A CONSIDERATION OF THE INFLUENCE OF HEREDITARY AS OPPOSED TO ENVIRONMENTAL FACTORS IN THE GENESIS OF ASTHMA

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I N T R O D U C T O R Y

The word 'asthma' connotes a number of conditions of diverse etiology, characterised by paroxysmal dyspnoea, mainly of expiratory type. Whereas cardiac asthma signifies a dyspnoea, the origin of which lies in a relative insufficiency of the two sides of the hypertrophied heart (Volhard), and the renal variety a terminal event in a train of symptoms arising from a failure of kidney function, bronchial asthma does not necessarily imply primary disease of the lungs or bronchi, but on the other hand, is a symptom of various states not necessarily related to each other. This is shown by the difference in the pathological anatomy of cases reported as bronchial asthma. For instance, there is a report in the British Medical Journal

Nov. 16th, 1935, of a case of what was thought to be typical bronchial asthma which occurred in a patient following a severe electric shock. In this case the post-mortem examination showed dilated bronchi and absence of hypertrophy of the bronchial musculature, whereas bronchial constriction and hypertrophy of muscle are the usual findings. Nevertheless profusion of eosinophiles in the mucoid secretion of the lungs was present as in other more typical cases. Asthma, then, must be looked upon as merely a symptom, and unless otherwise stated in what follows, refers to the true spasmodic or bronchial variety, which, in the opinion of most, is distinct from and unrelated to the types of renal and cardiac origin.

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In recent years the science of eugenics has received increased attention, and new light has been shed on the etiology of many diseases. Old concepts, wherein by the study of pedigrees, the inheritance of certain diseases has been suspected, have been substantiated in many cases by scientific calculation and observation, and in many others, have been contested and proved to be erroneous. Up till now, the results of such inquiries have had their greatest utility in the study of mental deficiency, but such other conditions as epilepsy, epiloia, rheumatism, allergy,

haemophilia, albinism, tuberculosis and cancer have received attention, and although no definite opinions have been forthcoming in the majority of diseases studied, nevertheless new and fruitful methods of approach have been established and data elucidated which will lead ultimately to a more complete understanding of numerous morbid conditions. The importance of the respective parts played by nature, in the form of heredity, and nurture, by the influence of environmental conditions, and each in conjunction with or opposed to the other having been ascertained, attention will be orientated in the direction most likely to be fruitful in combating the influence at fault.

Since asthma became recognised as a clinical entity, it has been observed by clinicians as well as by the laity that the disease shows a distinct tendency to run in families and in successive generations; and speculations have been made repeatedly as to inheritance. Such great early authorities as Sir John Floyer (1698) Hyde Salter (1868) and Cullen (1784) maintained that the majority of asthmatics inherited their trouble from their predecessors. Sir John Floyer (1) said " As my asthma was not hereditary from my ancestors, so, I thank God, neither of my two sons are inclined to it, who are now past the age in which it seized me." The implication to be made is that Floyer recognised two types of the disease, the hereditary and the sporadic. At the present time, the

same views are held, but the greater emphasis is laid on the hereditary aspect, especially by the American workers, and the sporadic type considered unusual. The result of this conception has been the adoption in many cases of a fatalistic attitude towards the disease, with consequent delay in seeking advice and with unnecessary suffering by many affected individuals.One is not infrequently confronted by the statement, "Of course, my mother suffered from asthma" as if to say that under such circumstances it is only to be expected that the patient should be similarly affected, or, as Rackemann(2) says"The origin of the capacity to develop hypersensitiveness is partly concerned with heredity and there is little to be done about it." An attitude such as this in a patient suffering from an ailment which almost always is accompanied by a state of expectancy and apprehension is obviously prejudicial to treatment and the good health of the individual.

It is proposed in this thesis to inquire into the parts played by heredity and environment respectively in the etiology of asthma, with the hope that the responsibility of each of these factors may be more correctly evaluated and treatment adopted accordingly; or in the instances where heredity is important, "if," as Penrose (3) aptly remarks, "we can by artificial means neutralise the injurious hereditary effects, the importance of heredity from the medical point of view is very much diminished."

HEREDITY

In the consideration of the question of heredity as a fundamental factor in the pathogenesis of any disease, the study of pedigrees may lead to erroneous conclusions as the result of faulty methods in the selection of data. The occurence of a morbid condition in more than one member of a family can only raise the suspicion of heredity, but of itself is no proof. This may be well illustrated in the instance of leprosy. Before it was discovered that leprosy was the result of an infection by a specific bacillus, it was universally maintained on account of its familial occurence, that it was a hereditary disease, and in some parts of the world legislation was introduced to prevent propagation of affected persons by castration. The discovery of the true causal agency in the lepra bacillus transferred the major responsibility to the infective environment, with consequent alteration in the outlook, and increased emphasis on prophylactic methods. Again, environmental influences are more prone to exercise their effects on groups of people living in proximity and under similar conditions, so that the presence of any abnormality manifested as a familial peculiarity may be only an expression of faulty environment exerting its influence on many people simultaneously. Thus, in the lower animals, the well-known example of Drosophila, the fruit fly, may be cited. When grown in an atmosphere of moisture, Drosophila develops

the pathological condition called 'vestigial abdomen', whereas in the more natural dry conditions, development results in the formation of the perfect species. Whereas, for many obvious reasons, it is difficult, if not impossible, to demonstrate directly and conclusively environmental and hereditary factors in the case of the human species, the problem in the simpler animals is not so difficult, and from the results of these, inferences may be drawn which can be considered applicable to man.

The investigation of the question of heredity may be approached cheifly in two ways. The first method consists of the critical study of a large number of pedigrees in which the morbid condition occurs. Here the investigator sets out to determine the frequency of occurence of the morbid condition in the various members of the family as compared with its frequency in a sample of the population chosen at random; and its mode of transmission from generation to generation. The decision as to the heritability of the condition rests on the discovery of certain numerical ratios between affected and unaffected members. In such an enquiry, it is important to remember that an unduly high ratio may be obtained by considering in the survey only those families wherein the condition occurs frequently, and only those branches of the family with at least one affected member. Individuals

suffering from a particular disease are more likely to have their attention called to the existence of the same ailment in relatives, than non-sufferers. The recording of family histories must, then, be critical and unbiassed.

In the second method, the presence of a particular biochemical or morphological variation from the normal occurring in the siblings constitutes the basis for determining the presence or absence of the disease. This is well exemplified in the condition called 'familial acholuric jaundice'. Here latency of the disease in the siblings may be confirmed by the investigation of the "fragility" of the red blood cells. While failing to manifest the more obvious symptoms of the disease such as jaundice and enlarged spleen, members of a suspected family may possess bloods which become laked in a solution of sodium chloride of a specific gravity higher than that which lakes the cells of normal blood, thereby affording proof of the presence of the disease.

In the method of pedigree studies, additional information may be acquired by studying the incidence of the disease in members of twins. Additional evidence of the inheritance of a particular trait, morbid condition, or diathesis can be adduced also from observations on the transmission from generation to generation of characters known to be hereditary, such as the colour of eyes, and the blood groups with which the matter under consideration might

be associated.

In the elucidation of the problem proposed here, each of these methods of inquiry will be used, and its value assessed relative to the subject.

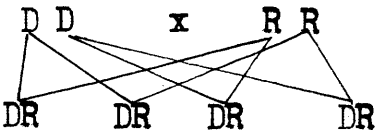
The numerical ratios referred to in pedigree studies are those based on the hypotheses of Mendel. Although the classical experiments of this pioneer were made early in the second half of last century, it was not until the commencement of the present one that their great importance was realised. Since then his theories have received increased application. His experiments were made on plants and by the workers who succeeded him, on simple animals; and although it is manifest that breeding experiments as performed in plants and animals cannot be applied in humans, nevertheless, the truth and implications of these results have been accepted as applying also to the human species.

The experiments based on Mendel's work demonstrate that certain characteristics of a species are transmitted through successive generations by agencies or particles called "genes", located on the chromosomes. To this the name "particulate inheritance" has been given. The exact geographical distribution of the genes has been located on the chromosomes of simple animals; in the case of the higher animals however, this has not been achieved owing to the

large number and complexity of the chromosomes, which in man, for example, reaches the large number of twenty- four pairs. There is no reason to doubt that the theory of particulate inheritance is applicable also to the higher animals, and proof of the inheritance of a particular character rests on the ability to demonstrate the passage of the gene carrying the character from one generation to the succeeding one. This latter can be achieved in practice by establishing the numerical ratios by the Abbot Mendel in his breeding experiments and may be discussed briefly in the following:-

By means of self-pollination through a succession of generations, Mendel was able to obtain pure races of tall and dwarf plants.

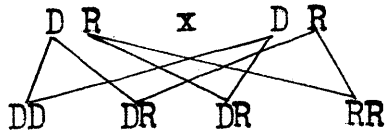
If the factor for tallness is represented by D in each gamete, the zygote formula for this property may be written as DD, and in the language of genetics described as homozygous for factor of tallness. Similarly, pure dwarfism may be represented by the formula RR. If, now, pure talls are pollinated by pure dwarfs, the second generation will be tall but impure, hybrid, or heterozygous for tallness.



In other words tall is dominant to dwarf.

Pollination by two members of F1 generation will give the following results:-

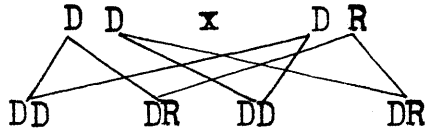
F (2)



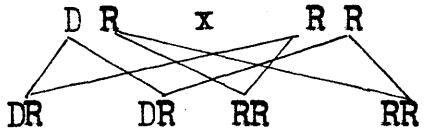
— 75% talls
25% dwarfs

Of these, 25 per cent are homozygous talls, 50 per cent heterozygous talls and 25 per cent dwarfs.

Other combinations may be written thus:-



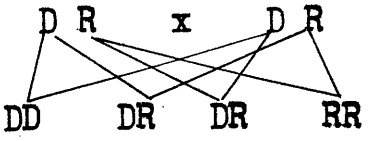
— 100% talls
50% homozygous
50% heterozygous



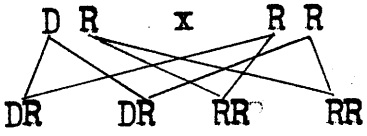
— 50% talls, heterozygous
50% dwarfs, homozygous

In the case of recessivity, the recessive trait must be present in both parents before the character can ve manifested in the offspring. The sudden appearance of any property in several children, in the absence of manifestations in the parents, is strong presumptive evidence of a recessive factor, provided of course, nurture can be excluded.

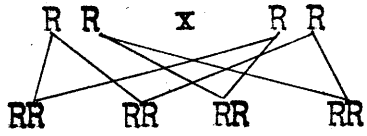
The formulae may be written as follows:-



— 25% recessives, homozygous.



— 50% recessives, homozygous.



— 100% recessives, homozygous.

To summarise:-

The law of heredity requires that the offspring of parents exhibiting a dominant trait should show the trait in the following proportions:-

(1) 100% if one or both parents are homozygous.

(2) 75% if both are heterozygous.

(3) 50% if one is heterozygous and the other does not carry the trait.

and in the case of recessivity:-

(4) 25% if both parents are heterozygous.

(5) 50% if one is homozygous and other is heterozygous.

(6) 100%if both are homozygous.

The assumption that a particular disease or group of diseases is hereditary in nature, can be proved only if the author is able to obtain an incidence of morbidity in the family approximating to the ratios enumerated above.

It is proposed now to examine the etiology of the disease since any view regarding the heredity of asthma must be in accordance with the known theories of causation.

ETIOLOGY.

Many theories have been advanced to explain the ultimate factors constituting the basal state predisposing to paroxysms of bronchial asthma.

THE EXUDATIVE DIATHESIS was proposed by Czerny of Germany. The term denotes a tendency to exudative processes in the skin and mucous membranes, and is exemplified by urticaria, eczema, conjunctivitis, asthma and convulsions. Lapage (4) considers exudative symptoms as outlets for metabolic errors, from which it may be concluded that environment plays a more important rôle than heredity in the causation of the syndrome. The term does not connote a fundamental state, but rather the

expression of many.

THE AUTONOMIC SYSTEM. Eppinger and Hess attempted to elucidate the problem of asthma and allied disorders by postulating imbalance of the opposing components of the vegetative nervous system. Their conclusions were based on experiments using adrenaline, atropine and pilocarpine. Asthma, they say, is a manifestation of vagotonia as opposed to sympatheticotonia, the disturbance resulting from an underdevelopment of the chromaffin tissue and overgrowth of lymphoid tissue. Cases of pure vagotonia or sympathetic-otonia are rare, the individual showing symptoms of over-action, frequently also evidencing the signs of deficient activity elsewhere. Thus, while the asthmatic paroxysm is considered by the majority to imply a vagotonia affecting the bronchial muscles, the cause of death during an asthmatic attack is believed by many to be the result of vagal inhibition. Christopherson (5) blames autonomic dysfunction for chronic bronchitis and asthma, the inco-ordination resulting from disordered nutrition (6) and C. Paget Lapage (7) subscribes to the view of autonomic dysfunction by suggesting a sensitive autonomic nervous system for allergic phenomena. Lapage believes the fault is mainly an hereditary endowment but considers that in many cases the production of sensitization results from overloaded metabolism (see under toxaemia). Hyde Salter, too, thought asthma was characterised by a

general irritability of the nervous system commonly caused by diseases of the lungs. Imbalance of the autonomic nervous system is found in conditions other than asthma and totally unrelated to it, and so with regard to the problem under discussion cannot be considered an entity.

L'ARTHRITISME. The French apply the term "L'ARTHRITISME" or Neuroarthritic diathesis" to describe the ultimate mechanism by which the predisposition or diathesis operates, but as in the case of the autonomic system this conception offers little help in the solution of the problem.

ENDOCRINES. In close relation to the autonomic nervous system, the endocrines fall to be considered. These have been incriminated by a majority of workers, (Kern, Levy, Gallino, Terrada, Maranon, et. al.) (9). It is conceded by them, however, that not all cases of asthma result from irregular action of these glands. No intimate association between asthma and sub- or hyperthyroidism has been adduced. The same applies to the pituitary, while thymic asthma is a condition distinct from the bronchial variety. Witts has investigated the endocrine factor is 500 cases of asthma, 350 of whom were over the age of fifteen years and his figures were (10) :-

Myxoedema (Active) ..... ·6%
Hyperthyroidism (arrested)..... ·2%
Frohlich's Syndrome ..... ·4%
Diabetes mellitus ..... ·2%

The gonads have a more intimate influence. It is well known that the sexual epochs in an asthmatic's life often corresponds to periods of aggravation or amelioration of the severity of the condition, and this more particularly in the female in whom the state of activity of the gonads is more easily apparent. It is agreed, however, that the gonadal activity or inactivity cannot of itself initiate the asthmatic state.

There is much evidence to support the theory of adrenal dyscrasia. Prov. Burn, in an address to the Royal Society (11) suggested an insufficiency of the adrenals as the underlying condition. Conclusive evidence from post-mortem material is lacking, probably because the demonstration of any but gross changes in those glands is beset with enormous difficulty. James Adam (12) has reported the findings in the adrenals in three asthmatic deaths in which extensive damage to these glands was present, but in a fourth case (No. 59), in the examination of which I was associated with Dr. Adam, no gross or microscopic deviation from the normal could be discovered. The dramatic relief afforded to the sufferer from an acute attack by the hypodermic

injection of adrenaline suggests hypoadrenalinaemia, but Kuntz (13) maintains that the relief obtained from adrenaline is the result of constriction of the vessels of the bronchial mucosa. Pigmentation of the skin so commonly seen in the chronic asthmatic raises the same question. But asthma, or allied diseases is a rare concomitant of Addison's disease, the pathological basis of which is disintegration of the adrenals. Recently, a reference in the British Medical Journal (14) expressed the view that adrenaline circulating in the blood exerts an antitoxic action on the system, and vice versa; it is maintained by others that toxaemia exhausts the adrenals. Garretson (15) associates asthma with neuro-endocrine disturbance and considers hypoadrenia the cause of asthma. He comments on the toxic look of allergic people, and refers to the pigment frequently observed in the skins of asthmatic patients. Evidence is adduced from observations on frogs, the depth of the pigment in the chromatophores in these amphibia having been traced to adrenal activity.

The problem of deficiency of circulating adrenaline is being approached by various methods, but none has yet proved sufficiently delicate and reliable.

