THE GENETICS OF RAGWEED HAY FEVER

by

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I. INTRODUCTION

Ragweed hay fever makes thousands of people miserable every year. These people have an allergy to ragweed pollen. The characteristic symptoms include rhinitis, sneezing, nasal blockage and itching of the nose, eyes and throat. These symptoms appear in sensitive people soon after ragweed pollen is introduced into the environment. They occur every year from about the middle of August until the first frost, during the time that the wind-pollinated plant is dispersing its heavy load of pollen. The plants causing most trouble are the short ragweed, Ambrosia artemisiifolia L. var. elatior (L.) Descourtils, giant ragweed, Ambrosia trifida L., and western ragweed, Ambrosia psilostachya DC. var. coronopifolia (T. & T.) Farw. (Bassett and Frankton, 1961).

A. Definition of Allergy.

Allergy has been recorded from the time of the early Greeks (Vaughan, 1948), but von Pirquet (1906) was the first to call the condition "allergy" and to define it. He stated that allergy was "the change in the condition of the organism brought about by the contact with some organic toxin or other", i.e. a "changed reactivity" of the individual toward a substance (Schwartz, 1952). This is an extremely general definition and may include almost any pathological condition.

A more limited meaning is implied when "allergy" is used as a synonym for "hypersensitivity". The term "allergy" is sometimes used in the still narrower sense of being a "true hypersensitivity", i.e. a hypersensitivity which occurs spontaneously in only a small proportion of the population and cannot be induced in the remainder. By this definition, one implies an intrinsic factor which is most easily thought of as being hereditary in nature. This point of view in a study designed to determine whether heredity plays a part in the etiology of the condition would introduce an immediate bias. The same criticism can be applied even more rigorously to use of the word "atopy" interchangeably with allergy, since Coca defined atopy as "a type of hypersensitiveness peculiar to man, subject to <u>hereditary</u> influence, presenting the characteristic immediate whealing type of reaction, having the circulating antibody reagin, and manifesting peculiar clinical syndromes, such as asthma and hay fever" (Schwartz, 1952).

Because of such obvious bias in these definitions, it was decided to define allergy from the clinical picture observed. For the purpose of this study, major allergies are hay fever or asthma or atopic dermatitis or some combination of these. Other lesser allergic manifestations included are urticaria, drug sensitivity and gastro-intestinal upsets produced by known foods. These conditions are generally

found only in man, but there are now reports of allergic dogs (Wittich, 1941; Patterson, Chang and Pruzansky, 1963).

Early workers in allergy felt that the allergic manifestations that they were seeing were quite different from those observed in protective immune reactions as they knew them because no precipitating antibodies were demonstrable in the sera of allergic patients, because the allergic conditions occurred in only a small proportion of the population (about 10%) and because the end result could be harmful or undesirable rather than protective. Now allergy is accepted as being probably another variation of the general immunologic response and is probably due to the union of an antigen with a specific antibody which initiates a chain of events resulting in allergic symptoms.

B. Antigens.

An antigen is any material foreign to the circulation of the host which will result in the production of specific antibodies which will, in turn, react only with that antigen, or perhaps with only a very few other closely related, cross-reacting antigens which happen to have a common configuration. The majority of antigens are proteins, although other substances such as carbohydrates can, on occasion, act as antigens. Some substances, termed haptens, only become antigenic after union with protein. In some drug sensitivities, the

drug acts as a hapten. Generally, a substance must have a molecular weight of more than 10,000 to be antigenic, but there are exceptions, such as insulin. The shape of a molecule plays some part in determining antigenicity and most antigens are globular in shape. The type of antibody produced depends on the type of determinant group (such as acid radicals or the constituent amino acids in a protein) present, on the position of the determinant group and on the spatial configuration of this group. The number of sites on an antigen capable of reacting with antibodies is the valence of the antigen. Antigens are usually multivalent (Raffel, 1961).

Other factors determining whether a substance will be antigenic include route of injection, vehicle used for injection, e.g. Freund's adjuvant increases antigenicity, length of time the antigen is in the host, nutritional state of the host, etc.

The antigens most important in clinical allergy are the pollens of wind-pollinated plants, mould spores, animal danders, dust, feathers and many foods, and are usually termed allergens. Allergens are usually poor antigens.

C. Antibodies.

Raffel (1961) defines an antibody as a "humoral globulin produced in response to an antigen and capable

of reacting with the antigen in some observable way." Antibodies are gamma globulins which are not in any way different from normal serum gamma globulins except that they react with antigens. Gamma globulins can be characterized by centrifugal or electrophoretic means. When using centrifugal means, the characterization into 7S and 19S gamma globulins is on the basis of sedimentation constant, determined by molecular weight. When using electrophoretic means (immunoelectrophoresis), the characterization into $gamma_2$, $gamma_1A$ and $gamma_1M$, is on the basis of electrical charge and antigenicity. Antibodies are found in all classes of gamma globulins. For instance, most of the anti-bacterial antibodies are found in the $gamma_2$ globulins, the rheumatoid factor is found in the 19S $gamma_1M$ globulin fraction and the circulating ragweed reagins are probably 7 to 15S $gamma_1A$ globulins (Franklin, 1962).

In 1940, Pauling reached the conclusion that precipitating antibody molecules must have a valence of at least two, i.e. two combining sites, in order for precipitation to occur. In 1950, Porter verified this hypothesis. By digestion with papain, he was able to break the antibody molecule into three polypeptide chains, which he designated as chains I, II, and III. Chains I and II are similar and are believed to contain the antibody-

combining sites because these fragments do react with antigen to form a soluble complex. However, they inhibit precipitation and this provides good evidence that at least two combining sites are necessary for precipitation. The larger chain, III, probably governs the antigenic specificity of the gamma globulin molecule as it shows no antibody activity but contains the antigenic sites of the original molecule (Porter, 1959).

Antibodies can be detected by a number of tests varying in sensitivity. The ring test and the precipitin test, which detect antibody by the formation of a precipitate upon union of the antibody with soluble antigen at optimal concentrations, are the least sensitive in vitro methods. More sensitive techniques are the agar gel techniques, the Coombs test, and the collodion particle and agglutination methods. The last three methods involve adsorption of the antigen to larger particles before reaction with the antibody. Still more sophisticated methods include complement fixation, passive cutaneous anaphylaxis and fluorescence techniques (Raffel, 1961).

There are still many unexplained phenomena in immunology such as the question of the site and regulation of antibody synthesis. Although a great deal of controversy still exists, most immunologists feel that the plasma cell is the most likely cell in which antibody is produced (Burrage et al., 1956). There is presently no explanation for the

continued production of antibody in the absence of antigen or for the diversity of antibodies synthesized in the body. The characterization of the Gm and Inv genetic loci is one small step toward an answer (Harboe, Osterland and Kunkel, 1962).

D. Antibodies Found in Allergic Patients.

Several antibodies are found in the sera of allergic patients but the characteristic antibody found in these patients is known as reagin. This antibody has a special affinity for the skin and therefore is also known as skin-sensitizing antibody (SSA). It is a non-precipitating antibody and its presence was first detected by skin tests. Reagin migrates electrophoretically with the $gamma_1$ fraction of gamma globulin and is probably a 7 to 15S $gamma_1A$ globulin. This antibody, which is heat labile and has a molecular weight of about 500,000, does not cross the placenta and hence is not passively acquired by the foetus (Rosen, 1962; Boyden and Roth, 1963). Reagin can be passively transferred to non-allergic individuals in what is known as the Prausnitz-Küstner reaction (after Prausnitz and Küstner who first described it (1921)). This was the reaction which initially demonstrated the presence of circulating reagin. If serum from an allergic patient is injected intradermally into a

non-allergic patient and the site of injection is challenged 24 to 48 hours later with the specific allergen, a positive skin test (wheal and flare reaction) will occur. Similarly, a transfusion of allergic serum will result in a temporary skin sensitivity and possibly, temporary symptoms in the recipient (Boyden and Roth, 1963). In vitro, reagin, in the presence of the specific allergen, causes release of histamine from peripheral white blood cells (Katz and Cohen, 1941; Noah and Brand, 1954). Reagin probably cannot be induced in non-allergic individuals, although recent work with new repository treatment has provided some evidence to the contrary (Sparks, Feinberg and Becker, 1962). Also, there has been no direct evidence until very recently that reagin is responsible for the clinical symptoms of allergy. The study of Connell and Sherman (1964) has indicated the possible existence of a correlation between reagin titer and severity of clinical symptoms. These workers found, after collecting and testing the sera from 109 ragweed hay fever patients, that the group of patients with the highest titers of skin-sensitizing antibody also had the most severe symptoms.

Besides reagin, other antibodies detected in the sera of treated allergic individuals include blocking antibody, hemagglutinating antibody and the conventional "immune" antibody. All are alike in that they have a sedimentation constant of 7, a molecular weight of about 150,000, no particular

affinity for the skin, and do not give a Prausnitz-Küstner reaction. They can be induced in normal people and do cross the placenta (Rosen, 1962; Boyden and Roth, 1963). There is a great deal of controversy concerning hemagglutinating antibody. Blocking antibody will be discussed later in connection with hyposensitization treatment.

E. Mechanism of Hypersensitivity Reactions.

The initial event in any hypersensitivity reaction is the union of an antigen with its specific antibody. Under the appropriate conditions, the combination of antigen and antibody will result in the release of histamine from the mast cells and from other body cells. In immediate hypersensitivity, such as found in clinical allergy, it is known that the release of histamine from sensitized cells is most important, but it is not known whether this release is limited to the target organ only, e.g. lungs or nasal mucosa, or occurs in the body generally (Raffel, 1961).

Histamine, the major chemical mediator in allergic reactions, is a derivative of the amino acid, histidine, and is found in high concentration in the mast cells. It produces smooth muscle contraction, vasodilation and increased capillary permeability (Guyton, 1956). These three characteristic actions are sufficient to explain many allergic hypersensitivity reactions.

In addition to histamine, other chemical mediators such as serotonin, slow-reacting substance, bradykinin, acetylcholine and heparin are also thought to play some role in hypersensitivity responses (Boyden and Roth, 1963) so it is not surprising that anti-histamines used in symptomatic treatment do not give complete relief to all allergy sufferers.

F. Skin Tests.

The skin test is one of the methods used in the diagnosis of allergy. The test consists of the introduction of the allergen into the skin, either by a scratch or puncture technique, or by intradermal injection. The latter method is the most sensitive of the three (Fineman, 1926). Most allergic patients have immediate skin sensitivity. Thus, when the appropriate allergen is introduced, a wheal and flare reaction appears in 10 to 20 minutes and denotes the presence of reagin and hence, sensitivity.

The mechanism for this immediate reaction, although controversial, seems to be similar to the triple response of Lewis. Union of antigen and antibody results in histamine release, which in turn causes local dilation of the small vessels, which appears as erythema. The dilation is also accompanied by increased permeability of the vessels and

consequent escape of the plasma into the tissue spaces, resulting in edema or wheal formation (Crawford, 1963).

Skin tests show a reasonable correlation with clinical symptoms. The best correlation is found in testing with pollens and tests for other inhalants stand second in value. Tests with food allergens are much less reliable (Sherman and Kessler, 1957). Thus, a positive skin test may appear in the absence of clinical symptoms, perhaps indicating past or future sensitivity (Bissell, 1958). More rarely, the opposite situation obtains, i.e. a negative skin test in the presence of definite symptoms.

G. Hyposensitization Treatment of Allergy.

The idea of hyposensitization treatment dates back to the discovery that a temporary relative refractoriness to anaphylaxis could be induced with injection of minute quantities of the antigen at regular intervals. Noon (1911) applied this method in the treatment of allergy and found it to be effective. He gave multiple injections of increasing quantities of the allergen. This method is still followed today with variable success. About 80 to 90% of hay fever patients and 50 to 60% of those with asthma get marked relief (Criep, 1958).

The mechanism of relief in clinical allergy is not understood. It is apparently different from the mechanism

of desensitization in anaphylactically sensitized animals, where the concentration of circulating antibody is diminished by repeated injection of small amounts of antigen. In clinical hyposensitization, there is usually no decrease in circulating reagin concentration in the sera of treated patients, although the symptoms may have improved (Levine and Coca, 1926).

A new antibody was found in treated patients (Cooke et al., 1935). It was called "blocking antibody" because it appears to block or inhibit union of antigen and reagin by having a greater affinity for the antigen than does reagin. In addition, this "blocking antibody" can be distinguished from reagin by differences in molecular weight, placental transfer, affinity for the skin and the other characteristics mentioned earlier (Boyden and Roth, 1963). Blocking antibody can be induced in normal individuals who have received allergen injections (Cooke et al., 1937). These observations would suggest that the induction of blocking antibody is responsible for clinical improvement but the evidence is not strong as studies have indicated that there is no direct correlation between amount of allergen injected and amount of blocking antibody present or degree of relief from symptoms (Levin, 1959; Delorme et al., 1961).

II. LITERATURE REVIEW

The recognition of a possible familial tendency in allergy is not new and investigations into the problem date back at least to the seventeenth century. However, for the purpose of this study, only more recent works will be discussed since they are the most relevant to the interpretations which have directed thinking in this area. Most of the reports which simply quote prevalence figures suggesting a familial tendency, but which do not expand on the nature of this tendency, have been omitted.

Although few of the major studies deal exclusively with hay fever, most of them include this allergy. Consequently, by reviewing these reports, it is possible to form some definite ideas concerning the heredity of hay fever.

It is important to note that most of the investigators in the studies being reviewed use the "percentage positive family history" approach, i.e. they compare the percentages of positive family histories in an "allergic" and "non-allergic" series and accept an elevated frequency of positive family histories in the probands of the former group as evidence for a familial tendency. Such an approach is valid only if the "non-allergic" are comparable to the "allergic" groups in all relevant features including the degree of thoroughness with which they are investigated, and this has usually not been the

case. Furthermore, allergy afflicts from 10 to 20% of the population, so that even if there were no familial tendency, most of the population would have at least one affected relative simply on a probability basis. The number of affected relatives, and hence indirectly, the prevalence of positive family histories, depends on the number of relatives included in the family history. The following table illustrates this point.

Table 1. Probability of at least one family member being affected with "allergy" by chance alone (assuming a 10% allergy incidence). (Adapted from van Arsdel and Motulsky, 1959).

Family Size (n)	Probability $1-(.9)^n$
1	.10
2	.19
3	.27
4	.34
5	.41
6	.47
7	.52
8	.57
9	.61
10	.65

A. Studies Which Favour Heredity in Allergy.

1. Studies of Allergy in Large Samples.

Cooke and Vander Veer (1916) were the first to undertake a large scale study to determine whether there was an hereditary factor in allergy. The study is comprehensive and very good for the time at which it was done. The experimental material consisted of 504 patients who had hay fever, bronchial asthma, angioneurotic edema or acute gastroenteritis after ingesting certain foods. They were chosen from people who had been observed over a 5-year period, presumably at a hospital, but this is not stated. Their ages ranged from one to 77 years. Comparable information concerning ages of the 68 and 76 members in the two small control series is lacking, so there is no indication of whether the composition of the three groups is similar. Also there is no specific information about the criteria for choice of the probands in any of the groups.

A population frequency of allergy of 7% was calculated from the observation that 14 of the 204 persons in one control series (the 68 random persons plus their parents) had an allergic history. Of the 504 allergic cases, 48.4% had a positive family history of allergy as compared to 9.5% and 14.5% in the two control series. The elevated percentage of positive family histories in the allergic group suggests a familial tendency. The interpretation is that one inherits not a

specific sensitivity, but rather "an unusual capacity for developing bioplastic reactivities to any foreign proteins." This capacity is inherited equally from the maternal and paternal sides.

Analysis of the data concerning allergic persons with a positive family history indicates that the stronger the family history of allergy, the lower the age of onset of clinical symptoms. Both Ratner et al. (1941) and Schwartz (1952) disagree with this interpretation because many of the probands had hay fever, which has a late age of onset (Markow and Spain, 1930; Bray, 1931), and many of these probands reported a negative family history, so it is conceivable that this disease had not yet developed in some family members, but the impression would be that those who develop allergy late in life have a negative family history.

When the number of offspring affected (there is no indication of whether the probands were included, but it is likely that they were) and the distribution of age of onset was taken into consideration, it was estimated that, in the group with bilateral inheritance, 67.5% of the offspring would eventually develop symptoms, and in the group with unilateral inheritance, 60.0% would eventually be affected. Schwartz (1952) feels that these calculations are unjustified, probably because he is not satisfied with the age of onset data. However, these estimated percentages were thought to

be near enough to 75% and 50% to make dominant inheritance a logical interpretation of the results. It must be recalled that the analysis deals with families with at least one affected, and this would result in an increase in the observed affected offspring, unless the probands were excluded. There is no indication of what was done here. Also, for this interpretation of dominant inheritance, it is assumed that all those who are affected are heterozygous for the gene. The authors are probably justified in making this assumption as, even with a frequency of allergy of 7%, less than 2% of those affected will be homozygotes. The high frequency of allergic probands with a negative family history, 51.6%, is attributed partly to underreporting, especially in the case of hay fever where symptoms may go unnoticed, and partly to the possibility that some people have a latent allergy which can be transmitted to and expressed in their offspring.

