

CRITICAL ANALYSIS OF THE HEREDITARY CONCEPT OF ALLERGY

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PRESENT-DAY knowledge of human inheritance is meager and unsatisfactory. Direct experimental methods available in botany and zoology are obviously impossible in man. In plants and in lower forms of insect life experimental matings can be made to determine the operation of the laws of heredity, the mode of transmission of various characters, and their modifiability in the presence of other characters. In the study of human inheritance we are not confronted with pure lines, but with the most complicated admixture of different lines. Matings are random; the genetic constitutions of the parents entering into the matings are not known. The breeding period is so delayed that it is seldom that any one observer can watch the effects of the condition on more than two generations. The number of offspring is usually so few that there are seldom enough children to express all of the possibilities of the mating with respect to any one character.

The student of human inheritance, therefore, is limited to a study of pedigrees to observe the incidence of pathologic disorders. Much of the evidence on which these deductions rest is based on hearsay. Records are generally inadequate, not always accurate, and certainly liable to subjective interpretation by the investigator.

In view of the conflicting conclusions that have been drawn by different investigators thus far in an attempt to apply Mendelian laws to allergy, the difficulty in obtaining adequate material, and the inadequate definition of essential criteria, we agree with Hogben¹ that no hypothesis can be made to fit the existing data.

The tendency of asthma and hay fever to occur in families has been reported frequently in the literature. In 1909, Drinkwater² concluded that asthma is inherited as a simple Mendelian dominant character on the basis of a single family pedigree. A more extensive study was made by Cooke and Vander Veer³ in 1916, and Adkinson⁴ subsequently published the results of an investigation which agreed with Cooke and Vander Veer in that genetic influences played a major role. The former investigators concluded that the capacity to become sensitized is transmitted as a simple Mendelian dominant character, while the latter inferred that bronchial asthma is inherited as a simple recessive trait. Genetic transmission as a simple dominant character failed to explain why, in more than one-half of the cases, no history of allergy could be elicited in any of the antecedents. The conclusion that bronchial asthma is inherited as a simple recessive trait is untenable because of

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the presence of pedigrees in which both parents were affected, yet some children were normal.

In 1924, Spain and Cooke⁵ presented additional material and suggested that the genetic factor is dominant and multiple, the component parts of which are separately inherited. Wiener, Zieve, and Fries⁶ postulated that allergic individuals may be classified according to the age of onset of symptoms into pure normals, those whose symptoms began before puberty, and those who are either normal transmitters or who develop allergy after puberty.

It is generally agreed that isolated pedigrees such as those of Drinkwater and others are unsuited for a study of inheritance. We carefully reviewed the excellent protocols of Cooke and Vander Veer. They concluded, first, that the capacity to become sensitized is inherited, and that the degree of inheritance influences the age of onset of symptoms. The evidence for the inheritance of allergy is based on a comparison of the incidence of positive allergic family histories in their patients, as compared with that observed in a group of a random selection of so-called normal individuals. They found a wide divergence in the incidence of positive family histories in the allergic group as compared with the nonallergic group. Since they indicated in one of their control groups that their inquiry was limited to the presence of allergy in the parents alone, we believe that the wide divergence that they observed in the incidence between the allergic and nonallergic groups may better be explained by the difference in the extent of inquiry in the two groups compared.

In support of this criticism, we re-examined our data with respect to this point. When we limited our inquiry of allergies in the family to parents and collaterals, parents and grandparents, or to the parents alone, different figures were arrived at (Table I). The inference of the existence of hereditary factors in allergic diseases, predicated on the data subjected to the criticism just made, should be re-examined in the light of more strictly defined criteria.