Many observers believe that multiple agencies

operating simultaneously are responsible for the syndrome produced. Von Strumpell (16) thniks that asthma is a manifestation of a certain type of constitution appearing in individuals with a pronounced psychopathic or nervous irritability, who exhibit a tendency to exudative processes all over the body, as a result of external or internal stimuli of not unusual nature. Hofbauer (17) states that asthma is the expression of disturbed respirations in a person exhibiting weakness of the peripheral circulation which he calls "Angiotonie" He says "Die Asmatiechie Anfall ist demgemäss aufzufassen als Folge der angiotonen Reaktion der tieferen Atemwege auf Reize, welche beim Fehlen von Angiotonie als unterschwellige keine nachweisbare Folge nach sich ziehen."

Increase in amino acids of the blood has been reported on by Adam(18) Oriel (19) Cameron (20) McDonagh (21) identifies the paroxysm of asthma with disruption of the ionic balance of the blood caused by toxaemia and manifested by increase in size and clumping of the colloid particles of the blood together with decreased Brownian movement. An investigation of the calcium content of the blood of asthmatics has revealed no deficiency (22). Alteration in acid-base balance has been shown by numerous investigators. Following on the work of Tiefensee (23) a condition of alkalosis has been suggested particularly by supporters of the allergic theory. That this is based on insufficient

evidence has been proved by Adam(24) Cameron (25) Oriel (26) and Kenneth Phillips (27) by whom investigations of the alkali reserve have been performed. A low carbon-dioxide combining power of the blood together with increase of the ammonia-combined acid offers convincing evidence of the tendency to acidosis.

In none of the above hypotheses has evidence been found to justify the view that heredity, in the Mendelian sense, plays a major role in the establishment of the asthmatic constitution, nor has it been substantiated by those who stress neurotic disabilities.

Psychological Factors. In the major psychoses bronchospasm is not more frequent than in a random sample of the population; perhaps less so. In many hundreds of patients admitted to the mental wards of a general hospital I have seen only two cases. In one patient treatment of an infected maxillary sinus brought about recovery from both the asthma and the toxic confusion. In the other, attacks were infrequent and did not occur during her stay in the asthma ward. (case 29)

Case No. 75. Female, aged 21, employed as waitress in a smoke-room. Asthma of two years' duration. Admitted from mental wards, where she was being treated for confusional insanity. Operation for appendicitis in 1934. After drainage of the maxillary antra which contained pus and reduction of enlarged turbinals, recovery from both the mental condition and the asthma occurred. A brother, sister and paternal grandmother are asthmatics.

Perhaps sympathetic preponderance in these cases renders the manifestation of bronchospasm unlikely. In the neuroses or psychoneuroses, asthma is more frequently encountered. The state of heightened nervous tension in asthmatics has already been mentioned. In children, a history of attacks at times of excitement, such as prior to school examination or a children's party, is often obtained, while in adults, worry and emotional upsets are known to be harmful influences. These, however, appear to act as exciting causes, rather than determinants, and in some cases conform to a type of conditional reflex. In the neuroses and psychoneuroses still more subtle psychological processes are said to be active and at times, primary, the asthma arising as a result of subconcious mental conflict, the present locus of the ailment having been suggested by a situation in which difficulty of breathing has occurred. Cures by psychoanalysis or anamnesis have been claimed. Cases of pure psychic origin are admittedly unusual, but have been reported by J.A. Hadfield (28) Millais Culpin (29) Karl Hansen (30) Moos and Strauss (31).

Kuntz (32) says that temporary psychic and emotional disturbances of a purely functional character in many instances also are accompanied by parasympathetic hyperirritability and Hoff and Werner (33) maintain that

the threshold between autonomic and psychic centres is appreciably lowered in neurotic patients, leading to obvious disabilities. Of interest here, also, is the finding that asthmatic children show a higher level of intelligence as measured by the Binet-Simon scale than normal children of comparable age, and this in spite of the greater amount of absenteeism from classes (34).

Assuming that the concept which regards asthma as a respiratory neurosis is acceptable, does an enquiry into the inheritance of the mental disorders help to solve the question? It is common knowledge that there are families in which the incidence of major psychoses (Schizophrenia and manic-depressive) is high. A hereditary factor has never been proved to be the rule in these cases; rather it is acknowledged that faulty home conditions caused by greater or lesser degrees of mental inaptitude in parents predisposed to the evolution of psychotic states in children. The same holds good in the minor psychoses in which asthma is not infrequent, and similarly also for the more simple highly-strung, unstable, nervous types. It is almost an axiom that a nervous temperament in the parent is reflected in a similar disposition in the child, for even at a very early age the infant becomes conscious of instability and nervousness in the parents, particularly in the mother. The psychological

factor in asthma has been referred to by Langdon Brown, Gillespie, McDowall, Ziegler and Elliott (35), and it is believed by Gillespie that asthma may in some cases be a true respiratory neurosis. Berkart (36) concluded that an inherited neuropathic constitution was the basis of all asthmas, but for the foregoing reasons, and without necessarily invoking heredity, it is not difficult to understand why children of mentally unstable parents should be more susceptible to those ailments which are characterised by faulty inhibition. It may be this latter which is largely responsible for the "inherited autonomic dysfunction" considered to be so important by Lapage (see page 12).

VASOMOTOR SYSTEM. Instability of the vasomotor system is a theory advanced by Alexander Francis (37). The author maintains that the sensitive vasomotor system is easily upset by emotions and by peripheral reflexes, and particularly by a condition of hyperpyraemia or excess of heat-producing substances in the blood (Francis Hare). These latter are produced by faulty circulation causing insufficient oxidation of the products of digestion. Benefit is achieved by stabilisation of the vasomotor system, by exercise, etc., and cauterisation of "asthmogenic areas" in the nose. The author attaches little or no importance to the hereditary factor.

ALLERGY. Reference has already been made to the rôle of allergy, atopy or hypersensitiveness in the pathogenesis of asthma. Allergy was defined by Von Pirquet (1906), with whom the conception originated as the result of his observations on the tuberculin reaction as follows:-

"The capacity to react in an abnormal way to contact with foreign substances". (38)

He named the condition "Reaktionfähigkeit". Coca (39) in 1922, considered "atopy", which means " a strange disease", a more suitable name to describe the phenomena which characterise the condition, namely, contraction of smooth muscle and vascular exudation; and considered asthma and hay fever to be the two atopic diseases. More recently, the term atopy has been adopted to signify hypersensitivity which can be transmitted from one individual to another. (Conybeare, 40). Here the term 'allergy', which is better known, will be used.

With many, the word 'allergy' implies heredity. In Coca's (41) definition of atopy, the term atopy has been coined " to designate those clinical forms of hypersensitiveness in man which are hereditary in nature" and the importance he ascribes to heredity in asthma is easily understood from his definition of bronchial asthma as follows (42) :-

" Bronchial asthma may be defined as that form of ATOPIC illness which manifests itself in recurrent attacks of paroxysmal dyspnoea particularly pronounced in the expiratory phase".

Others, while considering allergy essentially hereditary, admit at the same time that the hypersensitivity may exceptionally be acquired (43). Others, again hold that whereas the capacity to become allergic may be transmitted from generation to generation, the allergic manifestation is almost always the result of faulty environment (44).

It will be convenient to study the nature of allergy as a basis for further inquiry.

The observation that the emanations from animals or inhalation of pollen dust may provoke an attack of asthma, was made many years before Richet's experiments on anaphylaxis. Hyde Salter (45), himself a victim of cat asthma, referred to emanations from animals as an important extrinsic cause of dyspnoea. Again, urticaria has long been associated in the lay mind with the ingestion of certain types of food, particularly shell-fish and strawberries. Accordingly, following on the work on anaphylaxis by Richet, and hay fever by Blackley and Dunbar, observations

were recorded in many parts of the world resulting in the conclusions held at the present time, that

(a) many morbid conditions are caused by hypersensitivity or idiosyncrasy to the ingestion, inhalation, injection, contact or parenteral administration of a large number of foreign proteins or even as a result of physical agencies.

(b) that these pathological conditions tend to occur in the same allergic individual, in members of the same family, and in predecessors and descendants; or, in short, that the allergic condition is hereditary.

The original conception of the inheritance of a specific condition such as asthma, hay-fever or eczema, has been superseded by the view that what is inherited is the capacity to become sensitive or allergic, while recognising that a particular manifestation of the allergic complex when present in a parent, is more likely to be reproduced in a child than any other allergic manifestation (46); or, as Coca (47) says, " Heredity exercises its influence on the 'shock' tissues independently of antibodies".

The conditions embraced by the nosological term " allergy" are many and the number is being enlarged from time to time. Proof of the allergic nature of many members

of the group is indeed very flimsy and lacking substantial foundation, while in others, an allergic etiology can be proved only in a proportion of the cases. The list includes the following:-

Asthma
Hay-fever
Urticaria
Eczema
Migraine
Food upsets
Angioneurotic oedema
Vasomotor rhinitis
Drug allergy
Physical allergy
Dermatitis venenata
Serum disease
Epilepsy
Haematuria
Mucous colitis
Enuresis and Dysuria
Cyclical vomiting
Dysmenorrhoea
Rheumatism

Sensitivity to a particular substance arises in susceptible individuals when that substance is introduced into the body some time after a previous exposure to it. When no previous exposure can be proved, it is assumed that in many cases the noxious substance or allergen has gained entrance to the foetus through the placental circulation. There are many instances where no previous exposure could have been at all likely. These include reactions to drugs, poison ivy and serum disease. In these cases it is difficult to reconcile the manifested phenomenon with this hypothesis.

The points of entrance of the allergen are many and

various. In children, the alimentary tract is said to the common one; in adults, the respiratory tract, while the different layers of the skin or the blood vessels may at times be the portal of entry. The exact mode of action of physical allergy(Duke), and whether or not the physical agents may be called specific allergens, is still in doubt.(48) The presence of the offending substance in the tissues, circulating fluids or both gives rise to the formation of specific antibodies, called 'allergens', which differ from antitoxins in one important essential, namely, that they do not contain precipitins. · These antibodies or allergens become attached to particular tissues, and when allergens are introduced into the body, a reaction takes place in those tissues which expressed as asthma, hay-fever, urticaria or other disorder. Coca (49) calls the site of the reaction the "shock organ", and while maintaining that sensitivity and not the specific allergic disease is passed on from generation to generation, he also asserts, as do others, like Balyeat, that there is tendency for the sensitivity of the particular shock organ to be transmitted also.

As has been mentioned previously, the modern conception of allergy originated as an outcome of the skin reactions noted by Von Pirquet when he injected tuberculin subcutaneously, and by Dunbar, recorded similar reactions

with pollen extracts. These skin tests nowadays constitute the principal means of detecting or confirming sensitivity in suspected individuals, and in researches in heredity, of discovering latency in related persons. Allergists maintain that whereas positive responses to skin tests may be expected in a maximum of 10 per cent normals, in allergic individuals and their relatives estimates varying from 25 to 95 per cent may be obtained, the number depending on the technique of the author, the number of reagents employed and the type of allergy, viz.

Rowe, 400 reagents used ...	91%	(50)
Brown ...	83%	"
Meyer ...	76%	"
Coke ...	58%	"
Thomas ...	70%	"
Cooke ...	73.4%	(51)
Larson and Bell ...	44%	(52)
Rackemann ...	45%	"
Walker ...	48%	"

Average of forty-four observers, 11,443 cases of allergy, positive reactions occurred as follows (53):-

Hay-fever ...	93.2%
Vasomotor rhinitis	55.7%
Eczema ...	52.7%
Asthma ...	52.7%
Gastro-intestinal allergy	26.5%

It has been supposed, therefore, that the difference between allergic and normal individuals lies in the greater

capacity of the former to become sensitive, and is evidenced by the increased incidence of positive skin reactions in them. Doerr (54) says "The capacity to become sensitive is present in all human beings in merely different degrees depending on disposition and exposure"; and argues against a distinct separation between allergy and asthma according to their dependence on heredity. He refers to Ancona's cases to support his arguement. (vide infra.)

Adequately controlled experiments have not yet been completed. A recent investigation by Pearson (55) gives the following results for skin reactions.

Normally healthy adults ... 20% positives
Asthmatics ... ... 75% Do.

It is believed by many that the incidence of allergy in the general population is greater than is usually supposed. Vaughan (56) concluded from an investigation of an isolated community that the incidence of minor allergy amounted to as much as 50 per cent, but more persistent forms were less frequent. (10 per cent.)

The phenomena of the allergic reactions as manifested by skin tests are imperfectly understood. Adequate reasons have not been advanced to explain the presence of positive skin reactions in subjects in whom the absence of clinical

sensitivity is beyond doubt and to substances with which the individual has never come in contact. Nor can an explanation on a hereditary basis be offered for the variable response of closely related persons exhibiting allergic symptoms. Examples are not infrequent where, with what is presumably a strong hereditary taint, a person may show evidence of hypersensitivity and fail to react to tests, or where non-reacting parents have strongly reacting children and vice versa, or some affected members of a family may exhibit positive cutaneous tests while other members clinically sensitive do not. Moreover, the allergic hereditary theory fails to explain the considerable number of cases of frank allergy with negative family history. Outstanding examples of the development of asthma accompanied by positive cutaneous reactions and the presence of reagins in the blood are recorded where the family history is completely negative. Thus, laboratory workers handling ascaris manifest positive skin reactions to the intradermic or hypodermic injection of ascaris extract — (Casoni Reaction) — and many suffer from asthma (57). Ancona's cases are even more striking (58). In Florence an 'epidemic' of asthma was investigated by Ancona. It was noted that all those who were working with grain infected with the mite, pedicolosis ventricosus, developed asthma or dermatitis or both. Positive skin

reactions were obtained. These results have been confirmed by Storm Van Leeuwen(59). In these cases, although typical of allergy, there was no question of heredity. Finally, the average eosinophilia in asthma has been found to be as high in the non-allergic as in the allergic (60).

These findings support the contention held by many that allergy is not necessarily a hereditary condition.

For the evaluation of the skin tests as popularly applied, Cooke's postulates (61) may be quoted here.

"1. Sensitisation must be demonstrated by one of the following:-

a. A positive local reaction, cutaneous or ophthalmic.

" b. The original allergic manifestation must be artificially reproduced at will on introduction of the substance, inhaled, ingested, or injected.

"2. It must be shown that the individual has come in contact, in some way, with the suspected substance in order to permit it to act as an aetiologic factor.

Regarding the above, it is conceded by most allergists that under certain conditions, the cutaneous tests cannot be elicited. Bray (62) states that it is notoriously difficult to elicit skin reactions in children after they have been in hospital for a few days, and A.J. D. Cameron (63) and others affirm that following detoxication,

individuals may no longer react positively to foreign proteins to which they have previously shown a marked response. Skin tests in angio-neurotic oedema, drug hypersensitiveness and urticaria are according to Coca(64) almost always valueless. The same applies also to eczema.

That many people suffering from the various so- called allergic diseases are sensitive to animal emanations and dusts cannot be refuted. On the other hand that all who manifest a positive skin reaction to animal dander are sensitive to that substance, is just as untrue. Van Leeuwen (65) records that 67 per cent of asthmatics give a positive response to horse dander although so-called horse asthma is very rare. The patient who is immediately seized with a paroxysm of asthma in proximity to a cat or horse is seen from time to time, although but seldom. James Adam (66) records that he has not seen a single case of cat asthma in sixteen hundred cases of asthma. From the immunological point of view the manifestation of the Prausnitz-Küstner* reaction offers

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* Prausnitz- Küstner reaction is the passive transfer of allergy and is carried out by injecting intradermally into any individual serum from the person to be skin-tested. The skin of the recipient now becomes locally sensitive. The subsequent injection of an allergen will produce the formation of a wheal at the site of the injection.

Convincing evidence of a substance circulating in the blood of the patient which is closely associated with the exhibition of the clinical condition. But what of the asthmatic who, after repeated and exhaustive tests fails to evidence a positive response? Is the asthma from which he suffers of a type fundamentally different from the allergic variety? The value of the skin tests can be measured by the efficacy in its application to clinical medicine. James Adam (67) says he uses skin tests when he needs them, which is not often, Garretson (68) considers skin tests a waste of time, and James Maxwell (69) found only a few positive reactions with scant success on avoidance. Lastly, Van Leeuwen states that " Although positive reactions were found in practically all our cases of asthma it was relatively seldom possible to incriminate one of the known allergens as the causitive agent of the attack (70).

While accepting the results of these investigators who have found an increased incidence of positive skin reactors in hypersensitive people and their relatives, it is nevertheless my opinion that the interpretation of these results is in some part fallacious and that they afford insufficient evidence of the inheritability of allergic conditions and of its etiologic importance. Families there undoubtedly are, in which heredity can be invoked, but these are in the minority and in them the hereditary factor can be

minimised by concentrating on the correction of the prejudicial effects of various extrinsic influences (V.infra).