To verify the findings of Cooke and Vander Veer (1916), Spain and Cooke (1924) carried out a second similar study on a different series. The methods used were almost identical and the same criticisms concerning size of the control population, composition of the groups, methods of analysis of data, etc., also apply. An additional criticism concerns use of the word "atopy" meaning "inherited human hypersensitiveness" in a study designed to determine whether heredity does play a part in the development of an allergy. Nevertheless,

the study is again very thorough and is this time limited to asthma and hay fever. The 462 allergic probands had either asthma or hay fever and a positive cutaneous reaction to confirm the sensitivity. There is no indication of whether the 115 non-allergic control probands were skin-tested, nor of how many relatives of the allergic probands were tested.

The frequencies of positive family histories in the allergic and control series were 58.4% and 7%, respectively. This last figure of 7% is obviously too low because, as Table I indicates, even if each proband had a family consisting of only one member, with a population frequency of allergy as low as 7%, the frequency of probands with a positive family history would be 7%. However, the increased occurrence of positive family histories in the allergic group over that in the allergic group of the previous study perhaps implies that one is now dealing with specific inherited factors rather than more general ones. At any rate, the calculated values of 71.6% and 56.1% for anticipated affected offspring from cases with bilateral and unilateral histories, respectively, fit more nearly the expected values for dominant inheritance than did the corresponding values in the first study. In this second study, the conclusion is that hypersensitivity is due to a dominant and multiple gene, the component parts of which are separately inherited. Inter-

pretation of this conclusion in modern genetic terms is difficult, if not impossible.

Adkinson (1920) made an extensive study of the families of 400 individuals with bronchial asthma and concluded that allergy is inherited as a recessive condition. No information about the frequency of allergy in families of non-asthmatic persons is presented for comparison so there is initially no basis from this study for any statement concerning inheritance. Nevertheless, her conclusion that recessive inheritance was operating was based on the observation that normal parents, who are supposedly heterozygous because there was asthma in their families, are able to transmit the disorder. Adkinson's data do not support this conclusion. Theoretically, in a heterozygote x heterozygote mating, one-quarter of the offspring should be affected, and Adkinson's results show three times as many allergic as normal children from such matings. She accredits the discrepancy to incomplete records of normal individuals and does not consider the possibility of incomplete dominance by which some of her pedigrees could equally well be explained (Richards and Balyeat, 1933). She also finds, as did Spain and Cooke (1924), that a positive family history lowers the age of onset of symptoms. Further, the sensitivities of parent and offspring are not necessarily the same. In those asthmatics with a positive family history, it is found that equal numbers of

males and females inherit the condition from the father, but twice as many females as males inherit it from the mother. This would imply that in a sample of asthmatics, more females than males would be affected, but nearly all investigations disclose a slight preponderance of affected males (Schwartz, 1952). Schwartz has directed other criticisms at Adkinson. He suggests that the pedigrees presented were selected, and states, "There was no substantiation of the different diseases and there is no indication whether the same amount of effort went into collecting each pedigree." This study is not well accepted today.

Coca (1927) hypothesized that hay fever and asthma, rather than being controlled by the same single hereditary factor, as suggested by previous workers (Cooke and Vander Veer, 1916; Adkinson, 1920; Spain and Cooke, 1924), were controlled by three different hereditary factors, one determining the shock organ, another determining the age of onset of symptoms, and the third determining the allergen to which one responded. Most of Coca's work was concerned with evidence for the hereditary determination of the shock organ. Some support for this view is the presence of the same reagin in two individuals, one of whom may have hay fever, and the other asthma; and, the induction of a "constitutional reaction" upon injection of worm extract into three worm-sensitive people, who were also asthmatics for a different reason

(Walzer and Brunner, 1927). This evidence scarcely justifies the conclusion that shock organs "are in general and individually subject to hereditary influence."

A subsequent investigation of the "pure" antecedents of "pure" hay fever and "pure" asthma probands (Clarke, Donnally and Coca, 1928) was designed to test the supposition of a separate hereditary tendency in these allergic manifestations. Of 180 asthmatics, 81.1% had one or more antecedents with asthma only, and 18.9% had one or more antecedents with hay fever only. Of 251 hay fever probands, 62.9% had ancestors with hay fever only, and 37.1% had ancestors with asthma only. This implies that all the probands have "pure" ancestors of one kind or the other, but not of both kinds. Since both conditions appear in the families of both sorts of probands, one would expect to find both conditions within the individual families also, but this does not appear to be the case. While this evidence is puzzling, as it stands it is compatible with Clarke et al.'s interpretation that each allergic manifestation is transmitted independently. These authors make no suggestion as to the possible mode of transmission.

The study of Peshkin (1928) is commendable for the thoroughness with which information was collected. In order to ensure a reliable family history, parents of 278 asthmatic children, three months to 14 years of age, were first

familiarized with allergic symptoms and with the purpose of the method of treatment employed for their child. After the child had been under observation for about two years, the parents were asked to complete a questionnaire regarding allergy in the family.

There was a family history of allergy in 42.57% of the probands. Unfortunately, there was no control series with which to compare this response. The 278 children were also tested by the scratch method for sensitivity to at least 65 proteins. Skin test response was independent of family history so the same conclusions apply to both the protein-sensitive and protein-nonsensitive groups. In the children who had developed asthma during the first five years of life, 35% of the total protein-sensitive group and 32% of the total protein-nonsensitive group had a positive family history of allergy, whereas in these two groups, 43% and 40%, respectively, had a negative family history. The conclusion, based on this evidence, is that asthma can be acquired as well as inherited. This conclusion does not necessarily follow from the data because the existence of a positive family history in a given proportion of the probands is not evidence for inheritance. Some (Schwartz, 1952) do not feel that this study is representative of allergy in the general population because all the probands were children.

The hereditary nature of allergy has been confirmed by Balyeat (1928) and Bray (1930, 1931). Balyeat found a positive family history in the families of 60.1% of 1000 cases of "atopy" (asthma and hay fever) as compared with 8.3% in "relatives of the first degree" of 1117 normal university students. This figure of 8.3% is below the general population figure and hence is suspect. The indication of earlier age of onset of symptoms with a positive family history, plus information from pedigree studies led to the conclusion that the ability to become sensitized is inherited as a single Mendelian dominant trait, and that "in the linkage, eczema and migraine are interchangeable with hay fever and asthma." Three pedigrees are included as evidence for this last statement. It was noted, too, that the earlier one becomes sensitized, the greater is the tendency to develop multiple sensitivities. Because the proportions of the patients with asthma or hay fever are not stated, the age of onset data means little (Schwartz, 1952). In addition, the control probands (university students) are too uniform a group to constitute a valid comparison with the allergic probands.

Bray (1930, 1931) found a positive family history of allergy (asthma, hay fever, eczema, urticaria and migraine) in 68.5% of 200 asthmatic probands, 12 years of age and younger, and accepts the prevailing view that allergy is inherited as

a dominant trait. There is no control series for comparison. In the first analysis (1930), it was stated that there was no evidence for family history affecting age of onset of symptoms in the first decade, but later (1931), this statement was modified and the idea that family history affects age of onset, even in the first decade, was accepted. In studying sex incidence, it was found that up to puberty, twice as many males as females were affected with allergy, and after that, there was an approximate equality of numbers (Bray, 1931). It was also noted that inheritance from the maternal side was twice as frequent as from the paternal side (see also Adkinson, 1920). This observation introduces the possibility that <u>in utero</u> sensitization, as well as Mendelian inheritance, is responsible for allergy. Alternatively, it might indicate the presence of psychogenic factors, the mother having a stronger psychological influence on the child than the father. Schwartz (1952) attributes a similar trend in his data to the fact that females know more about their families than do males.

Wiener, Zieve and Fries (1936), while they accept the premise that allergy is inherited, find that the evidence refutes both dominant and recessive modes of inheritance. They propose a third manner of inheritance to explain the bimodal distribution of age of onset of symptoms seen in the data (Cooke and Vander Veer, 1916; Spain and Cooke, 1924;

Bray, 1930), i.e. modes before and after puberty. They assume the existence of two alleles, h and H, where h is responsible for the allergic constitution, and H is its normal allele. Three genotypes are possible, HH, hh and Hh. Individuals of genotype HH are normal, those of genotype hh will develop allergy before age 10. Of the heterozygotes, Hh, 18% will develop symptoms after 10 years of age and the rest will remain symptom-free throughout their lives. Therefore, allergic individuals can be of two genotypes. On the basis of such an explanation, expected frequencies of bilateral, unilateral and negative family histories, calculated from data in other reports (Cooke et al., 1916; Spain et al., 1924; Bray, 1930), fit remarkably well with the observed frequencies. Part of the reason for the good fit seems to be that the argument is somewhat circular. The authors derive a gene frequency from a population, then apply these figures back to the same population. This is a minor part of the calculation, however. The postulated mode of inheritance cannot be completely tested because the number of critical matings (affected x affected) necessary for verification was not available. Despite the fact that this hypothesis does not explain the observation that twice as many males as females are affected with allergy in childhood, it has been well received because it seems logical (Vaughan, 1948).

Tips (1954) undertook a comparable statistical investigation in which he initially assumed an hereditary predisposition in atopic hypersensitivity and then went on to examine possible mechanisms of transmission and to test an alternative to Wiener et al.'s hypothesis (1936). Information about frequencies of general atopy, hay fever, asthma and eczema was collected by questioning a survey sample of 99 couples about these manifestations in themselves. The frequencies so obtained were then used to calculate the expected frequencies of the various mating types in a population if hay fever, asthma and eczema were each due to a recessive allele of a different gene pair. These expected proportions fit very well with those observed in a second population of 226 matings, which had been tested and found to fit the expectation for random mating. The conclusion reached therefore, is that three different loci are responsible for the three different conditions. Such a conclusion is complicated by the close relationship of these conditions. For example, Ratner (1938) finds that "eczema is a forerunner of asthma in many instances." This would favour a common factor being responsible, at least for eczema and asthma.

Although some skin-testing was done in earlier studies (Spain and Cooke, 1924; Peshkin, 1928), only in the more recent reports (Brem and Colmes, 1940; Bissell, 1958; Critz, 1961) has there been any emphasis placed on this method of

diagnosis in studies of the familial tendency in allergy. Brem and Colmes compare the frequencies of allergy and of positive skin tests to 35 allergens in 135 members of the families of 40 experimental probands who had any kind of allergy, with these frequencies in 17 members of 4 control families. They do not specify how any of the probands were chosen. In the allergic families, 30% of the members had a history of allergy as compared to none in the control series, but since the latter group is so small, results are not reliable. There was also a higher frequency of positive skin reactions in the allergic families, 3.5% (171/4860), than in the control series, 0.7% (4/612). Fifty-five of the relatives in the allergic families had at least one positive skin test. The corresponding figure for the control families is not given but at least two and perhaps four of the 17 had a positive skin test. This trend to an increased frequency of positive skin tests in allergic families was later confirmed by Bissell (1958).

Critz (1961) began with the good intention of correlating skin tests and family history data to evaluate more precisely the evidence for familial allergy. He has compared family history and number of positive scratch tests to 36 foods and 36 inhalants in families of 50 allergic children with the same information obtained from the sibs of 44 adults with no personal and no family history of allergy. Such a

control series is certainly not representative of the general population and comparison of the allergic group with it is meaningless.

Schwartz's comprehensive study on heredity in bronchial asthma (1952) originated because many were still skeptical about inheritance in allergy. Rather than defining some diseases as allergic in nature and then determining whether they were inherited, Schwartz began with a large number of diseases of a possible allergic nature, then let the statistics confirm their hereditary, and hence, definite "atopic" nature. He investigated the presumably allergic diseases, bronchial asthma, hay fever, vasomotor rhinitis, Besnier's prurigo (atopic dermatitis), eczema, urticaria, migraine, Quinke's edema, gastro-intestinal allergy, epilepsy, ichthyosis and psoriasis, in the families of three groups of probands: (1) 191 asthmatics with asthma of mixed etiology, (2) 50 asthmatics with baker's asthma, and (3) 200 control probands who did not suffer, or never had suffered, from any of the diseases included in the study. Disease in the asthmatic probands was well documented by a thorough examination and clinical tests. The control probands were well matched with the 191 asthmatics for age and sex ratio, but van Arsdel and Motulsky (1959) point out that the two groups are not strictly comparable since the control series, consisting of groups of individuals such as medical

students, differed in structure from the experimental group. Also, the baker's asthma group, in which special conditions were required for development of the disease, was of a different structure.

Personal or mail contact was attempted with all relatives of the probands to obtain accurate information, and whenever possible, skin tests were done for further verification, except in the case of healthy relatives of control probands. Detailed comparisons were made among the three groups for each disease. Because there was a higher frequency of asthma, vasomotor rhinitis, Besnier's prurigo and hay fever in the allergic groups than in the control group, and because these disorders show a positive correlation with one another, Schwartz concluded that the four disorders were genetically related. Ratner (1953) is disturbed because no correlation was found between asthma and eczema (including infantile eczema). Perhaps their individual definitions of the disorders could explain some of the divergence here. At any rate, in addition to the four conditions being genetically related, because asthma is the predominant disease in relatives of asthmatics, a "localization factor" for asthma, genetic in nature, is also suggested. From these results, Schwartz is willing to accept Coca's concept of atopy for asthma, vasomotor rhinitis, Besnier's prurigo and hay fever.

From a survey of 5818 college students, van Arsdel and Motulsky (1959) reported that 16.7% has asthma and/or hay fever. The prevalence of these two allergic disorders in the families of the allergic and non-allergic students was then compared. There was a positive family history more often in the former than in the latter group (56.5% versus 22,2%) and parental allergy was more frequent in the former than in the latter group (19.7% versus 5.6%). When both parents were affected, there were more affected offspring than when only one or neither parent was affected. In addition, those students with both asthma and hay fever had a higher frequency of positive family histories and a higher frequency of bilateral family histories than had the group with just one of these manifestations.

Although many of the results, such as the observed prevalence of 56.5% with a positive family history in the "allergic" group, could be explained by chance, the trend to an increased frequency of allergy in the allergic group was so consistent that an hereditary, or at least a familial factor, appeared necessary to explain it. An explanation by the mechanism suggested by Wiener et al. (1936) is possible, as is Penrose's idea of a polygenic system (1953), although the latter is more difficult to test.

For the study, all the information was obtained via questionnaire. Van Arsdel and Motulsky are aware of the

shortcomings of this method of data collection but feel that their questions were so designed as to limit a great deal of ambiguity, although they still recognize under-reporting as a problem.

A study on heredity in bronchial asthma was done recently in India (Viswanathan and Bharadwaj, 1962). The investigators state that they began with no preconceived notion about the role of heredity, if any, in the etiology of allergy. They personally interviewed 191 male and 143 female asthmatics, over 15 years of age, and took family histories from these people. This family history data was then compared with that from a control sample of 160 individuals obtained in a survey of two areas in Delhi.

Incidence of asthma in parents of allergic and control probands was 29.6% and 10.0%, respectively. This difference suggested a familial tendency in asthma. By examination of representative pedigrees for mode of inheritance, and by subsequent elimination of some of the modes, the conclusion that asthma could be due to an autosomal recessive gene was reached. This conclusion was further supported by evidence from different types of matings. Matings of normal x normal individuals (Aa x Aa), and normal x affected individuals (Aa x aa), showed twice as many affected offspring from the second type of mating (33.8%) as from the first (18.6%). This would be expected on

the basis of recessive inheritance. The later age of onset in some cases was thought to be the reason for obtaining 18.6% affected rather than the 25% expected for the normal x normal matings. Yet earlier reports (Bray, 1930) indicate that asthma generally has an early age of onset, and therefore, this disorder should have appeared in most of the family members studied.

It is difficult to evaluate this investigation because insufficient data is presented and because it is not clear how the average frequency of affected offspring was determined, but it does seem as if the proband was included in the initial totals of those affected.

2. Studies of Allergy in Individual Families.

Probably the first account of heredity in allergy in the twentieth century was a short publication by Drinkwater (1909) in which he presented a single pedigree involving three generations of a family. Because 10 of the 23 family members suffered from asthma, this single pedigree has been extensively quoted as evidence that asthma is inherited as a simple Mendelian dominant character.

Many similar reports of single pedigrees have been used to document the hereditary nature of allergy. Smith (1927) reported on 64 descendants in four generations, from

a marriage of first cousins, both of whom were hypersensitive. From information obtained by questionnaire, it was found that 56.2% of the family members had symptoms of hay fever, asthma, vasomotor rhinitis, urticaria, angioneurotic edema or eczema or any combination of these, while only one of 23 control subjects (spouses of family members) had any of these symptoms. This control series is obviously not suitable. However, because of the elevated frequency of allergy within the family, plus other considerations, the author states that hypersensitivity shows a dominant inheritance.

Bucher and Keeler (1934) report another large family in which 102 of 454 individuals in five generations were affected with allergy. Most of them had asthma, hives or eczema, although those with hay fever, allergic rhinitis, migraine, gastro-intestinal upsets and anaphylaxis were also termed allergic. Because migraine and intestinal upsets are questionable allergic manifestations and bacause anaphylaxis is not clearly defined but is not usually an allergic reaction, the authors' postulate that allergy is inherited as a simple unit dominant character becomes doubtful.

Apperley (1930) suggests that the ability to become sensitized behaves as a simple Mendelian dominant character because in a pedigree of 16 family members over 10 years of age, "12 to 13" had various allergies including migraine,

epilepsy and hyperacidity symptoms.