TABLE I. INCIDENCE OF POSITIVE FAMILY HISTORY IN NONALLERGIC AND ALLERGIC CASES, VIEWED FROM THE EXTENT OF ANTECEDENT PEDIGREE INQUIRED INTO

SOURCE	TYPE OF CASE	NO. OF CASES	EXTENT OF ANTECEDENT PEDIGREE INQUIRED INTO			
			DIRECT AND COL-LATERAL	DIRECT		NOT SPECIFIED
				PARENTS AND GRAND-PARENTS	PARENTS	
Cooke and Vander Veer	Nonallergic	63	—	—	9.5%	—
Cooke and Vander Veer	Nonallergic	76	—	—	—	14.5%
Spain and Cooke	Nonallergic	115	—	—	—	7.0%
Balyeat ⁷	Nonallergic	403	—	—	9.0%	—
Cooke and Vander Veer	Allergic	504	48.4%	—	—	—
Spain and Cooke	Allergic	462	58.0%	—	—	—
Wiener, Zieve, and Fries	Allergic	66	—	—	28.7%	—
Ratner and Silberman	Allergic	250	54.4%	43.2%	22.4%	—

With regard to the influence of the type of family history on the age of onset, we were unable to confirm their findings.³ In our study of 250 children and their families, there was no relation between the type of family

history and the age of onset of symptoms.⁸ This finding is in accord with those of Peshkin⁹ and Bray¹⁰ and has most recently been corroborated by Schwartz.¹¹

It is agreed that the general incidence of the major allergic syndromes in the random population is from 7 to 10 per cent. We, in careful questioning of a total group of 3,000 individuals consisting of medical students, physicians, and nurses, found that the general incidence was from 10 to 19 per cent. This inquiry took place over a period of fifteen years up to the present time. In the latter few years these inquiries show a somewhat greater incidence of allergy in this professional group. For comparison, we studied the so-called allergic population, in this instance composed of the combined fraternities of 250 patients, which was first collected fifteen years ago. The total population of these families was 6,244 individuals, including the patients. Of this total, 617 were allergic. The frequency of allergy in this so-called allergic population, therefore, is 9.8 per cent. Bray,¹² in a similar study, found an incidence of 14.3 per cent.

The notion that one of the characteristic features of allergy is the great frequency with which it may appear in a family has been accepted and reiterated by many authors. A search for evidence in support of this idea reveals that it is based chiefly upon a few striking family pedigrees such as those reported by Drinkwater,² Smith,¹³ and Bucher and Keeler.¹⁴ Attention is drawn to the varying criteria with respect to the interpretation of the allergic state in these three studies.

We analyzed our own data with regard to this problem. There was an average of 25 persons per family history. In about 40 per cent of the families, there was only one allergic member, who was the patient himself. In an additional 25 per cent of the families, only one other relative showed allergy. Less than 1 per cent of the families have an allergic membership similar to the oft-quoted pedigrees of Drinkwater and Smith. This indicates the extremely low incidence of such an occurrence.

We also consulted the protocols of Cooke and his co-workers on this point. From their data we noted that the distribution of allergic members per family in their material is identical with ours²⁰ (Fig. 1).

When the incidence of allergic offspring in the family group is correlated with the type of family history classified according to the presence of allergy in the branches, we discover a somewhat larger number of individuals is affected when it is present on both sides or on one side than when there is a negative family history, but the incidence of allergic offspring is the same in those families where allergy appears on both sides and where it is unilateral.

Schwartz¹¹ this year published a monograph in which he studied the problem of inheritance of bronchial asthma. He concluded that bronchial asthma is a genetic entity, and that a genetic relationship exists between asthma, vasomotor rhinitis, and probably infantile eczema in which the specific offending allergen is clearly demonstrable. On the other hand, a large category of eczemas, urticaria, angioneurotic edema, and gastrointestinal allergy he found to be not significantly associated with asthma, and therefore separated

them pathogenetically from bronchial asthma. He also concluded that asthma is inherited as a Mendelian dominant with failing manifestations, so that only 40 per cent who carry the genes would ever develop symptoms.

