THE BEHAVIOR OF BRONCHIAL ASTHMA AS AN INHERITED CHARACTER[1]

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In a study of 400 cases of bronchial asthma, some attention was given to the behavior of the disease as an inherited character. In the series of 400 cases, 192 or 48 percent gave a history of the occurrence of asthma among other members of the family, and 208 cases, or 52 percent, gave a negative family history. Of the group of 191 patients who were sensitive to proteins as demonstrated by positive skin tests (WALKER, 1916), 96, or 24 percent, of the 400 cases gave a history of the occurrence of asthma or hay-fever in the family, and in 85 cases, or 21.25 percent, the family history was negative. Of the 209 cases which were negative with all the proteins tried in the skin tests, 96, or 24 percent, reported asthma among other members of the family, and 123, or 30.75 percent, knew of no relative who had asthma or hay-fever. In the group of cases sensitive to proteins, 52 percent gave a history of asthma in the family, while

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Study XIV, ibid. **36:** 423, 1917.

Study XV, ibid. **37:** 51, 1917.

Studies XVI and XVII, Jour. Med. Res. [Boston] **37:** 277, 287, 1917.

Study XVIII, Jour. Am. Med. Assn., **70:** 897, 1918.

Study XIX, Jour. Med. Res. **40:** 229.

The cause and treatment of bronchial asthma, Med. Clinics of N. Amer., Boston, **1:** No. 4, 1918.

A clinical study of 400 patients with bronchial asthma, Boston M. and S. J. **179:** 288, 1918.

Treatment of bronchial asthma with proteins. Arch. Int. Med. **22:** 466, 1918.

The treatment of bronchial asthma with vaccines. Arch. Int. Med. **23:** 220–234. Feb., 1919.

Sensitization and treatment of bronchial asthmatics with pollens. Amer. Jour. Med. Sci. **157:** 409. March, 1919.

in the non-sensitive group, only 41 percent knew of the occurrence of asthma or hay-fever in the family. This proportion, 59 percent, of patients in the non-sensitive group with no known family history of asthma or hay-fever is probably unduly large, because the data are based almost entirely upon the statements of the patients themselves, often in answer to questions on several different occasions, and sometimes corroborated by other members of the family. Time and opportunity were lacking for interviewing members of the families and investigating the records of distant relatives, as would have been done, in accordance with the methods of C. B. DAVENPORT (1911), if a field-worker could have been assigned to the problem. Some of the patients were foreigners with very limited understanding of English. Others had come recently from distant parts of the country or had lost their parents in early childhood, with the result that they could give very little information concerning their family history. On the other hand, since there is no stigma attached to the occurrence of asthma or hay-fever in the family, the patients had no motive for concealment and their statements can probably be accepted as fairly truthful. The accuracy of the data is somewhat vitiated by the fact that other conditions, such as dyspnoea caused by disease of the heart or kidneys, and severe bronchitis in old age, often simulate bronchial asthma and are reported as asthma in the family history, thus occasionally giving a falsely positive family history. But with due allowance for error, the larger proportion of positive family histories among the patients who were sensitive to proteins seems too great to be accidental, and the conclusion may be drawn that asthma of the anaphylactic type has a greater tendency to run in families than does the non-sensitive asthma which approaches more nearly an intensified bronchitis. This result is in accord with the much more remarkable figures of Dr. F. M. RACKEMANN (1918), who found that "a history of either asthma, hay-fever, or food poisoning, in the immediate family, occurs in 58.7 percent of the cases of extraneous asthma, but in only 10.5 percent of the cases of intrinsic asthma." Roughly speaking, and allowing for differences in result from the fact that Dr. RACKEMANN uses the intradermal tests in the diagnosis of protein sensitization, whereas in this series of 400 cases the cutaneous method (WALKER and ADKINSON 1917) was used, which test gives a smaller proportion of positive cases, RACKEMANN's "extrinsic asthma" corresponds to WALKER's (1918 b) "sensitive group" and the former's "intrinsic asthma" to the latter's "non-sensitive asthma."

The group of 96 cases which were sensitive to proteins and which reported the occurrence of asthma in the family contains 48 males and

48 females. Twenty-nine patients began asthma before the age of five years, nineteen between five and ten years, nineteen between ten and twenty, twelve between twenty and thirty, twelve between thirty and forty, and five between forty and fifty. Thirty-eight inherited asthma directly from the mother or from the mother's family and thirty-nine from the father or the father's family, while in six cases asthma occurred in the families of both parents. Among the 96 cases with asthma in the family and who were not sensitive to proteins, eleven began asthma before the age of five years, thirteen between five and ten years, thirteen between ten and twenty, sixteen between twenty and thirty, twenty between thirty and forty, seventeen between forty and fifty, and five after fifty. This group presents a contrast to the sensitive 96 in that forty-two of the non-sensitive patients began asthma after thirty, while among the 96 sensitive patients only seventeen began asthma after thirty. This difference in the age of onset between sensitive and non-sensitive groups has been demonstrated by WALKER (1918 b), and is not affected in any way by the family history of the patient. Among the 96 non-sensitive cases there were 38 males and 58 females. In thirty-eight cases asthma occurred in the mother or the mother's family, in thirty-five cases in the father or the father's family, and in four cases asthma occurred in the families of both parents. In the whole series of patients who had asthma in the family, it occurred in the father's family in seventy cases, in the mother's family in seventy-two cases, and in the family of both parents in ten cases,while in forty cases a sister or brother was the only relative known to have asthma. Thus among both sensitive and non-sensitive cases with a known family history of asthma the disease occurs equally in the family of father and mother, and cannot definitely be said to be "inherited" more frequently from either parental side. Among the 85 cases which were sensitive to proteins but gave a negative family history, there were forty-eight males and thirty-seven females. Of this group of cases, nineteen began asthma before the age of five years, eleven between five and ten, twelve between ten and twenty, twenty between twenty and thirty, seventeen between thirty and forty, and six between forty and fifty. In the group of 103 non-sensitive patients with negative family histories, there were fifty males and fifty-three females. The age of onset was as follows:—under five, seven cases; between five and ten, seven cases; between ten and twenty, sixteen cases; between twenty and thirty, twenty-one cases; between thirty and forty, thirty-three cases; between forty and fifty, eleven cases; over fifty, seven cases. Here is shown the difference in age of onset between sensitive and non-sensitive groups already noted

among patients with a positive family history; among the 85 sensitive cases, twenty-three or about a fourth of the entire number began asthma after thirty, but among the 103 non-sensitive cases, 51 or one-half the cases began asthma after thirty. In both sensitive and non-sensitive groups, there is a large number of patients with an age of onset under thirty among patients with a positive family history, and more who began asthma after thirty among those with a negative family history. In the sensitive group, 85 percent of the cases with a known family history began asthma before thirty, while among those with a negative family history only 73 percent began asthma before thirty years. In the non-sensitive group, 55 percent of those with a known family history began asthma before thirty, while among those with a negative family history only 48 percent have an age of onset under thirty years. An earlier age of onset is found among patients where asthma is known to occur in the family.

Of the patients with a positive family history, the record in eleven cases was too incomplete for analysis and these must be discarded as unsatisfactory. The fathers of thirty-seven patients had asthma. In this group there were seventeen males and twenty females, nineteen patients were sensitive and eighteen were non-sensitive. Of the women seven were sensitive and thirteen not sensitive, and of the men, twelve were sensitive and five not sensitive. The mothers of nineteen patients had asthma. Of these nineteen patients, there were six men, only one sensitive, and thirteen women of whom four were sensitive. The fathers of two patients, a non-sensitive man and a sensitive woman, had hay-fever. In thirty-nine cases the father had asthma or hay-fever. The mothers of six patients, three males and three females, all sensitive, had hay-fever, and the mothers of two patients, a man and a woman, both non-sensitive, had bronchitis. Therefore twenty-five patients altogether gave a history of asthma or hay-fever in the mother. The sisters of seven patients, four men and three women, had asthma, and the sisters of three women, two of whom were sensitive, had hay-fever. The brothers of ten patients, six men and four women, had asthma, and the brothers of four patients had hay-fever. Four patients, two non-sensitive men and two sensitive women, whose parents did not have asthma or hay-fever, had paternal grandfathers suffering from asthma. Eleven patients, four sensitive and two non-sensitive males, three sensitive and two non-sensitive females, whose parents were normal, had maternal grandfathers with asthma. Four patients, two non-sensitive and one sensitive male, and one non-sensitive female, with normal parents, had paternal grandmothers with asthma. Eleven patients, one non-sensitive and three sensitive males, four sensitive and three non-

sensitive females, whose parents were normal, had maternal grandmothers with asthma. Thus in eight cases the asthma while skipping the generation of the father, may have been inherited from the ancestors of the father. One non-sensitive boy, whose parents and grandparents were normal, had a paternal great-grandmother with asthma. In the families of eighteen other patients, asthma was reported collaterally in the father's family, but not in the direct line of inheritance. Twenty-two patients with normal parents may have inherited asthma from the maternal grandparents, the disease skipping a generation. In the families of fourteen other patients, asthma was reported collaterally in the mother's family, and in three other families hay-fever was reported. Taking the summary, sixty-six patients may have inherited asthma from the father's family, thirty-nine directly, eight skipping a generation, one skipping two generations, and eighteen collaterally. From the mother's family sixty-four patients may have inherited asthma, twenty-five directly, twenty-two skipping a generation, and seventeen collaterally. Thus taken altogether, the chance of inheriting asthma from the family of either parent is equal. The number of men and women inheriting asthma from the father is nearly equal, with a slightly larger number of women, but twice as many women as men inherit asthma from the maternal side, and although this proportion is less when the number inheriting hay-fever is added, the balance is heavier for the women. Altogether, thirty-six women inherit asthma directly from the parents, which is 25 percent larger than the number of men inheriting directly from the parents.

A comparison of sensitization between the groups with asthma in the family and those with a negative family history yields results as follows: In the first group eight patients were sensitive to horse alone; two to cat alone; four to bacteria alone; twenty-eight to pollens alone; two to wheat alone; one to feathers alone; one to wheat and potato; one to egg and wheat; one to the cereals, wheat, corn, rye, and rice; one to corn and egg; one to casein and potato; one to casein and wheat glutenin; one to casein, asparagus and the pollens; one to mackerel and beef; one to cod, halibut, and egg; one to oat and *Staphylococcus aureus;* one to green coffee and feathers; one to wheat, corn, casein, and ragweed; one to flaxseed and ragweed; one to feathers and tobacco; two to horse and egg; one to feathers and ragweed; one to horse, corn, potato, rice, red top, and timothy; one to feathers and wheat leucosin; twenty-five to horse and other animal hairs, pollens, food and bacteria; thus showing multiple sensitization in great variation. But the same condition and variety of sensitization is found in the second group, where the sensitization may be summarized

as follows: To horse only, four patients; to cat only, two patients; to wheat only, four patients; to bacteria only, eleven patients; to pollens only, twenty-seven; to cereals, one; to egg, three; to wheat and other cereals, three; to chicken and salmon, one; to rye, rice, potato, and haddock, one; to dog, feathers, and casein, one; to horse and pollens, eight; to cattle and lobster, one; to cattle and pollens, one; to dog, feathers, and casein, one; to horse and pollens, eight; to bacteria and pollens, one; to boxwood and pollens, one; to horse hair and other animal hairs, food, bacteria and pollens, in various combinations, twelve. Hence there is no apparent distinction in kind, variety, or degree of sensitization, as demonstrated by cutaneous tests, between patients who give a family history of asthma and those who do not.

In the group of 85 sensitive cases with a negative family history, there occurred several patients whose remote ancestry and distant relatives were well known, with no other case of asthma in the family. In these cases the disease seemed to have developed as a sporadic phenomenon from apparently normal stock, with no previous intimation in the life of the individual or in the family history of a predisposition to asthma. One such case, C. S., (WALKER 1918 a) a girl of ten years, had eczema as an infant and at the age of two years began to develop asthma in attacks with running of the eyes and nose, wheezing and difficult breathing from hay-dust and tall grass and when she was near horses. Skin tests were positive with horse-dandruff protein and with timothy pollen, and after treatment with the proteins of horse hair it became possible for her to take riding lessons and to care for her pony without symptoms of asthma. During the course of treatment with timothy pollen, eczema developed upon her back and legs in an irritating form which seemed always worse just after an injection of timothy. When the timothy pollen treatment was stopped, the eczema disappeared. In this girl the cause of the asthma was sensitization to horse dandruff as was proved by the development of the symptoms of asthma when near horses, by the positive skin tests to the proteins of horse dandruff, and by the marked improvement of the patient when treated with horse-dandruff protein. The twin sister of this girl, who resembled her closely in appearance, except that she was larger and more vigorous, had no eczema, asthma or hay-fever, and was not affected by horses or hay. In the family of six children, one older, and three younger than the twins, and in a large circle of cousins and other relatives, the patient was the only member of the entire family known to have asthma, eczema or hay-fever.

Another patient, M. D., (WALKER 1917) a woman, aged thirty-eight,

who had suffered from severe asthmatic attacks for ten years, and who always developed a rash from contact with fur, or the hair of dogs and cats, gave positive skin tests with the proteins of cat hair. She recovered from her asthma under treatment with the proteins of cat hair, and after much treatment with cat-hair proteins she gave a nearly negative skin reaction to the cat-hair proteins. No other member of her family was known to have asthma.

F. L. D., a man of thirty-eight, developed asthma suddenly at the age of twenty-three, after a long ride on horse back, although he had ridden horses all his life with impunity. Skin tests with horse-dandruff proteins were positive. After treatment with horse-dandruff proteins the skin tests were much diminished in intensity, and the patient had no trouble when riding horses. This patient knew of no asthma among his sons, or among other relatives. These three cases are presented to illustrate the fact that from the presence or absence of asthma in the family history, it is not possible to draw any inference as to the cause, severity of the disease, or prognosis in any given patient with bronchial asthma.

From the standpoint of heredity, no clear distinction can be drawn between bronchial asthma of the sensitized or purely anaphylactic type as demonstrated by positive cutaneous tests with proteins, and a second or non-sensitive type, which, always giving negative skin reactions with the proteins tried, is more like an intensified bronchitis and is probably not due to anaphylaxis at all. These two types of asthma are distinct in clinical history, cause, treatment, and prognosis, but from the standpoint of heredity they seem to be equivalent and interchangeable. Like the anaphylactic type of asthma, the non-sensitive type seems to run in families, and almost invariably the two types of asthma do not run pure in the family histories but both types occur in the same family. Among the patients who have been tested with proteins, these two types of asthma occur among members of the same family without distinction or rule. Among asthmatic patients, the mother may be sensitive, the son not sensitive; the father not sensitive, the son sensitive; the mother sensitive, the daughter not sensitive; both parent and child sensitive, or both not sensitive; one sister sensitive, the other not sensitive; one parent sensitive and suffering from both hay-fever and asthma, the other parent sensitive and having hay-fever, the child not sensitive and not suffering from either hay-fever or asthma.