Crawford (1936) presents a pedigree which shows allergy in five generations of a family. She does not postulate any possible mode of inheritance for the condition but believes that a permanent metabolic error is responsible. In this report, train and car sickness were counted as allergies, but persons with these disorders also always had other, more legitimate, allergic manifestations, so these inclusions make little difference to the results.

Stiles and Johnston (1946) discuss a pedigree of five generations of a family which includes 232 persons, 22.4% of whom have respiratory allergies as compared to a frequency of 7% in the general population. Analysis of the data led the authors to adopt the view that the tendency to become hypersensitive was inherited as an incompletely dominant condition with low penetrance and variable expressivity.

3. Studies of Allergy in Twins.

Twin studies are a good way to detect or confirm an hereditary factor in a condition under study if they avoid the many biasses that tend to enter such studies (Metrakos, 1953). Unfortunately, twin studies have contributed little to clarify the situation regarding heredity in allergy

because early zygosity determinations were not precise, but chiefly because the investigator is hampered by the small numbers of twins available. Consequently, most of the reports, many of them appearing only in reports of verbal discussions on the subject, involve only one, or a few, sets of twins and results vary widely.

Richards and Balyeat (1933) mention one set, Benson (1937) two sets, and Fineman (1942) three sets of identical twins in which both members of the set had the same allergic symptoms. Buffum and Feinberg (1940) refer to three pairs of identical twins in which age of onset and severity of asthmatic symptoms were similar but skin test reactions differed somewhat. The case of monozygotic twins reported by Simon (1940) is quite striking in that the members of the pair, who both had similar clinical symptoms, also reacted similarly to all 96 allergens tested, with the exception of one, dust. In Hebald's single twin pair (1942), both members had hay fever, but the ages of onset differed. Credille (1937) reports one set of identical twins and Vaughan (1942) reports two sets of "look-alike" twins in which both twins had allergy, but the clinical manifestations were different. On the other hand, Kahn (1937) mentions one twin pair and Cohen (1937) "several" pairs in which only one member was allergic.

The report of Cooke et al. (1916) included six pairs of twins, zygosity not stated, three of which showed the same symptoms. Criep's (1942) seven sets of identical twins (zygosity determined by sex and physical appearance) showed a marked degree of intrapair correlation regarding symptoms.

No conclusions about the inheritance of allergy can be drawn from such reports except that since some monozygotic pairs are discordant, the allergy concerned cannot be entirely genetic in origin.

One would expect that Bowen's study (1953) would be more conclusive than the others already mentioned because large numbers (59 twin pairs) were involved. Unfortunately, only monozygotic twins were included, so the necessary comparison of the result that seven out of 59 were concordant for allergy, with a corresponding response in dizygotic twins, cannot be made. Again, however, the large number of discordant monozygotic pairs argues against any simple genetic basis for the disease.

The most reliable results come from a report by Spaich and Ostertag (1936) which included 71 unselected sets of twins, monozygotic and dizygotic, chosen from 2500 twin pairs about whom information regarding allergic diseases had previously been obtained. These twins were classified for presence or absence of hay fever, asthma, migraine and dermatoses. Concordance rates were calculated for allergic dis-

position and for specific allergy. For hay fever, the concordance figures for monozygotic twins were 100% for allergic disposition and 80% for specific allergy (hay fever), as compared with 100% and 0% (only two cases) for the dizygotic twins. The corresponding values for the other manifestations, except for asthma, are in the same direction. For asthma, the rates in identical twins are 57.1% and 28.6% as compared with 57.1% and 7.1% in dizygotic twins. This implies that environment plays a large part in the development of this disorder.

The general picture obtained was that if one twin had an allergy, the chance that the other would also have it, was increased, Because this was particularly true in monozygotic twins, a genetic factor, which the authors suggest is dominant, was indicated.

Ratner (1952) and Schwartz (1952) criticize the study because migraine and dermatoses are much more doubtful allergic manifestations than are asthma and hay fever and should not be considered as equivalent to them.

4. Studies of Minor Allergies.

Up to this point, the role of heredity in hay fever, asthma or simply allergy in general, has been emphasized. The minor allergies have not been neglected and an appreciable amount of literature exists on this subject. Suffice it here

to point out that these studies do exist and to give a few examples. There are reports of an hereditary tendency in urticaria (Baughman and Jillson, 1963), angioneurotic edema (Landerman, 1962), food allergy (Rowe, 1928), migraine (Buchanan, 1920; Richards and Balyeat, 1933), etc. Here again, views are as diverse as they are in the case of major allergies and again, no acceptable conclusions can be drawn.

B. Studies Which Oppose Heredity in Allergy.

Since the idea of heredity in allergy was first proposed, there has been dissention as well as agreement. Ratner has been a staunch and outspoken critic of the view and many of his criticisms are justified. He points out that almost every investigator differs in his interpretation of allergic conditions (1938). Some include conditions others would omit and vice versa, to the point that the allergic nature of some of the disorders included is questionable and comparison between studies is impossible. This variety of standards can best be illustrated by noting the different criteria employed in the reports of individual pedigrees (Drinkwater, 1909; Smith, 1927; Bucher and Keeler, 1934; Apperley, 1930; Crawford, 1936; Stiles and Johnston, 1946). Ratner (1953) severely criticizes Schwartz (1952) for setting

up his own criteria in his study. Another criticism concerning previous reports on familial allergy is that methods of data collection and extent of inquiry into the family history differ. In addition, definition of a positive family history varies. To some, a positive family history could mean that one of the grandparents' sibs was affected (Wiener et al., 1936), whereas others may not include first cousins in the determination. Further, the probands in some cases are children, in other cases are adults, and in still others, are a mixture of the two. This makes comparisons difficult. Lastly, Ratner's point that "there is a danger of concealing assumptions which have no factual basis behind the impressive façade of flawless algebra" (1953) is illustrated in some studies.

Ratner's results, in many cases, lead to conclusions contrary to some of the accepted ideas. Determination of the effect of family history on the age of onset of symptoms is a case in point. To determine whether a positive family history does lower age of onset of symptoms, Ratner (1938) examined 250 allergic children who had asthma, eczema, hay fever or urticaria. He found that 52% of those under one year of age had a positive family history. Examination of children up to the age of 10 years revealed no effect of heredity on age of onset. In another study (1956) of 62 allergic children, two to five years of age, 31 had a

positive family history. Similar results were obtained by O'Keefe (1936) from a study of 300 children, and by Stiles and Johnston (1946). Ratner (1938) also found that about 50% of allergic adults began having allergic symptoms as children. The implication is that family history has no effect on age of onset of symptoms. These results are opposed to those of Cooke and Vander Veer (1916), Spain and Cooke (1924), Bray (1930, 1931), but the studies of Cooke et al. and Spain et al. included mostly adults, many of whom have no definite recollection of the age at which symptoms first developed and this introduces error. Also many of the allergic probands in these two studies suffered from hay fever which has a known late onset. This late onset could give the appearance of a high frequency of negative family histories in hay fever sufferers and this outcome would favour the original interpretation. Ratner's interpretation is that variation in age of onset of any allergic symptoms is due to an exposure factor. This idea is acceptable, for many who have conducted surveys on allergy are willing to admit that even though they favour an hereditary factor, environment does play a large part in the development of the disease (Schwartz, 1952; Maternowski and Mathews, 1962).

A comparison of the prevalence of affected individuals in the families of 250 allergic probands with the

prevalence of affected individuals among 3000 medical students, nurses and doctors, disclosed no difference in the frequencies of allergy in the two groups. The frequencies are 9.8% and 10.0%, respectively (Ratner and Silberman, 1952). As added proof that this difference does not exist, the allergic probands were included in the calculation of the first figure, 9.8%. This, however, leads to the equally questionable conclusion that there is less allergy in the families of allergic probands than in the general population. Ratner has ignored this implication. He feels that the percentage of affected individuals one obtains is a question of criteria, since Vaughan (1933) found a 50% incidence of minor allergies in the general population. Therefore, when the same criteria are applied to two populations, there should be no difference in the percentages affected in an allergic and control group. That this statement is not valid is demonstrated by the many studies mentioned in which the same criteria have been applied to two groups and such a comparison has been made. On the other hand, Ratner's control group in this study of frequencies of allergic symptoms (1952) is not of the same structure as the experimental group to which it is being compared and hence, this comparison is not strictly correct.

It is true that much of the evidence for the idea of inheritance in allergy is based on a few striking pedigrees

(Drinkwater, 1909; Smith, 1927; etc.). Calculations using the 250 families studied by Ratner (1952) reveal that in only 0.8% of these families were there as many affected members as in the families reported by Drinkwater and Smith. Hence, conclusions supported by such pedigrees are obviously biased.

Besides Ratner, there are others who spurn the idea of heredity in allergy. One of these is Smith, who is disappointed with the lack of originality in thinking about allergy (1961). His purpose is to point out that "an inherited tendency to produce abnormal antibodies is by no means the only possible explanation of the allergic diathesis." The alternative he proposes, probably for argument's sake, is that allergy is an infectious disease. He draws parallels between the course of allergy and the course of infectious diseases. His study of 432 allergic patients discloses a high rate of close contact with other allergic persons for those who have no family history of allergic disease.

Prigal (1958) has also voiced this opinion. He suggested that perhaps asthma is associated with infection and intra-familial contagion and this could account for a seeming hereditary tendency.

Rapaport (1958) takes the compromising and probably most rational approach to the heredity versus environment

conflict and asks the question, "Why can't allergy be both inherited and/or acquired?" Hereditary cases would be those with a strong family history. When a single family member developed an allergic condition, then this could be the result of the environmental factor, exposure to a large amount of allergen.

III. PURPOSE OF THE PRESENT STUDY

The fact that most medical authorities invoke heredity as the underlying cause of allergic disease would make further investigation seem unnecessary. However, it is obvious that much conflict and confusion exists in the literature. Ratner (1952) has pointed out many of the reasons for disagreement. In addition, in many cases, information was obtained by questionnaire only and was not verified by objective means. Furthermore, the studies generally lacked an adequate control series.

It was therefore our purpose to clarify some of the aspects of the problem of heredity in allergy by designing a study which we hoped would minimize previous oversights. We focussed on one allergic disorder, ragweed hay fever, and sought answers to the following questions:

1. Is the prevalence of ragweed hay fever higher in the near relatives (parents, sibs, and by second-hand information, uncles, aunts, first cousins and grandparents) of probands with ragweed hay fever than in the same relatives of probands selected on the basis of <u>no personal history of ragweed hay fever and negative skin tests for the allergens tested</u>?

2. Is the prevalence of positive skin tests for ragweed pollen higher in the parents and sibs of ragweed hay fever patients than in the parents and sibs of the control group?

3. Is the prevalence of other types of allergy (asthma, eczema, etc.) higher in the near relatives of ragweed hay fever probands than in the near relatives of control probands?

4. Is the prevalence of positive skin tests for grass pollen and egg albumen higher in the parents and sibs of ragweed hay fever probands than in the parents and sibs of control probands?

5. Does the familial pattern (if any) of positive skin tests for ragweed pollen (or if 4 is answered "yes", any positive skin test) fit a Mendelian expectation?

6. Is the frequency of positive skin tests higher in mothers than in fathers of ragweed hay fever probands (evidence of trans-placental or trans-milk sensitization)?

IV. MATERIALS AND METHODS

If the frequency of ragweed hay fever and/or other allergy in the relatives of a child with ragweed hay fever is no higher than in the relatives of a child who does not have such a condition, one might assume that ragweed hay fever and/or other allergy is not inherited. This is the basic assumption of the present study. If, on the other hand, there is a familial tendency, one may proceed to the question of whether the familial tendency is genetic, or the result of familial environmental factors. Accordingly, two groups of individuals were chosen for the comparisons: families of probands with a positive skin reaction to ragweed pollen extract and the clinical symptoms of ragweed hay fever, and families of probands with no positive skin reactions to the three allergens tested and no clinical symptoms of ragweed hay fever. The existence of other allergies in the probands was taken into consideration in the data analysis.

Because the control probands are members of twin pairs, another method used in human genetics to determine whether a condition is inherited, the twin study method, can also be applied in analyzing this material. If, in using the twin method, it is found that the concordance rates are higher in monozygotic twins than in dizygotic

twins, this is further evidence that the condition under consideration is inherited.

It was decided that 50 probands in each group would be sufficient to indicate whether allergy is familial. Probands in each group were children from the ages of 5 to 15 years inclusive, who, with their parents, had lived in Montreal (or another locality with a comparable ragweed pollen count) for at least five years. The last stipulation would ensure adequate exposure to the allergen, ragweed pollen. Allergic probands were chosen, without knowledge of their family history, from the files of children attending the Allergy Clinic at The Montreal Children's Hospital or were private patients of allergists affiliated with The Montreal Children's Hospital.

The control probands were the first born members of twin pairs on file in the Department of Medical Genetics at The Montreal Children's Hospital, and consisted of 20 monozygotic, 14 like-sexed dizygotic and 16 unlike-sexed dizygotic twin pairs. Appearance appraisal, blood tests and fingerprint analyses, in various combinations, were used for zygosity determination. In cases in which two sets of twins in the same family were in the age range of 5 to 15 years, the first born member of the oldest set was chosen as the proband. In

sib analyses, monozygotic twins were counted as one individual, dizygotic twins as two individuals. If the "control" proband had both a positive skin test to ragweed pollen and the clinical symptoms of ragweed hay fever, he was placed in the experimental group. Many of the "control" probands, who did not fit into either the control or experimental groups because they had positive skin tests but no ragweed hay fever symptoms, could be used in the determination of concordance rates.

Families of probands meeting the necessary requirements were first contacted by mail. They received a letter, which, in a general manner, indicated the nature of the study, including the type of tests to be done and the information required. After allowing sufficient time for discussion, the family was contacted by telephone to determine its willingness to participate. If an interest in the study was expressed, an appointment was made for a home visit.

During the visit, the probands' parents and sibs, five years of age and older, were skin-tested and an allergy history of each was recorded. Also, allergy histories of grandparents, aunts, uncles and first cousins of the probands, 10 years of age and older, were obtained. Histories were verified whenever

possible and were also reviewed by two allergists.

A. Skin - Testing.

Skin tests were done for an indication of sensitivity to ragweed pollen, to another air-borne allergen, grass pollen, and to a food allergen, egg albumen. About 0.02 cc. (Crawford, 1963) of the following preparations: ragweed pollen extract, 100 protein nitrogen units/cc., grass pollen extract, 100 protein nitrogen units/cc., egg albumen, 1000 protein nitrogen units/cc. and buffered saline control solution, were injected intradermally at four separate sites in a single vertical row on the forearm. The materials were prepared and supplied by the Department of Allergy and Clinical Immunology at The Montreal Children's Hospital. The order of injection remained constant throughout the study with the saline control always at the most distal site. Since drainage in the lymph vessels in the arm is from distal to proximal, the distal location was chosen for the saline injection so there would be no drainage to this site to give a false positive control reaction.

Skin tests were read by examining the sites of injection 10 to 20 minutes after administration of the allergen. The reaction was compared with that elicited

by the saline control (negative reaction). Generally, a positive cutaneous reaction is an itching wheal surrounded by a flare (Figures 1a and 1b). By our criteria, any reaction with a wheal four millimeters in diameter or larger, accompanied by some area of erythema, was considered positive.

The allergic probands were not usually retested when the other family members were being tested and their earlier skin test results were used in analyses. The earlier results were thought to be the most reliable because many of the probands were being treated for allergy and treatment may reduce the intensity of the skin test reaction (Lamson et al., 1928).

B. History - Taking.

The form used for taking the allergy history of immediate members of the family is reproduced in Figure 2. Questions similar to those appearing on these sheets were asked regarding the more distant relatives.

Only those individuals having characteristic symptoms of seasonal allergic rhinitis, perennial allergic rhinitis, asthma or eczema were considered to have a major allergy. Specifically, allergic rhinitis was diagnosed by a history of nasal drainage and the existence of at least two of the

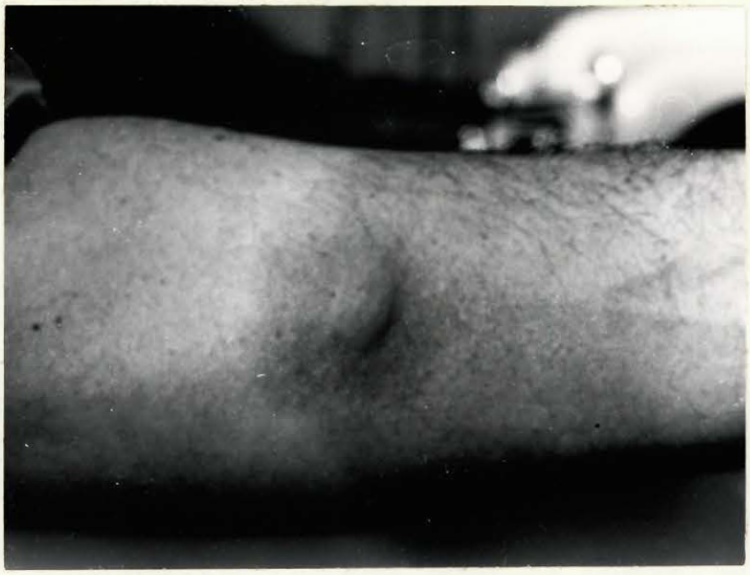

Figure 1a. Positive skin reaction showing raised wheal and surrounding flare.