He stated that it is not reasonable to maintain, as previous workers have done, that all allergic diseases are genetically related. In this connection, the recent studies of Ratner, Collins-Williams, and Untracht¹⁵ on the allergic dermal-respiratory syndrome corroborate the findings of previous workers that dermal and respiratory allergies are related and give further evidence that there is an evolution from dermal to respiratory symptoms, and that 59 per cent of children with allergic eczema later have respiratory allergy (asthma and hay fever).

Schwartz's results are based on a statistical study of material consisting of 191 asthmatic patients, 200 controls, and 50 patients with baker's asthma. He employed the Weinberg statistical genealogic method, which he considers reliable for the demonstration of inheritance factors, if one can assume the absence of exogenous differences between the patients and the control series.

The study is included in an extensive monograph, in which the author in his introduction states that there is hardly any branch of medicine in which the theories have been so numerous, the classification so vague, the nomenclature so divergent, and the definitions so varied. One can only be impressed with the enormous amount of time and effort expended by the author in the collection of his material and in its statistical evaluation. In discussing criteria he, too, emphasizes the lack of uniformity with regard to the material studied by previous workers, and is of the opinion that the question of heredity in allergic diseases cannot be considered as solved and that it will remain unsolved so long as the limitation of the concept of allergy remains uncertain. In this we heartily agree. We are further impressed by the remarkable parallelism between his and our points of criticism of previous workers. We refer to the limitations of isolated pedigrees, data which are not directly comparable, undefined and sparse control material, and the controversial correlation between the age of onset and the type of family history, upon which the hereditary hypothesis of Wiener, Zieve, and Fries rests.

The difficulties encountered in obtaining adequate control material are shown in Schwartz's study, in which one-half of his 200 control subjects were patients receiving ambulatory treatment at the Clinic of the National Polio-myelitis Society in Copenhagen. We will not attempt to evaluate the influence of this type of selection, but we do not believe that it constitutes a random sample. We emphasize this because his study will stand or fall on its validity.

Schwartz divided his asthmatic patients into allergic and nonallergic groups, which corresponds with what he calls the American classification of "extrinsic" and "intrinsic" to ascertain whether the two groups show the same characteristics from a statistical standpoint. He concluded that the two groups are not distinguishable, and that therefore asthma constitutes a syndrome which behaves as a genetic entity. Urticaria, which is almost universally regarded as an allergic disease, the author concluded was not genetically related to asthma. It seems to us, from the data of Schwartz, that

what may be inherited is not the capacity to become sensitized, but a respiratory tract which may react with the production of asthma or rhinitis, due to a multiplicity of stimuli, one of which may be the antigen-antibody mechanism.