Not only must non-sensitive asthma be accepted as the equivalent of the anaphylactic type from the standpoint of heredity, but it is necessary

also to accept as equivalents hay-fever, some urticarias, and occasionally eczemas caused by the ingestion of foods or other proteins, notably the eczemas in young children caused by eating eggs, milk or wheat. All of these symptoms indicate the existence of the anaphylactic state, i.e., sensitization to proteins. This point is well illustrated by the case, C. S., already presented, who in addition to asthma from horses had hay-fever from grass pollen. In the course of treatment with timothy pollen she developed an eczema which disappeared when the treatment was stopped. In cases sensitive to pollens the symptoms are more commonly hay-fever, but they may show asthma alone, or both hay-fever and asthma. Both hay-fever and pollen asthma are types of pollen sensitization, giving positive skin tests with the pollens and improving after treatment with the pollens to which they are sensitive. Among the patients sensitive to pollens, the mother may have hay-fever and asthma, the two sons hay-fever; the mother hay-fever, a son horse asthma, and an infant child an idiosyncracy for eggs; the mother horse asthma, the son fall hay-fever; the mother asthma and fall hay-fever, the son non-sensitive asthma; the father asthma and bronchitis, the son asthma; one brother asthma from foods, with bronchitis, the other brother fall hay-fever; one sister horse asthma and eczema and vomiting from eating eggs, another sister spring hay-fever, the niece asthma, the brother and aunt hay-fever; one sister with bronchitis and non-sensitive asthma although sensitive to wheat leucosin, the other sister sneezing when sifting wheat flour. Sometimes the sensitization to animal hair or to bacteria is manifested by sneezing and running of the nose rather than by asthma. Large doses of the proteins given in the course of treatment occasionally produced an immediate and temporary attack of asthma, and sometimes of hay-fever, urticaria, or eczema. From experiences like these, one is inclined to accept asthma, hay-fever, and sometimes urticaria and eczema, always coördinated by the skin tests or by the history and the symptoms, as different manifestations of the same anaphylactic state. The studies of family history were not extensive enough to show the occurrence of these other manifestations of sensitization to proteins in all the families where they may have been present, and with further study some apparently negative family histories might show the occurrence of some of these other manifestations. Although hay-fever, urticaria and eczema are accepted in this paper as the equivalent of anaphylactic asthma in the family history, all the patients included in the series of 400 cases had bronchial asthma. From the limitations of the investigation, and because asthma is sometimes caused by protein sensitization and sometimes not, this paper is restricted to the study of

asthma as an inherited character, without attempting to solve the larger problem of the inheritance of sensitization to proteins in general.

In table 1 is presented a record of cases where two or more members of a family were tested with proteins. Thirteen instances are recorded in table 1 where the relationship was parent and child. In six of these both parent and child gave positive skin tests; in five, only one gave positive skin tests, while the other was non-sensitive; and in two, both gave negative reactions. Of the six pairs where both were sensitive, in only two did the parent and child react to the same protein, namely, ragweed pollen; the mothers, (M. F.) and (C. E. H.), had fall hay-fever with asthma, and in one case one son, (C. F.), in the other, two sons, (E. B. H. and W. H. K.), had fall hay-fever. Of the four sensitive pairs who did not react to the same proteins, in one the mother (G. H. I) who had spring hay-fever gave positive reactions with the pollens of red-top and timothy, whereas the son (F. I.) who had asthma was sensitive to horse. In another case the mother (J. G. W). with asthma was sensitive to horse and the son (J. M. W.), although he gave a positive reaction to cat hair, had only fall hay-fever and reacted positively to ragweed pollen. In one case the father (F. L. C.) with asthma in the spring and fall was sensitive to the pollens of golden-rod and ragweed, and the daughter (L. C.) with asthma and a loose cough was sensitive to egg and wheat bread, and was relieved by the omission of these foods from her diet. In another case the mother (R. L.) who had asthma and eczema was sensitive to horse and egg, whereas the daughter (B. L. S.) who had spring hay-fever was sensitive to red-top and timothy pollens. Of the group of five pairs where only one was sensitive, in one instance the father (W. B.) was sensitive, the son (J. B.) was non-sensitive; in two where the mothers, (A. G.) and (V. M.), were sensitive, the child, in one case the son (V. G.), in the other the daughter (E. M.), was not sensitive; in one instance both parents (M. L. P. and M. L. P.) were sensitive and the son (L. P.) not sensitive; and in another the father (H. D.) was not sensitive but the son (P. D.) gave positive skin tests with horse, cat, and dog. In two instances, (L. C. and R. C.) and (L. L. and V. N.), both mother and daughter gave negative reactions with all the proteins tried.

Among this group of thirteen pairs of relatives, in seven the child began asthma earlier than the parent, and the age of onset in the child was earlier by anywhere from six to thirty-five years than in the parent; in two instances the parent and child had approximately the same age of onset; in one case the age of onset in the mother was indefinite but probably later than that of her son; in two cases the daughter developed

TABLE 1

The sensitization of relatives as shown by cutaneous reactions to various proteins

(A) Parent and child, both sensitive

Name	Age	Age of onset	Sex	Relation	Symptoms	Sensitization	Family history
G. H. I.	35	28	F	Mother	Spring h.-f.*	Timothy, red-top	Infant daughter has urticaria from eggs
F. I.	7	8 mo.	M	Son	Asthma	Horse, bacteria	
J. G. W.	44	12	F	Mother	Asthma	Horse	Mother's sister had asthma
J. M. W.	14	12	M	Son	Fall h.-f.	Cat, ragweed	
M. F.	35	Chi.	F	Mother	Asthma, fall h.-f.	Ragweed, golden rod	None
C. F.	13	3	M	Son	Fall h.-f.	Ragweed, daisy	
C. E. H.	49	4	F	Mother	Fall h.-f. with asthma	Ragweed, daisy, red top, timothy	Of five sons, the second and fifth have hay-fever
E. B. H.	23	18	M	Son	Fall h.-f.	Ragweed, daisy	
W. K. H.	12	9	M	Son	Fall h.-f., asthma once	Ragweed	
R. L.	64	4	F	Mother	Asthma, eczema	Horse, egg	Daughter has hay-fever
B. L. S.	45	27	F	Daughter	Spring h.-f.	Red top, timothy	Sister has h.-f.
F. L. C.	32	Infancy	M	Father	Asthma, spring and fall	Ragweed, golden rod	None
L. C.	1½	Birth	F	Daughter	Asthma, loose cough	Egg, wheat	

(B) Parent and child, one sensitive

A. G.	30	20	F	Mother	Asthma, fall h.-f.	Ragweed, red top, timothy	Paternal uncle and aunt, and another uncle's three children have asthma
V. G.	12	6	M	Son	Asthma	None	
H. D.	67	40	M	Father	Asthma	None	Brother had asthma
P. D.	11	5	M	Son	Asthma	Horse, dog, cat	

* h.-f. = hay-fever.

TABLE 1 (Continued)

Name	Age	Age of onset	Sex	Relation	Symptoms	Sensitization	Family history
V. M.	50	13	F	Mother	Asthma, fall and winter	Ragweed	Mother had asthma
E. M.	16	7	F	Daughter	Asthma	None	
W. B.	39	33	M	Father	Summer asthma	Daisy, corn, clover	None
J. B.	16	14	M	Son	Frequent colds once wheezing	Red top, corn = slight	
M. L. P.	33	23	F	Mother	Spring h.-f., with asthma	Timothy, red top	None
M. L. P.	35	29	M	Father	Fall h.-f.	Ragweed	None
L. P.	9		M	Son	None	None	
(C) Parent and child, neither sensitive							
L. C.	42	20	F	Mother	Winter asthma	None	None
R. C.	16	Chi.	F	Daughter	Winter asthma	None	
L. L.	40	11	F	Mother	Winter asthma	None	Mother had asthma
V. N.	22	20	F	Daughter	Summer asthma	None	
(D) Aunt, nephew, and niece, all sensitive							
E. E. B.	47	31	F	Aunt	Fall h.-f.	Ragweed	Brother has asthma
R. B.	23	Chi.	M	Nephew	Fall and spring h.-f., asthma in childhood	Ragweed, golden rod, timothy	Mother, maternal grandmother had asthma
G. B.	17	1½	F	Niece	Asthma, eczema, bronchitis	Horse, ragweed, golden rod, wheat	Same
K. V. F.	46	39	F	Aunt	Fall h.-f., asthma	Ragweed, golden rod	None
R. G. V.	16	6	M	Nephew	Asthma	Ragweed, cattle, feathers, lobsters	Aunt has hay-fever
(E) Sibs, one sensitive; the other normal							
M. L. S.	31	12	F	Sister	Asthma, bronchitis	Oat, bacteria	Mother's mother, patient's brother had asthma
M. F.	14	Inf.	F	Sister	Frequent colds	None	Same

TABLE 1 (continued)

(F) Sibs, both sensitive

Name	Age	Age of onset	Sex	Relation	Symptoms	Sensitization	Family history
H. D. T.	16	6 mo.	F	Sister	Asthma, bronchitis	Dog, horse, cat, chicken, ragweed	Grandfather and father have asthma
C. T.	11	3	M	Brother	Asthma, eczema, bronchitis	Horse, ragweed, wheats = slight	Same
W. E. C.	31	24	M	Brother	Asthma	Ragweed, linden leaves, horse = slight	Father and two brothers have asthma
C. F. C.	25	10	M	Brother	Asthma	Horse, red top	Same
M. B.	13	Inf.	F	Sister	Asthma, eczema, vomiting from eggs	Horse, dog, egg, wheat	Mother has some hay-fever
J. O. B.	11	7	F	Sister	Spring h.-f.	Ragweed, golden rod, timothy, red top	Same
F. G.	42	22	F	Sister	Asthma summer and winter	Wheat leucosin	Father had asthma
H. M.	37	31	F	Sister	Hay-fever from wheat flour	Wheat, and other cereals	Same
W. M. O.	26	23	M	Brother	Asthma	Potato, casein	Maternal grandfather had asthma
F. O.	31	27	M	Brother	Hay-fever	Ragweed	Same
M. N.	46	Chi.	F	Sister	Asthma, hay-fever, eczema	Horse, ragweed	Mother had hay fever; brother had asthma
J. A. N.	36	Chi.	M	Brother	Hay-fever	Ragweed, timothy	Same

(G) Sibs, none sensitive

P. J. O.	48	31	M	Brother	Summer asthma	None	Brother has asthma
D. J. O.	33	21	M	Brother	Winter asthma	None	Same

asthma later than did the mother, in one case nine years later, and in the other thirteen years later than did the mother; and in one case where both parents were sensitive to pollens, the mother (M. L. P.) suffering from spring hay-fever with asthma and the father (M. L. P.) from fall hay-fever, the son (L. P.) has not yet shown symptoms of either disease and is non-sensitive, but he is still fourteen years younger than the earliest age of onset of his parents. It is interesting that this child was born before the father developed hay-fever and that the symptoms developed in the mother during pregnancy with this son. The failure of maternal transmission of sensitization in this case during pregnancy is contradicted by another case where the mother (G. H. I.) developed spring hay-fever during pregnancy and the son (F. I.) began to have asthma at eight months, but this mother and son do not have the same symptoms nor do they react to the same proteins. Therefore even in this case, which is the best example of the series of a condition of sensitization to proteins transmitted from mother to offspring during pregnancy, the sensitization if transmitted at all is not specific. Since in nine and probably in ten cases out of the thirteen, the age of onset in the child was the same or earlier than that in the parent, there may be some tendency for children of asthmatic parents, if they do develop asthma, to develop it earlier than did their parents.

Two family groups are presented, one including aunt and nephew, the other aunt, nephew, and niece, the latter two being brother and sister, all of whom happened to be sensitive to ragweed pollen. In the first family group, the aunt (K. V. F.), who was the father's sister, had fall hay-fever, and her nephew (R. G. V.), who began to have asthma thirty-three years younger than the aunt began to have hay-fever, was sensitive to cattle, feathers, and lobster, as well as to ragweed. The parents of this boy had neither asthma nor hay-fever. In the second family group, the aunt (E. E. B.) had fall hay-fever, the nephew (R. B.) had asthma as a child and later on he developed both spring and fall hay-fever at a much earlier age than did the aunt. The niece (G. B.) began to have asthma and eczema at eighteen months, and in addition to the fall pollens, she gave positive reactions to horse and wheat. The mother and the maternal grandmother of this brother and sister had asthma; the father seems to have no trouble, but in addition to the sister whom we have tested, he has a brother with spring hay-fever.

Of seven pairs of sibs tested, as recorded, two brothers (P. J. O. and D. J. O.), both with asthma, gave negative reactions to all the proteins tried. A brother and sister (H. D. T. and C. T.) both asthmatics,

reacted alike to horse and ragweed. Two brothers (W. E. C. and C. F. C.), both with asthma, gave positive reactions to horse, one (C. F. C.) was strongly positive, the other (W. E. C.) only slightly, and both were sensitive to a pollen, one to ragweed, the other to red top. Of two sisters, one (F. G.) with asthma and bronchitis, happened to give a positive reaction to wheat leucosin, but she was not sensitive to the other proteins of wheat, neither did she improve when treated with wheat leucosin nor when wheat was omitted from her diet; the other (H. M.) who sneezed whenever she sifted wheat flour, gave positive reactions to wheat and other cereals but was as unresponsive as her sister to treatment with wheat and to the omission of wheat from her diet. Of a sister and brother, the sister (M. N.) who has asthma, hay-fever and eczema, is sensitive to horse and ragweed; the brother (J. A. N.) who has only hay-fever is sensitive to the pollens of timothy and ragweed. Of two sisters, one (M. B.) who had horse asthma, and eczema and vomiting whenever she ate eggs, was sensitive to horse, egg, and wheat, whereas her sister who had only spring hay-fever, reacted only to pollens. Of two brothers, one (W. M. O.) with asthma gave positive reactions to potato and casein, the other (F. O.) with fall hay-fever was sensitive to ragweed pollen. An eighth pair of sibs were tested, two sisters, of whom one (M. L. S.) with asthma and bronchitis was sensitive to oat and bacteria; the other with frequent colds but no asthma, gave negative reactions with all the proteins tried. But these two could be duplicated in almost any family in which a sensitive patient has a brother or sister, since in no family have we found every member suffering from hay-fever or asthma, and the normal individuals of course do not give positive skin reactions; hence this mixed pair, one sensitive and the other not, was not included in the series. Of the seven pairs of sibs presented, four pairs reacted alike to one or at the most two proteins; namely the brother and sister (H. D. T. and C. T.) both sensitive to horse and ragweed, two brothers (W. E. C. and C. F. C.) somewhat sensitive to horse, two sisters (F. G. and H. M.) who gave more or less adventitious reactions with wheat proteins, and a brother and sister (J. A. N. and M. N.) one with horse asthma, hay-fever, and eczema the other with fall hay-fever, both sensitive to ragweed. Two pairs, the sisters (M. B. and J. O. B.) and the brothers (W. M. O. and F. O.) where one had hay-fever and the other asthma, were both sensitive but not to the same pollens, and one pair (W. J. O. and P. J. O.) two brothers, were not sensitive.