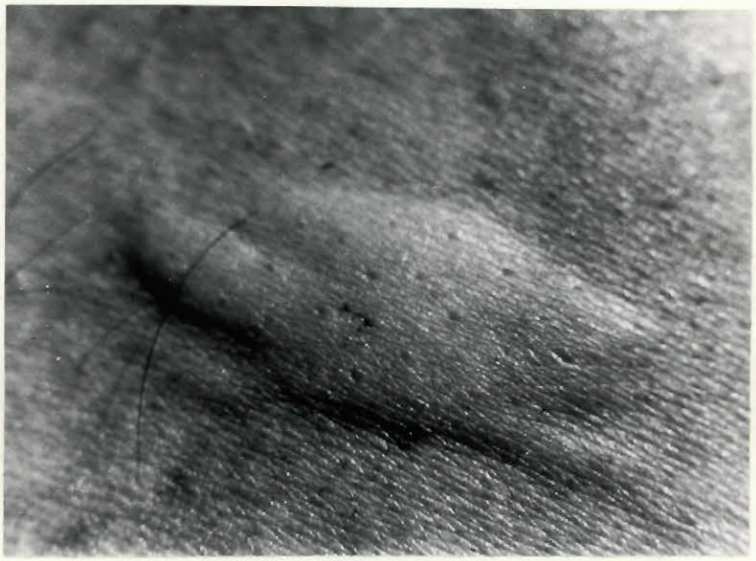

Figure 1b. Enlargement of wheal to show pseudopodia.

THE MONTREAL CHILDREN'S HOSPITAL
Departments of Allergy and Genetics -- Genetics of Hay Fever Study
Personal History Form

NAME_____ Relationship: Proband M. F. Sib

I. SEASONAL ALLERGIC RHINITIS During the period	Ragweed Aug. 15 -frost	Trees Apr.- May	Grasses June- July	Moulds July 15 -Dec.
(1) Paroxysms of sneezing				
(2) Itching of the nose				
(3) Blocked nose & clear discharge				
(4) "Cold" without fever				
(5) Red, itchy eyes				
(6) Tearing				
(7) Swollen eyelids				
(8) Coughing				

II. PERENNIAL ALLERGIC RHINITIS (record + or -)

	Diagnosed by: doctor	self	other
(1) History of P.A.R.			
(2) Continuously blocked nose	___		
(3) Paroxysms of 3 to 10 sneezes	___		
(4) Nasal discharge, thin and watery	___		
(5) Or purulent	___		
(6) Constantly itching nose	___		
(7) Constantly rubbing nose	___		
(8) Recurrent throat clearing	___		
(9) Post-nasal drip	___		
(10) Recurrent cough			
(11) Continuous cold, no fever	___		
(12) More than 1 adenoidectomy	___		
(13) Polyps	___		
(14) Nosebleeds			
(15) Croup	___		

Figure 2.

Personal History Form NAME_____

III. ASTHMA (record + or -)

(1) History of bronchial asthma Diagnosed by: doctor self other

(2) Periodic attacks of:

wheezing ___ audible laboured breathing ___

coughing or bronchitis___ short of breath without exertion___

(3) Well between attacks?_____

(4) Time of attacks: Spring Summer Fall Winter Duration_____

(5) Precipitated by: Food___ Inhalants___ Drugs___ Contactants___

Nonspecifics: Exercise___ Emotion___ Humidity___ Others___

(6) Treatment_____ (7) Response_____

IV. ATOPIC DERMATITIS (ECZEMA) (record + or -)

(1) History of eczema Diagnosed by: doctor self other

(2) Itchy rash on creases of arms and legs____ on neck____

face____ body____

(3) Does rash come and go?_____ moist____ dry____ scaly____

V. DRUG ALLERGY

Penicillin_____ Sulfa_____ Aspirin_____ Other_____

Describe reaction_____

VI. URTICARIA (HIVES)

(1) History of hives Diagnosed by: doctor self other

(2) Recurrent reddish welts, that come and go without leaving marks?_____

(3) Are welts itchy?_____

(4) Recurrent swellings of face____ lips____ eyes____ hands____

Personal History Form NAME_____

VI. URTICARIA (HIVES)

(5) Precipitating factors: Food (specify)_____

Drugs: Penicillin_____ Sulfa_____ Aspirin_____ Other_____

Infection_____ Emotion_____ Inhalants_____ Contactants_____

VII. MISCELLANEOUS

(1) Migraine_____

(2) Unusual vomiting, diarrhoea, or other intestinal upset after eating any particular food_____

(3) Contact sensitivity: poison ivy_____ other_____

VIII. SKIN TESTS

Ragweed	Egg Albumen	Grass	Control

Date_____ _____
Interviewer

other symptoms listed in the questionnaire. Asthma was diagnosed by the presence of wheezing and shortness of breath plus supporting information regarding the nature of the attacks, their duration, etc. Diagnosis of eczema was made chiefly by a history of chronic pruritic eruption and by the areas affected--face, trunk, popliteal and cubital fossae.

Slightly different criteria were used for the minor allergies. Urticaria was considered only when recurrent, and gastro-intestinal allergy only when the offending food was identified. Drug sensitivities were diagnosed when the specific agent was known and the symptoms were well-defined (urticaria, dermatitis, exanthem).

People were questioned concerning contact dermatitis due to wool, poison ivy, etc., but in compiling the data, this information was omitted since it was felt that reactions of this nature did not usually constitute an allergy.

A history of migraine was obtained because some believe it to be an allergic manifestation. However, although it was omitted in the analyses of major and minor allergies, a comparison was made of the prevalence of migraine in the experimental and control groups. Migraine was diagnosed if the individual had an aura (flashing lights, etc.) with nausea and unilateral headache of great severity.

V. RESULTS

When this study originated, it was proposed to compare the prevalence of allergic symptoms and positive cutaneous reactions in two groups, an "allergic" experimental group with probands chosen from the Allergy Clinic at The Montreal Children's Hospital and from private allergy practices, and a "non-allergic" control group chosen from files of twins. However, it soon became evident that those allergic probands who were private patients must be placed in a separate group from those who were clinic patients because the two groups were selected by different people (their allergist in the first case, and the present investigator in the second) and because the two groups appeared to differ in a number of ways. To distinguish these groups in the following discussion, the group of 50 families obtained through the Allergy Clinic will be known as "Experimental Group I" and the group of 12 families from the private allergy practices as "Experimental Group II". The third group is the Control Group.

There were two families in Experimental Group I which might have been ascertained twice (because a sibling met proband requirements) but since counting

these families once or twice would make little difference to the final totals, they were included only once.

The pertinent facts concerning the structure of each group are given in Table 2. The table shows mainly that the siblings and parents of the probands in Experimental Group I and the Control Group are older than those in Experimental Group II, that Experimental Group II families are the smallest, and that there is an excess of males in the siblings of allergic probands. The twins (Control Group probands) are usually among the younger members of their families because of the known correlation of twinning with maternal age (Enders and Stern, 1948). The differences in the three groups are not so great as to make comparisons invalid and they actually aid in explaining the results. The question of abnormal sex ratios will be discussed elsewhere.

Separate analyses were done for prevalence of positive cutaneous reactions and of clinical symptoms because the correlation between the existence of a positive cutaneous reaction to an allergen and the development of clinical symptoms from exposure to that allergen is not absolute, and because not all the allergens responsible for clinical symptoms are being tested. The results should, however, be similar in both cases.

Table 2. Comparison of the structure of Experimental Group I, Experimental Group II, and the Control Group.

	Exp. Group I	Exp. Group II	Control Group
Average age of proband (years)	10.3±3.0	9.6±2.6	9.1±3.0
Average maternal age[1] (years)	39.9±5.8	36.4±5.8	39.6±5.6
Average paternal age[1] (years)	43.4±5.9	39.8±5.5	42.7±7.2
Average age of sibs[1] (years)	12.9±6.2	8.1±2.1	13.1±4.6
Birth rank of proband[2]	2.4	1.5	3.2
Average family size[3]	2.8	2.3	2.9[4]
Sex ratio[5] in probands	2.6	1.0	1.3
Sex ratio[5] in sibs of probands	2.1	4.3	0.8

1. At testing.
2. Including stillbirths, miscarriages and abortions.
3. Including only living children five years of age and over.
4. Excluding twin.
5. Males per female.

A. Results from Skin-Testing.

Table 3 presents the results from 1338 skin tests performed on 446 near relatives of 112 probands in the period from October, 1962, to February, 1964. Generally, the number of positive skin reactions to ragweed pollen extract accounts for the majority of positive reactions. Figure 3 illustrates the relative frequencies of positive skin tests to ragweed and grass pollen for Experimental Group I and the Control Group. There are so few reactions to egg albumen that these tests will be included only in discussion of Table 3 and will be omitted from further analyses.

The consistent increased frequency of positive skin tests to ragweed pollen, grass pollen or to at least one allergen in the two Experimental groups over that in the Control Group implies a familial tendency. The frequencies of positive reactions to ragweed pollen, grass pollen or to at least one allergen were significantly higher in the mothers, fathers and siblings in Experimental Group II than those in the Control Group. In Experimental Group I--Control Group comparisons, only the differences in reactions between the siblings are significant. Numbers of positive skin tests are significantly higher in all comparisons between Experimental Groups I and II, except for the cases of siblings with a positive skin test to ragweed pollen and of mothers with a positive reaction

Table 3. Reactions to all skin tests in mothers, fathers and siblings of probands.

Positive Reaction to	Exp. Group I N	#	%	Exp. Group II N	#	%	Control Group N	#	%
At Least One Allergen									
Mothers	50	14	28.0	12	6**	50.0	50	9	18.0
Fathers	50	14	28.0	12	8**	66.6	50	10	20.0
PARENTS	100	28	28.0	24	14**	58.3	100	19	19.0
SIBLINGS	82	25**	30.5	16	9**	56.3	124	10	8.1
Ragweed Pollen									
Mothers	50	12	24.0	12	6**	50.0	50	8	16.0
Fathers	50	14	28.0	12	8**	66.6	50	9	18.0
PARENTS	100	26	26.0	24	14**	58.3	100	17	17.0
SIBLINGS	82	23**	28.0	16	6**	37.5	124	8	6.5
Grass Pollen									
Mothers	50	6	12.0	12	4**	33.3	50	3	6.0
Fathers	50	5	10.0	12	7**	58.3	50	5	10.0
PARENTS	100	11	11.0	24	11**	45.8	100	8	8.0
SIBLINGS	82	12**	14.6	16	6**	37.5	124	6	4.8
Egg Albumen									
Mothers	50	1	2.0	12	0	-	50	1	2.0
Fathers	50	1	2.0	12	0	-	50	3	6.0
PARENTS	100	2	2.0	24	0	-	100	4	4.0
SIBLINGS	82	1	1.2	16	0	-	124	2	1.6

N total number
\# number positive or affected
% percent positive or affected

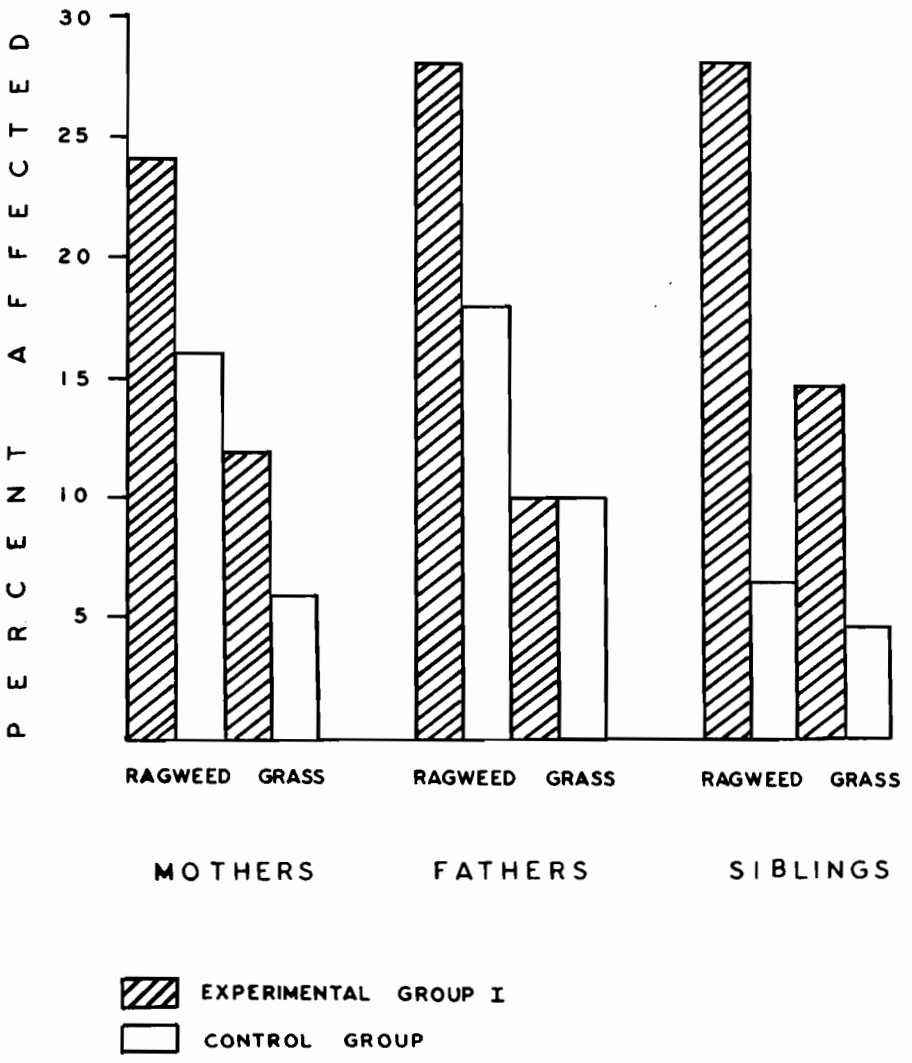

Figure 3. Skin test reactions to ragweed and grass pollen in near relatives of probands.

to "at least one allergen." (All probability values quoted are obtained from a "one-sided" Student's t table since the comparisons are all clear-cut cases of expectations for the experimental series being higher than for the control series, when the values being compared are not equal.)

The results from Experimental Group I indicate a similar frequency of positive skin tests to ragweed and grass pollen, or to at least one allergen, in the mothers, fathers and siblings of the probands, i.e. there is no increase in the number of positive reactions with age (Table 3). The frequency of positive reactions to grass pollen is about half the frequency of positive reactions to ragweed pollen. Detailed analysis of the skin test responses to ragweed pollen only, grass pollen only, or to both of these allergens (Table 4) shows that almost half of those who react to ragweed pollen also react to grass pollen (20/49), and that nearly all of those who react to grass pollen also react to ragweed pollen (20/23). Only three of the 182 persons in this group react to grass pollen extract alone.

There are proportionally more positive cutaneous reactions in Experimental Group II than in the other two groups. Approximately the same percentages of siblings as parents of the probands react to at least one allergen,

Table 4. Reactions to skin tests for ragweed and grass pollen in mothers, fathers and siblings of probands.

Positive Reaction to	Exp. Group I			Exp. Group II			Control Group		
	N	#	%	N	#	%	N	#	%
Ragweed Pollen Only									
Mothers	50	7	14.0	12	2	16.7	50	5	10.0
Fathers	50	9	18.0	12	1	8.3	50	4	8.0
Siblings	82	13	15.9	16	3	18.8	124	4	3.2
Grass Pollen Only									
Mothers	50	1	2.0	12	0	-	50	0	-
Fathers	50	0	-	12	0	-	50	0	-
Siblings	82	2	2.4	16	3	18.8	124	2	1.6
Both Ragweed and Grass Pollen									
Mothers	50	5	10.0	12	4	33.3	50	3	6.0
Fathers	50	5	10.0	12	7	58.0	50	5	10.0
Siblings	82	10	12.2	16	3	18.8	124	4	3.2

and to grass pollen extract, but fewer siblings than parents react to ragweed pollen extract, although the difference is not significant (P=.05-.10) (Table 3). More than half of the parents who have a skin test reaction react to grass pollen as well as to ragweed pollen (11/14), but none of the 14 parents with a skin sensitivity reacts to grass pollen alone (Table 4). On the other hand, some siblings (3/16) do react to grass pollen alone, but a lower proportion of siblings than parents reacts to both pollens (3/16 of the siblings versus 11/24 of the parents). This internal distribution (Table 4) accounts for the results seen in Table 3.

In the Control series, the prevalence of positive cutaneous reactions is significantly higher in the parents of the probands than in their siblings ($P<.01$), i.e. the number of positive skin reactions increases with age (Table 3). Again, as in Experimental Group I, about one-half (8/17) of the parents who show a positive cutaneous reaction to ragweed protein also respond to grass protein (Table 4). None of the 100 parents tested reacts positively to grass pollen alone. In the sensitized siblings, the distribution of positive reactions to ragweed pollen, or to grass pollen, or to both, approximates a 1:1:1 ratio. This ratio is

similar to that observed in sibs in Experimental Group II, but there the proportions affected are much greater than in the Control Group.