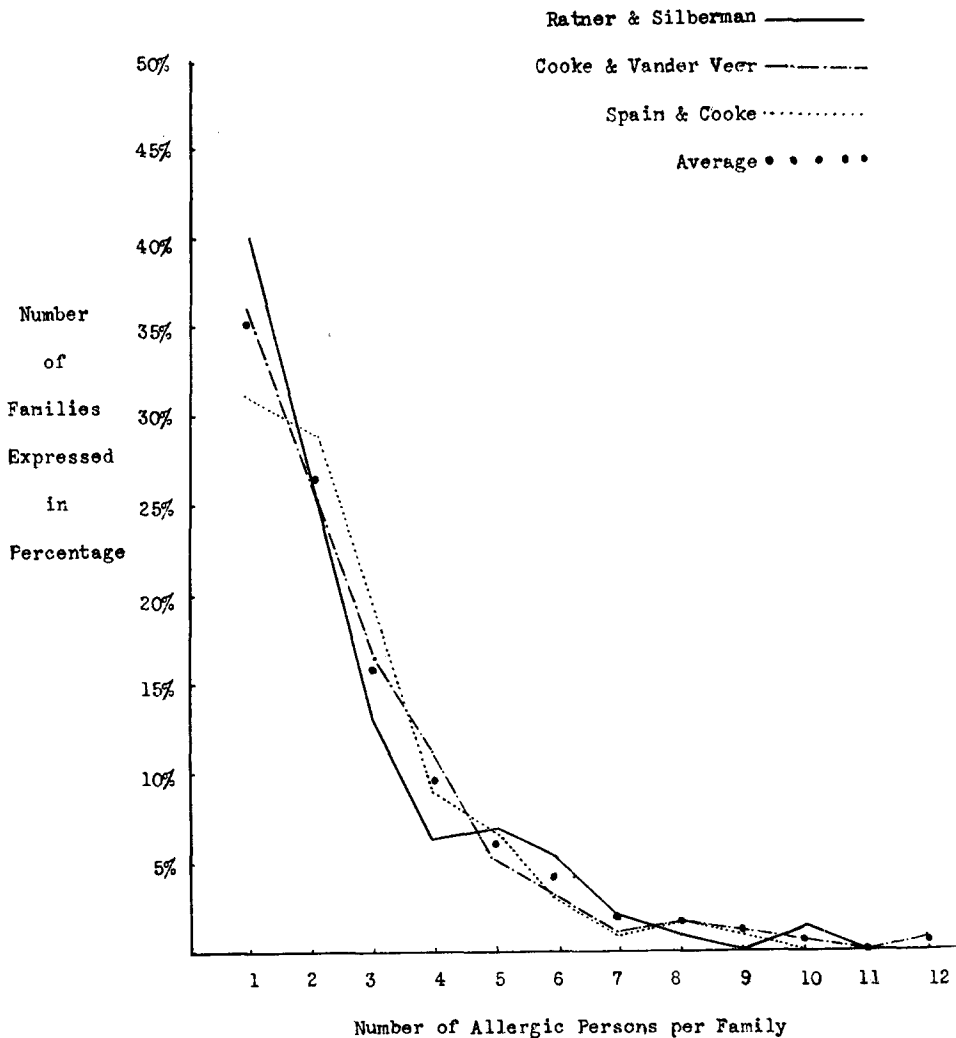


Fig. 1.—Comparison of the number of allergic individuals per family in our 250 cases, the 503 cases of Cooke and Vander Veer, and the 439 cases of Spain and Cooke.

Schwartz states further that the study of baker's asthma does not permit the general conclusion that all cases of occupational asthma must be due to an inherited predisposition. We feel that there is a contradiction in his conclusion that baker's asthma is inherited as a Mendelian dominant in view of the fact that in 60 per cent of the bakers who suffered from asthma there was a negative family history.

Other points of interest that are brought out by this investigator are that all persons may be sensitized and that different occupational substances

possess different capacities to sensitize. We are in accord with this and believe that what Schwartz was dealing with is an occupational group of asthmatics who are exposed to an unusual concentration of a highly allergenic substance. It must be further commented upon that the sensitization period to flour that he found in his cases averaged more than ten years.

In a study that we made in guinea pigs on experimental asthma we determined that quantity and certain temporal factors played an important role in the shortness of period in which the animals became sensitized. As we increased the intensity of the exposure of the guinea pigs to the inhalation of an antigenic dust, we learned that sensitization occurred earlier in direct proportion to the amount of exposure. However, there seemed to be an optimal point at which this occurred, and, as the time of exposure was increased beyond this point, sensitization did not necessarily occur as early as at the optimal point.¹⁶

One of the surprising things in Schwartz's work is that no mention is made of the percentage of bakers that develop asthma. Do 75 per cent of bakers develop asthma or do 10 per cent develop it? It would have been interesting if Schwartz had used the bakers who had not developed asthma as controls. Under the conditions of their exposure, those who did not develop asthma would certainly have constituted an excellent group of nonallergics.

In our guinea pig experiment referred to previously, 93 per cent of the animals developed experimental asthma. Seven per cent appeared to be resistant, the reason for which we did not determine. We concluded that our findings lend support to the belief that asthma may be regarded as an acquired condition.