Twenty-two family groups are presented altogether where more than one member has been tested on the skin with proteins. Of these twenty-

two groups, in fourteen both members reacted to some protein; in five pairs, one member was sensitive to some protein, the other was not sensitive, and in three pairs, both members were not sensitive. Of the five mixed pairs, all were parent and child; in four the parent was sensitive, the child not sensitive, and in one the father was not sensitive when the son reacted to proteins. Of the four non-sensitive children of sensitive parents, in two cases the mother was sensitive, and in one case the son, in the other the daughter, was non-sensitive; once the son was not sensitive when the father was; and in the fourth case both parents were sensitive, while the young son was non-sensitive and was free from both asthma and hay-fever. Of the fourteen groups of relatives, all sensitive, six did not react to the same proteins, and eight did to some extent. Of the six not sensitive to the same proteins, four (G. H. I. and F. I.), (J. G. W. and J. M. W.), (F. L. C. and L. C.), and (R. L. and B. L. S.), were parents and children, two mothers and sons, one father and daughter, and one mother and daughter, and two were sibs, two sisters (M. B. and J. O. B.) and two brothers (W. M. O. and F. O.). Of these six pairs giving heterogeneous reactions, there were five pairs of which one member had hay-fever and the other asthma, the varying reactions corresponding to the different symptoms. In only one pair of these did both members suffer from asthma, and even in this pair, father and daughter (F. L. C. and L. C.), the reactions followed the symptoms and not the relationship, since the father had pollen asthma and the infant daughter had asthma from foods. Of the eight groups of relatives where all members were sensitive to the same protein, one pair was the two sisters sensitive to wheat leucosin where the symptoms did not altogether correspond to the skin reactions five groups included one of mother and son (M. F. and C. F.), one of mother and two sons (C. E. H., and E. B. H., and V. K. H.), an aunt and nephew (K. V. F. and R. G. V.), an aunt, nephew and niece (E. E. B., R. B., and G. B.), and one of brother and sister (M. N. and J. A. N.) where the element of pollen asthma and hay-fever explained the identical cutaneous reactions. The seventh pair were the brothers (W. E. C. and C. F. C.) somewhat sensitive to horse, but in neither brother was horse the fundamental cause of the asthma, and finally the brother and sister (H. B. T. and C. T.), both sensitive to horse and ragweed, but with many other individual factors which affect the asthma and the multiple sensitization. The evidence from this series of twenty-two tested groups of relatives, which included forty-seven individuals, of whom only thirty were included in the series of four hundred cases studied, indicates that sensitization to specific proteins is not transmitted from parent to child

even when both have asthma and both are sensitive to foreign protein; that the child may be sensitive even when the parent is not; that the parent may be sensitive and that this sensitization is not necessarily transmitted to the child even when the asthma seems to be inherited. In other words, the cutaneous test is an index of the cause and symptoms of the individual case of bronchial asthma, but it bears no specific relation to the family history or to the problem of inheritance. When members of the same family have identical symptoms they may give identical skin reactions, but so may all other persons not related, who have the same identical trouble. For this reason, family histories and skin reactions in patients with hay-fever will correspond much more closely and seem to prove much more conclusively the existence of a specific inherited tendency than can any group of asthmatic patients. This series of relatives tested also lends support to the statement that sensitive and non-sensitive asthma, as well as hay-fever and some skin disturbances caused by the ingestion of proteins, must be accepted as equivalents from the standpoint of heredity. This detailed discussion shows also that in considering the behavior of bronchial asthma in inheritance the grouping into sensitive and non-sensitive types which is useful for diagnosis and treatment cannot be followed in studying family histories.

Many experiments have been performed on animals to discover the laws which govern anaphylactic shock in animals artificially sensitized, and the tendency has been to apply the reasoning by analogy from the results obtained in these experiments to the condition in patients suffering from asthma, hay-fever or other anaphylactic phenomena. It was the similarity between experimental anaphylactic shock in guinea-pigs and the asthmatic attack in the human which led MELTZER (1910) to advance the hypothesis that asthma is an anaphylactic phenomenon caused by sensitization to foreign protein. A brief review of the literature of animal experimentation will be given, in so far as it touches upon the problem of heredity. EHRLICH (1892), in studying the transmission in mice of immunity to certain substances, showed that female mice, immunized to ricin, abrin and robin, gave birth to young which possessed distinct resistance to these substances four weeks after birth, but that this resistance was lost by the beginning of the third month. This increased resistance was not transmitted to the grandchildren, and was transmitted only by the mothers. Immune fathers did not transmit immunity to their offspring. Normal offspring of untreated parents gained a considerable degree of immunity by nursing immune mothers. Later this study was extended to tetanus (EHRLICH and HUEBNER 1894), and it was

shown that immune mother guinea-pigs and mice transmit immunity to young, but fathers do not, and the immunity transmitted to the offspring disappears in the second or third month. In guinea-pigs treated with diphtheria antitoxin by WERNICKE (1895) and guinea-pigs and rabbits rendered immune to tetanus, anthrax, and cholera, by VAILLARD (1896) it was found that the treated female always transmitted some resistance to her offspring, often to successive litters; the immunized father does not transmit immunity; the increased resistance in the offspring disappeared after the third or fourth month; experiments upon increased immunity through lactation were uncertain or negative; and except for one case of resistance in the second generation observed by VAILLARD, no increased immunity was found among the grandchildren. THEOBALD SMITH (1907) in an article on the transmission of passive immunity by immunized female guinea-pigs to their offspring says:

"In a preliminary paper published several years ago, the writer called attention to the fact that certain female guinea-pigs under observation gave birth to young which had more than average resistance to diphtheria toxin. This increased resistance was observed in all litters until the death of the mother, and was nearly constant in amount for any given mother. . . . . The conclusions finally reached were that the manifestation of increased resistance in the young is due to the preliminary treatment of the mother with toxin-antitoxin mixtures, but the degree to which the mother reacts to treatment,—that is, the degree of passive immunity transmitted to the young,—is probably an individual or family factor. . . . . In no instance did the offspring of the treated resistant males possess any more than average or normal resistance. . . . . The transmission of increased resistance by the mother to her offspring is regarded by EHRLICH, WERNICKE and others, as a passive process in the young. The immunizing antibodies are transmitted through the placenta *in utero*, and perhaps to some extent in the milk. This passive immunity is gradually lost with the increasing age of the offspring. This passive immunity is, therefore, of limited duration, most observers regarding it as lasting two or three months. . . . . All observers . . . have found that the grandchildren of the immunized females have the usual resistance. . . . . VAILLARD traced the persistence of active immunity in the immunized female through four litters of the same female. BULLOCH found traces of hemolysins in an immunized rabbit three hundred and eighty-seven days after innoculation. . . . . The writer has records of a considerable number of guinea-pigs which transmitted immunity to their offspring for over a year. . . . . Though the male parent does not transmit directly any passive immunity, there is no evidence to show that he does not equally with the mother transmit the capacity for producing antibodies, which capacity varies much from family to family, quite independently of the treatment."

ROSENAU and ANDERSON (1907) clearly separate the anaphylactic reaction to horse serum and the immunity to diphtheria produced by the injection of diphtheria antitoxin.

"In our previous work we showed that hypersusceptibility to the toxic effects of horse serum may be transmitted from the mother guinea-pig to her young. Later one of us (ANDERSON) showed that the female guinea-pig may transmit hypersusceptibility to horse serum and immunity to diphtheria toxine at the same time. . . . . Our present studies corroborate the fact that hypersusceptibility to the toxic action of horse serum is always transmitted from the mother guinea-pig to her young. This function is solely maternal; the male takes no part whatever in the transmission of these acquired properties. Whether this maternal transmission is hereditary or congenital cannot be definitely stated. We are able to exclude milk as a factor in transmitting the hypersusceptibility to the toxic action of horse serum, by a series of exchange experiments. 'Exchange' experiments consist in at once placing guinea-pigs born of a susceptible mother to nurse with an untreated female and, in exchange, the young of the untreated female are at the same time placed to nurse with the susceptible female. From these 'exchange' experiments we learn that hypersusceptibility is not transmitted from the young through the milk. We also learn from our experiments that hypersusceptibility may be transmitted from mother to young whether the mother is sensitized before or after conception. The fact that this influence may take place after conception might be taken to indicate that the condition is congenital and not hereditary. . . . . We have never seen symptoms resulting from the first injection of horse serum in the guinea-pig born of an untreated mother."

GAY and SOUTHARD (1907) show conclusively that this transmitted hypersusceptibility to horse serum is passive artificial sensitization.

"There is further evidence that guinea-pigs refractory to horse serum still contain the sensitizing substance of the serum unneutralized. The offspring of refractory animals, born at a period when the mother is resistant to the toxic action of horse serum, are sensitive, not resistant."

Guinea-pigs immunized by repeated doses of horse serum, bore young which when injected at ages varying from six to nine weeks, with much smaller doses of horse serum than the mother had received before the birth of the young, without ill effects, had typical anaphylactic shock, and showed the pathological findings produced by that condition.

"There is an analogy between these last experiments on the transmission of sensitivity of offspring from refractory mothers and certain experiments of ROSENAU and ANDERSON, and of ANDERSON; these authors found that the young of sensitized guinea-pigs were also sensitive to horse serum. It was only a step further for us to demonstrate that normal pigs may be rendered sensitive to horse serum by injecting them with the serum of sensitive pigs and awaiting the proper incubation."

VAUGHAN (1913) says:

"The transfer of the condition of sensitization from the mother to her offspring is an illustration of homologous passive anaphylaxis. This has been studied especially by ROSENAU and ANDERSON, GAY and SOUTHARD, and OTTO. The latter has found the young sensitive at forty-four hours after birth." . . . .

The first injection of the foreign protein is without manifest effect, but in reality it has a most profound effect. It induces changes which may continue throughout life and may be transmitted from mother to offspring."

In experimental anaphylaxis GROER and KASSOWITZ (1914) showed that the diphtheria antitoxin demonstrated by SCHICK to be present in blood and tissues of some human beings, were transmitted passively from the mother to infant through the placenta. VON DUNGERN and HIRSCHFIELD (1911) have claimed that iso-agglutenins are inherited, often according to Mendelian law.

Passive artificial sensitization transmitted from the treated female guinea-pig to her young, behaves as a different phenomenon from bronchial asthma in man. The artificial condition is transmitted only from the treated mother to her offspring, whereas asthma occurs with equal frequency in the families of either parent. The young of an artificially sensitized animal are most sensitive soon after birth, and the sensitization is lost within a few months, whereas in the human, asthma, or sensitization to proteins may be manifested in very young infants, begins most frequently in children under five years, but it may be shown for the first time at any age under thirty. The successive litters of a sensitized guinea-pig are all equally sensitive, whereas of the five sons of a woman who has hay-fever, the second and fifth may have hay-fever, while the first, third, and fourth sons are not affected by pollens; that is, normal children may be born between and following sensitive ones. The sensitization in animals is never transmitted by the offspring of treated mothers to the third generation, except possibly in one case observed by VAILLARD whereas asthma or sensitiveness to proteins may be manifested in man through three or even four successive generations. In asthma the condition may be present in grandparent and grandchild, but not manifested in the parent, thus skipping one and sometimes two generations, or the asthma or protein sensitization may be present in aunt or uncle and nephew or niece, while the parents are normal. In animals the young of untreated females never react without a previous sensitizing dose, but according to TALBOT, infants may react to the very first cow's milk or egg with which they are fed, and in four infants a positive skin test to egg was obtained before egg had ever been eaten, but there is no positive proof that the mothers of these infants were sensitive to egg. In the two cases of the present series, where the mother developed first symptoms of sensitization to pollens during pregnancy, one child is normal, and the child of the other mother developed asthma when eight months old. Moreover, the sensitization in the young of treated females is always for the

specific protein with which the mother was treated, and the anaphylactic shock produced by the first injection into these sensitized young of the protein to which they are sensitive differs in no respect from the anaphylactic shock which might be produced in the mother or in a normal pig transfused with blood from the mother. Sensitiveness to foreign protein in the human, if it is inherited at all, is almost always not specific, either as to the particular protein, or as to the symptoms produced. The evidence from family histories of asthmatics is against inheritance of specific sensitization. All the evidence indicates therefore, that bronchial asthma is not maternal transmission conveyed from mother to child through placenta or milk, not congenital, caused by any action during pregnancy upon the cells of the foetus that produce sensitization, but if it is inherited at all, it behaves as a character transmitted equally by the germ-plasm of either parent, independent of any manifestation of asthma or sensitiveness to protein in the somatic cells of the parent. The nearest approach to this condition in animals is noted in the quotation from THEOBALD SMITH, that some families of guinea-pigs vary much in their ability to develop antibodies to diphtheria toxin.

Throughout the literature which deals with bronchial asthma as an anaphylactic phenomenon, suggestions and statistics as to the behavior of the disease in inheritance are given by many authors. S. J. MELTZER (1910), one of the first to interpret asthma by the phenomena of anaphylaxis, says:

"Heredity also seems to be an influential factor in some cases . . . . . The sensitizing effect may be transmitted from mother to offspring, which however may gradually dwindle away. . . . . The sensitization to anaphylaxis may be hereditary or acquired; so is the disposition to asthma either hereditary or acquired."

EDWARD LESNÉ and CHARLES RICHET fils (1913), discuss the same problem (translation by the present writer):

"Anaphylaxis caused by eggs is found sometimes among many members of the same family; hence there seems to be a hereditary predisposition to it. An interesting case is that of GELPKE, who has observed in mother and child an absolute intolerance to eggs. One of us has published, with LAROCHE and SAINT GIRONS, an observation which shows through four generations the existence of an anaphylaxis to eggs: the great-grandfather, born in 1775, was afflicted with an absolute intolerance for eggs and cream; this intolerance became proverbial in the family who have kept it in mind; the grandfather, born in 1807, presented an anaphylaxis much less marked; he however could not eat the slightest bit of meringue without being sick. Of his four children, the first is normal, two others are intolerant of eggs and cream and look upon egg as a poison; the fourth was intolerant of eggs until the age of twenty-five years, since then his

intolerance has diminished. Of the three present grandchildren, one is unaffected, the other two are intolerant, the one lightly, the second strongly. This case is comparable to the cases of anaphylaxis to milk which occur among the children of a single family."

K. K. KOESSLER (1913) reports three cases of asthma caused by eggs, two with no family history of asthma, and a third patient, a woman aged twenty-eight, whose father was subject to hay-fever and had an intolerance for eggs in childhood, had asthma from eating eggs and asparagus.