Many of the allergic probands also are sensitive to both ragweed and grass pollen. Sixty-six percent (33/50) of the Experimental Group I and 58.3% (7/12) of the Experimental Group II probands show double sensitivities (Appendix Tables A-1 and A-4).

To verify the apparent increase in frequency of positive skin tests with age seen in the control series, the frequencies of individuals (excluding the probands) with at least one positive skin test, in the various age groups from age five upwards, were calculated for all three groups (Table 5) and graphed (Figure 4). The frequencies of individuals with at least one positive skin reaction in Experimental Group II are consistently high and there is a marked fluctuation because the numbers in each group are small. The frequencies in Experimental Group I begin at 30.3% for the age range 5 to 9 years, and increase somewhat with age to a peak frequency of 42.9% in the 35 to 39 years range, then decrease quite abruptly. For the Control Group, the frequencies are lower than in the experimental groups, as would be expected, and the peak frequency, 26.7% is in the age range 30-34

Table 5. Parents and siblings with at least one positive skin test, classified by age group.

Age Range (years)	Exp. Group I			Exp. Group II			Control Group		
	N	#	%	N	#	%	N	#	%
5 - 9	33	10	30.3	11	5	45.5	43	3	7.0
10 - 14	26	9	34.6	5	4	80.0	52	3	5.8
15 - 19	18	6	33.3	0	0	-	25	4	16.0
20 - 24	3	0	-	0	0	-	3	0	-
25 - 29	4	1	25.0	1	1	100.0	2	0	-
30 - 34	12	5	41.7	6	4	66.7	15	4	26.7
35 - 39	21	9	42.9	10	5	50.0	27	7	25.9
40 - 44	31	6	19.4	4	3	75.0	24	3	12.5
45 - 49	23	5	21.7	2	1	50.0	26	5	19.2
50 and over	11	2	18.2	1	0	-	7	0	-

N total number
number positive or affected
% percent positive or affected

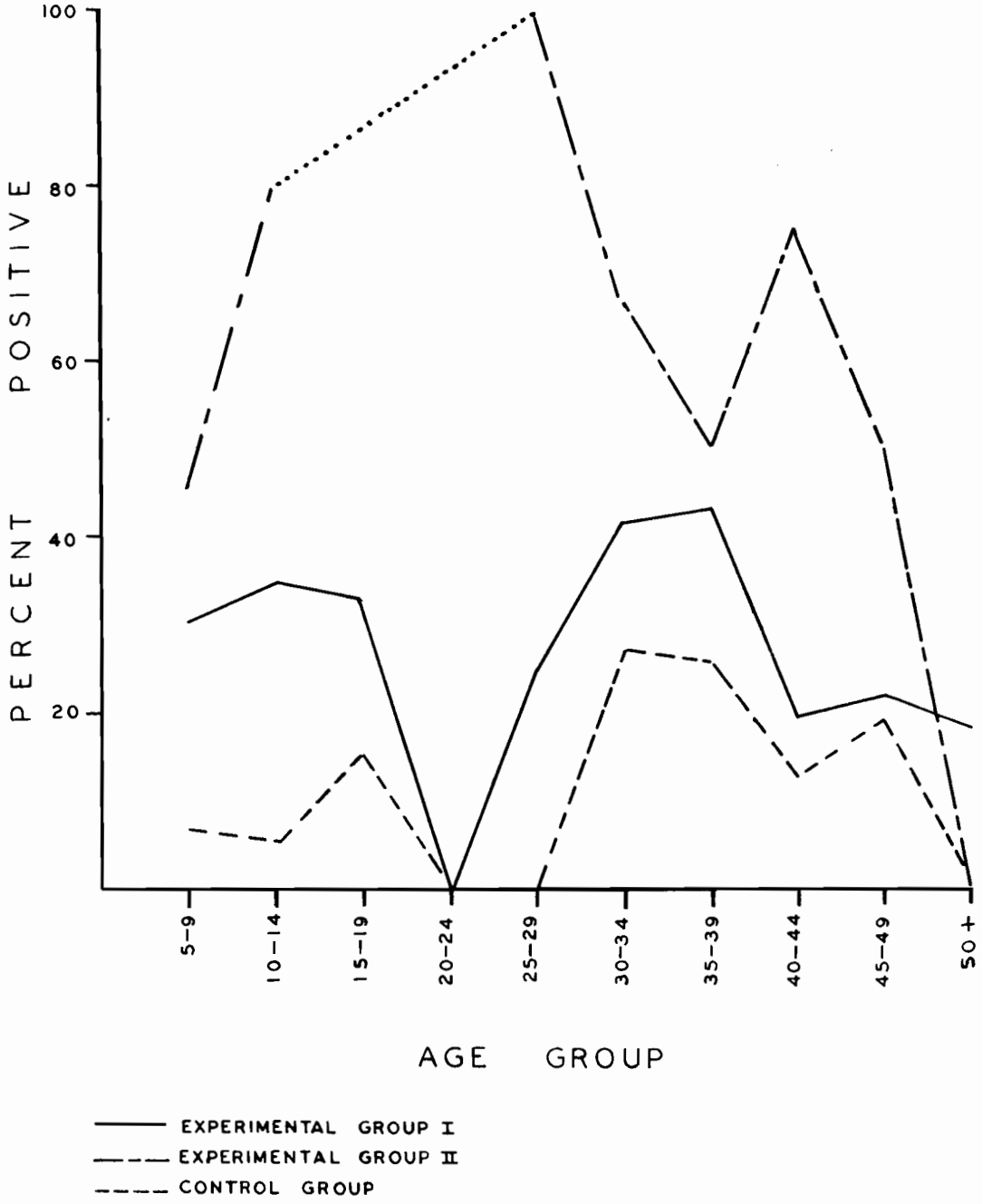

Figure 4. Response to skin tests in different age groups.

years but the frequency here is not very different from that (25.9%) in the age range 35-39 years. A similar plateau from 30-39 years occurs in both groups. Also, in the Control Group as in Experimental Group I, there is a noticeable decrease in skin sensitivity after the peak is reached. In the Control Group there appears to be a somewhat greater increase in sensitivity with age than noted in the other groups, but unfortunately, the numbers of individuals necessary for definite conclusions are lacking, especially in the late teens and twenties, where the trend would be expected to be most prominent.

This approach to the results has revealed that there is a higher frequency of positive skin reactions in the experimental than the control groups. The difference is significant in all comparisons between Experimental Group II and the Control series, but only between the siblings of Experimental Group I and those of the Control series. The Control Group demonstrated that there may be increased sensitization with age. This trend was not as obvious in the experimental groups. In addition, it became evident that sensitization to grass pollen was nearly always accompanied by sensitization to ragweed pollen, but the reverse was not true.

If a familial tendency for the ability to form skin-sensitizing antibodies is assumed, the next logical step is to determine the frequencies of affected offspring when both, one or neither of the parents is affected. This analysis has been done for positive skin tests to ragweed pollen and to grass pollen (Table 6). The data for "any positive test" are very similar to those for ragweed pollen alone and are, therefore, omitted.

In many cases, the numbers are small and little difference is observed in the frequencies of affected offspring when one or both parents are affected and, indeed, in Experimental Group II, it appears that the greatest proportion of offspring are sensitized to ragweed pollen when neither parent is sensitized, but this is presumably a random fluctuation resulting from the small numbers involved. The overall indication in that when one or both parents are sensitized, the offspring are more likely to be sensitized. A X^2 test for differences in sensitivity to ragweed and to grass pollen in Experimental Group I confirms this indication for there is a significant difference between numbers of affected siblings when parents are or are not affected ($P < .01$ for both ragweed and grass pollen).

Table 7 presents the outcome of concordance

Table 6. Affected siblings from matings in which both, one or neither parent has a positive skin test to ragweed or grass pollen.

	Exp. Group I			Exp. Group II		
	total sibs	aff. sibs	% aff.	total sibs	aff. sibs	% aff.
Ragweed-positive Tests						
affected x affected	8	3	37.5	6	2	33.3
affected x normal	25	13	52.0	6	2	33.3
normal x normal	49	7	14.3	4	2	50.0
Grass-positive Tests						
affected x affected	2	1	50.0	3	1	33.3
affected x normal	12	4	33.3	9	5	55.5
normal x normal	68	7	10.3	4	0	-

studies on skin test reactions in 18 twin pairs in which at least one member of each pair had at least one positive reaction. The data reveal a slightly higher concordance rate in monozygotic twins than in dizygotic twins in both

Table 7. Concordance rates for skin tests in twins.

	No. of pairs	Any allergen Concordant no.	%	Specific allergen Concordant no.	%
Monozygotic	8	4	50.0	4	50.0
Dizygotic	10	3	30.0	2	20.0
		X^2=.8		X^2=1.8	
		P=.15-.20		P=.05-.10	

of the categories, response to a "specific allergen" (4/8 versus 2/10) and response to "any allergen" (4/8 versus 3/10). There is no change in the rate of concordance (50.0%) in the two categories for the monozygotic twins, implying that when both twins are sensitized, they are both sensitized to the same allergen. This is not so much the case for dizygotic twins. Further, the average

age of the concordant monozygotic twins (11.8 years) is somewhat lower than that of the discordant monozygotic twins (12.8 years). The opposite situation is true for the dizygotic twin pairs where average age for the concordant dizygotic pairs is 10.7 years and for the discordant pairs is 7.7 years (for the category, response to "any allergen".

A sex ratio of 3.25 (26 males : 8 females) for the total affected siblings of allergic probands in Experimental Groups I and II was calculated from data regarding sensitization to ragweed pollen. A similar excess of affected males is seen in the twin data where, of the 18 twin pairs in Table 7, all eight pairs of monozygotic twins and four of the seven pairs of like-sexed dizygotic twins were male pairs.

B. Results from History-Taking.

The data for analyses of clinical symptoms includes only 45 of the 50 control families since five of the control probands, although they had no positive skin reactions to the allergens tested and no ragweed hay fever symptoms, did have some other allergic symptoms (Appendix Table A-7). All living sibs on whom a history was obtained were included, regardless of whether they had been skin-tested. The results from symptoms confirm the trends seen in the skin-test data, but these trends are not as well-defined as in the first case.

Most individuals with an allergy usually have more than one type of allergic disorder. For example, of the probands in Experimental Groups I and II, all but three in each group had symptoms of at least one other major allergy besides ragweed hay fever (Appendix Tables A-1 and A-4).

Table 8 summarizes the findings regarding various allergic symptoms in the three groups being compared and indicates the significant differences between the experimental and control series. Many of the differences between Experimental Groups I and II, although not indicated, are also significant. Figure 5 compares the prevalence of ragweed and grass hay fever in Experimental Group I and the Control Group. It is immediately evident that, whereas the fathers and siblings in the experimental groups usually have a higher overall proportion of symptomatic allergy than those in the control series, the prevalence of symptomatic allergy in the mothers in Experimental Group I is generally lower than in the Control Group mothers, except in the cases of asthma and grass hay fever.

Because of this discrepancy between symptoms and skin sensitization, Tables 9a and 9b were drawn up to determine the relationship between a positive skin reaction to an allergen and the development of clinical

Table 8. Allergic symptoms in mothers, fathers and siblings of probands.

	Exp. Group I			Exp. Group II			Control Group		
	N	#	%	N	#	%	N	#	%
Any Major Allergy									
Mothers	50	13	26.0	12	8**	66.7	45	12	26.7
Fathers	50	20**	40.0	12	7**	58.3	45	6	13.3
Siblings	90	24**	26.7	16	6**	37.5	126	14	11.1
Ragweed Hay Fever									
Mothers	50	5	10.0	12	6*	50.0	45	8	17.8
Fathers	50	9*	18.0	12	5**	41.7	45	3	6.7
Siblings	90	11*	12.2	16	4**	25.0	126	6	4.8
Grass Hay Fever									
Mothers	50	2	4.0	12	4**	33.3	45	1	2.2
Fathers	50	4	8.0	12	2	16.7	45	3	6.7
Siblings	90	4	4.4	16	4**	25.0	126	1	0.8
Perennial Allergic Rhinitis									
Mothers	50	5	10.0	12	5*	41.7	45	7	15.6
Fathers	50	10	20.0	12	3	25.0	45	0	-
Siblings	90	11	12.2	16	2	12.5	126	5	4.0
Asthma									
Mothers	50	6	12.0	12	2	16.7	45	3	6.7
Fathers	50	4	8.0	12	4**	33.3	45	2	4.4
Siblings	90	7	7.8	16	0	-	126	4	3.2
Any Minor Allergy									
Mothers	50	11	22.0	12	4	33.3	45	16	35.6
Fathers	50	14	28.0	12	1	8.3	45	9	20.0
Siblings	90	17	18.9	16	3	18.8	126	20	15.9

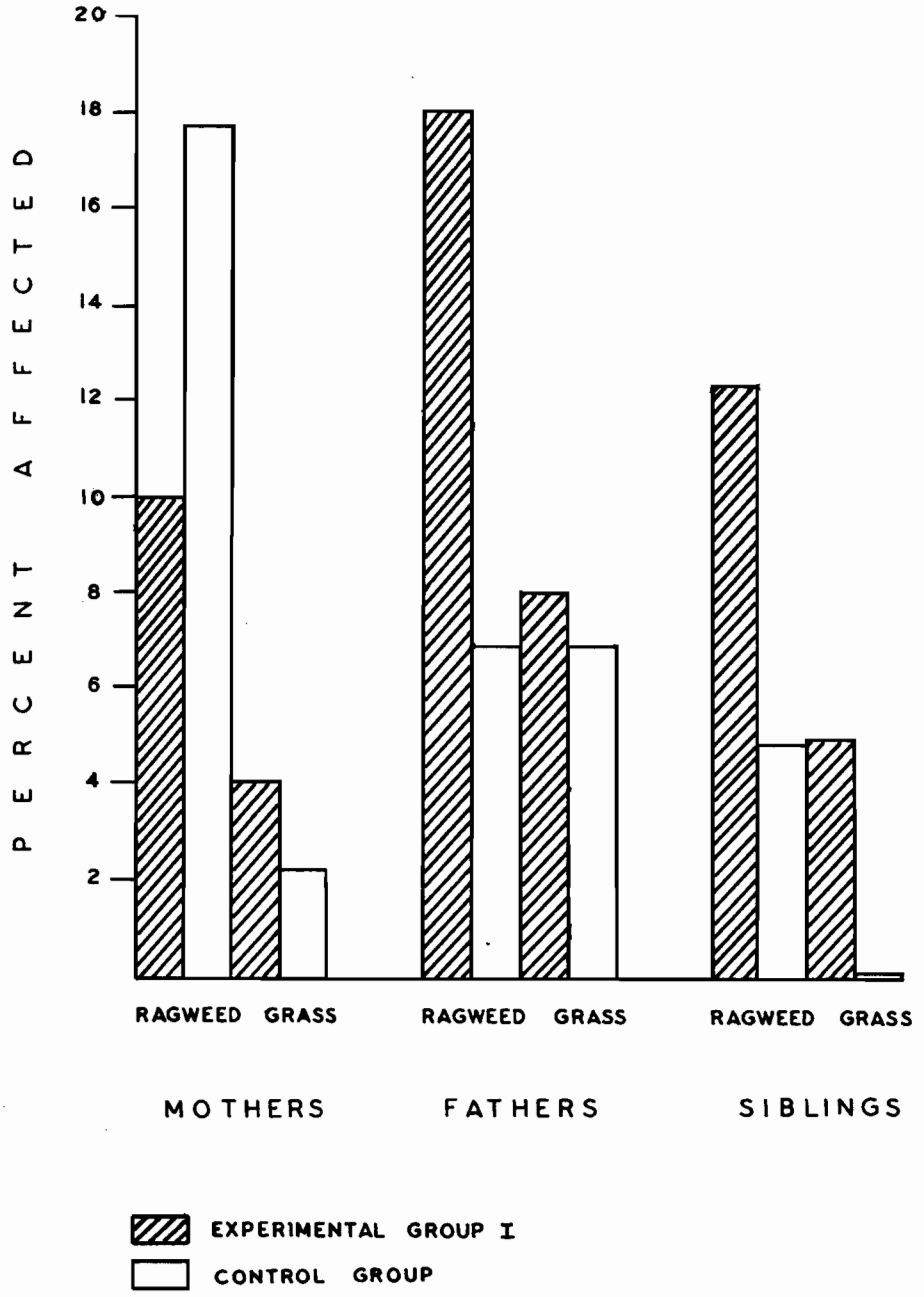

Figure 5. Ragweed and grass hay fever in near relatives of probands.

Table 9a. Positive skin tests and hay fever symptoms from ragweed pollen in mothers, fathers and siblings of probands.

	Exp. Group I			Exp. Group II			Control Group		
	N	#	%	N	#	%	N	#	%
MOTHERS	50			12			45		
Skin test only		7	14.0		0	-		1	2.2
Symptoms only		0	-		0	-		1	2.2
Both		5	10.0		6	50.0		7	15.6
FATHERS	50			12			45		
Skin test only		5	10.0		3	25.0		6	13.3
Symptoms only		0	-		0	-		0	-
Both		9	18.0		5	41.7		3	6.7
SIBLINGS	82			16			117		
Skin test only		12	14.6		2	12.5		3	2.6
Symptoms only		0	-		0	-		1	0.9
Both		11	13.4		4	25.0		5	4.3

Table 9b. Positive skin tests and hay fever symptoms from grass pollen in mothers, fathers and siblings of probands.