Schwartz states finally that he cannot rule out the possibility that certain varieties of asthma are pathogenetically different from the spontaneous variety. We have always been at a loss to know what constitutes a spontaneous variety of asthma. Asthma is not an intrinsic disease but depends largely on exogenous factors. The antigen invading the respiratory tissue sets up a sensitization based on the antigen-antibody mechanism.

Schwartz regards Ancona's endemic asthma as a special variety of asthma to be distinguished from baker's asthma. Ancona¹⁷ studies a group of bakers with asthma which he showed immunologically to be due to infested wheat grain and, in addition, proved that extracts made from the particular infectious agent, *Pediculoides mites*, did induce skin reactions when injected and produced asthma when inhaled by these subjects.

We see no difference in this form of asthma from baker's asthma due to the inhalation of flour. Though the type of allergen may differ in its innate qualities for establishing allergy with greater or lesser ease, they all operate in the broad domain of the antigen-antibody mechanism.

Finally, Schwartz takes exception to including tropical eosinophilia and Löffler's syndrome, which are often associated with asthma, under the category of asthma and suggests placing them in a special group.

We therefore are critical of his establishing new sets of criteria for the various groups of antigen-antibody forms of allergy and believe that the

sole criterion for allergy must rest on proof that the allergic syndrome is or is not initiated by an antigen-antibody mechanism.

One is not justified in eliminating eczema, urticaria, gastrointestinal disturbances, and certain forms of asthma such as Ancona's and Löffler's. If, in these conditions, one can elicit positive skin tests in the individual and establish a causal relation between the allergen and the syndrome through clinical test, then the condition must be accepted as allergic in character and not arbitrarily eliminated from consideration.

In discussing investigations of identical twins in relation to the problem of the inheritance of cancer, Little¹⁸ points out that the data obtained from this type of material do not prove the genetic transmission of such tumors. If cancer were due to an agent or agents present in the fertilized ovum or in the maternal blood in a form transferable through the placenta, similar results would be expected. Such an agent might be a gene, a part of or a whole chromosome, or any component of a reproducible type in the egg cytoplasm, or a viroid or serologic substance of maternal origin.

We would like to quote the comment of Chase¹⁹ on the subject; he states, "Indeed, with certain allergies such as hay fever, the genotype of the individual has been said to exert absolute control over the capacity for sensitization; this matter has not yet been subjected to adequate examination."

Further analyses of the hereditary concept are discussed in a previous communication.²⁰

CONCLUSION

The discrepancies noted in published observations on the distribution of allergy and its relation to heredity and the inferences drawn therefrom are largely due to the different methods of collection of data, the criteria employed in defining the allergic state, and the extent to which inquiry was made into the individual family incidence of allergy.

An evaluation of the available data does not satisfactorily demonstrate that, within the scope of the antigen-antibody mechanism, the capacity to become sensitized is controlled by genetic influences. On the other hand, we do not imply that we have shown that the gene does not play a role in the production of the allergic state. The frequency with which the hypersensitive state occurs in the lower animal and in man makes it extremely difficult to dissociate acquired from genetic factors in its establishment. Chromosomal and other factors which may simulate genetic influences require further elucidation.

In view of the conflicting conclusions that have been drawn by different investigators thus far in an attempt to apply Mendelian laws to allergy, the difficulty in obtaining adequate material, and the inadequate definition of essential criteria, no genetic hypothesis can be made to fit the existing data.

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Errata

In the article by Lloyd E. Seyler and S. William Simon entitled "Bristamin, a New Antihistaminic Drug," which appeared on page 261 of the July issue of the JOURNAL, in the Conclusion it was stated that good or excellent response was observed in 62 per cent of the patients. This figure should be 82 per cent.

In the list of members advanced to fellowship at the business meeting of the American Academy of Allergy, Feb. 27, 1953, which appeared on page 282 of the July issue of the JOURNAL, the following name was omitted:

Henry D. Ogden, M.D.