"The little daughter of the patient, five years old, eats eggs without ill effects. . . . . In our cases . . . the first sensitizing dose seems not to have been given. But this is not essential. For the substances which split the protein in the blood to toxic products may be present from birth in an abnormally high amount, through a peculiar diathesis of the individual. . . . . Anaphylaxis is a condition which may be inherited, so is asthma. . . . . The identification of asthma as a manifestation of an inherited or acquired allergy or anaphylaxis is able to unite and explain in a satisfactory manner the heterogeneous theories of the underlying mechanism of the asthmatic crisis."

RICH (1914), presenting cases of infantile sensitization to egg albumen, observes:

"One of the most interesting features of this disorder is the frequency with which it appears in a family. In five of my ten cases there was good evidence of this disorder in the previous generation. In two the mother, once the father's sister, once the father's brother, once the mother's brother. VAUGHAN also found that experimental sensitization to protein may be transmitted to the young."

FRITZ B. TALBOT (1914) reports six cases of "egg poisoning," two with no family history, four with a family history of some anaphylactic phenomenon, but none with a history of specific sensitization to egg, except that the younger brother of one patient had some idiosyncrasy to egg. Three times the father had hay-fever, and twice the son, in addition to intolerance to egg, had hay-fever.

"The family history suggests that a sensitive condition of the blood may be transmitted from one individual to another. . . . . If this is not inherited directly, a predisposition toward sensitization may be inherited. It seems to be more probable that the sensitivity may be acquired."

HYMAN ISKOWITZ (1915) says:

"Asthma may be hereditary or acquired. A large percentage of cases of bronchial asthma have either a hereditary history or a history of protein sensitization. . . . . A predisposition to the condition is nearly always present."

OPPENHEIMER and GOTTLIEB (1915), in an article on hay-fever, speak of inheritance:

"In all likelihood, there exists in the patient an individual susceptibility to this particular disease, which seems to have some relation to heredity, for this and other allied ailments are frequent in given families. Among our patients there are two brothers with hay-fever, a brother and sister with hay-fever; a woman with hay-fever whose son suffers from asthma; two cases in which a father and one or more of his children suffer from hay-fever; a young woman with hay-fever, who had intense eczema as a child and whose mother suffers with eczema that is rebellious to treatment."

The same authors, writing on the subject a year later (OPPENHEIMER and GOTTLIEB 1916) are even more impressed with the tendency of hay-fever to be inherited.

"Heredity plays a very important rôle in the etiology of pollen disease, as we have shown that over 90 percent of our patients have other members of their families who suffer with allied complaints. . . . . Any denuded surface of the body is a suitable place for the parenteral absorption of the proteins of pollen, so that given a patient whose antecedents, either in collateral or direct line, have shown themselves to be sensitive to any of the above mentioned substances, that patient if so exposed, will in all likelihood develop pollen anaphylaxis."

F. B. TALBOT (1916), in a second article on asthma in children, says:

"The histories of most of the patients studied have shown that there is a hereditary predisposition to allergy; that the parents or close relatives of the children have asthma, hay-fever, or an idiosyncrasy to some food. During the year 1914–15 the writer made a routine skin test for egg albumin on all of the children and infants admitted to the Children's Ward at the MASSACHUSETTS GENERAL HOSPITAL, and out of 85 admissions, three infants gave a positive skin test to egg albumen. They were respectively, three, four, and eight months of age. The mothers of the infants on being carefully questioned, said that the babies had never eaten egg in any form. A fourth case, in private practice, aged fourteen months, which had never eaten egg, gave a positive skin test to egg white. SCHLOSS and WORTHEN report the same results in two infants, and BLACKFAN in one nine weeks old. It seems certain therefore, that these infants had a hereditary and not an acquired sensitization to egg albumen."

Later in the same article, Dr. TALBOT continues:

"A family history of asthma, hay-fever, rose colds, eczema, or idiosyncrasy to some food, was present in 19 out of the 23 cases, while in the remaining four cases, there were no notes in the family history on these points. BERKHEAD also found a 'hereditary element' strongly marked in 16 percent of his cases. It seems therefore that there is a strong family predisposition to asthma."

In an article on idiosyncrasy to cow's milk, the same author (TALBOT 1916 b) says:

"Certain individuals whose parents and close relations give a history of such anaphylactic phenomena as asthma, hay-fever, chronic urticaria, or idiosyncrasies to foods, have a hereditary predisposition to sensitization. . . . . In other instances the first cow's milk, and all subsequent bottles that are given to the baby are vomited immediately, in which case we must assume that sensitization was hereditary, and present at birth."

In discussing the third paper of TALBOT on "Asthma in childhood III," ALEXANDER C. HOWE (1917) spoke of the bearing of the family history on the individual case:

"These subjects that are sensitized have an inherited taint. You will never find a case of hay-fever or asthma in a child but you will find that its ancestors had hay-fever or asthma, or acute gastric attacks from eating certain articles of food, or hives, or some other form of anaphylaxis. . . . . That is to say, if there is a decided history of sensitization in both parents, the child will frequently in a large percentage of cases develop some form of anaphylaxis by the fifth year. If there is a strong taint in only one side of the family they will surely develop it before the tenth or fifteenth year, and when the taint is only a slight one on one side, and there is none on the other, it may run to the twentieth or twenty-fifth year. By taking these facts into consideration, you can frequently determine by the history when it is possible for the subject to become sensitized—and to protect them accordingly."

FRANCIS M. RACKEMANN (1918), reporting on one hundred and fifty cases of bronchial asthma, says:

"The family history is here very interesting and important. There was a history of either asthma, hay-fever, hives, or violent poisoning from food in forty-four of this group of patients; twenty-seven on the mother's side and two on both; not stated in thirty-three. . . . . From this we may say that a positive family history indicates the probability of a particular case of asthma belonging to the extrinsic rather than the intrinsic group."

WARFIELD T. LONGCOPE (1915) in his Harvey Lecture on "*The susceptibility of man to foreign proteins*," discusses the problem of heredity at length, from both the experimental and theoretical aspects:

"The history of idiosyncrasies in certain families, such as the tendency to asthma or hay-fever or the susceptibility to certain foods, has long been recognized as very common. . . . . Hypothetically this may take place in one of three different ways: (1) as true inheritance through the germ-plasm of the cells, either of the father or mother; (2) by direct influence of the immunizing agent that affects the mother, upon the cells of the foetus which produce active immunity in the child; (3) by passive transference of the immune bodies from the mother to foetus by way of the blood or milk. . . . . The facts so far collected, regarding the familial tendency of idiosyncrasy to foreign protein do not accord absolutely with those found in experimental immunity and anaphylaxis from mother to offspring. In the first place, sensitization in man is not transient, but often of years' duration. In the second place it may occur through

four generations, and in the third place, as occurred in the extraordinary family described by LAROCHE, RICHET and ST. GIRONS, in the male members. And finally the sensitization may not always be to the same protein. In at least one family which we have studied, the father was sensitive to horse serum and the son to egg white. If inheritance is a factor, therefore, it cannot be by means of passive transfer from mother to infant, but in some instances at least may be a true inheritance of cell characteristics derived either from the father or mother. The whole problem, since it is one of greatest importance, needs careful study, but one is inclined to suggest that occasionally sensitization towards foreign protein may be an inherited characteristic of the germ-plasm and often not highly specific in character. . . . . The high degree of susceptibility in some people, the multiplicity or lack of specificity of sensitization, and the distinct tendency for it to occur in families differentiate these individuals from the artificially sensitized and suggest that there is some unknown factor here which is absent in men and animals subjected to artificial sensitization."

ROBERT A. COOKE and ALBERT VANDER VEER (1916), give data upon 621 cases of sensitization:

"The antecedent, direct, or collateral history was negative in 260, positive on one side in 205, positive on both sides in 39, and discarded as incomplete in 117. . . . . Of 504 cases with satisfactory history there was positive antecedent, direct or collateral history in 48.4 percent. . . . . Inheritance therefore does exert a distinct effect upon the age of onset of symptoms of sensitization; the more complete the inheritance the earlier the manifestation. . . . . The offspring of a sensitive parent are not born sensitive. . . . A parent may transmit a tendency to sensitization without himself being sensitized. . . . . That placental sensitization is not an important factor is evidenced by the fact that the inherited character is as frequently paternal as maternal and that in cases where the inheritance has been maternal, the clinical form in the child is much more apt to be different from the mother (45.4 percent) than it is to be identical (18.6 percent) and is no more apt to be identical with the mother than with the father. . . . . We must say that the results of a clinical study compel us to conclude that sensitized individuals transmit to their offspring not their own specific sensitization but an unusual capacity for developing bioplastic reactivities to any foreign proteins."

Analyzing their data statistically the authors conclude that this capacity behaves as a dominant Mendelian character.

Before attempting an analysis of individual family histories for evidence that bronchial asthma is inherited according to MENDEL'S law, a brief summary of the fundamental conceptions of heredity is in order. According to WEISMANN'S doctrine of the continuity of the germ-plasm, race characteristics are transmitted in a continuous stream of material from the germ cell of the parent to that of the child, independent of the environment or of the manifestation of inherited characteristics in the somatic cells of the individual body, which from the standpoint of heredity is only the vehicle of the germ cells. From the fact that during the

maturation of the germ cells, before the union of egg and sperm to form the first cell of the new individual, the number of chromosomes is reduced to one-half the somatic number, so that, before their union, egg and sperm cells or gametes possess half the nuclear content of the normal soma cell, arose the conception that each inherited character has its material origin or basis in determiners present in the chromosomes of the germ cells; that these determiners are paired until the reduction division, but single in the mature egg and sperm. In the zygote which results from the fusion of egg and sperm—the first cell of the new individual, from which develop both soma and germ cells of the offspring—these determiners are again paired, but one member of each pair is derived from the egg, the other member from the sperm. Hence half the inheritance comes from either parent. If in any particular pair of determiners, the inheritance from the two parents is exactly the same, the child is said to be pure or homozygous with respect to that single character, but if the determiner from one parent differs from that derived from the other parent, the child is hybrid or heterozygous with regard to that character. If in the germ cells only one determiner is present, that is, the individual is heterozygous, the person is said to be simplex with regard to that character, but when the individual is homozygous or pure, and consequently bears in the germ cells two determiners for the character, he is said to be in the duplex condition. According to the laws formulated by MENDEL, and substantiated by DE VRIES, CORRENS, TSCHERMAK, and many others, the characteristics inherited from the two parents do not blend, but are segregated unmixed in the germ-plasm and are so transmitted. The offspring resembles one parent or the other with regard to any given character, but he is capable of transmitting to his offspring the characters inherited from both parents. A character which prevails in the soma cells whenever it is present in the germ cells is called a dominant character, while a character which may be present in the germ cells without manifesting itself in the soma cells is said to be recessive. Thus people who show a dominant character, may be pure dominant and capable of transmitting only the dominant character to their offspring, or they may be heterozygous with respect to that particular character. In the latter case, the hybrid individual has germ-plasm that is simplex with respect to the dominant and its corresponding recessive, and the germ cells which he produces will be of two sorts, one bearing the dominant character alone, and the other the recessive, according to which of the two determiners happens to be eliminated in the reduction division of the germ cell. Theoretically these two kinds of germ cells are produced in equal

numbers; hence half the offspring of a hybrid individual mated to a recessive, would show the dominant character, and the other half the recessive. The recessive character, when present in the germ-plasm of a hybrid or heterozygous individual is not manifested in the soma cells, but is transmitted, as has been said, by one-half the germ cells. When only the recessive determiner is present in the fertilized egg (zygote) the individual is duplex (homozygous or pure) with respect to that character, and the soma cells manifest the recessive character, and all the germ cells produced from that zygote bear the recessive character.

On the theory that inherited characters are either dominant or recessive, and that a homozygous individual bears germ-plasm in which the determiners for any given character are alike, hence duplex, while in a heterozygous individual the germ-plasm is simplex, there are six possible types of mating, which may be represented diagrammatically as follows: *D* stands for a determiner of any dominant character and *R* for the corresponding recessive, the two together standing for the gametic character of parent and offspring.

Mating	Parents	Offspring
1	$DD \times DD$	All *DD*; all showing the dominant character and transmitting it only.
2	$DD \times DR$	$DD + DR$; all show the dominant character, but only one-half are duplex, and the half which are simplex are capable of transmitting the recessive character to one-half their offspring.
3	$DD \times RR$	All *DR*; all show the dominant character, but are capable of transmitting the recessive to half their offspring.
4	$DR \times DR$	$DD + 2DR + RR$; three-fourths of the offspring show the dominant character; one-fourth are duplex or homozygous, and can transmit only the dominant character; one-half are heterozygous dominant, transmitting the dominant character to one-half, the recessive character to the other half of their offspring; one-fourth show the recessive character, and transmit only the recessive character to their offspring.
5	$DR \times RR$	$DR + RR$; half are pure recessive, and half, while showing the dominant character, will transmit it to half their offspring.
6	$RR \times RR$	All *RR*.

If bronchial asthma is inherited in the manner of a Mendelian trait, the disease is probably either dominant or recessive to the normal or non-asthmatic condition. If the asthmatic condition is dominant over the normal, it will show as a somatic character wherever it is present in the germ-plasm, whether the individual is a pure dominant, that is, inherits

asthma from both father and mother, or whether he is a heterozygous dominant, inheriting asthma from only one parent, and capable of transmitting the normal condition received from the other parent to one-half his offspring. If the asthmatic condition is dominant, then any normal individual would be a homozygous recessive, and not capable of transmitting the asthmatic character. On the other hand, if bronchial asthma is recessive to the normal condition, all asthmatic individuals must have inherited the character from both parents and are capable of transmitting the condition to all their offspring. Normal individuals by this hypothesis would be of two sorts, homozygous normals, not capable of transmitting asthma, and heterozygous normals, who, while not having the disease, have inherited it from one side of the family, bear it recessive in their germplasm, and are capable of transmitting it to one-half their offspring.

□ = ♂ normal male.

○ = ♀ normal female.

■ ● = asthmatic male and female.

◨ ◑ = male and female with hay-fever.

□ O = male and female with other asthmatic tendencies.

E Ⓔ = male and female with eczema.

m = miscarriage.

KEY TO SYMBOLS

By this hypothesis, it would be possible for two apparently normal parents, if both carried the asthmatic character in the simplex condition, to bear asthmatic children.

To determine whether bronchial asthma behaves as a Mendelian character in heredity, it is necessary to examine individual family histories in which asthma and allied conditions occur. In the G. family, there is evidence of protein sensitization in three generations. The mother of the patient has had hay-fever for many summers; the father of the patient was normal. The patient, A. G., a physician, aged 28, has had hay-fever for seven summers, and similar symptoms whenever he goes near horses or guinea-pigs, and with the hay-fever and with changes of weather he sometimes has asthma. By the cutaneous tests, he is sensitive to horse, guinea-pig, pollens of the grass and composite families, and various bacteria. Following injection of pollen he had urticaria,

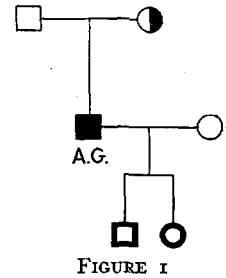

FIGURE 1

sneezing, choking and marked constitutional symptoms. His two children, a boy and a girl, aged eight and five years respectively, both have urticaria after eating strawberries and lobster. The wife of the patient, of unknown family history, is normal. In this family history, the asthma seems to behave like a Mendelian trait, dominant over the normal condition.