Treatment based on the theories of sensitization has proved disappointing, and on this account as well as for the reasons discussed above, discredits in great measure, the assumption that allergy is a fundamental state. Coca (71) expects a maximum of only 30 per cent cures or relief lasting for years with desensitization or avoidance, a figure not any higher than that obtained by simple hygienic regime (72). Van Leeuwen (73) stated that it was seldom possible to incriminate one of the known allergens, although he found positive skin reactions in practically all his cases, and Hurst (74) attaches little value to cutaneous tests and desensitization. Avoidance of the suspected food-stuff or inhalant has given disappointing results on the whole (75). But more striking than this is the fact that desensitization does not appear to modify tolerance as shown by the intensity of the skin reaction (76). Most authorities have accordingly reached the decision that allergic phenomena are merely the expression of a more fundamental condition (Coca, 77, Rackemann 78, Adam 79, Cameron 80, Peshkin 81, Witts 82, McDonagh 83, Connybeare 84, et.al.)

With the adoption of this view, the value of such data such as increased frequency of positive skin reactions

amongst relatives, as evidence of heredity, must be materially diminished.

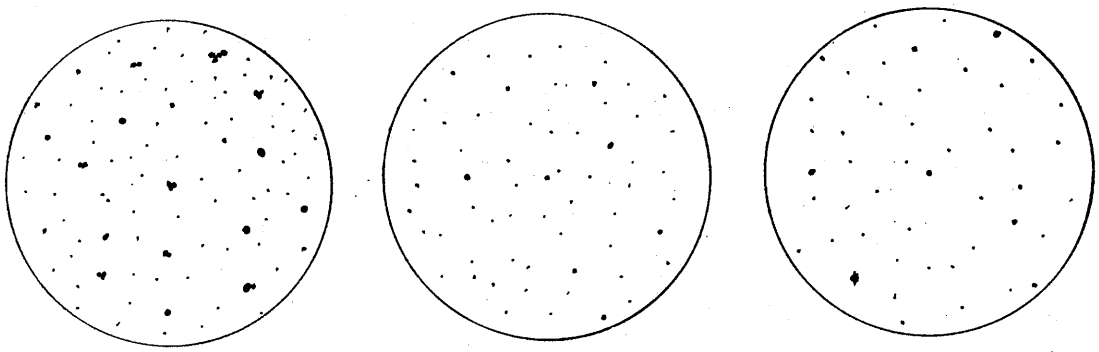
With the exception of Kahn(85) who maintains that all cases of asthma show a hereditary incidence of 100 per cent., it is freely acknowledged by all students of the subject that environmental conditions play a greater or lesser role in the origin and maintenance of the asthmatic proclivity. In the proportion as the environment receives greater or less emphasis in the pathogenesis of bronchial asthma, so the importance of the hereditary factor may be evaluated. It is now proposed to discuss the principal environmental influences associated with the development of asthma. It may be remarked at this juncture that from the moment conception takes place, the zygote at once comes under the influence of the environment through the maternal and placental circulations. The faults in nutrition and vitality of the mother are consequently reflected in the state of health of the offspring, and conditions of hypersensitivity as of immunity in the mother, may be transmitted to the foetus without necessarily invoking particulate inheritance. This has been proved by Rosenau and Anderson Walzer and others(86) in their experiments on anaphylaxis in animals and allergy in man. A similar process occurs also in the case of breast feeding(87). A distinction must therefore be made between inherited and congenital hypersensitivity;

and when one remembers that, according to Bray(88), heredity is twice as important when the mother transmits than it is when the father is the antecedent, one may reasonably suspect that placental, in contradistinction to germinal transmission, is to be incriminated in many cases, and due allowance made in statistical studies. To assess even approximate figures to the placental origin of hypersensitivity is obviously impossible.

The first of the environmental conditions to be discussed in view of its and value in treatment is toxaemia.

TOXAEMIA or TOXICOSIS. First proposed and elaborated by James Adam at the beginning of the century, this theory has since then gained many adherents. Burton Haseltine(89),La Forge,(90) Cameron (9I),McDonagh (92), Wolfe (93),Jordan,(94) Naish (95), Lapage (96)and others have corroborated from their extensive experience the successful results to be obtainedby paying attention to the general hygiene of the body, and my own sreies of cases has impressed on me also its very considerable value. Toxaemia as a factor in the genesis of pathological conditions, has to a large extent fallen into disrepute. The trend of medicine to-day, is to evaluate of a theory in proportion as that theory receives greater or less substantiation from physiological, pathological, or biochemical findings. A condition like toxaemia can occasion few changes sufficiently

gross to manifest themselves by such tests. Mitchell (97) has affirmed, however, that in bronchospasm, the test for indicanuria is frequently so marked as to be outstanding, and McDonagh (98) and others have shown that in intestinal intoxication, as in toxaemias of other origin, the colloidal particles of the blood, when examined by ultramicroscopy, are usually enlarged, massed together, and relatively



(a) (b) (c)

Colloidal particles of the blood as seen in dark ground microscopy

(a) during the asthmatic spasm
(b) 15 minutes after adrenaline
(c) 75 minutes after adrenaline

immobile. While not having been able to examine bloods in the preparoxysmal stage, on two occasions I have compared the sera during the paroxysm, a quarter and one and a quarter

hours after the administration of adrenaline and in both cases I was able to note that with the resolution of the spasm, a greater degree of dispersion occurred, with increased Brownian movement of the colloidal particles. Jordan (99) has X-rayed the intestinal tracts of asthmatic patients and has demonstrated stasis of the bowel. He has reported successes by attending to this disturbance. He concludes, in agreement with others, that intestinal toxaemia is in many cases largely responsible for asthma. Clinically the signs of toxaemia are no less striking. The coated tongue, dry pigmented skin, chloasma under the eyes and constipation are usual in chronic sufferers, and their disappearance with general hygenic measures, serves only to accentuate their prior condition by contrast.

Toxaemia may be described as a condition of chronic intoxication of the body, which manifests itself clinically as lowered vitality and physiologically as a defective power to secrete hormones and enzymes necessary for the assimilation and utilisation of food materials and the excretion of waste products.

Referring specifically to asthma, Adam (100) epitomises as follows:-

"Asthma is primarly a toxaemia.
This toxaemia arises partly in the bowel, partly in the tissues; it arises partly by absorption of nitrogenous poisons resulting from intestinal

"putrefaction under microbic action; but mainly is due to an error in nitrogenous metabolism, the result of imperfect oxidation or enzyme action. In short the poison arises from protein food or protein tissue.

"The error in protein metabolism is closely connected with excess of carbohydrate in the diet.

"The oxidation of the excess of the simpler carbohydrate molecule seems to interfere with proper oxidation of the more complex protein molecule. In other words, the excess of energy-food interferes with the metabolism of the tissues and tissue-foods; the imperfectly metabolised products so resulting, set up asthma.

"The toxaemia, whether arising in bowel or tissues or both, tends to show itself first as catarrh, later as spasm, in the respiratory tract. This toxaemia shows itself in conditions, catarrhal and spasmodic, other than, but closely related to, asthma."

That excessive carbohydrate is important in the production of catarrhal states has been expressed by others. Alexander Francis (101) refers to "hyperpyraemia or excess heating substances (Hare)" as an irritant of the vasomotor system. Paton (102) has furnished cogent evidence that the increased consumption of carbohydrate is responsible for the great incidence of catarrhal conditions of the upper respiratory tract. When it is remembered that the consumption of concentrated carbohydrate has increased enormously during the past half century, and that metabolic diseases like asthma and diabetes have become much more frequent also, it is easy to associate the increased frequency of these diseases with the greater intake of carbohydrate. True it

is, as is pointed out by Adam (103), that the incidence of asthma and, incidentally hay-fever, varies with the race, and those races in which asthma is absent or infrequent have been shown either to spend the greater part of the day outdoors or consume a diet in which concentrated carbohydrate does not bulk largely. These races include Eskimos, Indians of the American reservation, Chinese, Manchurians, and the Aborigines (104). Rackemann (105) cannot understand why hay-fever is found more frequently in the eastern than the western states of America, and why in the latter, the condition is treated with so much more success in spite of disadvantageous geographical conditions. Does not the answer lie in the habits of the people living in these districts? The eastern states are characterised by large cities, tall buildings and indoor amusements derived principally from theatres, cinemas, ets., while the consumption of carbohydrate as candies and chocolates is considerable. Food in excess of energy requirements, resulting in insufficient and improper combustion combined with lack of outdoor exercise might be invoked with justification and in agreement with Adam (106) Paton (107) Francis (108) et alii. Important here is the statement by McDowall (109) that when an individual is at rest, vague activity is at its maximum. In plants, too, over-nutrition prejudices proper development, its effect causing "fasciation or flattening of the stems - and

is then, as a rule at least not inherited at all ". (Ruggles gates (107).

The following case histories demonstrate the beneficial effect of outdoor exercise on asthma:-

Case No. 35. Male, age 55. Asthma for 22 years. Occupation, school teacher. Gave up exercise several years ago because of shortness of breath. In evenings he now sits over the fire and eats chocolate. Rather overweight, heart flabby, with rhonchi on both side of chest. Nasal obstruction due to enlarged turbinals. B.P. 145 / 100. Family history, negative. Was an only child. Treated with mercurial and saline once weekly, belladonna and iodide mixture, reduction and simplification of diet and encouraged to take up golf again. After fifteen months, he is almost completely asthma-free. "Can play two rounds of golf and walk six miles after it".

Case No. 4. Female, age 48. Asthma for four years. No allergic diseases in relatives. She improved to a large extent with general hygienic and medicinal treatment, but still had occasional spasms. She was encouraged, much against her will, to walk and later to run in the grounds of the hospital with resulting complete cessation of attacks. She has remained well for two years.

Case No. 12. Male, 59 years, engineer. Always healthy until fifteen ago when he had influenza. This was followed by asthma which has continued without interruption. Worse in the evenings and so unable to spend any time outdoors. Family history, negative for allergic diseases. Constipation severe, nose healthy, B.P. 260 / 150. Eosinophiles, 6 per cent. Treatment of constipation and recommendation of walking and breathing exercises in spite of severe dyspnoea resulted in complete cessation of wheeze and cough. Recovery has been maintained.

Intoxication from other sources is important also. Avitaminosis B can be included under this category. Kuczynsky (111) has shown in convincing experiments that "special vagus irritation" may be produced by deficiency of vitamin B. Wolfe (112) of Washington, a surgeon, states that his interest in asthma was first stimulated by the occassion of a recovery from asthma of a patient on whom he operated for chronic appendicitis, the operation having been performed for reasons other than the asthma. Since then, he has witnessed many other cases of complete recovery following the eradication of a focus of infection. Recently, I saw an asthmatic lady who, several months earlier, I had successfully treated by diet and exercise, mercurial, iodide and belladonna. She had remained free of asthma until the onset of symptoms which suggested a diagnosis of cholecystitis, when her paroxysms recurred with renewed severity. With treatment for her cholecystitis her asthma has again disappeared and she has now remained well for many months. Of interest here, is the report on one hundred consecutive cases of gall-bladder disease by Murray Black (113). This writer records that of these hundred patients, 4 per cent suffered from asthma, an incidence four to eight times as frequent as the presumed proportion of asthmatics in a random sample of the population. It is presumed that in the cases where a focus of infection or

irritation is incriminated, asthma is caused either by a condition of toxicosis, or by the formation of a reflex, whose central connections are in the nucleus ambiguus or adjacent nuclei, and from which stimuli are referred to the bronchi through the vagus motor fibres.

Certainly, the number of cases cured by operative interference alone, does not form a high proportion, but the fact of its occurrence is striking and must always be remembered.

La Forge (114) and Cameron (115) affirm that following detoxicating measures, allergic skin tests, where positive prior to treatment, now become negative. The question, naturally arises whether there can be any relationship between toxaemia and the exhibiting of positive skin tests with which the conception of heredity is so intimately associated.

It has been shown by Rosenau, Anderson and Walzer (116), that in normal infants, the addition of a fresh protein food to the diet is followed by the presence in the blood of that protein or its derivitives. The addition of these foodstuffs seldom cause asthma or other allergy; or to put it another way, foreign proteins may circulate in the blood without provoking anaphylactic or allergic phenomena. It would therefore appear that the entrance into the blood-stream of foreign protein might be considered a normal process and under conditions of good health the protein is broken down

by enzymes, hormones and catalysts, elaborated by the organs. In the toxaemic or allergic individual, on the other hand, this destruction of foreign proteins does not take place on account of enzyme insufficiency, and antibodies, or allergins are formed to neutralise them. The subsequent introduction of an allergen results in an interaction between allergen and allergin with the liberation of a histamine-like substance (Lewis) and production of the asthmatic seizure.

Depressed enzymatic activity is evidenced by the low gastric acidity (Adam, 116, Bray 117, Hurst 118,) increased amino-acids of the blood (Adam 119, Oriel 120, Cameron 121) and by defective action of the liver as shown by increased bilirubin (Bray 122) abnormal blood sugar (laevulose) curve (123); and Manwaring (124) has shown that anaphylactic shock does not occur in the experimental animal if the liver is excluded from the circulation.

It is not difficult to understand, therefore, why, with toxaemia as a factor in the production of the asthmatic tendency, clinical sensitivity disappears with improvement in bodily health.

An observation recorded by Rackemann(125), an enthusiastic advocate of the allergic and hereditary theories is relevant here. This writer records that in San Quentin

prison " despite a heavy exposure to jute dust, no new cases of asthma or other manifestation of other allergy developed, although a number of inmates had asthma before arrival". The same author (126) has treated sixty-six cases of asthma on simple hygienic lines and without reference to allergy, and was "amazed" at the improvement in many cases. He remarks that " Dietary defects as a basis for asthma must always be considered".

The following three cases of asthma were examined for sensitization by skin tests. In one, positive reactions were obtained to fish and fowl, but avoidance of these gave no relief. (Case No. 21).

Case No. 27. Female, age 48. Bronchitis each winter since childhood. Hay-fever till a few years ago. Rheumatic fever at eighteen; coliform infection of urinary tract for 25 years; pelvic viscara removed eight years ago. Was in Bridge of Weir sanatorium for four months without benefit; No T.B. found. B.P. 140/95; polypus in right nostril. Family history, nine out of forty-two relatives with asthma. Severe attacks occur at leat once a day. Very thin, chloasma and pigmented spots in the skin. Constipated; bedridden. Removal of polypus refused. Skin tests with twenty reagents, negative. Attacks treated with adrenaline, diet and bowels regulated, mercurial and saline twice weekly and encouraged to perform respiratory exercises. After one year, attacks occur at intervals of two to four weeks. After eighteen months, almost completely asthma free. During the past three months, kidney function has decreased with heavy albumen in the urine and oedema. Heart is showing signs of failure. In spite of fairly good response to diuretics the prognosis is unfavourable.

Case No. 21. Female, age 41. Asthma for eight years following chill when sea-bathing. Allergic skin tests performed several years ago and positive reactions to fish and fowl discovered but no improvement followed avoidance. Dietetic and general hygienic treatment together with outdoor exercise resulted in complete disappearance of the asthma. The patient can eat any kinds of food.

Case No. 56. Boy, age 16 months, breast fed. Asthma for three months at fortnightly intervals, attacks lasting three to five days. Eczema since six months. A large series of skin tests performed by an eminent dermatologist failed to reveal any substance which might be incriminated. One maternal uncle had asthma. Fed almost exclusively on milk puddings. Overclothed, and hands, arms and knees covered to prevent scratching. Skin wrinkled and inelastic, with dry, scaly eczema covering body, face and limbs. Weight, four pounds below average; mentally precocious. Treatment, grey powder twice weekly, complete elimination of milk from diet. Fruit, vitamins, eggs, fish and fowl added. Reduction of clothing, exposure of limbs and cold sponge each morning. Exercise encouraged. After ten months eczema present only in small patches on the wrists and has had only two mild attacks in the past five months. Weight, two pounds above average.

Closely linked with the subject of toxaemia is PERIODICITY, one of the most characteristic features of asthma. It is well known that the asthmatic paroxysm shows a marked tendency to occur at certain periods of the day, month or year. This periodicity would be difficult to account for by the assumption of the allergic basis only, since it is known that in proven allergic cases a definite time relation exists between contact with the allergen and the onset of the paroxysm. The 2 to 4 a.m. period often mentioned may receive its

explanation in one or more of the following ways:-

1. The depressed metabolism occurring during the sleeping period.

2. Adoption of the horizontal position and consequent high position of the diaphragm.

3. Increased pressure in the venous as compared with the arterial system, facilitated by recumbency, a condition calculated to cause congestion of the pulmonary circulation and mucous membrane (128). (It is to be noted here, that inequality of pressure in the two sides of the heart has been postulated by Volhard (129) as a cause of cardiac asthma.)