	Exp. Group I			Exp. Group II			Control Group		
	N	#	%	N	#	%	N	#	%
MOTHERS	50			12			45		
Skin test only		5	10.0		0	-		3	6.7
Symptoms only		1	2.0		0	-		1	2.2
Both		1	2.0		4	33.3		0	-
FATHERS	50			12			45		
Skin test only		3	6.0		5	41.7		3	6.7
Symptoms only		2	4.0		0	-		1	2.2
Both		2	4.0		2	16.7		2	4.4
SIBLINGS	82			16			117		
Skin test only		8	9.8		2	12.5		5	4.3
Symptoms only		0	-		0	-		0	-
Both		4	4.9		4	25.0		1	0.9

symptoms upon exposure to that allergen. In the case of ragweed, it is quite common to have a positive skin test to ragweed pollen without symptoms but only rarely do those who have clinical symptoms not have a positive skin test. Proportionally fewer of the skin-test positive Experimental Group I mothers have developed clinical symptoms of ragweed hay fever (5/12) than have the skin-test positive Control Group mothers (7/8) but the difference is not significant. With respect to the development of symptoms, the Experimental Group II mothers are similar to the Control Group mothers. The fathers and siblings in all three groups respond in a manner similar to the Experimental Group I mothers, i.e. many with a cutaneous reaction do not develop clinical symptoms.(Table 9a).

The correlation between skin tests and history is not as good for grass pollen as for ragweed pollen sensitivities. (Table 9b). This poorer correlation is noted in Experimental I and the Control Groups where there is a total of five individuals who apparently have a history of seasonal allergic rhinitis from grass pollen but do not have a skin reaction to it. It is also seen in the Control Group mothers where three have a positive cutaneous reaction, one has clinical symptoms of hay fever, but none has both.

Experimental Group II is most consistent in these comparisons since all of those who have symptoms also have a positive skin test. This is a result of the allergists giving a positive diagnosis of allergy only if the symptoms were confirmed by skin sensitivity.

To examine further the correlation between skin reactions and symptoms, the data for seasonal allergic rhinitis from ragweed and grass pollens was approached in the same manner as was the data for skin tests to these allergens (Table 10). The results from clinical symptoms confirm those from skin tests in all groups in that a relatively larger proportion of those affected with hay fever suffer from ragweed hay fever alone, or from both ragweed and grass hay fever, than suffer from grass hay fever alone. In the Control series, there is no definite pattern of increase in frequency of hay fever symptoms with age. Confusion exists because the number of mothers suffering from hay fever (8/45) is significantly higher ($X^2=7.5$, $P<.01$) than the number of siblings affected (6/126), but there is no significant difference between the number of fathers (4/45) and the numbers of mothers affected ($X^2=1.5$, $P=.10-.15$) or between fathers and siblings affected ($X^2=.6$, $P=.20-.25$).

Despite the low prevalence of some allergic manifestations in Experimental Group I mothers, further

Table 10. Ragweed and grass hay fever in mothers, fathers and siblings of probands.

	Exp. Group I			Exp. Group II			Control Group		
	N	#	%	N	#	%	N	#	%
Ragweed Hay Fever Only									
Mothers	50	4	8.0	12	2	16.7	45	7	15.6
Fathers	50	6	12.0	12	3	25.0	45	1	2.2
Siblings	90	8	8.9	16	1	6.3	126	5	3.9
Grass Hay Fever Only									
Mothers	50	1	2.0	12	0	-	45	0	-
Fathers	50	1	2.0	12	0	-	45	1	2.2
Siblings	90	1	1.1	16	1	6.3	126	0	-
Both Ragweed and Grass Hay Fever									
Mothers	50	1	2.0	12	4	33.3	45	1	2.2
Fathers	50	3	6.0	12	2	16.7	45	2	4.4
Siblings	90	3	3.3	16	3	18.8	126	1	0.8

analyses were performed, partly to determine the effect, if any, of the discrepancy on confirming or rejecting the view that an allergic tendency is inherited. The percentages of probands in Experimental Groups I and II and the Control series having one or both parents affected with a major allergy are 54.0%, 100.0% and 32.0%, respectively. The differences between experimental and control series are significant in both cases ($P<.01$) and this strengthens the idea of a familial tendency in allergy. A mating analysis was performed (Table 11) which shows that when one or both parents have major or minor allergies or ragweed hay fever, slightly more of the siblings will have these conditions than when neither parent is affected. However, the similarity in the proportions affected is more remarkable than the difference and is most marked in the case of ragweed hay fever symptoms where 13.6% (3/22) of the siblings have ragweed hay fever when the parents are affected as compared with 11.8% (8/68) when the parents are unaffected. (The same comparison concerning skin reactions to ragweed pollen shows a significant difference between the groups with affected and "normal" parents).

Since the differences were so slight and it appeared as if, rather than inheriting a predisposition

Table 11. Affected siblings from matings in which both, one or neither parent has the specified allergic symptoms.

	Exp. Group I			Exp. Group II		
	total sibs	aff. sibs	% aff.	total sibs	aff. sibs	% aff.
Major Allergies						
affected x affected	8	1	12.5	3	2	66.7
affected x normal	33	13	39.4	13	4	30.8
normal x normal	49	10	20.4	0	0	-
Minor Allergies						
affected x affected	11	2	18.2	0	0	-
affected x normal	33	8	24.2	7	1	14.3
normal x normal	46	7	15.2	9	2	22.2
Ragweed Hay Fever						
affected x affected	2	1	50.0	3	1	33.3
affected x normal	20	2	10.0	7	2	28.6
normal x normal	68	8	11.8	6	1	16.7

to develop ragweed hay fever, one inherits a general predisposition to develop allergic manifestations or perhaps the ragweed hay fever gene has reduced penetrance, the proportions of siblings with ragweed hay fever, when parents had or did not have specified allergies other than ragweed hay fever, were determined for Experimental Group I. (Table 12). The most striking results are for perennial allergic rhinitis where parents with this allergic manifestation have more children with ragweed hay fever than parents who do not have perennial allergic rhinitis. The difference is significant (X^2=3.0, P=.025-.05) but there is no indication of whether it is real. The numbers in each group would be too small to make a similar analysis for Experimental Group II useful.

The summary of the data on allergic symptoms in twins (Table 13) can merely be used to indicate a trend. For twin pairs in which at least one member is affected with symptoms of at least one major allergy, there is a higher concordance rate in monozygotic than in dizygotic pairs for both "any major allergy" and a "specific major allergy" (3/6 versus 1/11) but the difference is not significant (P=0.099, Fisher's Exact Method). The concordance rates do not vary for the two classifications of allergy. The average age of

Table 12. Siblings with ragweed hay fever from matings in which both, one or neither parent has other specified allergies, but not ragweed hay fever. (Experimental Group I).

Allergic Symptoms in Parents	Affected Siblings N	#	%
Major Allergies			
One or both parents affected	19	3	15.6
Neither parent affected	49	5	10.2
Seasonal Allergic Rhinitis Other Than Ragweed Hay Fever			
One or both parents affected	1	0	-
Neither parent affected	67	8	11.9
Perennial Allergic Rhinitis			
One or both parents affected	11	3	27.3
Neither parent affected	57	5	8.8
Asthma			
One or both parents affected	8	0	-
Neither parent affected	60	8	13.3
Eczema			
One or both parents affected	2	0	-
Neither parent affected	66	8	12.1

the concordant monozygotic twins is 11.3 years and of the discordant monozygotic twins is 10.3 years. The corresponding figures for concordant and discordant dizygotic

Table 13. Concordance for symptoms of major allergies in twins.

	No. of pairs	Any allergy concordant no.	%	Specific allergy concordant no.	%
Monozygotic	6	3	50.0	3	50.0
Dizygotic	11	1	9.1	1	9.1

twins are 5.0 and 8.9 years, respectively.

The frequencies of grandparents, uncles, aunts and first cousins affected with any allergic manifestation was calculated for each of the three groups. These frequencies are 7.9% for Experimental Group I, 24.4% for Experimental Group II and 7.0% for the Control Group. In both Experimental I and the Control Groups the frequencies of symptoms in grandparents was 10 to 14%, and in uncles, aunts and cousins was approximately 5 to 9%. The frequency of migraine in the near relatives (parents and sibs) of Experimental Group I probands is 8.4% and for the Control Group is 6.2%. There were no

reports of migraine in near relatives of Experimental Group II probands.

The sex ratio in the 24 allergic sibs of Experimental Group I probands is 2.4, and for the sibs of Experimental Group II is 6.0. Of the three concordant sets of monozygotic twins, two are male pairs. The concordant dizygotic twin pair is unlike-sexed.

VI. DISCUSSION

Numerous investigators, using a variety of approaches, have confirmed the hereditary nature of allergy (Cooke and Vander Veer, 1916; Wiener et al., 1936; Van Arsdel and Motulsky, 1959; etc.). Many also acknowledge the large part played by the environment in the development of allergic disorders (Schwartz, 1952; Rapaport, 1958; Maternowski and Mathews, 1962; etc.). The findings of Adkinson (1920) and Bray (1930), which demonstrate a higher frequency of allergic disorders in the mothers than the fathers of allergic children, are the only results which could conceivably be used as evidence for acquisition of allergic disorders by trans-placental or trans-milk transmission. The present study supports the view that both hereditary and environmental factors are necessary for the development of allergic disorders, but there is no evidence of trans-placental or trans-milk transmission of these disorders.

Most of the conclusions of the present study are based on skin-test results because skin tests were the most reliable source of information. The data for clinical symptoms reflect the trends observed in the skin-test results, but are a less valuable source of information because of their subjective nature.

The higher frequencies of positive skin tests to

ragweed pollen, grass pollen or to at least one allergen (including egg albumen), in the near relatives of the experimental probands as compared with the frequencies in the same groups of relatives of the Control Group (except in the identical responses of Experimental Group I and Control Group fathers to grass pollen) is evidence for familial tendency in the development of skin sensitivity, although not all of the differences are significant. Table 14 displays representative results from reactions to ragweed pollen extract. This pollen is the most prevalent allergen of the three tested and therefore accounts for the greatest proportion of skin reactions.

Table 14. Skin test reactions to ragweed pollen extract in mothers, fathers and siblings of probands.

	Exp. Group I			Exp. Group II			Control		
	N	#	%	N	#	%	N	#	%
Mothers	50	12	24.0	12	6	50.0	50	8	16.0
Fathers	50	14	28.0	12	8	66.6	50	9	18.0
Siblings	82	23	28.0	16	6	37.5	124	8	6.5

Table 14 also shows that the frequency of positive skin tests in Experimental Group I is the same in the

parents as in the siblings while in the Control Group, the parental frequency is significantly higher than the sibling frequency ($P<.01$). Furthermore, the frequency of positive skin tests among the Experimental Group I siblings is significantly higher than the frequency among the Control Group siblings ($P<.01$), but the difference in response between the parents of the two groups is not significant. The most obvious interpretation of these results is that, in Experimental Group I, where an hereditary factor is presumably operating, individuals become sensitized with minimum exposure to the allergen and the sensitivity persists until late in life. In the Control Group, on the other hand, where there is presumably no hereditary factor acting, but where there is an observed increase in the frequency of skin sensitization with age, individuals apparently develop a sensitivity from a large exposure to the allergen. This is probably an oversimplification of the situation since an attempt to verify the increase with age by plotting percentage with any positive skin test versus age failed to give a line with a marked positive slope. However, there were few individuals in any one age group, especially in the late teens and the twenties where the trend might reasonably be expected to occur. Hence,

this explanation is one of the possibilities and is biologically feasible.

The situation for Experimental Group II is somewhat different from that for the other groups and deserves special consideration. The first thing which is obvious is the high frequency of positive skin tests in both the parents and sibs as compared with Experimental Group I. Reasons for this can only be suggested. It is obvious that a different socio-economic group would see a private practitioner than would attend a clinic. It is hardly logical to believe that one group would have more allergy than the other. The reason for the elevated frequency of allergy is not apparent, but the answer would probably be found among the answers to the question "What makes a private practice different from a public practice?" There may be significant differences in racial composition, age distribution, and a variety of more or less subtle environmental factors that may render the two groups non-comparable. Possibly there may be selection for positive family history in the private practice in that a parent who knows about allergy from personal experience may take his allergic child directly to his allergist, whereas a non-allergic parent may take his child to a general practitioner or specialist

in internal medicine.

One must also consider the possibility that there was an unconscious selection, by the observers, for a positive family history of allergy, and especially of ragweed hay fever, in choice of the probands, some of whom were new patients requiring treatment for ragweed hay fever. In a good allergy practice of long standing, there will be a certain amount of interrelationship among the patients so the practitioner may, in many cases, have a good idea of the family history of a new patient before asking the routine questions. Further, one cannot be entirely objective in selecting patients from his own practice because of the personal relations aspect. Some patients and their families are very willing to participate in a research project while others would be offended at being asked.

It appears, then, that this method of obtaining probands results in an artificial population which can give rise to contradictory results such as seen in Table 15, where a higher proportion of affected siblings results from matings in which neither parent is affected than from those in which one or both parents are affected. Granted, the numbers are small and the results very prone to chance fluctuations, but one of the reasons that the number of siblings in the group with a negative

parental history is proportionally smaller than in Experimental Group I, is that the number of probands

Table 15. Siblings with a positive skin test to ragweed pollen when both, one or neither parent has a positive skin test to ragweed pollen.

	Exp. Group II			Exp. Group I		
	N	#	%	N	#	%
One or both parents affected	12	4	33.3	33	16	48.5
Neither parent affected	4	2	50.0	49	7	14.3

with a positive parental history is proportionally higher.

The second obvious difference in Experimental Group II, noted from Table 14, is that although there is presumably the same hereditary factor acting here as in Experimental Group I, the frequencies of positive skin tests to ragweed and grass pollen are slightly (but not significantly) higher in the parents than in the siblings (Table 16). This suggests that the siblings have not yet had the necessary minimum exposure. The suggestion is acceptable for two reasons: (1) the siblings in this group are younger, on the average (average age 8.1 ± 2.1 years), than those in Experimental Group I (average age 12.9 ± 6.2 years), and (2) the parents

in Experimental Group II are in a higher income bracket than those in Experimental Group I, and hence are more

Table 16. Reactions to skin tests for ragweed and grass pollen in parents and siblings or Experimental Group II probands.

	Ragweed pollen			Grass pollen		
	N	#	%	N	#	%
Parents	24	14	58.3	24	11	45.8
Siblings	16	6	37.5	16	6	37.5

likely to spend the summer in areas relatively free of ragweed pollen, expecially since at least one member of the family, the proband, who is usually the eldest child, already has ragweed hay fever.

Although Experimental Group II is in general not comparable with the other two groups, it is included in the analyses, but will be discussed specifically only where it contributes additional information. We were very fortunate to have this series of allergic probands because it illustrates the large part heredity can play in allergy and also points out some of the pitfalls of which one must be aware in any study of human populations.

In both experimental groups, the frequencies of the

various allergic symptoms are higher than in the control, except for the cases listed in Table 17, and this provides limited evidence for an hereditary factor in the development of allergic symptoms. In the Control Group, the

Table 17. Comparisons in which there are higher frequencies of allergic symptoms in the control than in the experimental groups.

	Experimental			Control		
	N	#	%	N	#	%
Mothers						
Any major allergy	50	13	26.0[1]	45	12	26.7
Ragweed hay fever	50	5	10.0[1]	45	8	17.8
Perennial allergic rhinitis	50	5	10.0[1]	45	7	15.6
Minor allergies	50	11	22.0[1]	45	16	35.6
Fathers						
Minor allergies	12	1	8.3[2]	45	9	20.0

1. Experimental Group I
2. Experimental Group II

trend with age is uncertain since in most cases, the frequencies in sibs are very similar to those for one parent but much less than those for the other parent. The

situation for "any major allergy" is illustrative. The frequency in mothers is 26.7%, in fathers, 13.3%, and in siblings, 11.1%. One would expect that exposure would have some effect on the development and severity of symptoms. Broder, Barlow and Horton (1962) have observed an increase in the cumulative prevalence of hay fever in the second and third decade over that in the first, in studying members of a total community.

It is difficult to suggest what the physiological and genetic relationship between clinical symptoms and skin reactions might be, i.e. do symptoms appear after a given reagin titer has been reached? If this is the case, is reagin produced by a gene complex and then does it act as a regulator substance which causes a chain of reactions leading to the development of symptoms? This is purely speculative and only recently (Sherman and Connell, 1964) has there been evidence for a relation between reagin titer and degree of severity of clinical symptoms.

The low frequency of allergic symptoms in mothers of Experimental Group I is a puzzling feature of the study. It becomes even more puzzling with the observations that all but one calculated frequency for the fathers and siblings of the probands are in the expected direction (Table 17). The analysis for mothers

with a positive skin test to ragweed or grass pollen, or clinical symptoms of hay fever, or both a positive skin test and hay fever symptoms (Table 18), done in

Table 18. Positive skin tests and hay fever symptoms from ragweed or grass pollen in Experimental Group I and Control Group mothers.