In the N. family, the asthmatic condition appears twice in three generations, the victims in each case being the daughter of a normal father and an asthmatic mother. In the fourth generation are three young children who as yet have not developed asthma. There is no evidence (both the patient and her mother were tested with many proteins) in this family, of sensitization to proteins. In this family, the asthmatic condition seems to behave like a character dominant over the normal conditions, and in this particular case, to be transmitted from mother to daughter.

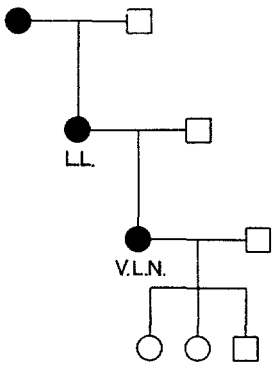

FIGURE 2

In the M. family occurs an almost identical family history, in that for two generations the daughter seems to inherit asthma from an asthmatic mother and a normal father. The mother of the patient, V. M., a woman aged 50, had asthma, but the older brother and sister were normal, her daughter, aged 16, has asthma, but three younger children, two girls and a boy, are normal. The mother is sensitive to ragweed pollen, the daughter was negative to all the proteins tried. Here again the asthmatic condition seems to be dominant over the normal, and to be transmitted from mother to daughter. The maternal grandmother, however, had a son and daughter who did not show the asthmatic condition, this could be explained by the hypothesis that the asthmatic grandmother was heterozygous with respect to the asthmatic character. The mating then would be like type 5, where half the offspring theoretically are pure recessive (normal if asthma is dominant), and half, while showing the asthmatic character, would be heterozygous and transmit the normal condition to half their offspring. The patient, V. M., must be of this heterozygous type; of her four children, one is asthmatic and three are normal.

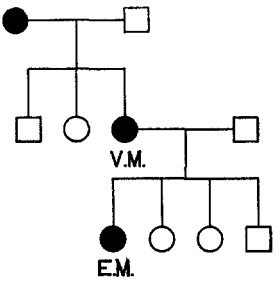

FIGURE 3

In the S. family the father of the patient had asthma; the mother, six sisters and one brother are normal; six other sibs died in infancy. The husband of the patient is normal, and none of her six young children have developed asthma as yet. The patient was sensitive to wheat, potato, and bacteria. Here asthma inherited from the paternal side seems to be dominant in the patient over the normal condition found in the mother; the seven normal children of the same parents could be explained, as in the M. family, by the hypothesis that the father was heterozygous and transmitted the normal condition to his other children; the theoretical number would be half the offspring normal and half asthmatic. This family history could also be interpreted by the opposite hypothesis, that asthma is recessive to the normal condition; the normal condition inherited from the mother is dominant over the asthmatic condition inherited from the father, in seven of the eight children, but these seven normal children are all heterozygous, and bear the asthmatic condition as a simplex character in their germ-plasm; the father, who must carry the asthmatic character in the duplex condition, if asthma is recessive, transmitted asthma to the patient, as to all his other children, and in addition, if the patient received the asthmatic character from the mother, who might be heterozygous, and hence capable of transmitting asthma, she would be a pure recessive, and hence asthmatic like her father. Marrying a normal man, the asthmatic condition would be transmitted by the patient to all her children, but none of them would have asthma because it would be in them recessive to the normal condition inherited from the father.

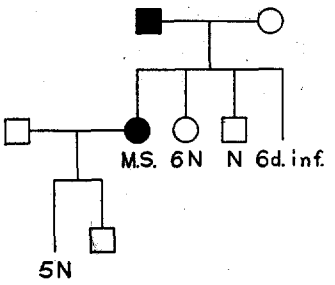

FIGURE 4

In the D. family the patient and his brother both had asthma of the non-sensitive type; of the eighteen children of the patient, by two mothers, all are normal except the youngest, a boy who has asthma and is sensitive to cat. If asthma is a dominant character, it was transmitted by the patient only once out of a theoretical nine times. If the asthmatic condition is recessive to the normal, and the first wife were a duplex normal, the ten children of the first family would all be normal; if the second wife were a simplex normal, she would be expected

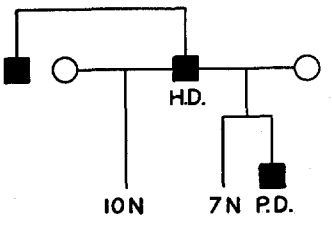

FIGURE 5

to transmit asthma to half her offspring; hence, if the patient, H. D., is a pure recessive, half the children of the second marriage would be expected to develop asthma; one out of a theoretical four is asthmatic. This last interpretation brings the theoretical expectation nearest the actual facts.

In the C. family, the grandparents of the patient are unknown. The father had asthma all his life, but after scarlet fever at the age of sixty the disease left him. Of the eight children of this asthmatic father and normal mother, four had asthma and four were normal. The patient, M. A. C., a woman, aged 56, the oldest of the family, suffering from asthma and diabetes, not sensitive to proteins, began to have asthma when she was a child, following scarlet fever. Her sister, three years younger, developed asthma after a cold contracted during scarlet fever when she was eighteen or nineteen years old. The brother began to have asthma following a cold contracted during measles, and he died from dropsy at the age of twenty-four. The youngest child, a girl, who had asthma,

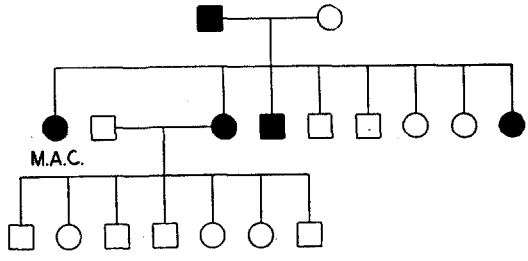

FIGURE 6

died from "heart failure" at the age of thirty. Two normal sisters are living and well. A brother who did not have asthma died from pneumonia. None of these eight children had offspring, except the second daughter who married a normal man and whose seven children as yet give no evidence of asthma. By the theory that asthma is dominant to the normal condition, if the father were a simplex asthmatic, half of the offspring would be expected to be asthmatic and half normal, which is exactly what happened. On the theory, that asthma is recessive to the normal condition, and an individual in order to show asthma must bear the tendency in the duplex condition, if the mother of the patient were a duplex normal, all the children would have been normal, but capable of transmitting asthma. But since half the children had asthma, it is possible that the mother was a simplex normal, that is not asthmatic but capable of transmitting asthma. In this case half the children would inherit asthma from both the father and mother, and would be asthmatic, while

the other half would be normal like the mother but capable of transmitting asthma. The asthmatic daughter who married the normal man, would be expected to transmit asthma to half her offspring, if asthma behaves as a dominant character; but if asthma is a recessive, and her husband was a duplex normal, all her children would be simplex normal. From the family history, it is difficult to render a decision in favor of either theory, but the fact that none of the children of the second daughter have asthma is in favor of the doctrine that asthma behaves as a recessive trait.

In the G. family, the history differs from the group which has just been discussed, in that the parents of the patient were both normal. The family history of the mother is unknown. A sister and a brother of the

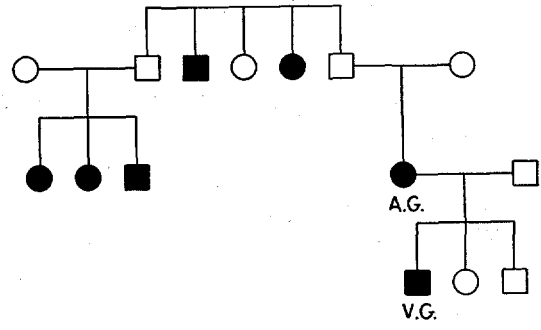

FIGURE 7

father had asthma, and the three children of a normal brother of the father also had asthma, so these first-cousins of the patient also present the phenomenon of asthmatic children born of normal parents. The patient, a woman, aged 30, has suffered from asthma for ten years both winter and summer, and is sensitive to pollens and bacteria. Her husband and young son and daughter are normal; her oldest child, a boy of twelve years, has suffered from asthma for six years and is not sensitive to proteins. By the theory that asthma is a dominant trait, and hence present as a characteristic of every individual who is capable of transmitting the condition, it is not possible to explain how the children of normal parents can inherit a tendency to asthma which runs in the family and is manifested in grandparents, aunts or uncles, cousins or more distant relatives. By the theory that asthma is recessive to the normal condition, this skipping of a generation can be explained; but by that theory, every asthmatic individual must be duplex with regard to that character, that is, must have inherited the asthmatic tendency from both parents; and where both parents are

normal this is difficult of demonstration, and sometimes seems absurd. That asthma occurred in the family of the father of the patient is manifest; and with an asthmatic brother and sister, it is not improbable that the father was a simplex normal, that is, capable of transmitting the trait to half his offspring. But there is no evidence that the mother of the patient was a simplex normal, who transmitted the asthmatic tendency to her daughter, the patient; yet this assumption seems to be necessary to an interpretation of this family history by the Mendelian law. Moreover it is necessary also to assume without evidence that the husband of the patient is a simplex normal transmitting asthma to half his offspring, in order to explain the asthma in the son.

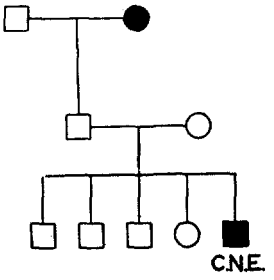

FIGURE 8

In the E. family the patient, a man, aged 25, who had eczema in childhood, has had asthma for twenty years, and by the cutaneous test is sensitive to animal hairs, foods, and pollens. The youngest of a family of five, whose sister, three brothers, and parents are normal, the patient seems to inherit asthma from his paternal grandmother. The father who is sometimes short of breath but does not have asthma, may thus be a simplex normal. There is no known history of asthma in the mother's family. In the histories of the D., Cr., and Co. families (figures 9, 10 and 11, respectively), the asthma, from which

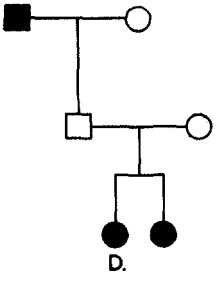

FIGURE 9

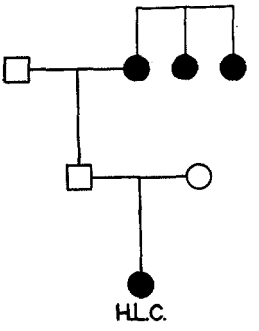

FIGURE 10

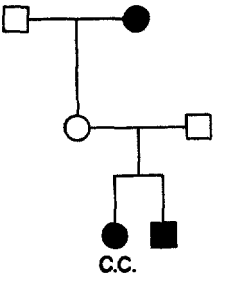

FIGURE 11

one of the grandparents suffered, skips the generation of the parents, and reappears in the patient. In the Ck. family, the parents are normal, the father's brother has asthma, and two of five children have asthma. According to the Mendelian law of inheritance, a dominant character appears in the direct line in every generation, but a recessive character

shows itself in the body of the individual only when present in the germ cells in the duplex condition, inherited from both parents. In this group of family histories, bronchial asthma behaves as a recessive character, because it is transmitted to the offspring when both parents are normal, its origin being demonstrated in the family of one parent, and unknown in the other.

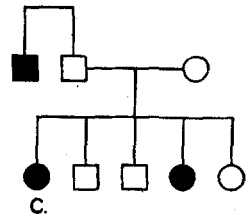

FIGURE 12

In the M. family (figure 13), asthma appears as a recessive character in the second and third generations, in that the offspring of apparently normal parents have asthma. But in the fourth generation the children of an asthmatic father and a normal mother have asthma, which might

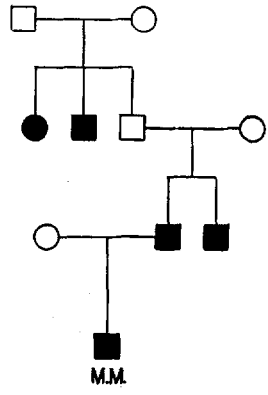

FIGURE 13

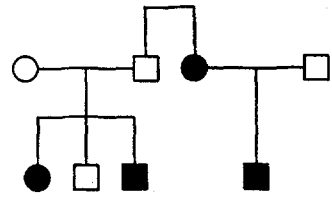

FIGURE 14

indicate that asthma is a dominant rather than a recessive character. In the Crz. family (figure 14), the asthmatic tendency behaves like a dominant character in that the son of an asthmatic mother has asthma, but like a recessive, where two of three children of non-asthmatic parents have asthma. In the P. family (figure 15), the father and paternal aunt of the patient had asthma, but the daughter of the normal brother and his normal wife shows beginning asthma with heavy colds. If the mother of the patient were a simplex normal, the patient might have inherited asthma from both father and mother, while her brother inheriting asthma only from the father is normal like the mother, but transmits the asthmatic tendency received from him. In the V. family (figure 16), the patient, R. V., a boy aged 14, is sensitive to pollen and lobster, has asthma in the summer; the parents are normal, but the father's sister has

hay-fever and is sensitive to pollens. Thus the father in all probability is a simplex normal, transmitting the tendency, but its presence in the mother's family cannot be shown.

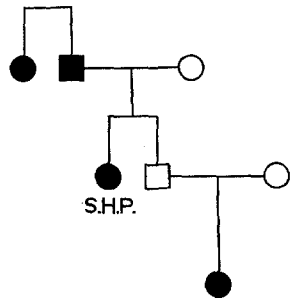

FIGURE 15

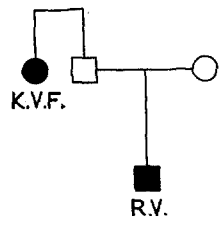

FIGURE 16

In the A. family, the oldest brother, a first-cousin, and the maternal grandmother have asthma. The oldest child of the asthmatic brother, whose wife is normal, has urticaria from eating egg, and the second child has eczema and asthma after eating egg, milk, and wheat. The patient, a girl, aged 17, has eczema, and had asthma as a child until four years of age, followed by a nearly free interval until she was eleven years old, and a return of the condition since that time. By cutaneous tests she is sensitive to cat hair and wheat, and she improved when removed from contact with cats and when wheat was omitted from her diet. The parents of the patient and her brother, and of the asthmatic first-cousin, are all non-asthmatic, the tendency may have been transmitted from the grandmother through the mother to the patient and her brother, and through the father of the cousin. Where both children of the asthmatic brother show protein sensitization, one as asthma and the other as urticaria, the simplest explanation is that the tendency is dominant over the normal condition; but it is not impossible that the mother transmits asthma also.