4. Engorgement of the turbinates due to the recumbent position and warmth. (130)

5. Increase of parasympathetic activity during rest;(MacDowall 131), or has been otherwise stated, during sleep, the adrenals sleep.

The week-end is a frequent time for the occurrence of the paroxysm. Adam points out that at this time there is for the working man, more food and less exercise, and that in them, asthma fails to make its appearance if more efficient combustion of food is achieved by increased exercise. He sights numerous examples in proof (132). The vicious effect of overloaded metabolism is also emphasized by Lapage (133). While believing, mainly on account of the occurrence of asthma and its allied disorders in more than one member of a family, of the importance of an inherited insecure metabolism, he points out that " overloaded metabolism has a distinct contributary effect in the production of allergy.

An autophil (a person who has inherited a tendency to allergic manifestations) who has been overloaded by defective metabolism is likely to develop allergy, but one who has not been so overloaded will probably remain healthy". Overloading may be brought about by faults in the diet, injudicious exercise, too much excitement and chronic sepsis.

Bray (134) incriminates the Friday night bath and syrup of figs. Regarding the hot bath, Adam (135) has shown that this produces an eosinophilia, and Cramer (136) points out that warmth causes suspension of adrenal activity. Winter is the period of respiratory infection; summer, that of irritation by pollen dust, whether or not there is special sensitivity to it. The sexual epochs are important. Bray, (137) states that after puberty, asthma is twice as frequent in the female as in the male, a fact explained by Adam as partly accounted for by the greater tendency to a sedentary habit. Increased severity often occurs at the menstrual periods and at the climacteric there is frequently amelioration, but asthma sometimes begins then for the first time. Pregnancy is usually a period of enhanced well-being and there is often cessation of the distressing symptons . In some, the condition makes its appearance for the first time as in the following case:-

> Female, age 32. Primipara, an active energetic woman, pregnancy advanced to third month. Her visit was occasioned by badly engorged varicose

veins. She was advised to take laxatives and rest after meals. Two weeks later, because there was no improvement, I recommended complete rest in bed. At the end of this time, she returned with mild dyspnoea, rales and rhonchi widely spread in her chest and a history of typical nocturnal dyspnoea and orthopnoea. There was no family history of asthma or allied disorder. On looking back on this case, I feel that had I applied elastic bandages to her legs and allowed the patient her usual exercise, I might have prevented the onset of a distressing illness.

Respiratory infection and the development of asthma appear to be intimately connected. By some, a bacterial allergy is postulated. Measles, whooping cough and pneumonia, bulk largely in the medical history prior to the onset of the asthma, and the common cold is often instrumental in precipitating a paroxysm in a susceptible individual. An Edinburgh investigation (181) into the heredity of asthma, found that 80 per cent of the patients gave a history of respiratory infection before the onset of the disease. The effect of these is firstly to exhaust the patient's resistance, and secondly, to irritate the pulmonary branch of the vagus and so facilitate a reflex. Immunologists offer a third reason. They say that during these illnesses, on account of the lower vitality, the patient is unable to combat successfully, the entrance of allergens such as horse-hair and feathers on which the patient lies, and so sensitization follows. Inasmuch as only 50 per cent of asthmatics are considered to be allergic, and the other 50 per cent not, and the frequency of infectious diseases is presumably the same in both groups, it would appear that the infection is more important than the assumed

inherent allergic susceptibility.

CLIMATE AND ALTITUDE. The effect of climate and altitude is well known, but no adequate explanation is forthcoming. Storm Van Leeuwen (138) postulated the presence of spores and fungi in the atmosphere which he called "climatic miasms", the latter, considered to be allergens acting on a hereditarily predisposed subject. Support for his contentions is to be derived from the fact that bronchial asthma does not occur at a height of 4,000 or more feet above sea level, altitudes at which moulds and spores are absent. He maintained, also, (139) that at this level, asthmatic patients can sleep on horse-hair and feathers with impunity. On the other hand, there is the possibility that the improved health may be the result of respiratory stimulation consequent upon the oxygen-want in the rarefied atmosphere, as well as by the quickened metabolism, increase of red cells and raised blood pressure which occurs at increased altitudes (Wittkower and Wolfer, 140). Fatigue, emotion, insomnia and mental strain, are important contributary factors, probably by causing sympathetic exhaustion.

NASAL FACTORS. La Forge and Burton Haseltine (141) maintain that almost every asthmatic has nasal pathology, but the onset of bronchospasm may be precipitated by any other condition that is capable of setting up a naso- pulmonary reflex.

Their conception of the cause of asthma is divided into two components, (a) a basal toxicosis which produces defective action of the adrenals and pituitary, and (b) a pulmonary reflex initiated mainly from the nose. The following figures indicate the frequency of nasal pathology found by various authors:-

Dundas Grant	... ...	63%	(142)
Haseltine and La Forge	...	Great Majority	(143)
Adam	... ...	68%	(144)
Moll	... ...	77.9%	(145)
Vaughan	... ...	71%	(146)

The association between enlarged turbinals, polypi, sinus disease or deflected septum and asthma, is the subject of controversy. Some say these conditions are responsible for the asthma, while others say they are merely incidental. Again, polypi, opacity of the sinuses and enlarged, blobby turbinals are believed by allergists to be the product of the allergic soil. Where there is nasal abnormality, it is easy to understand from the work of Brodie and Dickson (147) Sercer (148) and Phillips (149), that a nasal-pulmonary reflex might easily become established. Cases of unilateral asthma are recorded, where the more affected lung was on the same side as the abnormal side of the nose (Adam, 150, Sercer, 151) and a similar condition obtained in case No. 68, in which a large spur in the right nostril was associated with bronchospasm which was at times much more severe in the right lung. The value of nasal treatment has been decried by many.

Piness and Miller (152) for example state that in 704 operations for the nose, in 413 patients, there were no successes, but figures of these authors are extreme and other results are shown below:- (153)

	Improved	Cured
Dundas Grant ..	60.3%	20.8%
Heatley and Crowe ..	85.4	1.6
Tod ..	43.	10.
Lierle ..	80.	10.
Leopold and Fetterolf ..	50.	48.
Rackemann and Tobey ..	50.	5.
Lyon and Murray-Lyon ..	66.9	18.3
Moll ..	50.4	2.7

It is pointed out by those who recommend nasal interference that the latter is calculated only to eradicate the source of a nasal-pulmonary reflex and promote more efficient respiration, while attention to other causes of toxicosis is all-important.

The factor of improper breathing must also be emphasized. Coke (154) remarks that " The inability to breathe properly is one of the greatest defects of the modern child." The importance of mouth breathing in the genesis and aggravation of bronchial asthma has received striking confirmation from the work of Sercer(155), Sercer and Valutec (156) and Hofbauer (157). These observers have shown that in mouth breathing, respirations become superficial, the diaphragm but slightly mobile and high-standing ("Hochzwerchfelzustand" - Hofbauer). Owing to the faulty diaphragmatic breathing, the apecis of the lungs are

also imperfectly ventilated. The whole effect is to produce stagnation of the air, increased carbon dioxide tension of

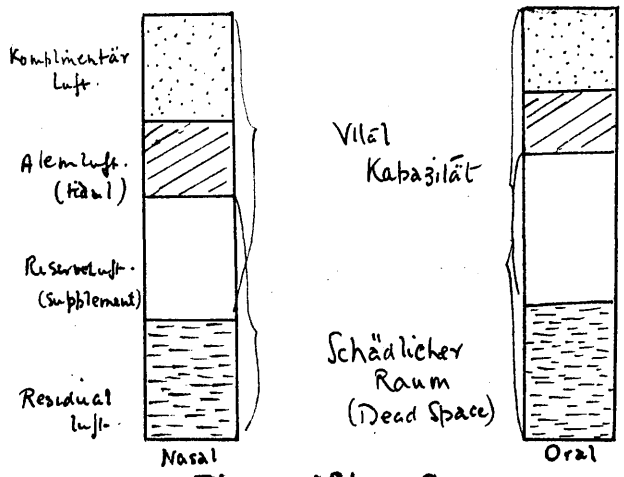


Fig. After Sercer.

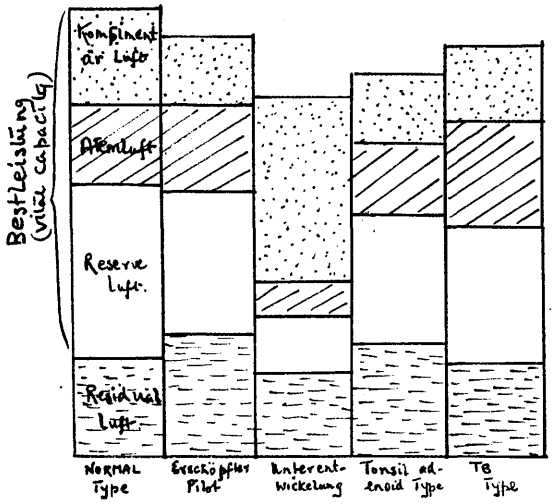


Fig. 2

from Hofbauer, after Flack.
Atemgrosse beim Gesund organisch, bzw. functional Kranken.

the blood, and consequent acidosis as well as defective oxygenation of metabolites. I have myself observed the absence of adequate diaphragmatic movement in several asthmatics with the aid of the X-ray screen and was able

to confirm the findings of Sercer and Hofbauer in this respect.

Sercer and Valutec(loc. cit.) in an ingenious series of experiments in which they used a specially constructed spirometer, demonstrated in a convincing manner the detrimental effect of the absence of nose breathing on respiratory ventilation (Fig.1.). They showed, that where there is occlusion of the nose, where there is mouth breathing due to other causes, and in laryngectomised patients, the physiological stimulus for diaphragmatic breathing is suspended, with consequent diminution of the vital capacity, increase of the dead space, and augmented tension of the CO_2 in the alveolar air. In asthmatics, Hofbauer (158) Sercer (159) Phillips (160) and Van Leeuwen (161) have noted a similar diminution of the vital capacity. In Figure 2. is represented the alteration in vital capacity produced by various conditions.

MONILIARY INFECTION. In a recent monograph, Gordon Oliver of Jersey (162) claims to have found monilia in the sputa of all of fifty-four cases of asthma investigated. The author contends that this mycotic infection is the cause of bronchial asthma and that successful treatment is achieved by measures calculated to overwhelm the infection. The author "holds no brief for the hereditary theory" but

maintains, rather, that the occurence of the disease in more than one member of a family may be accounted for by the frequent contamination of milk by the fungus, on the island. J.H. Barnard (163) found monilia in 108 of 410 cases of asthma investigated, and concludes that moniliasis is a common factor in bronchial asthma. Monilia have been found in many other chronic respiratory diseases, and conditions accompanied by emaciation and simulating pulmonary tuberculosis have been traced to infection with this fungus. Castellani (164) reports that moniliary infection is common in workers in tea factories and has isolated monilia from the tea itself. In an investigation of the significance of monilia in the sputa, Bertram Jones (165) concludes that "bronchomoniliasis cannot be diagnosed from the examination of the sputa alone".

Moniliary infection with reference to asthma is being investigated at the present time.

OBSERVATION IN ANIMALS.

Information derived from observations on animals has been both experimental and clinical. Studies in anaphylaxis have given rise to the assumption of an allergin-allergen reaction and so helps to explain the process which takes place in man when contact with an offending substance is made.

The conception that the asthmatic paroxysm is of the nature of an anaphylactic phenomenon was suggested by Meltzer in 1910. He noted a similarity between the condition of the lungs in the asthmatic attack in man and in Guinea-pigs dead of anaphylactic shock. The frequent occurence of a definite time-relation between contact with the nocuous substance and the onset of the allergic symptom suggests a mechanism of the nature of an anaphylactic (antigen-antibody) reaction in at least a proportion of cases although for reasons previously advanced the phenomenon is considered to be secondary to a more fundamental metabolic state. But the analogy ends here, for the points of resemblance between anaphylaxis in animals and allergy in man are fewer than their differences. Anaphylactic shock is a condition of the laboratory animal which is always artificially induced whereas the analogous state in man is most frequently spontaneously acquired. Again, anaphylaxis is always associated with the presence in the blood of precipitins, but in man these are absent, although the presence of a circulating antibody is suggested by the Prausnitz-Küstner reaction (see page 31). Furthermore, desensitization is easily achieved in anaphylaxis but in allergy it is exceptional, and where it occurs there is no decrease of antisubstances in the blood (166). For these reasons, amongst others, it is generally believed that

anaphylaxis and allergy are not identical, and that true anaphylaxis is rare in man. The term 'hypersensitiveness' has been used to embrace both conditions. The question thus arises as to the nature of serum disease. Is it an artificially induced allergy or anaphylaxis? Its occurence is frequent after the administration of serum for therapeutic purposes, and in a series of 150 cases to whom antistreptococcal serum was given for prophylaxis against puerperal fever, I observed serum reactions in a very large proportion if not in the majority. Bray (167) states that 90% of white people exhibit serum reaction following the intravenous injection of a large dose of serum. A feature distinguishing allergy from anaphylaxis according to allergists, is that in the former the condition is most frequently hereditary but in the latter it never is; but whatever the nature of serum disease, heredity is obviously not a factor.

With regard to asthma, urticaria, eczema, etc., the origin of which is presumed to be allergic, if it is assumed that anaphylaxis and allergy are both manifestations of a hypersensitive state, it is difficult to understand why one form, anaphylaxis, should be proved by experiment to be non-hereditary and that the less reliable clinical observation should indicate that the other, allergy, is only doubtfully hereditary.

The work of Kenneth Phillips (168) has furnished convincing evidence of the importance of toxaemia or toxicosis (La Forge) in the genesis of the asthmatic state. This worker is able to produce experimentally paroxysms of bronchospasm. By isolating a loop of bowel and varying the quantity of contents by periodic aspirations, he contrived to effect a condition of toxaemia of varying intensity. Thereupon, he superimposed a mechanical irritation by suturing wire rings into the middle turbinals or packed pus-soaked gauze into the antra. After a short period, the animals showed the signs and symptoms of asthma. The latter condition did not develop unless both the toxaemia and nasal irritation were induced. Similar results were obtained by the same author by producing a parathyroid toxicosis.

The question of heredity does not arise here and the evidence indicates that toxicosis and nasal irritation are the factors of fundamental and paramount importance.

Clinical observation on animals affords information of great value. Coca, with his theory that asthma is essentially hereditary, practically denies its occurence in animals. That it does occur in animals living under sophisticated conditions, in dogs, in canaries, and in horses, is well-known. Investigation has revealed that as in man, the condition is accompanied by an eosinophilia.

Adam (169), who has treated and cured various affected animals, has recorded his results frequently and has noted also that the return to an improved condition of health corresponds to a fall in the eosinophil count. The methods of treatment used have been attention to bowels and regulation of diet and exercise. His observations are in agreement with those of Law (170), a prominent veterinary surgeon, who emphasizes the importance of correct feeding in the prevention and cure of horses suffering from asthma, heaves, and broken wind.

Adam aptly remarks "In none of these can the question of heredity arise".

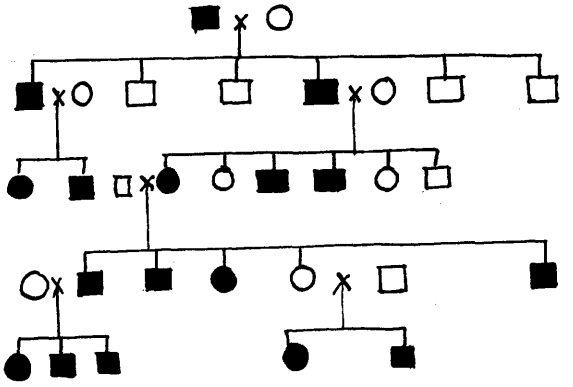
PEDIGREE STUDIES.

The foregoing has considered the principal current views of etiology of bronchial asthma, and an attempt has been made to review these theories with particular regard to obtaining evidence for and against the importance of the hereditary factor. Many of these hypotheses have assumed the presence of a diathesis. With some, such as Lapage, Bray and Coca, the term diathesis has been used to connote chromosomal inheritance or "continuance of germplasm". (Weissman) with others merely a constitutional tendency in accordance with Ryle, (171) who defines diathesis as

" A variation in the structure of function of tissues, which renders them peculiarly liable to react in a certain way to certain extrinsic stimuli". This definition does not necessarily imply heredity, although this is the meaning accepted by many. Inherited biochemical or biophysical make-up, however, may so influence nutrition as to render the individual peculiarly liable to certain disorders of function. Adam (172) says " The soil is inherited" and with this, everyone must agree, " Whether or not the disease will develop, depends on nurture".