	Exp. Group I			Control		
	N	#	%	N	#	%
Ragweed						
Positive skin reaction	50	7	14.0	45	1	2.2
Hay fever symptoms		0	-		1	2.2
Both		5	10.0		7	15.6
Grass						
Positive skin reaction	50	5	10.0	45	3	6.7
Hay fever symptoms		1	2.0		1	2.2
Both		1	2.0		0	-

order to clarify the problem, reveals that fewer Experimental Group I mothers who have a positive skin test to ragweed pollen develop symptoms of hay fever (5/12) than do Control mothers (7/8), but the difference is not significant. Since there was a slightly increased frequency of experimental mothers as compared with control mothers

suffering from asthma (12.0% versus 6.7%) and from grass hay fever (4.0% versus 2.2%), it was thought that the sensitized mothers might develop asthma rather than hay fever, or perhaps suffer from grass hay fever since some claim that the two pollens have common antigenic components (Lidd and Farr, 1963). This was not the case because only one of the seven mothers with ragweed pollen skin sensitivity had asthma and none had grass hay fever. Other attempts to explain this difference on a physiological basis also failed. If one postulates that females who develop skin sensitivity must develop clinical symptoms at the same time to fit the 1:1 sex ratio observed in allergic adults as compared with a 2:1 ratio in children (Bray, 1930), this immediate appearance of symptoms should occur in Experimental Group I mothers as well, but does not. On the other hand, if one postulates that those who acquire allergy (Control series) acquire skin-sensitizing antibody and symptoms concurrently, the fathers in the Control Group should respond in the same manner as the mothers do. Since neither of these postulates applies, one is forced to conclude that the difference in frequency of clinical symptoms in the two groups of mothers arises either from the sample or because the Control mothers are less critical in their definition of allergic symptoms than the Experimental

Group I mothers, who have usually had more experience with allergic disorders. There is some verification for the latter explanation in cases where individuals claim to have symptoms but no positive skin tests. Although this situation is possible because the skin-testing extract may not be sufficiently concentrated to elicit a reaction, it is more probable that the subjective history-taking is the cause of inaccuracy rather than objective skin-testing. The low value for minor allergies in fathers in Experimental Group II, 8.3% (Table 17), can probably also be attributed to inaccuracies in history-taking.

One should be able to make a decision in favour of a genetic component in a disorder if there is an increased prevalence of affected siblings from matings in which one or both parents are affected with the disorder, as compared with the prevalence when neither parent is affected. Such an analysis for positive skin reactions to ragweed and grass pollen (Table 19) strongly favours an hereditary determiner in the development of skin sensitivity to both of these allergens because the numbers of offspring with positive reactions when parents are affected is significantly higher than the numbers with a reaction when neither parent is affected. However, the frequencies of affected offspring when parents

have or do not have allergic symptoms is much less impressive evidence for an hereditary factor. None

Table 19. Siblings with a positive skin test to ragweed or grass pollen when both, one or neither parent has a positive skin test to ragweed or grass pollen (Experimental Group I).

	Ragweed pollen			Grass pollen		
	N	#	%	N	#	%
One or both parents affected	33	16	48.5	14	5	35.7
Neither parent affected	49	7**	14.3	68	7**	10.3

of the differences are significant. The results for ragweed hay fever are representative (Table 20).

Table 20. Siblings with ragweed hay fever when both, one or neither parent has ragweed hay fever (Experimental Group I).

	N	#	%
One or both parents affected	22	3	13.6
Neither parent affected	68	8	11.8

This lack of any marked difference for ragweed

hay fever symptoms might be explained if one accepts the view that rather than inheriting a very general predisposition to develop allergic symptoms or a very specific predisposition to develop ragweed hay fever, one inherits a kind of intermediate predisposition, to develop allergic rhinitis. Then it could be assumed that parents who did not suffer from ragweed hay fever, suffered from some other allergic rhinitis. The evidence for this is scanty. The best support comes from the analysis of numbers of siblings with ragweed hay fever when parents have, or do not have, perennial allergic rhinitis (Table 21). The trend is only suggestive because although the difference in the numbers of affected offspring in the two groups is significant at the 5% level ($X^2=3.0$), there is no indication of whether the difference is real. Further, there were not enough sibs in the other groups in which similar

Table 21. Siblings with ragweed hay fever when both, one or neither parent has perennial allergic rhinitis and does not have ragweed hay fever (Experimental Group I).

	N	#	%
One or both parents affected	11	3	27.3
Neither parent affected	57	5	8.8

analyses were done to get any idea of the trend. This is particularly true for the data for seasonal allergic rhinitis. It is not possible to verify the hypothesis of inheritance of a predisposition to develop allergic rhinitis from the skin-test data because the two allergens which gave the most valuable information, ragweed and grass pollen, usually cause an allergic rhinitis. If one were able to get a useful number of cutaneous reactions from non-inhalant allergens which produced symptoms other than rhinitis, it would be possible to elucidate further the problem of whether one inherits a general predisposition to become allergic or a predisposition to respond in a specific way. Certainly, some of the confusion could be cleared up with accurate histories.

The frequencies of those individuals responding to both ragweed and grass pollens is quite marked in the skin-test data and is reflected in the symptom data (Table 22). Almost half of those who have a positive skin reaction to ragweed pollen react to grass pollen (20/49) and almost all of those who react to grass pollen also react to ragweed pollen (20/23). For symptoms, almost one-third (7/25) of those with ragweed hay fever symptoms also have grass hay fever symptoms. Most of those with grass hay fever also have ragweed hay fever

Table 22. Mothers, fathers and siblings with positive skin tests to ragweed pollen, grass pollen or both, or with ragweed hay fever, grass hay fever or both (Experimental Group I).

	Skin Reactions			Symptoms		
	N	#	%	N	#	%
Ragweed Only						
Mothers	50	7	14.0	50	4	8.0
Fathers	50	9	18.0	50	6	12.0
Siblings	82	13	15.9	90	8	8.9
Grass Only						
Mothers	50	1	2.0	50	1	2.0
Fathers	50	0	-	50	1	2.0
Siblings	82	2	2.4	90	1	1.1
Both Ragweed and Grass						
Mothers	50	5	10.0	50	1	2.0
Fathers	50	5	10.0	50	3	6.0
Siblings	82	10	12.2	90	3	3.3

(7/10). The reason appears to be that if one possesses the ability to become sensitized, he will most likely become sensitized to ragweed pollen simply because it is one of the most prevalent allergens. A proportional number will develop symptoms. A second sensitivity to grass pollen may develop later. Or, if the first sensitivity were to grass pollen, the development of a second sensitivity to ragweed pollen is almost assured.

Huber (1930), who has studied hay fever symptoms, found that 80% of those with grass hay fever had ragweed hay fever, while only 30% of those with ragweed hay fever also suffered from grass hay fever. Therefore he has suggested that those who are sensitized to grass pollen may very easily become sensitized to ragweed pollen because their mucous membranes have not fully recovered from the assault by grass pollen in May and June, before they are exposed to ragweed pollen in August and September. The same argument could apply to skin-sensitizing antibody production where the antibody-synthesizing mechanism is still in a responsive state when the ragweed season occurs.

In Huber's series, the fact that 76% of the 80% with grass and ragweed hay fever, had grass hay fever first, supports his hypothesis. In other practices, the impression is that ragweed hay fever develops before grass hay fever, when both are present (Bacal, 1964). This would

seem more logical in view of the fact that ragweed pollen is usually more prevalent than grass pollen. In the present study, no information concerning this sequence was obtained. Nevertheless, the existence of double sensitivities implies that the predisposition is not specific for ragweed hay fever, but does not indicate how general it is.

Although the numbers of twin pairs are small and no significant difference exists in comparisons between monozygotic and dizygotic twins, the findings from the twin studies are not contrary to the hypothesis that an hereditary and an exposure factor are responsible for allergic disease. The concordance rates are slightly, but consistently, higher in the monozygotic than the dizygotic pairs for both skin-test and clinical-symptom data, but there are many discordant monozygotic pairs (Table 23). The concordance rates for both skin tests and allergic symptoms are the same for monozygotic twins, but there is a higher concordance for skin tests than for clinical symptoms in the dizygotic twins, implying that the development of symptoms is less genetically controlled than is development of skin-sensitizing antibody.

Study of the average ages of concordant and discordant twins should give some idea of the relative

role of exposure in the development of skin-sensitizing

Table 23. Concordance rates for skin test reactions and clinical symptoms.

	Skin tests					Symptoms				
		Any		Specific			Any		Specific	
	N	#	%	#	%	N	#	%	#	%
Monozygotic	8	4	50.0	4	50.0	6	3	50.0	3	50.0
Dizygotic	10	3	30.0	2	20.0	11	1	9.1	1	9.1

antibody and clinical symptoms (Table 24). The results are quite confusing because there is no consistent trend, probably because of the small numbers involved (the calculation

Table 24. Average ages, in years, of concordant (C) and discordant (D) twin pairs.

	Skin tests		Symptoms	
	C	D	C	D
Monozygotic	11.8	12.8	11.3	10.3
Dizygotic	10.7	7.7	5.0	8.9

for average age of dizygotic twins, concordant for symptoms,

involves only one twin pair). Consequently, all that can be said is that exposure is very important in development of allergic manifestations.

The minor allergies have not been emphasized in the analyses because we are concerned chiefly with respiratory allergies, and because minor allergies are difficult to diagnose and often go unnoticed because they do not cause much discomfort. This is one of the reasons it is difficult to correlate cause and effect in many cases. There is a trend to an increase in minor allergies in the experimental series over the control series except for the Experimental Group I mothers and the Experimental Group II fathers. The number of offspring with a minor allergy is greater, but not significantly so, when one or both parents have a minor allergy than when neither has such a disorder, which might indicate some hereditary factor present. There are reports in the literature which show that many minor allergies are inherited as separate entities (Rowe, 1928; Landerman, 1962; Baughman and Jillson, 1963; etc.). While many individuals in our data who have minor allergies, do not have major allergies, it is impossible to decide, simply on this basis, whether a minor allergy is just another expression of a general allergic predisposition, or is, indeed, a separate entity.

The fact that the frequency of any allergy (including minor allergy) reported in more distant relatives (grandparents, aunts, uncles and first cousins) is between 7% and 8% illustrates that families interviewed cannot give an accurate history of the disorders in more distant relatives since this frequency is lower than the generally accepted population value of 10% for major allergies. The fact that the two frequencies are nearly equal illustrates that little information can be obtained when data of this nature is grouped, especially when the family sizes are variable and the accuracy of the information is also variable. However, when frequencies were determined separately for grandparents, aunts and uncles, and first cousins, there were no significant differences between the experimental and control groups. In each group, more grandparents than aunts and uncles or cousins of the probands were affected with allergic symptoms.

Other workers (Bray, 1930; Wiener et al., 1936; Schwartz, 1952) have observed that up to puberty, there is an excess of males suffering from allergic symptoms. After this time, the sex ratio approaches equality as the relative number of females developing allergy increases (Nelson, 1933). In the present study a significant

excess of allergic males is observed in the Experimental Group I probands themselves (36 males:14 females), in the affected sibs of allergic probands (e.g. 26 males: 8 females with skin reactions) and in the twins with positive cutaneous reactions (all 8 monozygotic pairs and 4/7 like-sexed dizygotic pairs). Exposure differences are not sufficient to account for the abnormal ratio and explanations based on hormonal differences have not been satisfactory. None of the proposed mechanisms for inheritance of allergy has incorporated the abnormal ratio into the explanation and this observed sex ratio remains another of the unanswered questions.

Besides the excess of affected males, the data demonstrate a significant excess of male sibs of allergic probands in both Experimental Group I (sex ratio 2.1) and II (sex ratio 4.3). This could account for the abnormal sex ratio in allergic sibs, but it does not account for the initial abnormal sex ratio. Other reports have not indicated male:female ratios in the siblings of allergic probands so it is not possible to make any comparisons here. It seems highly unlikely that the occurrence of allergic manifestations would affect sex ratio, yet there is no evidence that by chosing allergic probands in the manner used in this study, one is selecting for families with a high pro-

portion of males. Further data concerning the sex ratio in allergic families is needed for confirmation of these results before an explanation can be sought.

The observations that (1) there is an elevated frequency of positive cutaneous reactions and clinical allergic symptoms in families of allergic children as compared with the frequencies in families of non-allergic children, (2) there are more affected offspring in families in which parents are affected than in families in which parents are not affected, and (3) the concordance rates for monozygotic twins are somewhat higher than for dizygotic twins, provide evidence that heredity plays a part in the etiology of allergy. The exact nature of this hereditary factor cannot be determined from the information available, but some assumptions can be made.

It appears that one does not inherit a specific predisposition to become sensitized to ragweed pollen and to develop ragweed hay fever symptoms, but because the numbers of persons with various symptoms were too small and because the allergens tested were not as representative of allergic disorders as would have been desired, it was impossible to determine whether one inherits a general predisposition to become allergic or a specific predisposition to respond to a given group of allergens in a characteristic manner. (In

speaking of predisposition, production of skin-sensitizing antibody and development of symptoms will be meant because the relationship between the two is unclear). The observations that (a) allergic persons usually have more than one allergic manifestation, and (b) when several family members have allergic symptoms, the symptoms are not necessarily the same, argue for the inheritance of a general allergic predisposition, while the indication that more parents with ragweed hay fever and perennial allergic rhinitis have children who suffer from ragweed hay fever than when they have other allergic symptoms, could be evidence for a specific predisposition, i.e. the ability to respond to inhalant allergens and develop allergic rhinitis.

The hereditary factor responsible is probably not a simple dominant with full penetrance because in such cases, one expects nearly all of the probands to have at least one affected parent. At least one parent of only 46% of the probands in Experimental Group I had a positive skin test to the allergens tested and at least one parent of only 54% suffered from symptoms of a major allefgy.

Those who possess the necessary genetic constitution apparently produce reagin or skin-sensitizing antibody with a very limited exposure to the allergen. Do

those who become sensitized only after repeated exposure also possess a similar hereditary constitution with different modifying factors which retard onset of the disorder, or are they the heterozygous individuals proposed by Wiener et al. (1936), or do they simply succumb due to constant exposure? The last alternative would imply that with adequate exposure to ragweed pollen, for example, everyone would eventually develop symptoms of ragweed hay fever. Although there has been no attempt to measure individual exposure, it would seem reasonable to assume that a large number of persons have had a great deal of exposure without developing symptoms. Therefore, one is led to postulate that there is probably a major gene or group of genes governing allergic predisposition (which seems to be correlated with skin-sensitizing antibody production) and numerous other modifying genes responsible for the eventual expression of the allergic disorder. Some of these modifying genes plus the homo- or hetero-zygous state of the major locus (loci), determine the degree of exposure necessary for development of skin-sensitizing antibody and symptoms. Those who possess none, or very few, or these factors do not develop the disease.

Future Investigation

The time has come to concentrate on the details of inheritance in allergy. However, one cannot design studies which would elucidate these details without first being aware of the value and limitations of studies such as the present one.

It is felt that the basic organization of the present study was good. The setting of definite criteria regarding age range and exposure, to be met by all probands, established quite comparable experimental and control series. Since this study was a pilot study, the numbers were small, but in another study, at least twice as many probands in each group would be recommended. The policy of home visits increased the proportion of families willing to participate, but did have some shortcomings in that there are many distractions in the home and there is the possibility, although remote, that testing will result in untoward reactions requiring immediate medical attention.

Ascertainment was essentially by single selection of families although there was the possibility of multiple ascertainment for two families. The biasses in the method include a greater probability of ascertainment in families with larger numbers of affected offspring and the complete exclusion of families with no affected offspring. It has

been found (Warburton, 1962) that by using the "proband" method, i.e. omitting the first proband and counting the number of affected and unaffected siblings, the families with more than one affected individual are exactly compensated for. In another study, where data are more extensive, it is recommended that the various methods of analyses be applied to determine whether the data is compatible with a recessive mode of inheritance.

There is always a difficulty in assembling an unselected, adequate control series because "healthy" people do not wish to submit to "unnecessary" tests. Because unco-operativeness is a problem in most population studies, and no less in this study, it is mentioned here. If at all possible, the control series should be chosen from a group with which good rapport has previously been established, for some other reason. This reduces the number of refusals and hence reduces selection and bias because it has been observed that if one contacts members of the general population, those most likely to assent are those who are familiar with the condition under study because "<u>it is present in my family</u>".

Few familial studies of allergy have supplemented history with skin-sensitivity tests. These tests are a valuable aid in the diagnosis of allergy provided their limitations, such as degree of correlation with symptoms,

are recognized and taken into consideration when choosing allergens to be tested in an investigation. Another consideration should be the frequency of positive reactions to the allergen. If the frequency of response is too low or too high (non-specific response), the tests will provide little information because they do not discriminate between allergic and non-allergic persons. In addition, the number of allergens tested should not be too large to seriously discourage participation in the study, nor so small as to obscure any existing trends.

To be useful in determining whether a general or specific predisposition is inherited, the allergens tested should be varied in nature and each capable of producing distinct and different symptoms. This suggestion is difficult to put into practice because the correlation between skin sensitivity and disease for non-inhalant allergens is poor and the frequency of reactions is low. Some foods, such as cocoa, codfish and nuts do produce characteristic symptoms such as generalized urticaria, but they can also produce allergic rhinitis. Furthermore, some, such as codfish, are very potent allergens and may elicit a severe reaction in sensitive individuals so that they must be used with caution. The alternative to using such unsatisfactory allergens is to use inhalant allergens which cause seasonal or perennial allergic

rhinitis and to try to determine whether there is a specific or general response to them but here one is faced with the problem of uniform exposure.