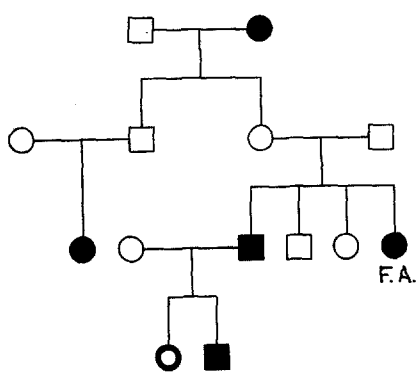

FIGURE 17

In the group of family histories presented next in order, the asthmatic tendency is found in the families of both parents. In the B. family, the maternal grandmother and her sister were asthmatic. She married a

man of unknown family history, but who according to the theory that asthma is recessive, must have transmitted the asthmatic tendency, because their daughter, the mother of the patient, had asthma. The father of the patient was normal, but since his sister had asthma, he probably was a simplex normal and transmitted the tendency. The patient, a woman, aged 41, who has had asthma for nineteen years, is not sensitive to any proteins tried. Her husband is normal, and none of the four children show any tendency to asthma or protein sensitization. Thus the asthmatic tendency in the patient is probably recessive in her children to the normal condition inherited from her husband; but theoretically all of them bear the asthmatic tendency recessive in their germplasm and are capable of transmitting the tendency to half their offspring. This family history may be interpreted in a different fashion, as were other family histories earlier in the paper where asthma appeared for three generations in the daughters of asthmatic mothers and normal fathers. If it is assumed that the tendency to asthma is dominant over the normal condition, the asthma inherited from the maternal grandmother is dominant over the normal condition in the maternal grandfather, and hence their daughter, the mother of the patient is asthmatic. Under this theory, the father of the patient, although his sister had asthma, was normal. In the patient, the normal condition transmitted from the father is recessive to the asthmatic condition inherited from the mother. Marrying a normal man, she would be expected to transmit the asthmatic condition to half her offspring, and the other half, inheriting the recessive normal condition from both father and mother, would be normal and incapable of transmitting asthma. The difficulty in the way of this theory, that all the children are normal, is not insurmountable, because the children are still young, and may develop asthma later in life.

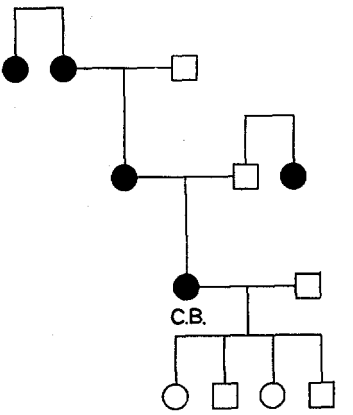

FIGURE 18

In the H. family, the paternal grandparents both had asthma; two sisters of the paternal grandfather, and the father of the paternal grandmother, were asthmatic; hence asthma was present in the families of both parents of the father, and this couple is more heavily tainted with the condition than any other pair found in the family histories. Of their five children, four had asthma. A non-asthmatic daughter, marrying

a normal man had two children, both with asthma. The father of the patient, marrying a normal woman, who does not know of the occurrence of asthma in her family, has three children, of whom the oldest, the patient, a girl aged eight, has asthma, but is not sensitive to proteins. An asthmatic daughter, marrying a normal man, has seven children, six normal and one with asthma. Under the theory that asthma is a dominant trait, if both paternal grandparents were simplex dominants, the mating would be like type 4, and three-fourths of their children would be expected to have asthma, and one-fourth to be normal, which is exactly what happened; but the normal children should not be capable of transmitting asthma; but the normal daughter did transmit asthma to her two

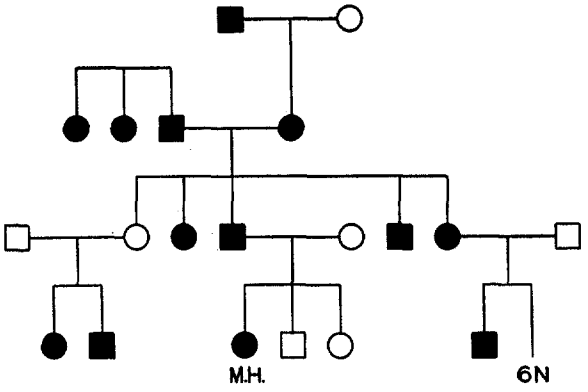

FIGURE 19

children. If the paternal grandfather were a duplex dominant, and the paternal grandmother a simplex dominant, as seems probable from the fact that her mother was normal, this mating would correspond to type 2; in that case all the children would be expected to have asthma, but one-half would be simplex; in this case the non-asthmatic daughter is not provided for. If asthma is recessive to the normal condition, the paternal grandparents must have both been pure recessives, and in that case the mating would correspond to type 6; the normal mother of the maternal grandmother would have had to be simplex, transmitting asthma, by this hypothesis, and the non-asthmatic daughter is not provided for. By the recessive theory also, all the normals who were married by these offspring would have to be simplex, in order to account for the appearance of asthmatics in each of the three families of grandchildren. But the theory that asthma is a dominant character does not provide for the two children of normal parents in the first family, and in the third family

half of the offspring should have been asthmatic, instead of one out of seven. All the grandchildren are young and may develop the trait later. On the whole, the theory that asthma is recessive seems to explain more of the facts in this remarkable family history, than the opposite theory.

In Moon, the patient is the daughter of an asthmatic mother and a normal father, the father's father had asthma, and hence he may have transmitted the tendency. All the children of the normal paternal

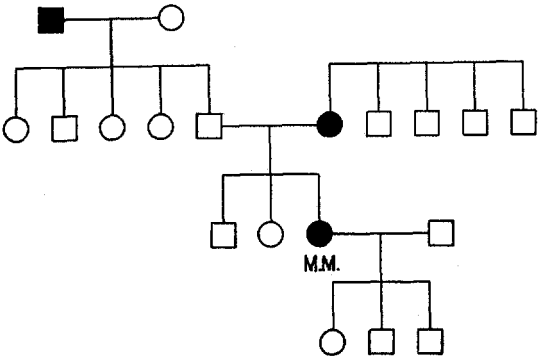

FIGURE 20

grandmother and the asthmatic paternal grandfather were normal, so in that mating at least, the asthma was recessive to the normal condition. If the father of the patient were a simplex normal, able to transmit asthma to half his offspring, and the mother whose parents and four brothers were normal, was a duplex recessive, transmitting asthma to all her offspring, their mating corresponds to type 5, where half the children would be expected to be pure recessive, that is asthmatic, and half, while normal, would transmit asthma. The facts of one asthmatic out of three correspond fairly closely. The normal condition of the husband of the patient is apparently transmitted to their normal grown children. This family history could of course be interpreted by the opposite theory.

In Biggs, the patient, G. B., a girl aged 18 has suffered from asthma and eczema all her life, and she is sensitive to horse hair, various foods, bacteria and pollens. Her brother, R. B., aged 21 has hay-fever, sometimes with asthma, and he gives positive reactions with pollens. The mother, and her brother and mother had asthma. The father has no asthma, hay-fever, or other sensitization to pollens, but his brother has asthma and his sister has hay-fever and gives positive cutaneous reactions to the pollens. By the theory that asthma is recessive to the normal condition, the mother of the patient would be supposed to be a pure recessive, inher-

iting asthma from her asthmatic mother and normal father; the father of the patient would be expected to be a simplex normal capable of transmitting the asthmatic tendency present in his family. If this is true, the older son who is normal, inherits the dominant normal condition from his father, but carries the asthmatic tendency inherited from his mother. His asthmatic and sensitive brother and sister inherit the tendency from both father and mother. This seems the most reasonable interpretation of the family history. If the normal condition is recessive to the asthmatic condition, the father cannot transmit the character, and the fact that it occurs on his side of the family has no bearing on the case.

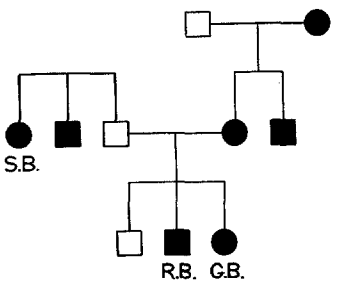

FIGURE 21

In Johnstone, the maternal grandfather was asthmatic, and he had two asthmatic brothers; hence by our theory, he was a duplex recessive. Marrying a normal woman, whether a simplex or duplex normal cannot

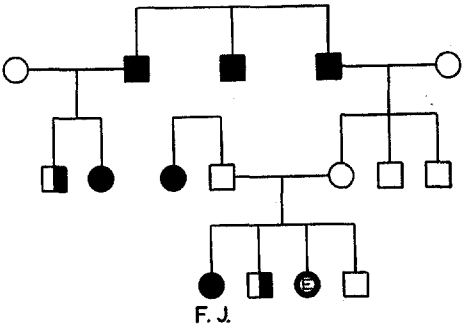

FIGURE 22

be determined from the history, he had a normal daughter, who by the theory was a simplex normal, capable of transmitting the asthmatic tendency. Her husband was normal, but probably simplex, because his sister had asthma. Of the four children of this pair of normal simplex individuals, a daughter, the patient, has hay-fever from, and by the cutaneous tests is sensitive to, cat hair; a brother has asthma, a sister has eczema, and a second son is normal, without evidence of protein sensitization. One of the asthmatic uncles of the mother married a normal woman, but his son has summer hay-fever and his daughter has cat hay-fever. It is impossible to explain this family history on the hypothesis that asthma is dominant to the normal condition, for in that case neither

parent would be capable of transmitting the asthma which is shown to be present in their families.

In Tucker, the asthmatic father married an apparently normal mother, who probably was simplex, inheriting asthma from her father. Of the three children of this couple, two have asthma, inherited, if asthma is recessive, from both father and mother. The normal child probably has inherited the asthmatic tendency from the father, but not from the mother. The asthmatic brother and sister are both sensitive to proteins.

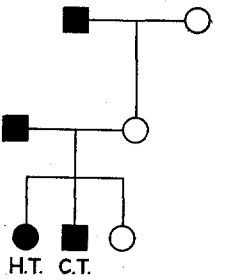

FIGURE 23

In the Guppy family, the maternal grandmother of the patient had asthma, but her husband and all their eleven children were normal, the asthmatic tendency in this mating behaving as a recessive character. Probably at least some of the children were capable of transmitting the tendency; theoretically all of them would have been simplex, if asthma is recessive; if it is dominant, at least half of them should have been asthmatic. The mother of the patient, normal but probably capable of

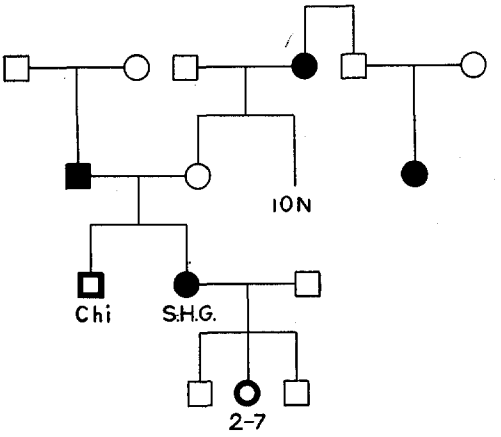

FIGURE 24

transmitting asthma, married an asthmatic, the son of normal parents, who according to the theory that asthma is a recessive character must have inherited the tendency from both parents, simplex normals bearing the tendency recessive in their germ-plasm. If the father was a duplex asthmatic, and the mother of the patient a simplex normal, the theoretical expectation would be that half the children would be asthmatic, and the other half normal but bearing the asthmatic character in their germ-

plasm. The two children of the mating were both asthmatic. The patient's brother had asthma in childhood, but recovered as he grew older. The patient, S. H. G., did not develop asthma until she was 26, but she has had asthma now for sixteen years, and by the cutaneous tests she is sensitive to horse, cat and bacteria. Thus both the patient and her brother show the asthmatic tendency, inherited perhaps from both parents. Her husband is normal and there is no history of asthma in his family. If he is a duplex normal and she a duplex asthmatic, all the children would be normal, but simplex and capable of transmitting asthma. If he is a simplex normal, he would transmit asthma to half his children, which, uniting with the tendency transmitted by the mother would mean half the offspring asthmatic, and half simplex normal. Of their three children, one, the daughter, had asthma with colds from the age of three to seven, but she has recovered as she grew older. In this family history, therefore, the asthmatic tendency behaves according to the Mendelian law, as an inherited trait recessive to the normal condition.

In Foye, both paternal grandparents had hay-fever; their son, inheriting the tendency perhaps from both parents, was asthmatic. The patient, the daughter of this asthmatic father and a normal mother has asthma, but is not sensitive to proteins. The first-cousin of the father, whose father had hay-fever, has hay-fever also. So in this family history the asthmatic tendency seems to behave consistently as a dominant character and the recessive theory can be made to apply only by supposing that the normal mother of the patient, and the normal father of the cousin with hay-fever, were both simplex normals and transmitted the tendency to their offspring.

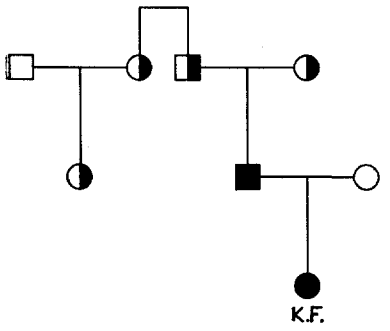

FIGURE 25

In the B. family, the maternal grandfather of the patient had asthma, his wife was normal, and their daughter, the mother of the patient had asthma, which would be expected if asthma is dominant; but which can be explained, if asthma is recessive, only by supposing that the maternal grandmother was simplex and able to transmit asthma. The father of the patient, the son of two normal individuals, has asthma, a condition which cannot be explained by the theory that asthma is dominant. On the theory that asthma is recessive, the appearance of asthma in the children of normal parents can be explained. Both parents are heterozy-

gous, and their mating corresponds to type 4; three-fourths of their offspring would be normal, but two-thirds of these normal offspring, or one-half the entire number, would be simplex normals, able to transmit asthma, the other normals would be duplex, not carrying asthma in their germ-plasm; one-fourth the offspring would be asthmatic, that is pure recessives, and would transmit the tendency to all their offspring. The father of the patient falls in this latter group. Both children of these asthmatic parents show the asthmatic tendency; the patient, a boy, aged eight, has had bronchitis all his life and asthma for the past two years, and his younger brother has bronchitis and is beginning to choke up with it. There is no evidence of protein sensitization in this family. Whether asthma is dominant or recessive cannot be judged from this last mating, because if asthma is dominant, the children of asthmatic parents would be expected to show the trait in all cases, if the germ-plasm were pure, and in all but one-fourth of the offspring, even if both parents were simplex, while if the asthmatic condition is recessive, the asthmatic patients must be pure recessive, and not capable of transmitting the normal condition.