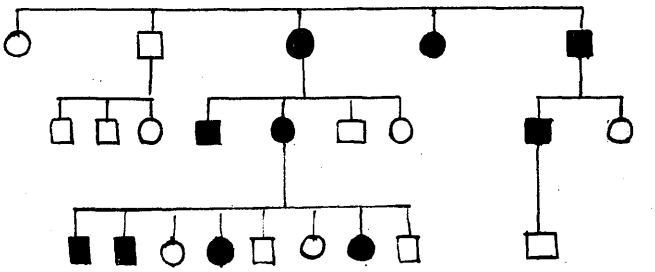
Before examining the evidence from the etiological aspect, it is proposed to proceed with an investigation of pedigrees and other material.

Fantham's (173) pedigree of cat asthma is probably the most striking of the hereditary asthmas.



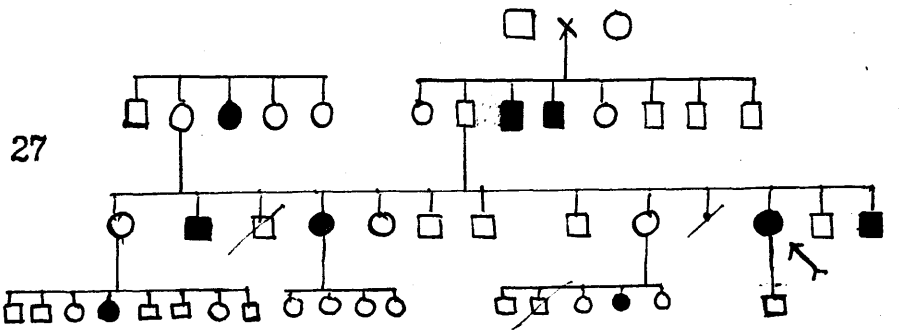
Here are seventeen asthmas in a total of 25 persons in five generations, giving a percentage of 68. In this case, a simple dominant factor is apparent.

Drinkwater's pedigree is also outstanding.

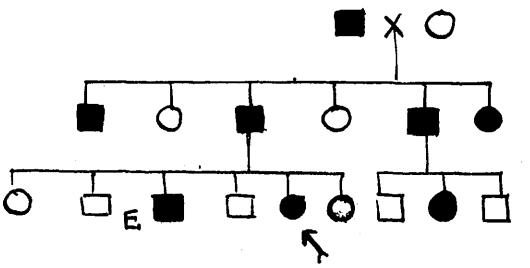


The most impressive pedigrees of my own series are those of cases Nos. 27 and 29

Case No. 27



Case No. 29



male = ○
female = □
affected = ● ■
patient = ↖
eczema = E

In 1916, Cooke and Vander Veer (174) in an article providing great wealth of clinical material, analysed their records of allergic diseases from the point of view of heredity. The evidence of hypersensitiveness was purely clinical and the following conditions were included;- bronchial asthma, hay-fever, urticaria, angioneurotic oedema and gastro-enteritis provoked by eating strawberries and shell-fish. Of 621 cases, 117 were discarded as being incomplete. In the remaining 504 with satisfactory history, a positive antecedent, direct or collateral history was obtained, one one side in 205 cases, on both sides in 39, and 260, there was no history of hypersensitivity in a relative. That is, 48.4 per cent gave a history of allergy in a near relative in marked contrast to 14.5 per cent of 76 normals investigated. The authors therefore concluded that inheritance is a definite factor in human sensitization. Further evidence they deduced from the fact that the greater the importance of the hereditary factor, the earlier the onset of symptoms, and this from the figures shown in Table 1. In short, in double inheritance, the maximum liability is in the first five years of life, when 36.3 per cent develop manifestations of allergy. Where inheritance is unilateral, maximum liability is in the ten to fifteen years age-period, and where the history is negative, twenty to twenty-five years.

TABLE No.1.

Showing a list of cases grouped according to age of onset and their inheritance.

From COOKE and VANDER VEER.

	1-5 yrs.	6-10 yrs.	11-15 yrs.	16-20 yrs.	21-25 yrs.	26-30 yrs.	31-35 yrs.	36-40 yrs.	41-45 yrs.	OVER 45
Negative Inheritance 253 cases										
No.ofcases % of total	13 5.1	32 12.6	29 11.5	29 11.5	39 15.4	35 13.9	36 14.0	22 8.8	4 1.6	14 5.5
Unilateral Inheritance 253 cases										
No.of cases % of total	29 14.3	36 17.7	44 2.7	25 12.4	28 13.8	19 9.3	10 5.0	6 3.0	2 1.0	4 1.8
Bilateral Inheritance 44 Cases										
No.of Cases % of total	16 36.3	13 29.9	3 6.8	4 9.0	2 4.5	1 2.2	3 6.8	2 4.5		

On the other hand one is compelled to admit that as Adam stresses, the greater the incidence of asthma or allied disorders in the parents, the more potent is the environmental factor in causing asthma in the child, for, since nurture is traditional, the indiscretions in the habits of life of the parents have their repercussions in the health of the child. Furthermore, it is pointed out, a large proportion of children acquiring asthma or allergy are "only" or first children (175), and the increased sheltering with which they are favoured is followed by disturbed metabolism, by decreased resistance to climatic changes as well as by the development of egocentricity, an opinion shared by Burton Wood (176), Coke (177) and others. In contrast to the findings of Cooke and Vander Veer, Coke (178) maintains that the incidence of the age of onset of allergic symptoms is the same for all age groups, a conclusion with which the Edinburgh investigation concurs.

In their thesis, Cooke and Vandeer Veer ask what the inheritance consists of, and come to the conclusion that it is the capacity to become sensitive, and this for the following reasons:-

(a) the offspring of a sensitive parent are not born sensitive; e.g. hay-fever does not occur till the age of ten to fifteen years, instead of two to three if inheritance were specific.

(b) a parent may transmit the sensitization without himself being sensitized. It has been found that in bilateral inheritance, a large proportion of the children become sensitized at an average age earlier than in cases of unilateral inheritance, notwithstanding that in more than one third of the former group the hereditary influence on one side of the family was not seen in the parent, but in a grandparent or a collateral, such as an uncle. It is here that the parent not clinically affected has transmitted some characteristic to his offspring, the nature of which cannot be specified. Conceivably, these have a latent sensitization.

(c) the inherited character is as frequently paternal as maternal; and the clinical form in the child is more apt to be different from the mother than it is to be identical, and as like to uncle as to parent (Contrast Coca who postulates the inheritance of a shock organ. Vide page 24.).

A study of the figures was made by the authors to see if Mendelian dominance or recessiveness was involved. Table 2 was extracted from their protocol.

They argue further;-

1. Double inheritance. In 26 families with 70 children, 39 show clinical sensitization at average of 23.

TABLE No. 2.

SHOWING THE PERCENTAGE OF SENSITIZED CHILDREN ESTIMATED TO DEVELOP IN THE THREE INHERITANCE CLASSES.

From Cooke and Vander Veer.

Inheritance	Number of Families	Total Children	Children Sensitized		Average Age of Total	% sensitied at average Age	Estimated Sensitized Children	
			No.	% total			No.	% total
Both parents...	26	70	39	55.7	23.0	82.6	47.2	67.5
One Parent.....	52	150	77	51.3	27.5	84.5	91.2	60.0
Negative.....	148	631	205	32.4	35.0	84.0	244.0	38.6

From an age of onset curve, we know that 82.6 per cent of such cases develop sensitization at this age. 39 children therefore represents 82.6 per cent and 47.2 children is equivalent to 100 per cent, and 47.2 is 67.5 per cent of the total number of 70.

2. Single inheritance. 60 per cent of 150 will become sensitive.

3. Negative history. 38.6 per cent of 636 children will develop sensitivity.

"Assuming all children though clinically sensitized are impure with respect to sensitization, (or heterozygous) we should expect, according to Mendelian laws, 75 offspring sensitive when both parents are affected, and 50 per cent where one is. Figures obtained are 67.5 per cent and 60 per cent." They conclude with the following "With regard to these cases of sensitization in which there is an absence of sensitization in the family history, nothing can be said. We can only surmise that here the failure to find the antecedent sensitization was due to the limitation of our methods of ascertaining the family history in this respect". In other words, Cooke and Vander Veer consider allergic troubles to be always hereditary and transmitted as a Mendelian dominant.

Significant facts emerge from a study of the protocols

submitted by these observers. In the first place, an analysis of Table 2. shows that the number of children per family of allergic parents is smaller than in cases where there is a negative family history, viz.,

Bilateral heredity	2.7	children per family
Unilateral "	3.0	" " "
Negative "	4.3	" " "

These figures support the contention to which reference has already been made, that asthma tends to be associated with small families and the increased protection, too rich food, etc., that goes with them.

Looking at individual families, one can see only one case in which Mendelian heredity can be assumed. In this case (571) four of the five children exhibited sensitivity, as follows:- Patient, female, age 55.Onset at 32. Brother, normal. Collaterals, paternal uncle, asthma. Others, mother asthma ; husband urticaria; three children, urticaria.

The age of onset of this patient's condition contrasts with the opinion expressed by the authors that cases where the inheritance is strong have an early onset of the disease, but conforms rather to the type in which nutritional factors might be incriminated.

In another family, with bilateral heredity, only

one sib of six showed sensitization. It is difficult to make these pedigrees support the contention that the heredity factor is a dominant and is of fundamental importance.

The authors' clinical material includes, as has been mentioned, cases of asthma, hay-fever, urticaria, angio-neurotic oedema, and gastro-enteritis. Of these, only hay-fever can be considered of undoubted allergic origin, because (a.) it is the commonest and most typical of the allergic group, (b) it has only one sensitivity which constitutes an entire disease. Other diseases have many sensitivities, (c.) it gives positive reactions in over 90 per cent of cases; others, in 50 per cent or less (v.p.27) In paroxysmal rhinorrhoea, all skin tests are negative (Connybeare 179). Van Leeuwen (180) considers this disease the expression of a non-specific alimentary toxaemia. Urticaria is considered to have an allergic origin in only 25 per cent of cases (Rackemann 181), and and hereditary angioneurotic oedema unrelated to the sporadic form . Gastro-enteritis gives positive cutaneous reactions in only 26.5 per cent of cases (see page 27). It would appear therefore, that with the exception of hay-fever, the conditions included in the allergic group of ailments are only secondarily allergic and are the expression of various more fundamental states.

Further scrutiny reveals more important information. Of the 623 cases of allergy there are 240 cases of asthma. Of these, only 48 are uncomplicated asthmas. The remainder are associated with hay-fever. In percentage figures, of 240 cases of asthma, 80 per cent are complicated by hay fever and 20 per cent are not, and of this latter, the majority are negative to pollen extract. This series of asthmatics contrasts in a striking manner with the Edinburgh series in which hay-fever occurred in only 7.5 per cent of the cases, and this figure seems to be the more usual in this country. James Adam (182) gives an incidence of less than 10 per cent and my own series, 7.7 per cent. In the sensitisations of the relatives, hay fever again predominates. It would seem likely therefore, that in the major group of 80 per cent, the onset of asthma is in some way related to the presence of hay fever at least in the majority of the cases, in the nature of cause and effect, and without knowledge of the ages of onset of the hay fever and asthma respectively, it is impossible to make definite pronouncement in the matter. It is well known that asthma frequently occurs in individuals who at an early age suffered from hay-fever (Witts, 183). (Balyeat, 184, Rackemam 185) That the reverse occurs, cannot be controverted, but these cases are infrequent. Balyeat, loc.cit., estimates that

in the south-west U.S.A. at least 60 per cent of hay fever cases will develop asthma. It is conceivable that in these patients, the hay fever sensitises the mucous membrane of the lungs in a manner similar to the exanthemata. Accordingly, we might consider, with ample justification, that the majority of those individuals of this series suffering from hay fever, with or without asthma show an increased familial incidence of sensitivity on account of a simultaneous massive exposure to pollen and in this respect are comparable to the cases of Ancona, already described, (see page 29).

Rackemann (186) reports that a family history of allergy occurs in only 35 per cent of his series of 344 cases of hay fever. Since hay fever is preeminently the allergic disease, it is difficult to account for its lower heredity incidence, except that it is assumed that asthma is occasioned by a prior hay fever in many cases. If then, allowance is made in the figures of Cooke and Vander Veer, for a large part of the 80 per cent group of asthma and hay fever, it becomes obvious that the incidence of positive family histories is considerably diminished.

It would be difficult to assess the true incidence of heredity in the cases of Cooke and Vander Veer. It is none the less my opinion that for the foregoing reasons, the figures of these authors are biassed by data which

cannot be considered unequivocal.

In 1929, the Edinburgh (187) investigators examined their pedigrees of asthma with the following results. 404 patients were considered; 55.2 per cent males and 46.8 per cent females. Urticaria was not included in this survey, since it was considered that a reliable history of this condition would be extremely difficult to elicit. 7.3 per cent had hay fever also. 51 per cent were below the age of 20, but it was found that when adjustments were made, the incidence varied little at different age periods. The report states that a history of asthma in some near relative was obtained in 38.7 per cent. Unfortunately, the total number of relatives was not stated, so that it is not possible to form an opinion as to the proportion of affected to unaffected individuals. No conclusion was drawn concerning the involvment of a Mendelian factor. Of the 139 cases, in whom inheritance was noted in the family history, 59.6 per cent had asthma before 20 years of age; but looking at the question from the point of view of age group, the authors concluded that there was no preponderance of inheritance cases at any period of life.

80 per cent of asthmatics gave a history of respiratory infection before the asthma commenced.

Bray's (188) investigations in asthma, hay-fever, urticaria, eczema, vasomotor rhinitis and migraine, lead him to conclude that heredity plays a most important role in from 50 to 70 per cent of cases according to the type of allergy displayed. The statistics are based on 200 cases. From a survey of the age of onset, he finds that 21 per cent develop symptoms before the age of ten, irrespective of hereditary influence, from which he concludes that heredity plays no part in determining the age of onset. In Bray's group, inheritance is twice as frequent when the mother transmits, and in the latter case twice as many offspring might be expected to be affected. At the same time, he comments on the difficulty of obtaining true figures for heredity, since in some instances, the hypersensitivity is known to be the result of placental transmission, and on that account must be termed 'congenital' rather than hereditary. A point of family history was obtained in 68.5 per cent of his cases, evidence of heredity having been presumed from a history of asthma, hay-fever, urticaria, eczema, migraine and vasomotor rhinitis in a relative. He remarks that it is difficult to obtain perfect agreement with Mendelian ratios. The total number of relatives included in his survey was 4,152 and the number of affected individuals, 597, giving a percentage incidence of 14.3, a figure very close to the incidence of hypersensitivity in a random sample of the population. Balyeat (189) found 8.3

per cent of 1,117 students with allergy, Spain and Cooke (190), 7 per cent of 115 cases, and Cooke and Vander Veer (191), 14.5 per cent. Bray recognises the vicious effect of prejudicial environmental conditions, and records (192) that 36 per cent of his children were "only" children and in a further 20 per cent, the affected child was the first of two or more. The average number of children per family, rarely exceeded two. Bray's figures are as follows:-

Unilateral family history, in 50 per cent of cases
Bilateral " " in 20 per cent " "

Conversely, bilaterally affected ancestry gave 70 per cent affected offspring; unilaterally, 60 per cent; negative, 45 per cent.

Bray's statistics are not convincing. His conception of allergy is too comprehensive, since only a minority of cases of urticaria and migraine are generally considered to be allergic. Ingram (193), dermatologist, has never seen an eczema due to cow's milk or other foodstuff, Dowling(194) cannot agree with those who say that infantile eczema is due to atopic sensitivity to foodstuffs, and Coca believes that there are really only two allergic diseases, asthma and hay-fever. Bray's figures of expected affected offspring with positive ancestry do not vary sufficiently from those with negative ancestry to be decisive.