Inaccuracies in the histories are probably the major problem encountered in any population study. Therefore, it is imperative that the investigator strive toward accurate history-taking. Some principles essential in obtaining an accurate history follow. First, the investigator himself should be certain of all the symptoms of the disorders with which he is working. Such knowledge can only be obtained from first-hand experience with the disease in question and for this reason, any person undertaking such a study should have this experience before beginning any research. Secondly, those being investigated should also be well-acquainted with the disorders under consideration and all participants should be equally well informed. The last aim is especially difficult to attain if a control series is involved because the subjects in this series presumably have had little previous knowledge of the condition. Peshkin (1928) and Schwartz (1952) in their investigations have been very thorough in educating the participants, although Peshkin had no control series with which to contend. Thirdly, during the actual history-taking, one should make an effort to avoid direct questions and let the person interviewed describe his symptoms. It

is known that many people give affirmative answers to direct questions because they feel that by doing so, they are of greater assistance to the investigator. Finally, all histories should be verified by a second interview and by at least one other reliable person (a relative) seen separately and at a different time because inaccuracies are more likely when the diagnosis is based on information obtained during a single interview with a single informant.

Because the exposure factor is obviously important, especially in pollen allergies, more attention should be paid to this aspect than has been previously. This is pointed out because few realize that comparisons of information about the occurrence of pollen allergies in relatives of two groups are quite useless if the exposure is not comparable. Similarly, age of onset data means little in pollen allergies if the extent of exposure is unknown. Therefore, questions concerning length of exposure before sensitization, i.e. length or residence in given localities, etc., should be included in any research programme.

VII. SUMMARY

A study of families of probands with a positive skin test to ragweed pollen and symptoms of ragweed hay fever (Experimental Groups I and II) and families of probands with no positive skin tests and no symptoms of ragweed hay fever (Control Group) was undertaken to determine the role of heredity, if any, in the etiology of allergic disease.

A higher frequency of positive skin reactions and of allergic symptoms in the parents and siblings of the Experimental groups than in the same relatives of the Control Group provides some evidence for the existence of a familial factor in allergic disease. Significant differences existed between the numbers of positive skin reactions in the siblings of Experimental Group I and the Control Group, but not between the parents in the two groups. The frequencies of positive skin tests to ragweed pollen are 28.0% and 6.5% for siblings, and 26.0% and 17.0% for parents, in Experimental Group I and the Control Group, respectively. The frequencies of allergic symptoms for the fathers and siblings in Experimental Group I were higher than the frequencies for fathers and siblings in the Control Group. The Experimental Group I mothers usually had a lower frequency of the various allergic disorders

than did the Control mothers. The only reasonable explanation seemed to be the inaccuracies in the history-taking method.

Experimental Group II showed a much higher frequency of positive skin reactions and symptoms than did either of the other two groups, but since this group was chosen from private allergy practices and differed in a number of ways, it was not directly comparable with the other groups. It did, however, provide valuable information concerning allergic disease.

Elevated frequencies of siblings with allergic manifestations from matings in which parents had allergic manifestations as compared with frequencies when parents did not have such manifestations, documents the existence of an hereditary factor. When one or both parents had a skin reaction to ragweed pollen, 48.5% of the probands' siblings also had a positive skin reaction to the allergen, whereas, when neither parent had a positive reaction, only 14.3% of the siblings had a positive reaction. Similar data from clinical symptoms provide less convincing evidence since, in most instances, differences were not significant.

In addition to the hereditary factor, there is evidence that an environmental factor is important in allergic disease because there was a significant increase in numbers of skin reactions in the parents

over the number in the siblings of the Control Group. A plot of age versus frequency of positive reactions is not contrary to the idea of increase in skin sensitivity with age due to an exposure factor, but provides no conclusive evidence for it.

Twin studies reveal a higher concordance rate in monozygotic than dizygotic twins for both skin tests (4/8 versus 3/10) and symptoms (3/6 versus 1/11) although the differences are not statistically significant. If larger numbers corroborated this trend, this would be evidence for an hereditary factor. The existence of many discordant monozygotic pairs (50% in each case) argues for an environmental factor as well.

Therefore, it is concluded that both an hereditary and an environmental factor are necessary for development of allergic disease. The genetic factor responsible does not fit any simple Mendelian expectation but the evidence is that a major gene, which is probably not a fully penetrant dominant, or a group of genes, either of which can be acted upon by numerous modifying genes, determine a general allergic predisposition.

A significant excess of males was observed in the allergic probands, in the siblings of allergic probands, in affected siblings of allergic probands

and in twins with positive skin tests. The observed excess of affected males up to puberty is in accordance with previous studies but the excess of male siblings of allergic probands needs confirmation.

The study has illustrated the relative value of information obtained by skin-testing and history-taking. Suggestions have been made for a future study to clarify some of the remaining problems.

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X. APPENDIX

Raw data concerning allergic symptoms and skin test reactions in probands and in mothers, fathers and siblings of probands.

Abbreviations

R.H.F.	Ragweed hay fever
S.A.R.	Seasonal allergic rhinitis
P.A.R.	Perennial allergic rhinitis
M	Mothers
F	Fathers
S	Siblings
Egg	Egg albumen

Table A-1. **EXPERIMENTAL** GROUP I. Allergic manifestations in probands, other than ragweed hay fever.

Family		Skin tests Grass	Egg	S.A.R.	P.A.R.	Asthma	Eczema
1.	Barrowcliffe	+		+			+
2.	Baylis	+			+	+	
3.	Besner					+	+
4.	Bukacheski						+
5.	Coughlin	+		+		+	+
6.	Cunningham	+		+			
7.	Dansereau						
8.	Dee	+		+		+	+
9.	Dollimore				+	+	
10.	Duffus					+	
11.	Faivre	+		+		+	+
12.	Fitzpatrick	+			+	+	
13.	Gilbert	+		+		+	
14.	Gough	+		+		+	+
15.	Grimes				+	+	
16.	Haladuick	+					
17.	Hale				+		
18.	Huber				+	+	
19.	Johnson				+	+	+
20.	Lacombe				+		
21.	MacDonald				+	+	
22.	Mc Connell	+		+	+		

Table A-1 Cont'd

Family		Skin tests Grass	Egg	S.A.R.	P.A.R.	Asthma	Eczema
23.	Mc Donald	+		+	+	+	
24.	Melnik				+	+	+
25.	Menard	+	+	+	+	+	
26.	Miron	+	+	+		+	
27.	Monaghan					+	+
28.	Morawski	+				+	+
29.	Murray	+		+	+	+	+
30.	O'Donnell	+	+	+	+		
31.	Palewandrem				+		
32.	Pearson			+		+	
33.	Peters	+		+	+		
34.	Pulvermacher					+	+
35.	Rowlands	+		+			
36.	Russo	+		+		+	
37.	Sansom	+	+				
38.	Sheppard	+		+		+	
39.	Simard	+					
40.	Sobol	+		+	+		+
41.	Stefankiewicz	+		+			
42.	Tomkinson	+		+		+	
43.	Tompkins	+				+	
44.	Trescak	+		+	+		+

Table A-1 Cont'd

Family	Skin tests Grass	Egg	S.A.R	P.A.R.	Asthma	Eczema
45. Walker	+		+	+	+	+
46. Weatherstone	+	+	+	+		+
47. Williamson	+		+	+	+	
48. Wyszogrodski	+		+			+
49. Young	+					+
50. Zeagman				+	+	

Table A-2. EXPERIMENTAL GROUP I. Allergic symptoms in parents and siblings of probands.

Family	R.H.F.			S.A.R.			P.A.R.			Asthma			Eczema			Total Sibs
	M	F	S	M	F	S	M	F	S	M	F	S	M	F	S	
1.									1							6
2.									1	+						3
3.																1
4.			1						1							4
5.		+	1			1		+	1		+	2				5
6.							+			+						1
7.																1
8.				+	+											1
9.																3
10.							+			+	+					2
11.																2
12.		+			+						+					2
13.																2
14.								+								1
15.			1					+								3
16.														+		1
17.		+														1
18.																2
19.								+								1
20.			1													7
21.																0
22.	+	+	1		+						+					2

Table A-2 Cont'd

Family	R.H.F. M	F	S	S.A.R. M	F	S	P.A.R. M	F	S	Asthma M	F	S	Eczema M	F	S	Total Sibs
23.	+		1	+		1	+			+			+			1
24.								+								1
25.																0
26.	+								1						1	1
27.		+			+		+									1
28.																2
29.								+								0
30.						1										2
31.	+	+					+	+								0
32.		+														2
33.			1			1		+	1							1
34.																1
35.						1				+						2
36.										+			+			0
37.			1													2
38.		+										2				4
39.																0
40.													+			1
41.																1
42.									1			2			1	4
43.	+							+								2
44.			1					+							1	1

Table A-2 Cont'd

Family	R.H.F. M.F S	S.A.R. M F S	P.A.R. M F S	Asthma M F S	Eczema M F S	Total Sibs
45.			1	1		2
46.	+		1			1
47.			1			2
48.	1					1
49.						1
50.	1		1			3

Table A-3. EXPERIMENTAL GROUP I. Skin test reactions in parents and siblings of probands.

Family	Ragweed			Grass			Egg White			Any			Total Sibs
	M	F	S	M	F	S	M	F	S	M	F	S	
1.			1									1	4
2.													3
3.													1
4.			1									1	3
5.		+	3		+	2			1		+	3	5
6.								+			+		1
7.		+									+		1
8.													1
9.													3
10.		+									+		0
11.													2
12.			+			+						+	2
13.													2
14.					+						+		1
15.			1									1	3
16.			+									+	1
17.		+	+								+	+	1
18.			+									+	2
19.													1
20.			1			1						1	6
21.													0
22.		+	+ 2		+	+ 1					+	+ 2	2

Table A-3 Cont'd

Family	Ragweed			Grass			Egg White			Any			Total Sibs
	M	F	S	M	F	S	M	F	S	M	F	S	
23.	+		1	+		1				+		1	1
24.		+	1								+	1	1
25.													0
26.	+		1	+		1				+		1	1
27.		+	1								+	1	1
28.													2
29.													0
30.		+				1		+			+	1	2
31.	+	+		+	+					+	+		0
32.		+	1								+	1	2
33.			1			1						1	1
34.													1
35.			1			1						2	2
36.													0
37.	+		1			1				+		1	2
38.	+	+	1			1				+	+	1	4
39.													0
40.													1
41.													1
42.													4
43.	+									+			0
44.	+		1	+						+		1	1

Table A-3 Cont'd

Family	Ragweed M	Ragweed F	Ragweed S	Grass M	Grass F	Grass S	Egg White M	Egg White F	Egg White S	Any M	Any F	Any S	Total Sibs
45.													2
46.	+	+			+					+	+		1
47.													2
48.			1									1	1
49.													1
50.		+	3			1					+	3	3

Table A-4. EXPERIMENTAL GROUP II. Allergic manifestations in probands, other than ragweed hay fever.

Family	Skin tests Grass	Egg	S.A.R.	P.A.R.	Asthma	Eczema
1. Benjamin				+		+
2. Blackwell	+		+	+		
3. Church				+		
4. Fox	+		+	+		+
5. Fraser	+		+			
6. Hunter						
7. Lazar	+					
8. Margolian				+		
9. Mauer	+		+	+		
10. Rabinovitch				+		
11. Sabler	+		+	+	+	
12. Sullivan	+					

Table A-5. EXPERIMENTAL GROUP II. Allergic symptoms in parents and siblings of probands.

Family	R.H.F.			S.A.R.			P.A.R.			Asthma			Eczema			Total
	M	F	S	M	F	S	M	F	S	M	F	S	M	F	S	Sibs
1.							+						+			2
2.								+			+					1
3.	+		1	+		1										1
4.							+									1
5.		+			+						+					2
6.	+			+			+						+			1
7.	+	+	1		+	1	+	+	1						1	2
8.	+	+		+						+			+			0
9.			1			1					+				1	2
10.	+	+					+				+					1
11.	+		1	+		1				+						2
12.		+			+			+	1							1

Table A-6. EXPERIMENTAL GROUP II. Skin test reactions in parents and siblings of probands.

Family	Ragweed			Grass			Egg White			Any			Total Sibs
	M	F	S	M	F	S	M	F	S	M	F	S	
1.			1									1	2
2.			1									1	1
3.	+		1	+		1				+		1	1
4.													1
5.		+			+	1					+	1	2
6.	+	+		+	+					+	+		1
7.	+	+	1		+	1				+	+	2	2
8.	+	+		+						+	+		0
9.		+	1		+	1					+	1	2
10.	+	+			+	1				+	+	1	1
11.	+	+	1	+	+	1				+	+	1	2
12.		+			+						+		1

Table A-7. CONTROL GROUP. Allergic manifestations in probands, other than ragweed hay fever.

Family	Skin tests Grass	Egg	S.A.R.	P.A.R.	Asthma	Eczema
1. Ancliffe						
2. Andrews						
3. Benjamin						
4. Bennett						
5. Beveridge						
6. Borshy						
7. Brunet				+		+
8. Carson						
9. Chaput						
10. Cheyne						
11. Cohen						
12. Descart						
13. Distilio						
14. Downes						
15. Drury						
16. D. Dunn						
17. J. Dunn						
18. Ellis						
19. Emmons						
20. Ettinger						
21. Feinstein						
22. Foot						

Table A-7 Cont'd

Family	Skin tests Grass	Egg	S.A.R.	P.A.R.	Asthma	Eczema
23. Fox						
24. Gagnier						
25. Goldsmith				+		
26. Hudson						
27. Isajuk						
28. Lamy						
29. Lanning					+	
30. Legault						
31. Lyrette						
32. C. Martel						
33. N. Martel						
34. Messacar						
35. Noakes						
36. Owchar						+
37. Parent						
38. Patterson						
39. Prunier						
40. Reitel						
41. Robillard						
42.. Shewchuk						
43. Sloan						
44. Spicer						

Table A-7 Cont'd

Family	Skin tests Grass	Egg	S.A.R.	P.A.R.	Asthma	Eczema
45. Thomas						
46. Todoeschuk					+	
47. Valade						
48. Vigeant						
49. Wade						
50. Watt						

Table A-8. CONTROL GROUP. Allergic symptoms in parents and siblings of probands.

Family	R.H.F.			S.A.R.			P.A.R.			Asthma			Eczema			Total
	M	F	S	M	F	S	M	F	S	M	F	S	M	F	S	Sibs
1.																3
2.																3
3.			1												1	1
4.							+									4
5.																2
6.							+		1							1
7.																2
8.																11
9.															1	6
10.	+						+			+						0
11.		+			+											2
12.																1
13.			1													2
14.																2
15.																2
16.																5
17.	+															4
18.		+							1							2
19.																5
20.					+											1
21.		+	1		+	1						+	1			2
22.																1

Table A-8 Cont'd

Family	R.H.F. M	F	S	S.A.R. M	F	S	P.A.R. M	F	S	Asthma M	F	S	Eczema M	F	S	Total Sibs
23.																1
24.																6
25.									1							1
26.																2
27.																2
28.																7
29.																0
30.	+			+					1			1				3
31.									1							5
32.																3
33.																3
34.			1									1			2	6
35.	+															2
36.																2
37.				+											1	4
38.	+					1	+			+						1
39.																3
40.							+									1
41.	+									+				+		2
42.																3
43.																2
44.																1

Table A-8.Cont'd

Family	R.H.F.			S.A.R.			P.A.R.			Asthma			Eczema			Total
	M	F	S	M	F	S	M	F	S	M	F	S	M	F	S	Sibs
45.																1
46.												1				2
47.			1						1							2
48.																4
49.	+			+	+		+			+						1
50.	+		1				+					1			1	1

Table A-9. CONTROL GROUP. Skin test reactions in parents and siblings of probands.

Family	Ragweed			Grass			Egg White			Any			Total Sibs
	M	F	S	M	F	S	M	F	S	M	F	S	
1.													3
2.						1						1	3
3.			1			1			+			+ 1	1
4.													4
5.													2
6.													1
7.													2
8.			1									1	4
9.													6
10.		+			+						+		0
11.			+			+			+			+	2
12.													1
13.													3
14.													2
15.													2
16.													5
17.		+			+						+		4
18.			+									+	2
19.													5
20.			+			+			+			+	1
21.			+ 1			1						+ 1	2
22.			+						+			+ +	1

Table A-9 Cont'd

Family	Ragweed M	Ragweed F	Ragweed S	Grass M	Grass F	Grass S	Egg White M	Egg White F	Egg White S	Any M	Any F	Any S	Total Sibs
23.													1
24.													6
25.													1
26.													2
27.													2
28.													7
29.		+			+						+		0
30.	+									+			3
31.						1			1			1	3
32.													3
33.	+		1							+		1	3
34.			2									2	4
35.	+									+			2
36.													2
37.													4
38.	+									+			1
39.													3
40.													1
41.	+				+					+			2
42.													3
43.													2
44.		+			+						+		2

Table A-9. Cont'd

Family	Ragweed M	Ragweed F	Ragweed S	Grass M	Grass F	Grass S	Egg White M	Egg White F	Egg White S	Any M	Any F	Any S	Total Sibs
45.													1
46.													2
47.		+	1			1					+	1	2
48.													4
49.	+	+			+					+	+		1
50.			1			1			1			1	1