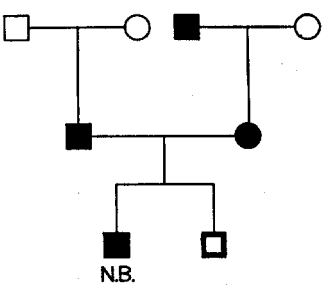

FIGURE 26

In Chadwick, the family history looks again like inheritance of a dominant trait. The patient, M. C., and her brother, both suffering from asthma, were the children of an asthmatic father and a normal mother; of her eight pregnancies, three children are normal, a daughter of four is choked up at times, one child died in infancy, and there were three miscarriages. Thus in the first generation, the asthma behaves like a dominant character, while in the third generation it is recessive to the normal condition in three out of four children. If asthma is a recessive character, for it to appear in the direct line in every generation, as it does in this family, the normal mother of the patient and her normal husband must have been heterozygous, carrying asthma in the simplex condition in their germ-plasm, and transmitting it to half their offspring.

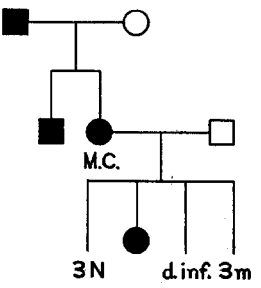

FIGURE 27

In Shewmann, an apparently normal maternal great-grandfather married an asthmatic, and of their ten children, one had asthma, and he had only wheezing and shortness of breath with colds. One apparently

normal son, marrying a normal wife, had a son who suffered from asthma. A normal daughter, marrying a normal, had five children, of whom two are normal, one daughter, the patient, M. L. S., has asthma and eczema and is sensitive to bacteria and some foods; a son has hay-fever, and in his youth had asthma, with colds; another daughter, non-asthmatic, and non-sensitive, has frequent colds. The patient, whose husband was normal, has three children, none of whom as yet has developed asthma, or any evidence of protein sensitization. In this family history, the asthmatic tendency does not behave like a dominant character; in the mating of the grandparents, if asthma were dominant and the grandmother were duplex, all the children should have had asthma, the mating then corresponding to type 3; if the grandmother was simplex, the mating would

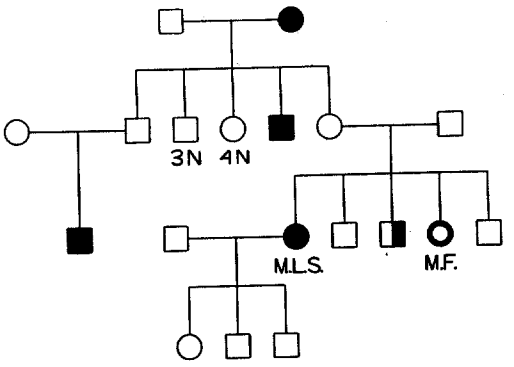

FIGURE 28

correspond to type 5, and at least half the offspring would have been expected to have asthma. If asthma is dominant, the two instances of asthmatic children born of normal parents cannot be explained, and at least half the children of the patient should develop asthma. If asthma is a recessive character, the normal grandfather, the mother of the asthmatic first-cousin, and the father of the patient, must all be supposed to have been simplex normals, capable of transmitting asthma; that the father of the first-cousin and the mother of the patient were simplex normals is rendered probable by the occurrence of asthma in their families.

In the family histories which follow, the data concerning normal members of families is incomplete, and for that reason proportions and percentages of offspring in given matings cannot be compiled for all cases. For this defect they are presented separately, although they are not different in any way from the three groups which have preceded. In the C. family, the father had slight asthma and three sons have asthma,

while the son of the mother by a former marriage, and a son and daughter by this second marriage have no asthma. In the mother's family, there is no known history of asthma. Here the asthmatic condition seems to be dominant, in that three out of five children apparently inherit it from the father, while the two normal children inherit the recessive condition from both parents. If the asthmatic condition is to be interpreted as a recessive trait in this family, it must be supposed that the mother was

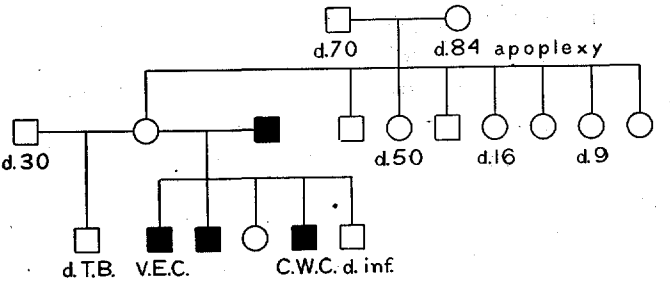

FIGURE 29

simplex and transmitted asthma to half her offspring, which seems a far-fetched theory. The patient, V. E. C., a man aged 31, has had asthma for the past seven years, with a history of sudden onset after an operation for appendicitis; he is sensitive to pollens and bacteria, and gives a slightly positive reaction to horse hair. The wife and four young children of this patient are normal. His brother, C. W. C., aged 25, has had asthma for fifteen years and is sensitive to horse hair and to red-top pollen.

In the Newell family, the mother had hay-fever but has gradually recovered; the patient, M. N., a woman aged 46, has fall hay-fever and with it asthma and sneezing and running of the eyes and nose when near horses; in childhood she had eczema. By the cutaneous tests she is sensitive to horse and pollens. A brother has asthma all the year; another brother, J. A. N., aged 36, has both spring and fall hay-fever, and is sensitive to pollens. Here the tendency to hay-fever inherited from the mother shows itself in three of her five offspring, one daughter having asthma and hay-fever, one son asthma, and another son hay-fever, while two daughters are normal. In this family the asthmatic tendency appears to act as a simple Mendelian dominant, the two normal daughters inheriting the recessive normal condition from both parents. If it is to be interpreted as a recessive character, the

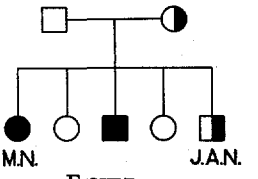

FIGURE 30

father, although normal, must be supposed to have been simplex, transmitting asthma to three of his five children.

In the Smith family, the father had hay-fever, the mother had asthma, the son hay-fever, and the daughter asthma. There may have been normal children not noted in the history, but taken as it stands the history looks like the inheritance of a pure trait, where both parents are duplex, transmitting the character to all their offspring, and by this interpretation, the mating might correspond to either type 1 or 6, the asthma and hay-fever being either dominant or recessive in this family.

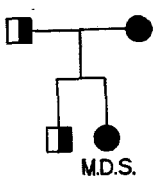

FIGURE 31

In the Poe family, the mother and maternal grandmother of the patient had hay-fever and the maternal great-grandfather had asthma. In the father's family, an uncle of the patient had hay-fever. The patient, a girl aged 24, has had asthma for nineteen years, and is sensitive by the cutaneous tests to horse hair and pollens. Her brother and his three children are normal. If asthma is a dominant trait in this family, it can be shown to have been passed down the direct line for four generations from parent to child; in each generation prevailing over the normal condition inherited from the other parent. In the last family, the daughter has inherited the asthmatic tendency from the mother and the normal from the father, while her brother has inherited the recessive normal tendency from both parents, and is not capable of transmitting it to his offspring. If asthma is dominant over the normal condition, the fact that the father's brother had hay-fever has no bearing on the case. But if asthma is a recessive character, the normal father may have been simplex, transmitting the normal condition to his son and the asthmatic tendency to the daughter. By this latter hypothesis, the mother would have to be duplex, transmitting the asthmatic character to all her children. The daughter, inheriting the tendency from both parents, is asthmatic; the son, normal like his father, bears the asthmatic character recessive in his germ-plasm and theoretically transmits it to half his offspring, but if his wife is a pure or duplex normal, none of the offspring will show the tendency. The hypothesis that asthma is recessive in this

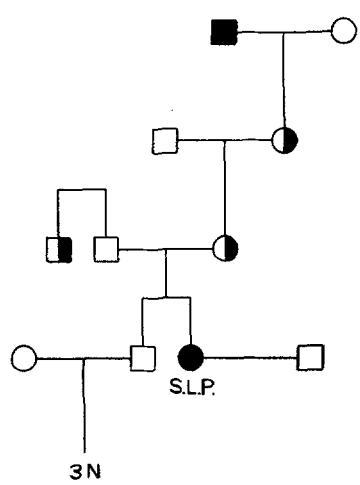

FIGURE 32

family makes necessary the supposition that the maternal great-grandmother and the maternal grandfather, in addition to the father of the patient, must have been simplex.

In the Brown family, the maternal grandfather had asthma, and four of his seven daughters were asthmatic. Three daughters, including the mother of the patient, and all six sons were normal. Although both parents were normal, the patient, A. B., a man aged 40, has had asthma

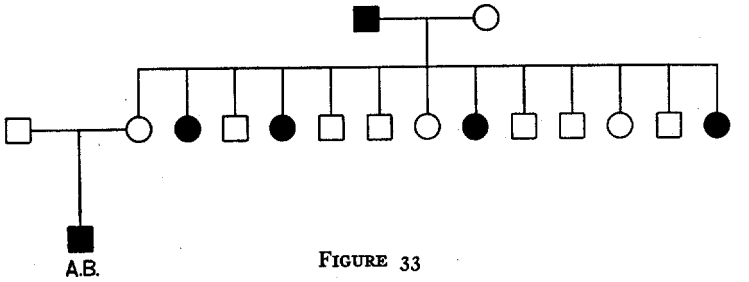

FIGURE 33

for two years, and is sensitive to bacteria. In the generation of the parents, the asthmatic character behaves as a dominant trait in four of the thirteen children. But if asthma is dominant, the fact that the maternal aunts and grandfathers had asthma, would not explain its appearance in the grandson, skipping the mother. On the other hand, if asthma is recessive, the maternal grandfather must have been a duplex asthmatic and his wife a simplex normal, capable of transmitting asthma; then four of the thirteen children would have inherited asthma from both parents, while nine would have inherited asthma from the father and the normal condition from the mother, and would be expected to transmit asthma to half of their children. In this case also, the father of the patient would have had to be a simplex normal.

In the following family histories, the parents of the patients are normal, but the asthmatic character appears collaterally in the family of one

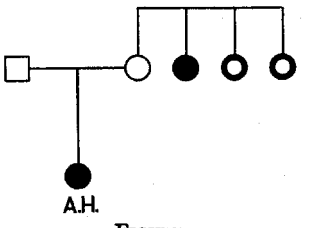

FIGURE 34

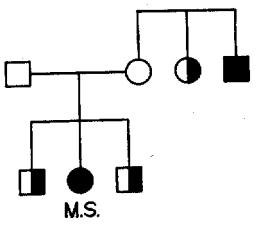

FIGURE 35

parent. In the H. family (figure 34), the patient, a woman, aged 37, has had asthma for two years, and is not sensitive to proteins; of her maternal

aunts, one has "wheezing spells like asthma," and two are made ill by eating eggs, In the S. family (figure 35), the patient, a woman, aged 25, has had asthma since she was three years old, and she is sensitive to horse hair, pollens, potato, and cereals. The two brothers of the patient have hay-fever, her maternal uncle has asthma, and her maternal aunt has hay-fever. In the G. family (figure 36), the patient, a boy, aged 12, began to have asthma at two years of age, and as an infant he had eczema. By the cutaneous tests he is sensitive to animals, pollens, wheat, and egg. One brother has fall hay-fever, another who had eczema in infancy has sneezing and running of the nose and eyes and a little choking up when he is near horses. The father's sister has hay-fever.

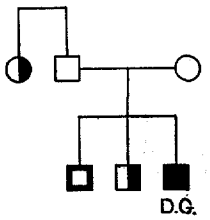

FIGURE 36

In the R. family, the asthma appears to have skipped two generations because both the father and the father's father were normal, but the brother of the latter had hay-fever. The patient, a man aged 40, has had fall hay-fever with asthma for sixteen years, and is sensitive to pollens; his sister has spring hay-fever, and a normal sister has running of the nose. The asthmatic character cannot be interpreted as a dominant trait in this last or the preceding family histories. In this last family, if the grandfather were a simplex normal, as appears possible from the presence of hay-fever in his family, he would have been expected to transmit the trait to half his offspring, but if his wife were a duplex normal, none of the children would have been asthmatic. If the father of the patient inherited the normal tendency from his mother and the asthmatic tendency from his father, he would have been a simplex normal and capable of transmitting asthma to half his offspring; and if his wife also were a simplex normal, the patient and his sister with hay-fever would have inherited the tendency from both parents, while the normal sister inherited the normal condition from one and perhaps from both. The wife and small son of the patient are normal.

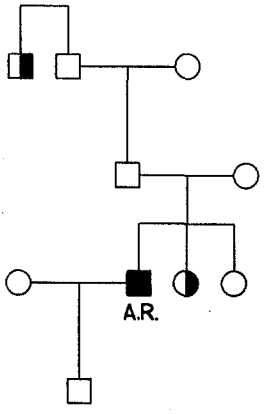

FIGURE 37

In the A. family, the history is exactly the same as in the preceding family, except that the asthmatic character skips two generations in the mother's family instead of the father's, the sister of the maternal grandmother having asthma, and in the fact that a first-cousin on the father's

side has asthma; this makes more plausible the hypothesis that the father is a simplex normal capable of transmitting asthma to half his offspring. In the last four family histories and in part of the P. and the S. families, the asthmatic tendency has behaved as a recessive Mendelian character.

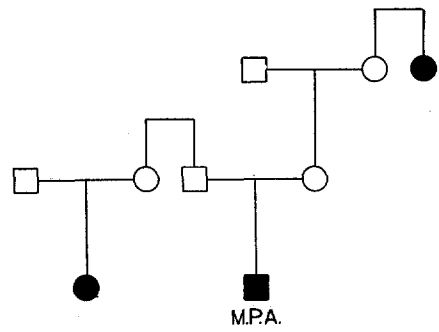

FIGURE 38

Thirty-eight family histories are presented with a more or less complete record of ninety-one matings in which parents or offspring are asthmatic or have hay-fever. In three matings, one producing only one child, both parents and all the children were asthmatic, five children in all being produced by this type of mating. In one mating, where both parents had asthma, four children were asthmatic and one was normal. In no mating where both parents were asthmatic were all the children normal. In nineteen matings where one parent was asthmatic, all the children were asthmatic, but in twelve cases only one child was born; from this group of matings twenty-five asthmatic children were produced. In nineteen families where one parent was asthmatic were born thirty-five asthmatic and sixty-seven normal children. In seventeen families where one parent was asthmatic, which included six matings where only one child was born, all the sixty children produced were normal. In twenty matings where both parents were normal, all the children were asthmatic, but this included thirteen matings with only one child; from this group, were produced in all thirty-one asthmatic children. In twelve matings where both parents were normal, fifteen normal children were born and thirteen asthmatic children.