L.J. Witts (195) examined 500 asthmatics and 100 controls. A family history in 60 per cent of the patients suffering from one or more of the following, was obtained:- asthma, hay-fever, urticaria, eczema, rhinorrhoea. In spite of this high figure, Witts remarks that "While there is no doubt that asthma and the other allergic diseases I have mentioned are closely related, our collateral investigations on apparently healthy people do not support the view that this group of diseases can be regarded simply as the manifestation of an inherited allergy or protein hypersensitiveness. Bruce Pearson(195) has found that 30 per cent of healthy adults have either a personal or family history of allergy. Much higher figures are given by the American worker Vaughan, whose conception of allergy is more embracing than ours. Study of skin reactions have also shown the great frequency of latent allergy as compared with overt allergic disease".

A series of 568 cases was investigated by Spain and Cooke (196) to see if a fresh investigation verified the results obtained by Cooke and Vander Veer in 1916. A positive family was obtained in 58.4 per cent of the cases as compared with 48.4 per cent in the earlier enquiry, but their conception of allergy embraced a larger number of diseases, viz., asthma, hay-fever, atopic coryza angio-neurotic oedema, gastro-enteritis, urticaria, migraine,

a and eczema. Figures of expected morbidity in this series were:-

Bilateral inheritance--71.6 per cent, instead of 75 per cent
Unilatral inheritance--56.1 " " " " 50 " ".

In the 41 per cent, which gave a negative family history the authors suggest as an explanation either an inadequate history, or failure of the relatives to come into contact with specific allergen.

Spain and Cooke concluded that asthma is definitely hereditary, and that either a single, or multiple dominant factors are involved.

In a series investigated by June Adkinson (197), a family history was obtained in 48 per cent. The author concluded that a Mendelian recessive was the fact involved. This has been controverted by all other workers, mainly for the reason that an incidence of only 71 per cent of expected affected offspring was obtained, instead of 100 per cent when inheritance was bilateral and furthermore, because recessive parents showing the disease rarely have recessive offspring (198).

Buchanan (199) is of the opinion that asthma follows none of the known laws of heredity.

Coke(200) in his volume on colds and hay-fever, finds on analysing his figures that 66 per cent of his hay-fever

patients give a family history of hypersensitivity in a near relative. Yet he belives that too much food and too little exercise with derangement of the liver are the commonest accessory factors. He remarks that " Some men were in such fit condition during the war that they developed no hay-fever at all though living in the open fields of France". Warren Crowe (201) cites an instance of a groom who was seized with asthma each time he was in proximity to horses. During the war, he was sent to the front and allowed to pursue his usual vocation, which he did, without the return of his trouble.

Hyde Salter (202) expressed the opinion that he had no doubt of heredity. He found a family history in 38 per cent of his cases. He remarked that the number of cases with familial incidence was greater than would be accounted for by chance.

Coca, Walzer and Thommen (203) have collected the records of thirty-three post mortem examinations of asthmatics. Of these, the family history is mentioned in twenty. Seven or 35 per cent of the latter showed a positive history in a parent or collateral. In thirteen or 65 per cent, the history was negative.

The histories were examined of 200 asthmatic patients under the age of sixteen, taken from the case records of Dr. James Adam, to whom I am greatly indebted for the material. Of these, 126 or 63 per cent were males and 74 or 37 per cent were females. A family history of asthma or associated disease was obtained in 30 per cent of the cases. In 14 per cent, the affected relative was a first relation. 100 cases were selected in whom the family history was recorded in detail. It was observed that 25 per cent were "only" children and in addition, in a large proportion the patient was the elder of two. Three or 12 per cent of the only children had a positive family history. In the group of 25 per cent "only" children, 60 per cent gave a history, past or present, of other symptoms of the allergic type, from which fact it may be assumed that "only" children are more prone to allergic disease, than others. The age of onset of asthma in the group of positive family history was compared with negative. In the former, it was 4.6 years and in the latter, 4.8. The close similarity in the ages of onset, agrees with the opinion of other observers that age of onset is not influenced by heredity, and contrasts with the opposite view held by Cooke and Vander Veer and Spain and Cooke. It was noted that in only 14 per cent, the affected relative was a parent or sibling. 494 relatives were embraced in the survey, and of these, 49 had symptoms, giving an incidence of 10 per cent, a figure comparable with the incidence of allergy

in the normal population. The average eosinophilia count for patients with affected relatives was 8 per cent, and for those without affected ancestry, 7.6 per cent. The results of the investigation of this series of cases indicate that no distinction can be made between the so-called hereditary and non-hereditary types, and that heredity as a factor in the pathogenesis of the disease must be held to be doubtful in the majority. The facts are rather in accordance with the supposition that environmental influences are more potent, for the group of "only" children of this series show a more pronounced tendency to acquire the allergic diseases in general, than other children.

The following case history taken from this series, is instructive (1572):-

> Male, age 10, asthma 7 years, suffered also from chilblains and eczema. Paternal grandfather, eczema; paternal uncle, asthma for eighteen years, now free; maternal uncle, hay-fever; brother and sister symptomless. Asthma first began after meals. After one year's treatment, the patient is asthma-free, and eosinophils reduced from ten to four per cent, a point of favourable prognostic import.

In this case, in spite of a strong bilaterally affected ancestry, the child has responded successfully to treatment.

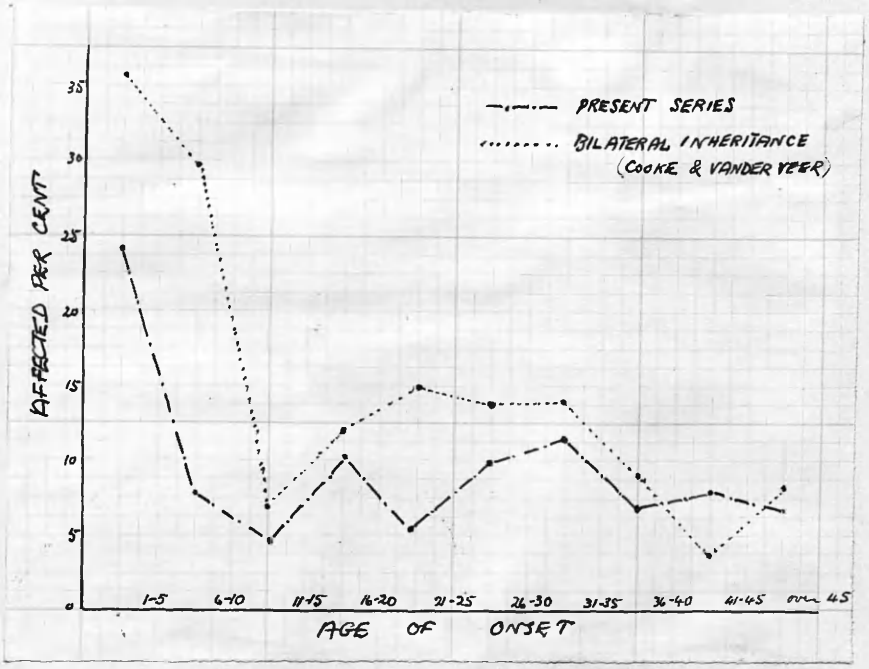
The present investigation is based on a series of ninety asthmatics, the majority of whom were investigated in Stobhill Hospital, Glasgow. To conform to the requirements

of other authors, a history of asthma, hay-fever, eczema, urticaria, migraine, vasomotor rhinitis and food-upsets was inquired for in the patients and relatives. A family history of one or more of these conditions was obtained in 34.5 per cent of the cases. The average age of onset was 24.2 years, an age slightly younger than that given by Cooke and Vander Veer and Spain and Cooke, although the familial incidence of the former authors was given as 48.4, and of the latter, 58.4 per cent. Hay-fever occurring as a complication of asthma was found in 7.7 per cent of the cases. The total number of relatives was 665, and the number affected 55, giving a percentage incidence of 8.2 per cent. Bray obtained 14.3 per cent affected individuals amongst the relatives of his allergic patients. It will be remembered that an incidence of 7 to 14 per cent of hypersensitivity in the relatives of normal people, was the presumed proportion.

A curve showing the age of onset in the patients of this series was plotted against and compared with that obtained in the bilateral inheritance cases of Cooke and Vander Veer. It is observed that the form taken in both is similar, contrary to what might be expected from the opinions of these authors.

The figure for morbidity in relatives obtained

in the 90 asthmatics of this series is lower than that of the majority of other authors. Possibly, the fact that a



large number of the patients are of the hospital class accounts for an increased difficulty in procuring information regarding illnesses in other relatives. It was seen th at the percentage of affected relatives was 8.2, a figure which could hardly be made to approximate to the Mendelian requirements. Even Bray's estimate of 14.3 per cent is still far below the required ratio, and much less than those given by the American allergists.

Summaries of the personal and family histories of the patients are recorded in the following tables.

□	=	Male
○	=	Female
■ ●	=	Affected Person
↖	=	Patient
F.	=	Father
M	=	Mother
B	=	Brother
S	=	Sister
Dtr	=	Daughter
G.F.	=	Grandfather
G.M.	=	Grandmother
Pat	=	Paternal
Mat	=	Maternal
Lt.	=	Light
D	=	Dark

TABLE 3. SHOWING DETAILS OF FAMILY HISTORIES.

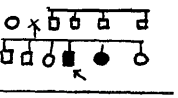
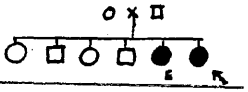
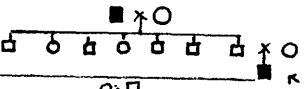
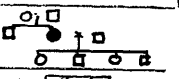
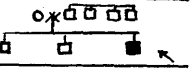
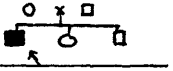
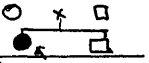
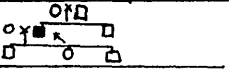
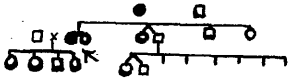
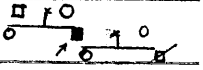
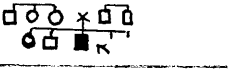
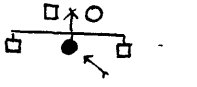
Case No	Age	Age at Onset	Relatives			Associated Symptom	Symptom of Relative	Pedigree
			Total	Aff.	Unaff.			
1	34	31	10	1	9		Sister Asthma	
2	29	28	7	1	6	Hay-fever	Sister Eczema	
3	10	1	10	1	9		Pat.G.f. Asthma	
4	48	44	7	0	7			
5	28	27	8	0	8			
6	60	57	4	0	4			
7	44	26						
8	40	39	3	0	3			
9	53	48	6	0	6			
10	57	51	19	1	18		Mother Asthma	
11	6	2						Adopted child
12	59	57	5	0	5			
13	8	3	7	0	7			
14	26	5	2	0	2			
15	33	25	4	0	4			

TABLE 3. (Contd.)

Case No.	Age	Age at Onset	Relatives			Associated Symptom	Symptom of Relative	Pedigree.
			Total	Aff.	Unaff.			
16	36	36	8	1	7			
17	6	3	6	3	2		F.Asthma Pat. G.M. Asthma	
18	11	9	6	0	6			
19	14	7	13	0	13			
20	25	24	7	0	7			
22	47	44	5	0	5	Aspirin Sensitive		
21	38	30	5	0	5			
23	59	58	8	1	7		Mother Asthma	
24	39	19	25	1	24		Brother Asthma	
25	6	3	18	2	16	Eczema	Mat.G.F. Asthma M.Migraine	
26	32	31	7	0	7			
27	48	38	42	9	33	Hay-fever	8 relatives Asthma.	

TABLE 3. (Contd.)

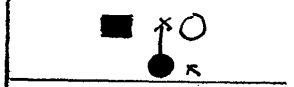
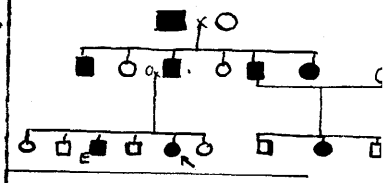
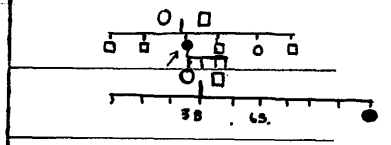
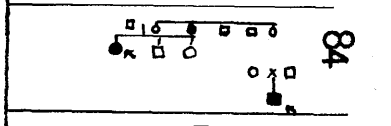
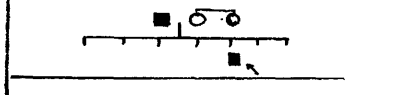
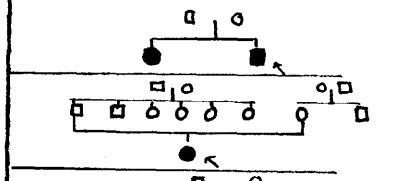
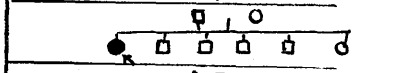
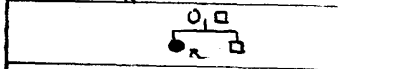
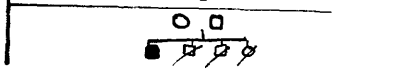
Case No.	Age	Age at Onset	Relatives			Associated Symptom	Symptom of Relative	Pedigree
			Total	Aff.	Unaff.			
28	4	2	2	1	1		Father Asthma	
29	19	1	17	7	10		Pat.3 uncs. 1 aunt 1 cous. asthma 1 cous. Eczema	
30	50	39	11	0	11			
31	44	14	9	0	9			
32	22	11	8	1	7			
33	55	33	2	0	2			
34	11	5	9	1	8		father asthma	
35	55	37	3	1	2		sister asthma	
36	3	1	12	0	12	urticaria		
37	32	6	7	0	7			
38	29	19	3	0	3			
39	41	31	2	0	2			

TABLE 3. (Contd.)

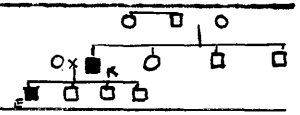
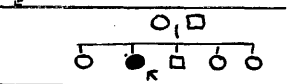
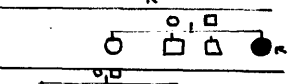
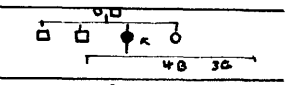
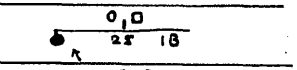
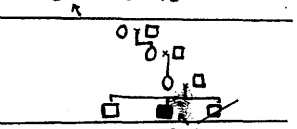
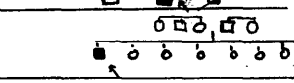
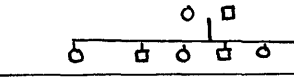
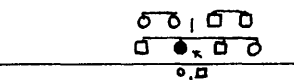
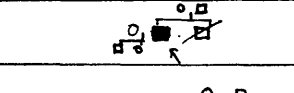
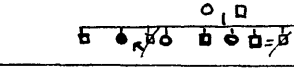
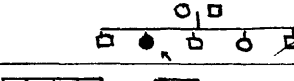
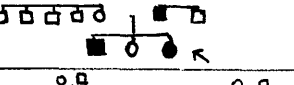
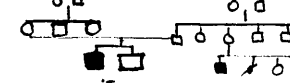
Case No.	Age	Age at Onset	Relatives			Associated Symptom	Symptom of Relative	Pedigree.
			Total	Aff.	Unaff.			
40	48	28	10	1	9		Son Eczema	
41	31	23	6	0	6	Hay-fever		
42	17	17	5	0	5			
43	48	46	12	0	12			
44	30	20	5	0	5	Hay-fever		
45	7	1	8	1	7	Hay-fever	Pat.G.F. Asthma	
46	44	42	11	0	11			
47	22	5	7	1	6		Sister Asthma	
48	32	32	7	0	7			
49	32	30	5	0	5			
50	39	37	10	0	10	Aspirin Sensitive		
51	59	59	5	0	5			
52	26	19	9	2	7	Hay-fever	F.Asthma B.Asthma	
53	12	2	19	1	18	Urticaria	Cous.Asthma	

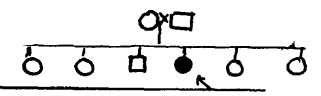
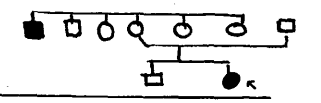
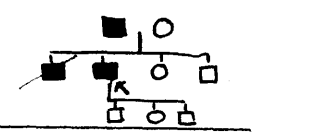
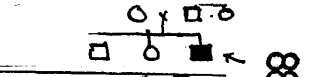
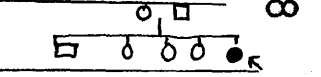
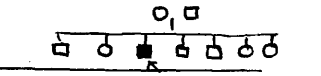
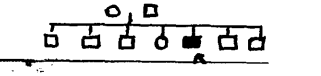
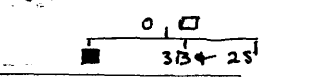
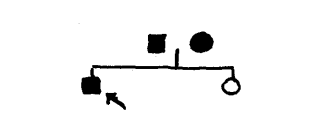
TABLE No. 3 (Contd.)

Case No.	Age	Age at Onset	Relatives			Associated Symptom	Symptom of Relative	Pedigree
			Total	Aff.	Unaff.			
54	34	33	6	1	5		Sister Asthma	
55	49	39	14	0	14			
56	1	1	12	1	11	Eczema	Mat. uncle asthma	
57	43	34	6	0	6			
58	49	43						
59	44	43	2	0	2			
60	54	53	11	0	11			
61	21	20	6	0	6			
62	52	42	8	0	8			
63	23	18	4	0	4			
64	39	32	7	1	6		Father asthma	
65	13	7	3	0	3			
66	50	35	4	0	4			
67	42	42	2	0	2			
68	31	30	5	1	4		Brother asthma	

TABLE 3. (Contd.)

Case No.	Age	Age at Onset	Relatives			Associated Symptom	Symptom of Relative	Pedigree
			Total	Aff.	Unaff.			
69	11	2	4	0	4			
70	40	33	9	0	9			
71	34	24	8	2	6		Father and Broth.Asth.	
72	63	61	6	0	6			
73	14	14	4	0	4			
74	21	6	5	0	5			
75	21	19	9	3	6		Brother h.-fever Bro.asthma Pat. G.M. Asthma	
76	26	25	5	0	5			
77	13	2	2	0	2			
78	31	27	10	0	10	Hay-fever Rhinorrrhoea		
79	35	28	6	0	6			
80	38	28	9	1	8		Father Asthma	
81	18	12	9	1	8		Pat. aunt Asthma	

TABLE 3. (Contd.)

Case No.	Age	Age at Onset	Relatives			Associated Symptom	Symptom of Relative	Pedigree
			Total	Aff.	Unaff.			
82	26	16	7	0	7			
83	3	1	8	1	7		Mat.uncle Asthma	
84	62	40	8	2	6		Brother Asthma Father Asthma	
85	12	3	5	0	5			
86	51	2	6	0	6			
87	24	18	8	0	8			
88	30	25	8	0	8			
89	47	40	7	0	7			
90	38	31	3	2	1		Mother Asthma Father Asthma	

The incidence of positive family histories obtained by various authors is presented in summary:-

Berkart	...	14 per cent
James Adam	...	26 " "
200 cases under 16 years (James Adam's) analysed by author	...	30 " "
33 post-mortems in which family history mentioned in 20 (Coca, Walzer, and Thommen)	...	35 " "
Present series	...	34.5" "
Rackemann	...	42 " "
Adkinson	...	48 " "
Cooke and Vander Veer	...	48.4" "
Van Leeuwen	...	50 " "
Vaughan	...	58.4" "
Spain & Cooke	...	58.4" "
Balyeat	...	60.1" "
Bray	...	68.5" "
Kahn	...	100 " "

Buchanan:- "Asthma follows none of the known laws of heredity".

It will have been seen from the foregoing pedigree studies, that the evidence in support of the inheritance of asthma according to Mendelian law, is not conclusive. It has been suggested by some that multiple factors may be involved, and that the combination of certain types is required to produce hypersensitivity. It has been shown by comparative experiments with plants and simple animals that this might hold good for at least some characteristics, but hitherto there has not been sufficient evidence forthcoming to substantiate the hypothesis as applied to man. For those who believe in the inheritance of asthma or allergy, there are many phenomena for which no explanation has been found. Some of these have been discussed previously. In pedigrees showing the occurrence of allergy in more than one generation, there is frequent skipping of a generation, but much more frequently than in diseases in which inheritance is indubitable. In Drinkwater's (204) pedigree of brachydactyly there is no skipping, and in Crowder and Crowder's (205) family of angioneurotic oedema containing twenty-eight cases in five generations and showing clear evidence of a simple Mendelian dominant, there is likewise no skipping. In the brachydactyly family, affected individuals mated with normals give 50 per cent affected offspring and 50 per cent unaffected, but the unaffected in no case produced affected individuals in the third generation. Once the condition disappeared, it did so

completely and irrevocably. Here, obviously, a simple dominant was involved, and the facts are in agreement with Blacker's (206) statement that a true dominant trait is not "Carried". and it can be prophesied with certainty that those members of a family who do not exhibit it will not transmit it. To accept Blacker's statement means that one must discard the many instances in which the evidence of heredity is adduced from the occurrence of the condition in collaterals, and so reduce considerably the figures for positive family histories. The acceptance of the hypothesis of the heredity of asthma is beset with still further difficulty, namely, the process whereby transmission is achieved. A brief review of the evolution of hereditary characters is apposite.

There are, at present, several schools of thought regarding the inheritance of new characters. The first is Darwin's theory of the "survival of the fittest" by which is understood the acquisition of somatic characters by natural selection to combat the hazards of the environment; and once formed, the transmission of these characters to the offspring. This theory postulates the presence of suitable characters to be chosen by the individual as necessity arises, since the function of natural selection is selection and not creation. Darwin's theory, therefore, does not explain the phenomena of the evolution of new characters. Lamarck maintained that structures developed or atrophied according to usage.

and the habit of the individual and that the new characters passed on in reproduction. Acceptance of this hypothesis necessitates the acceptance of its logical sequel that changes in the soma acquired during the lifetime of the individual can so influence the germplasm or gonads to secure the transmission of the acquired character to the progeny. This has been strongly controverted by Bateson, Punnett, De Vries and others (207). De Vries originated the "mutation theory" to explain the origin of new characters. According to De Vries the appearance of new characters, or "sports" in a particular species, can occur only as a result of a sudden change or mutation in the gene in the process of formation of the zygote; and that the germplasm, once formed, is distinct and separate from the soma and incapable of being influenced by it. The mutation theory is accepted by the majority of evolutionists, but as an explanation of the sudden appearance of asthma or its allied disorders, or its equally sudden disappearance in affected families, the theory is inadequate if other factors are not involved. Prof. E.W. McBride has taken a contrary view of the evolution of fresh characters. In an interesting paper entitled "Habit, the Driving Factor in Evolution" (208) he argues strongly in favour of Neolamarckism(fluctuations of Punnett), of the effect of habit and environment in the development of new characters and the possibility of transmission of these

latter to the offspring. He shows that from the examination of local races, taking the two types of eel as an example, that the morphological configuration of the animal corresponds to the habits of the species, and, from the examination of strata in geological formations, he has pointed out that changes in the teeth and feet of the camel have taken place in a manner appropriate to its change in environment — from the soft succulent food of swampy land, to the harsh herbage and hard unyielding ground of the steppes. He refers to the experiments of Dürkhen with the white butterfly and reports that according to the colour of the light in which the butterfly reproduces, so the colour of the pupae are modified, and that this colour change is passed on more completely to the third generation. When the butterfly is returned to normal conditions, the pupae still show the effects of the habit acquired by the parental generation. Dürkhen, he states, concludes that when a habit is acquired by one generation, the second generation exposed to the same conditions, acquires the habit more quickly and thoroughly. Finally, MacBride cites in support of his thesis, that certain fish in the Indian hill rivers have developed suckers to cling to the rocks and the degree of development corresponds to the velocity of the current. Experiments, similar to Dürkhen's have been made by Heslop Harrison with the gall-fly, Metalnikoff, Nuttall and others, with moths, loc.cit. Durkhen, MacBride and other experimentalists are convinced by these

results that ingrained habits are inherited and " to prove that habits and mode of growth in one generation do affect the next, all we require to show and all we could expect to see, would be that there was an intensification of the effect when the exposure to the new environment was continued ~~was continued~~ for several generations and a lag in the resumption of typical characters when the offspring of individuals which had been exposed to the new environment were replaced in the typical environment." (MacBride, loc.cit.)

These examples amongst others, appear to indicate that evolution occurs by a series of minute changes occurring in an orderly fashion, and cast doubt on the hypothesis that change in the soma can result only after mutation in the zygote. The likelihood of both processes operating, mutation and the influence of habit, must be kept in mind, and it is possible that as MacBride emphasizes, the gonad, although essentially distinct from the soma, might be influenced by environmental requirements, provided the transition from one morphological state to another is gradual and spread over a sufficiently long period of time.

These problems of heredity must be in the forefront of one's mind when one examines the occurrence of an ailment in more than one member of a family. Does the sudden appearance of allergy, or in particular, asthma, in a member

of a family hitherto healthy, indicate a mutation in the chromosomes of that person or the detrimental influence of some extrinsic factor or factors as infection, unhealthy nose, overloaded metabolism etc., and if the disease appears in the offspring, what conclusions is one to draw? Does it imply true Mendelian heredity or the continuation in the new generation of the faulty habits which caused the asthma in the parents, the progeny having acquired the condition with greater facility as a consequence of the continuation of the "driving force", as MacBride has shown. Experience in the treatment of the disease supports the latter assumption for results are obtained which would hardly be possible if the hereditary influence were stronger than the environmental. James Adam (209) reports that at least 90 per cent of asthmatic children can be permanently cured by regulation of habits and feeding in spite of family history, provided treatment commences before the age of sixteen, provided there is no mouth breathing and no deformity to prevent an active outdoor life; and La Forge(210) states" that heredity is not a prognostic factor. The asthmatic is made and not born. Certain conditions," he says, "produce asthma, and their correction willeradicate it regardless of the number of ancestors in whom such correction was not accomplished." These results contrast markedly with those of allergists. Desensitisation and avoidance can give only 30 per cent of permanent cures or relief for many years, in expert hands, (Coca, 211) and it

is probably for this reason that they attach the major responsibility to heredity. Recent research has been directed to the discovery of the nature of the allergic reaction rather than to the nature of the condition predisposing to it; and by the majority the outlook has been tempered by the initial assumption that the disease is hereditary.

LINKAGE OF CHARACTERS

A brief series of asthmatic patients and their relatives have been investigated for data which it was thought might be helpful to elucidate the problem.

It is common knowledge that physical characteristics tend to be transmitted from parents to children in groups. Stature, colour of hair, colour of eyes frequently resemble one parent more than another, and similarly for other characters. Linkage, in the modern sense, was first recognised by Bateson and Punnett in 1906. They noted (212, 213) that certain features of the members of a family are associated with each other in groups. This association of characters from the biologic standpoint implies the association of genes or allelomorphs* on one chronosome, or, as

- - - - - - - - - - - -

*Allelomorph:- In Mendelian inheritance, one of a pair of contracted characters which become segregated in the formation of germ cells. (Gould's Medical Dictionary)

Sutton (214) puts it "All the allelomorphs represented by one chromosome must be inherited together", and further "The same chromosome may contain allelomorphs that may be dominant or recessive independently". Accordingly, it was speculated whether asthma was associated with any known heritable property, since the finding of such a relationship in families with a high incidence of asthma or its allied disorders would afford strong evidence of a definite heritable factor in the pathogenesis of the disease. For this purpose, the blood groups or isoagglutinating elements of the blood were selected, since it has been proved by von Dungern and Herzfeld (215) that the law governing the inheritance of blood groups follows that of a single Mendelian dominant, and behaves as a unit in the process of crossing during the formation of the zygote (216). Moreover, the type of blood group possessed by an individual is easily determined. The colour of the hair and of the eyes were noted simultaneously, since these also are believed to follow the laws of heredity, although too often difficult of interpretation. Malignancy, mental deficiency, diphtheria (217), hay-fever (v. infra), goitre and other diseases have been investigated in respect of inheritance from this angle, but no linkage has been discovered. Snyder (218) states that blood groups are independent of eye colour.

Knowledge of the blood groups originated with

the work of Landsteiner and Shattock (1899) and much information has been added since then by such pioneers as Moss, Jansky, Bernstein, von Dungern and Hirzfeld. There are four types of isoagglutinins of the red corpuscles, named in international terminology, A, B, AB, O. The groups A and B are each dominant to their absence (219), and in their transmission through successive generations, follow the laws of Mendel.

In the series of group determinations carried out by the author, the technique recommended by Lattes (220) was followed. The blood to be tested was drawn off into a sterile tube containing citrate solution, and centrifuged. Thereafter, the corpuscles were washed once with normal saline, centrifuged again, and a 1-30 suspension in normal saline prepared. To begin with, the haemagglutinating test-sera were obtained from a well-known manufacturer, subsequently, it was prepared from patients of known type between ages 20-35 to ensure a high titre of agglutinin, as follows:-

The blood was withdrawn with aseptic precautions and allowed to stand for several hours at $0^{\circ}C$ to permit absorption of the auto-(pan) agglutinins. The serum was then separated and transferred to capillary tubes.

The 1-30 suspension of corpuscles to be tested was mixed with one drop of a 1-2 dilution of each of the sera

of types A and B. A drop of normal saline was used as a control. The slide was gently agitated and the mixtures observed by the naked eye for a period up to half-an-hour if necessary. When agglutination occurred, the result was indubitable in the great majority of cases. Where there was doubt, observation under the microscope was employed .

In all, 50 group determinations were carried out. This number represented 19 families, so that in most cases only a few representatives of each family were examined. The 50 individuals from a total of 705 patients and relatives constitutes only a small proportion of the whole, but this is accounted for by the extreme difficulty encountered in persuading relatives, both private and hospital, to present themselves for examination. The results are presented in the following tables with the observations on eye and hair colours.

TABLE 4. Showing Blood Groups, Colour of Hair and Colour of Eyes

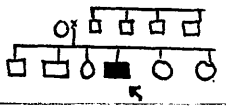
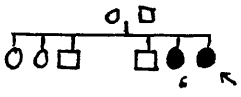
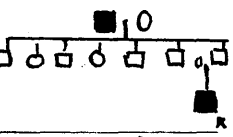
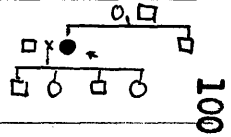
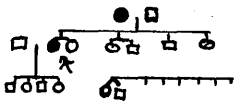
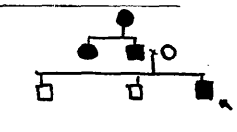
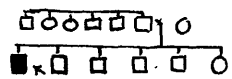
Case No.	Age at Onset	Assoc. Symptom	Relatives			Blood Group	Colour of		Symptom of Relatives	Pedigree
			Total	Aff.	Unaff.		Hair	Eyes		
1	31		10	1	9	Pat.....A Aff.S..B Unnaf S..A	black black black	brown brown grey	Asthma	
2	28	hay-fever	7	1	6	Pat.... O Aff.S.. O	black fair	grey blue	Eczema	
3	1		10	1	9	pat.... O F..... O M..... A	brown " black	brown " grey	G.F. pat. Asthma	
4	44		7	0	7	Pat.... A Son.... A Dtr.... A Son.... O	red fair red brown	hazel grey bl.gry. blue		
10	51		19	1	18	Pat.... A S(twin) A	brown "	gr.bl. "	Mother Asthma	
17	3		7	1	6	Pat..... M.....	fair "	gry.bl. "	Father Pat.G.M. & aunt Asthma	
19	7		13	0	13	Pat.... O M..... A F..... O B..... O S..... O B..... B..... B.....	brown " " " " " " "	bl-gry blue Bl-gry Blue " " " "		

TABLE 4 (Contd.)

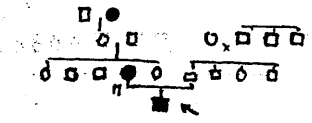
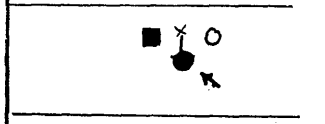
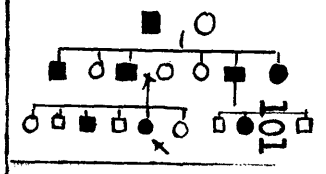
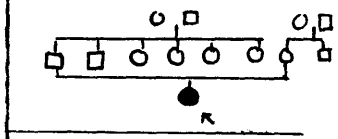
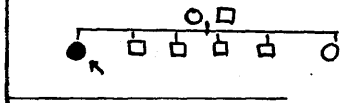
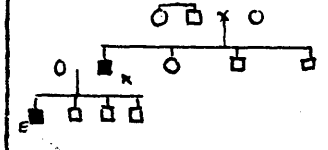
Case No.	Age at Onset	Assoc. Symptom	Relatives			Blood Group	Colour of		Symptom of Relatives	Pedigree
			Total	Aff.	Unaff.		Hair	Eyes		
25	4		18	2	16	Pat.... O F..... O M..... O	brown " "	bl-gry " "	G.G.F.(Mat) Asthma M.Migraine	
28	2		2	1	1	Pat.... A F..... A M..... O	lt.brn d.brn brown	gr-brn. lt.brn. gr-brn	Father Asthma	
29	1		17	8	9	Pat.... A	black	brown	Father, 3 uncles, 1 cousin, G.F. all pat. asthma B.Eczema	
36	1	urtic.	12	0	12	Pat.... A F..... O M..... A	fair brown fair	bl-gry hazel bl-gry		
37	6		7	0	7	pat... AB M..... A S..... O B..... A	black " lt.brn red	brown " d.brn. blue		
40	28		6	0	6	Pat.... O Wife... O Son.... O Son.... O Son.... O Son.... O	black lt.brn black " " "	brown grey brown " " "		

TABLE 4 (Contd.)