Where both parents had asthma or hay-fever, out of four matings in which ten children were born, only one child was non-asthmatic, and that child, although she married a normal, produced two children, both asthmatic. Hence the evidence seems strong that where both parents show the asthmatic condition, the character tends to breed true; if the asthmatic character is recessive to the normal condition, these four matings must be of type 6, and it is difficult to account for the one normal child by this hypothesis. If asthma is a dominant character, the matings which produced only asthmatic children might have been either type 1 or type 2, while the mating in which the normal daughter was born was probably type 4, where the theoretical expectation would have been three

asthmatic children to one normal; the actual ratio of one normal to four asthmatic is very close. In nineteen matings where one parent was normal and one asthmatic, twenty-five asthmatic and no normal children were produced; if asthma is a dominant character, this group would correspond exactly to mating of type 3, but if asthma is a recessive character this group is more like type 5, and in that case half the children would have been expected to be normal; the fact that in twelve of the seventeen matings there was only one child and in the remaining six only two each, makes this latter hypothesis somewhat more tenable. In nineteen matings, where one parent was normal and one asthmatic, sixty-seven normal and thirty-five asthmatic children were produced, a ratio of a little less than two normal to one asthmatic. If asthma is a dominant character, this type of mating would correspond most nearly with type 5, in which the theoretical expectation would be half the offspring asthmatic and half normal; the preponderance of normal offspring might be partly discounted by the fact that some of them are still very young and may develop the asthmatic condition later in life. If asthma is recessive to the normal condition, this group would still correspond most closely to type 5. In seventeen matings where one parent was normal and one asthmatic, sixty children were produced, all normal, an impressive number when compared with the mating of the same type where seventeen similar pairs of parents produced twenty-two asthmatic offspring. In this group, if asthma is a dominant character, the matings are necessarily either of type 2 or type 5, and the results correspond more nearly to type 5, where only half of the offspring would be expected theoretically to show asthma; here again some children are young and may develop the disease later on. But if asthma is recessive to the normal condition, this group would correspond exactly with type 3, where the theoretical expectation would be all normal.

The two groups of matings where both parents are normal, but have asthmatic children, cannot be explained by the theory that asthma is dominant to the normal condition. Twenty-two pairs of normal parents produced thirty-one asthmatic children, distributed in twelve families of one child, five of two and three of three children each. This group comes nearest to the mating of type 4, but even then it would have to be supposed that only the recessive fourth of the expected offspring had been born, while three times as many normal children as asthmatic would be the theoretical expectation. The twelve pairs of normal parents who bore fifteen normal and thirteen asthmatic children corresponds most closely to the type 4 mating; out of twenty-eight offspring the theoretical

expectation would have been twenty-one normal to seven asthmatic children.

A family history published by DRINKWATER (1909) not different in any essential from the family histories of asthma presented in this paper, shows asthma transmitted in the direct line for three generations, and in three families born of one normal and one asthmatic parent, exactly half the offspring have asthma and half are normal. while two other such pairs have normal children. He shows no asthmatic children born of normal parents. Three of his matings correspond to type 5, and two are of type 3, if asthma is taken to be recessive to the normal condition.

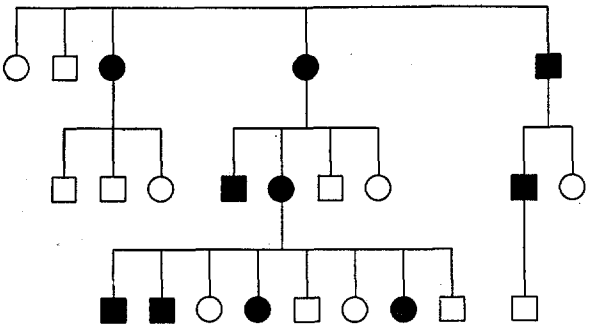

FIGURE 39

In the thirty-eight family histories presented above, the asthmatic condition behaves as a Mendelian dominant in seven; in twenty-five the character must be interpreted as a recessive character, if it is to be considered as inherited at all, while in six families it may be interpreted either way. In the more complete histories, both types are shown to occur in the same family, sometimes it behaves as a dominant, appearing in the direct line in two or more generations, and again as a recessive in that it skips one or more generations, or is present collaterally but not in the direct line. In the families most heavily tainted on both sides, the proportion of asthmatic offspring is greater than in families where it is present on only one side, or collaterally. By assuming that some normal individuals are simplex and transmit the character without themselves showing it, most family histories in which asthma occurs can be interpreted in accordance with the Mendelian law of heredity; the asthmatic trait behaves as a recessive character. But when an attempt is made to group the family histories according to the theoretical matings, the facts do not always meet the theoretical expectation. Where both parents have hay-fever or asthma, the correspondence with type 6 is very close, although two

normal children are shown, born of matings where both parents have hay-fever or asthma. Where one parent is normal and the other asthmatic, 127 normal children were born to sixty asthmatic, so that the normal condition prevails over the asthmatic in a ratio of more than two to one. The group where a normal and an asthmatic parent have all normal offspring would correspond exactly to type 3 if asthma were dominant, but since asthma behaves as a recessive, this must be taken as a variety of type 5 mating, where the expected normal half of the family was not born, and this view gains support from the small number of children and the fact that most of them are only children. If this group is united with the group where one asthmatic and one normal parent bear some children normal and some asthmatic, the typical type 5 condition, there are 60 asthmatic to 67 normal children, almost the theoretical expectation of one dominant to one recessive. Where from a normal and an asthmatic parent all the children are normal, the condition corresponds exactly to the theoretical expectation in type 5. Where both parents are normal but have some or all children asthmatic, the group corresponds most closely to the type 4 mating, with forty-five asthmatic offspring to fifteen normal, or three recessive to one dominant, which is the reverse of the expected condition. To summarize then, interpreting asthma as a recessive to the normal condition, seventeen matings of type 3 are shown, with 60 normal offspring; thirty-four matings of type 4, with fifteen normal and forty-five asthmatic offspring; thirty-four matings of type 5, with sixty asthmatic and sixty-seven normal offspring; and four matings of type 6, with nine asthmatic and one normal child, who transmitted asthma. No family history is presented which cannot be interpreted by the theory that asthma is recessive. By this theory also the apparently sporadic cases of asthma which occur frequently in families where no other case is known can be explained that the parents in question happen to be not pure but simplex normals, the recessive trait which each bears being transmitted from both to the child who develops asthma, but from only one to all the other children, a theoretical chance of one in four. Thus the 52 percent of cases with a negative family history can be brought under the same law of inheritance as those with a known history of asthma in the family.

SUMMARY

In a series of 400 cases of bronchial asthma, 192, or 48 percent, gave a positive family history; in the group of 191 patients sensitive to proteins 52 percent gave a positive family history while among the 209 non-sensi-

tive cases only 41 percent gave a family history of asthma; hence asthma of the anaphylactic type has a greater tendency to run in families than does the non-sensitive asthma. Asthma is inherited with equal frequency from father and mother; from the father's family 66 patients may have inherited asthma, 39 directly, 8 skipping a generation, 1 skipping two generations, and 18 collaterally. From the mother's family, 64 patients may have inherited asthma, 25 directly, 22 skipping a generation, and 17 collaterally. A nearly equal number of men and women inherit asthma from the father, but twice as many women as men inherit asthma from the mother, and 25 percent more women than men inherit asthma directly from the parents.

In both sensitive and non-sensitive groups a large number of patients who began asthma before thirty, are found to have a positive family history, and a larger proportion with an age of onset after thirty are found among those with a negative family history. An earlier age of onset is found among cases with a positive family history, and children of asthmatic parents who develop the disease begin asthma earlier than did their parents. There is no distinction in kind, variety or degree of sensitization to foreign proteins as demonstrated by the skin test, between sensitive patients who give a family history and those who do not. From the presence or absence of asthma in the family history, it is not possible to draw conclusions as to the cause, severity of the disease, or prognosis in a given case of bronchial asthma.

Sensitive and non-sensitive asthma do not run pure in the family histories, but both types occur in the same family; hence, from the standpoint of heredity, these two types of asthma and other manifestations of sensitiveness to proteins, such as hay-fever, and some skin disturbances, must be accepted as equivalent.

Twenty-two cases are presented where more than one member of a family has been tested on the skin with proteins; 14 pairs of relatives are both sensitive to some protein; in three pairs, both are non-sensitive; in five pairs, one is sensitive, the other not. Of the 14 sensitive pairs, 6 do not react to the same proteins, and the varying reactions correspond to the different clinical symptoms in the individual. In eight pairs who react to the same protein, in five cases the specific protein is a pollen and the identical skin tests are explained by the hay-fever and pollen asthma from which these patients suffer; in the other three pairs giving identical skin tests, all individuals show multiple sensitization, and the test is identical with respect to only one protein. Sensitization to specific protein is not transmitted from parent to child, or from pregnant mother to off-

spring. Parent may be sensitive and child non-sensitive, or *vice versa*. The sensitization is not transmitted even when the asthma seems to be inherited. The skin test is an index of the cause and symptoms of the individual, but bears no specific relation to the family history or to the problem of inheritance. Hence histories of hay-fever patients would seem to give evidence of the inheritance of protein sensitization, when really the identical symptoms explain the identical test, which, since there are only two principal causes, the pollens of ragweed and of timothy, must be identical in at least half the cases and will be identical in an even larger proportion of cases, since ragweed is by far the more common cause.

In the thirty-eight family histories presented, recording ninety-one different matings, the asthmatic tendency behaves as a recessive Mendelian character. Where both parents have asthma or hay-fever, all the children tend to show the condition. Where one parent has asthma and the other is normal in seventeen matings all the children were normal, 60 children in all; in a second group where one parent has asthma and the other is normal but probably simplex, half the offspring are normal and half are asthmatic, really 60 asthmatic to 67 normals. Where both parents are normal, but can be shown or must be assumed to be simplex, there were three times as many asthmatic as normal children, the reverse of the theoretical expectation but explained in part by incomplete records of normal individuals. By the theory that the tendency to asthma is recessive to the normal condition, even the sporadic cases which arise in normal families can be explained on the assumption that the two parents are simplex, and the asthmatic child inherits the character from both parents, the typical recessive expected in one-fourth the offspring of heterozygous parents.

To the practitioner therefore, the family history lends no aid on the individual case of bronchial asthma. With closer methods of diagnosis, the line between true bronchial asthma of the sensitive type and the non-sensitive asthma due to bacteria will be more tightly drawn; the family history will be more accurate, and the number of positive family histories will diminish. Thus eventually only the expected one-fourth of the offspring of normal parents who are capable of transmitting the disease will be reported. From the standpoint of eugenics, the advice against the marriage of two people who have a similar defect, particularly if they are related, holds good; but since over 50 percent of the cases gave a negative family history, this precaution would not prevent a large number of cases.

The nature of the inherited factor is unknown, whether it is the presence of something not found in the normal individual, or the absence of something usually present, all the theories of antibodies and protein split products fail to explain. Since sensitization to proteins is not inherited, it is a tendency or a power to develop asthma which is inherited.

CONCLUSIONS

1. In a series of 400 cases of bronchial asthma, 48 percent gave a history of asthma in the family and 52 percent gave a negative family history.

2. Asthmatics of the sensitive type more frequently give a positive family history than do non-sensitive cases.

3. Asthma is inherited with equal frequency from the family of either parent. An equal number of men and women inherit asthma from the father, but in this series, twice as many women as men inherit asthma from the mother, and 25 percent more women inherit asthma directly from the parents, without skipping a generation.

4. An earlier age of onset is found among patients with a positive family history.

5. Children of asthmatic parents that develop the condition begin asthma earlier than did their parents.

6. There is no distinction in kind, variety, or degree of sensitization to foreign proteins as demonstrated by cutaneous tests, between sensitive patients with a positive family history and those with a negative history.

7. From the family history it is not possible to draw conclusions as to the cause, severity of the disease, prognosis or treatment in any given case of bronchial asthma.

8. Sensitive and non-sensitive asthma run pure in the family histories only occasionally, but commonly both types occur in the same family without distinction or rule, hence, from the standpoint of heredity, these two types of asthma, and also hay-fever and some urticarias and eczemas caused by the ingestion of protein, must be accepted as equivalent.

9. According to cutaneous tests with proteins, members of a family may be both sensitive, or both non-sensitive, or one sensitive and the other non-sensitive.

10. Even when both members tested are sensitive, they are only rarely sensitive to the same protein.

11. Sensitization to specific proteins is not transmitted from parent to child.

12. Sensitization to foreign protein may run in families, but just as frequently it is found in only one member of a family.

13. Even when protein sensitization does run in a family, it is not identical as regards either specific proteins or the clinical symptoms developed among different members of the family.

14. The cutaneous test is an index of the cause and symptoms of protein sensitization in the individual, but bears no relation to the family history or the problem of inheritance. In family histories of hay-fever, different members of a family give identical cutaneous tests because they have the same symptoms; moreover, since there are only two common causes of hay-fever—the pollens of ragweed and timothy—tests and symptoms must be identical in at least 50 percent of the cases, and they will be identical in an even larger proportion of cases because ragweed hay-fever is by far the more common condition.

15. In the family histories presented, where the diagnosis of asthma except in the patients examined in this clinic, is based entirely on the clinical symptoms, the asthmatic condition is found not to be congenital or transmitted by the mother to the foetus or through the milk, but it behaves as a true inherited trait, transmitted in the germ-plasm of both parents alike, and following closely in the family histories the theoretical expectation of a Mendelian character recessive to the normal condition.

16. Where both parents have asthma or hay-fever, all the children tend to develop the condition.

17. Where one parent is asthmatic, and the other parent, although normal himself, has asthma in his family, and hence carries the asthmatic tendency recessive in his germ-plasm, half the children are asthmatic and half are normal but simplex, capable of transmitting the asthmatic tendency to half their offspring.

18. Where one parent is asthmatic and the other is normal and has no asthma in his family, all the children are normal but simplex.

19. Where both parents are normal but have asthma in their families and hence are probably simplex, theoretically one-fourth the children born would be asthmatic, and three-fourths normal; actually in this series, from this type of mating were produced three times as many asthmatic as normal children.

20. Where both parents are normal, but one is simplex, all the children would be normal, but half the children would be simplex and bear the asthmatic character recessive in their germ-plasm. Where both parents are duplex normal, all the children would be pure normal.

21. By the theory that bronchial asthma is inherited as a Mendelian trait recessive to the normal condition, the 52 percent of cases in this series, as well as the 51.6 percent in COOKE's series of 621 cases of sensitization, with a negative family history, can be interpreted. The asthmatic tendency can be transmitted if it is recessive, by individuals who are themselves not asthmatic, and it becomes manifest only in individuals who are duplex with respect to the character, that is, who inherit the tendency from both parents. Hence the tendency might be transmitted by several generations of normal individuals, but there is a theoretical expectation that when two normal persons, simplex with regard to the asthmatic tendency, marry, one-fourth their offspring will be asthmatic.

22. The nature of the inherited factor is unknown, whether it is due to the presence in the germ cells of affected persons of something not found in normal individuals, or the absence of something normally present, all the theories as to anti-bodies and protein split products have failed to explain. But it is the tendency or power to develop asthma, whether caused by sensitization to proteins or not, which is transmitted and not the condition itself.

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