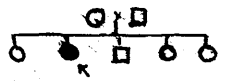
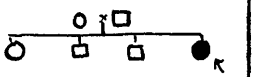
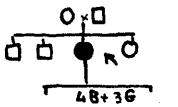
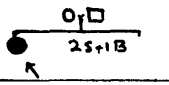
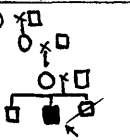
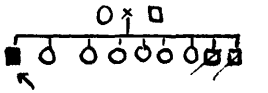
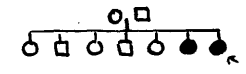
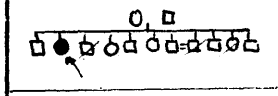
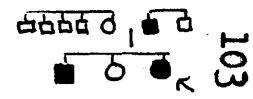
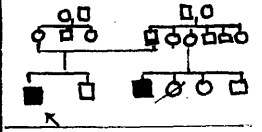
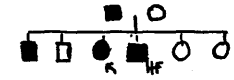
Case No.	Age at Onset	Assoc. Symptom	Relatives			Blood Group	Colour of		Symptom of Relatives	Pedigree
			Total	Aff.	Unaff.		Hair	Eyes		
41	23	hay-fever	4	0	4	Pat... B F..... M.....AB S.....AB S.....AB	black " " "	brown " " "		
42	17		5	0	5	Pat... S..... B..... B....	fair " D." "	blue brown d.brn. "		
43	46		12	0	12	Pat... A Husb.. O Son... O Dtr... O	l.brn black brown "	blue brown blue "		
44	20	hay-fever	5	0	5	Pat... S..... B..... S.....	black " " "	hazel " brown blue		
45	1	hay-fever	8	1	7	Pat... O M..... O F....	brown black fair	blue " grey	G.F.(pat.) Asthma	
46	42		11	0	11	Pat... S..... S..... S..... S..... S..... S.....	black " " " " " "	brown " " blue " "		

TABLE 4 (Contd.)

Case No.	Age at Onset	Assoc. Symptom	Relatives			Blood Group	Colour of		Symptom of Relatives	Pedigree
			Total	Aff.	Unaff.		Hair	Eyes		
47	5		7	1	6	Pat.... A S..... A	D.Brn black	Brown "	Sister Asthma	
50	37		10	0	10	Pat.... A B..... A B..... O				
52	19	hay-fever urtic.	9	2	7	Pat.... O F..... A B..... M..... O S....., O	black " " l.brn. brown	blue brown " blue brown	Father and brother asthma	
53	2	urtic.	19	1	18	Pat.... F..... M..... B.....	fair " " "	grey bl.gry " "	cousin asthma	
75	19		9	3	6	Pat.... A M..... B	brown black	blue hazel	father and brother asthma, brother hay-fever	

Blood Groups. The percentage proportion of the four groups in this series are Group A; 41.5, Group B, 5.2, Group AB, 7, GroupO, 46.5. These figures are in accordance with those given for European races.

Summary of results of Table IV :-

Five groups in which hypersensitivity occurred in two or more members of a family. Of these , the blood group was the same three times, case nos. 2, 28, and 47, and different twice, case nos., I and 52.

In eight groups, the blood groups of the patients and relatives were the same, but no symptoms occurred in the latter, case nos., 4 I0, I9, 36, 37, 40, 43, and 50.

In two groups, the blood groups of the patients were different from those of the relatives who were not affected, case nos., 37 and 41.

In two groups, the blood groups of the father and mother were the same as that of the patient, and therefore valueless in the study, case nos., 25 and 29.

In case no. 75, the antecedent asthma was paternal. The father was not available for typing , but presumably had the same group as the patient.

Case no. I0 is notable inthat the relative examined was an identical twin, but had no asthma or allied disorder.

Colour of Hair. Twenty three groups were studied, comprising eighty-one individuals. In five groups, patients and

relatives were the same, and therefore were not available for consideration, case nos. I, I9, 25 and 53. In four groups in which patients and relatives had symptoms of hypersensitivity, two had thesame hair colour, nos.47 and 52, and two different, case nos., 2 and 28.

In ten groups, the colour of hair in patients and relatives was the same without the latter ing suffering; case nos. 4, 10, 36, 37, 40, 41, 42, 43, 44, 46.

In ten groups, the colour was the same as the relatives in whose antecedent the asthma occurred, case nos. 3 and 45.

Colour of Eyes. Twenty-three groups, eighty-one individuals. In five groups, with patients and relatives having symptoms, the colour was the same in two, case Nos. 28 and 47, and different in three, case Nos., 28 and 47, and different in three, case nos., 2, 29, and 52.

Colour of eyes of patients and relatives similar, but no symptoms in the latter, case nos., 4, 36, 37, 41, 44, and 46.

Colour same as relative in whose antecedent the asthma occurred, case nos., 3 and 45.

In one group, the eye colour was different from other sibs who had no symptoms, case no. 42.

In cases 25, 40 and 53, relatives and patients had the same colour and therefore could not be considered.

The conclusions drawn from this brief genetic study

are that there is no relationship or linkage between the members of a family affected with asthma and its allied disorders and

1. The type of blood group inherited,
2. The colour of the eyes inherited,
3. The colour of the hair,

and therefore, no support for the hereditary theory of the asthma group of diseases can be adduced.

The failure to find linkage between asthma and the blood groups agrees with the result obtained by Levine (221) in his study of hay-fever. Levine examined twenty families in which at least one parent and one child were affected by pollen-fever. He excluded from his consideration those families in which parents possessed the same blood group. In six of his families, the normal parent was not available for grouping. Having assumed the heredity of hay fever, or atopy, he concludes that (a) the atopic offspring need not inherit the blood group of the atopic parent, and (b) atopic dominance may be connected with either of the factors of the blood groups or their allelomorph.

With regard to eye and hair colours, the analysis indicates that the colour properties of asthmatic patients resemble those of unaffected relatives as frequently as affected, and accordingly the same conclusions must be

drawn as in the blood group study.

ASTHMA IN TWINS.

A study of twins has been made by many genetists for the purpose of evaluating the hereditary factor in certain morbid conditions. The occurrence of facsimilar cancers in uniovular twins has been noted from time to time, and cases of tuberous sclerosis, and congenital pyloric stenosis in identical twins have been recorded recently.

In the consideration of twins, the distinction between binovular and uniovular (identical) twins must be remembered. Concordance of disease in twins need not necessarily imply a hereditary factor, but may only signify an environmental influence acting on both members simultaneously. On the other hand, the presence of the disease in one member of uniovular twins, under similar conditions of nurture, must be interpreted as signifying the unlikelihood of a hereditary causal factor. In a genetical approach to the pathogenesis of tuberculosis, a hundred and twenty-seven pairs of twins were studied by Diehl and v. Verschuer (222) who found after careful analysis that when environmental conditions of a pair of twins were such as to warrant the expectation of the disease in both, yet only one was tuberculous, by far the greatest proportion of cases occurred in binovular twins.

It is obvious that information derived from the investigation of uniovular twins is of greater value than from binovular twins.

The case records of Cooke and Vander Veer contain six pairs of twins summarised below, but no mention is made whether or not any are identical.

Case No.	Antecedent Sensitization	TWINS	
		a	b
144	Pat. and Mat	late h.f.	Same
336	Neg.	Urtic.-fish	Norm.
393	Pat. uncle	Early h.-f.	Norm.
500	Mat.G'mother	Late h. f.	Same.
622	Mat. aunt	Asth.-horse	Norm.
629	Pat. Gt. aunt	Early and late h.f.	Same.

Their findings indicate to them that no claim can be made for an inheritance of a specific sensitization. In only three of the six pairs does hypersensitivity occur in both members; in only one is inheritance directly antecedent.

My own series includes one pair of twins, proved to be identical by reason of(a) the close similarity of appearance — as girls they were distinguished by the presence in one of a deformed finger —, (b) identical hair colour

(c) identical eye colour (d) identical Blood group. (Weichmann and Pall, 223, accept blood groups as proof of identical twins).

Asthma occurred in only one. Her case notes are as follows:-

> Case No.10. Female age 58; onset of asthma seven years before. Only other illness, gall-stones when age 55. Her mother had asthma, otherwise the family history was negative for allergic diseases. Achlorhydria was present. She responded successfully to treatment.

In this case it is to be noted that the asthma did not commence before middle age, that is at a time later than would be expected had the condition been of hereditary origin. The age of onset would indicate, rather, nutritional faults. Had the asthma been hereditary, it is likely that both members of the identical twin would have acquired it. The different habits of life occasioned by their marriage might be supposed to be the reason for the disease in one and not in the other.

The following case, although not an instance of twins illustrates the same point.

> Case No.78. Female, 31 years, married, two children. Measles, whooping cough and chicken pox in childhood. Urticaria and appendicitis at 17 years. Septum resected seven years ago. Now suffers from vasomotor rhinitis and hay-fever. Asthma commenced four years ago six months after first confinement. Milk causes

wheeze, so seldom takes it. Has no exercise apart from a moderate amount of walking. Attacks at least once weekly, mostly at the week-ends. Turbinates enlarged. Family history negative for asthma in father and mother, five brothers and three sisters. Patient was adopted as an "only" child when six years old and lived apart from her relatives. She was much coddled and indulged. Regulation of diet, increased exercise and weekly mercurial has caused almost complete cessation of attacks.

SUMMARY AND CONCLUSIONS

The question of the inheritance of asthma has been in the mind of clinicians for very many years. The early observers reached their conclusions from observation of the frequency of the ailment in the relatives of sufferers. With increase in knowledge of allied disorders, nowadays grouped under the term "allergy", new data has been acquired by extending the survey to the whole group of ailments with resulting increased figures of incidence. The hereditary factor has been assessed variously from 14 to 100 per cent, partly according to the number of conditions embraced by the particular author's conception of the disease group, partly by ignoring the environmental conditions in various countries, and possibly by grouping under the label "asthma" totally different morbid states. Generally speaking, the larger figures are given by the supporters of the allergic theory and the smaller by those who consider the group to be the expression of a basic biochemical aberration of which allergy is symptom and bronchospasm a culminating event. In the survey of etiological factors, it will have been observed that each theory purporting to explain the ultimate cause of asthma can be supported by more or less convincing evidence to

warrant its assumption. In some, such as toxaemia and infection, the theory explains the cause of the metabolic upset; in others, like the exudative and allergic diathesis, the result, so that at the end of an enquiry into the pathogenesis of the disease, the impartial observer concludes that for asthma, as for its associated ailments, there is no single cause, and the success in treatment of alleviation of the trouble depends on the ability to locate the source of the fault. Special attention has been devoted to the discussions on allergy and toxicosis, for on the first depends the evidence produced in modern statistical studies to support a claim for heredity, and on the latter the justification for the hypothesis that the environmental are of greater importance than the inborn hereditary factors. An attempt has been made to disprove the view that allergy is a primary condition because of its implications, and case histories have been recorded to show the lesser value of the allergic approach to asthma, in practical medicine. The experiences of several prominant workers in the field of allergy have been cited. It has been pointed out earlier in this thesis that a family history of a disease is not proof of heredity, but that it often means traditionally inherited habit, or the effect of extrinsic influences exercising their effects on a group of people in proximity to each other. It has been noted in the course of reading on the subject of asthma, that the prevalent idea of the

striking inheritance figures for this disease is based to a large extent on the pedigree studies of Cooke and Vander Veer and Spain and Cooke, and that their views have been adopted by many authors and copied from book to book without adequate investigation. The statistics of these authors, as also of others have therefore been studied, with the resulting opinion that their evidence is in some part biassed by material not evaluated in its proper perspective. It has been pointed out that Cooke and Vander Veer's asthmas were complicated by hay-fever in 80 per cent of the cases and that further and more complete investigation would be necessary before a final decision could be made. The inclusion of other diseases like migraine and eczema, not yet proven to be allergic except in a minority of instances has further complicated the matter; but even with those, I have not been able to reach a figure near those of Cooke and Vander Veer, nor of Bray and his co-workers who are in agreement with the American ideas. The 200 case records of Adam and the Edinburgh investigation give figures much below these. One is therefore compelled to suppose that some other factors are at fault. Recently, Bray has volunteered the information that nearly 60 per cent of his children are "only" children, or first children, and much coddled and over-protected, an opinion for long emphasized by Adam, while the cases of Ancona amply demonstrate that heredity endowment is not necessary

for the acquisition of allergic symptoms, and that massive or lengthy exposure is sufficient. From this latter point of view, then, may be explained the greater frequency of hay-fever in the U.S.A., for in many parts of that country, ragweed, the principal offender, is found in abundance in every patch of uncared-for land, while the habits of the people suggest faults in the manner of living, a view which derives support from the fact of the absence of hay-fever in the Indians of the reservations, and of the comparative freedom also, of those for whom geographical conditions would be expected to produce a more intense effect.

Experimental work, on the whole, rather favours the environmental aspect; and here the work of Brodie and Dixon and Kenneth Phillips (page 56) has been outstanding. In the field of allergy, the cutaneous tests have been found to be more frequent in allergics and their relatives than in normal people, evidence which has been accepted by many to indicate an hereditary endowment. The fact of its occurrence in non-allergics disproves this, and raises the issue of some other factor common to both groups. To revert to the subject of individual pedigrees, such as those recorded by Drinkwater and Fantham and those of my own (cases 27 and 29), it would appear that a hereditary causal factor is important in some cases. These instances are published in virtue of their rarity. In 620 cases of Cooke and Vander Veer, there

is recorded only one instance in which four out of five siblings had symptoms. Geneticists warn us against generalisations on the strength of isolated instances. But even in spite of this warning, should we be convinced that there is an hereditary factor, a knowledge of the original causation is no further advanced by introducing this element, for a time must be reached in every family where there was no evidence of any predisposition, except we accept the mutation theory. If mutation occurs, it must do so very often. I have not been able to find a reference of any one accepting this theory in regard to asthma. More reasonable in my opinion is the assumption of the continuation in each generation of affected families of vicious nurture, an assumption which derives much support from MacBride, who maintains that habit is the driving force in evolution, and from Adam, La Forge, Haseltine and others who have proved in practice that the correction of faulty habits in the affected children of affected parents leads to permanent success in spite of the tainted ancestry. McDowall believes this practical test rather emphasizes the acquired aspect, and I agree with him, for a characteristic which has as its foundation a definite bioplastic variation in the chromosome, would not be so easily influenced.

The investigation of blood groups, colour of eyes and of hair, has only shown that there is no association between these properties and the disease. Here, a negative

conclusion is hardly of equal value to a positive; and if the hereditary theory were otherwise substantiated, would only indicate that in the zygote there is free assortment of genes.

The series of cases investigated contains only one pair of identical twins of which one member, alone, has asthma. The effect of heredity can be more correctly assessed if environment remains constant, and vice versa. In the case of identical twins, heredity is a constant, so that here the onset of asthma must be ascribed to environmental influence. The 200 cases of patients under the age of sixteen belonging to the case records of Adam, afford information which proves conclusively that little or no distinction can be made in the frequency of morbidity between those showing a positive family history and those a negative, and no distinction between the so-called hereditary and the non-hereditary, in other respects. The fact emerges, however, that "only" children are more prone to other allergic diseases than the other children, and so the acquired aspect of allergy is emphasized.

The occurrence of asthma in animals living under sophisticated conditions also strongly supports this view, but this fact is constantly ignored by allergists who stress heredity.

Buchanan believes that asthma follows none of the

known laws of heredity, whereas Vaughan states that " We cannot cure the allergic tendency. Born with the predisposition, one will transmit it to one's offspring and will carry it with him to his death". The former view gives hope to the asthmatic sufferer, the latter, a problem which must be solved by eugenics. To avoid an issue because it is unpleasant is unscientific; to accept a statement such as Vaughan's without adequate substantiation is definitely harmful. The material which has been available to me for examination leads me to believe that heredity is but seldom a factor in the development of bronchial asthma, and that environment or nurture plays a much more frequent and important role in its genesis; and with adequate attention to the latter much can be accomplished in aleviating a distressing disease.

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