ATOPIC DERMATITIS IN INFANCY

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INTRODUCTION

Of all the diseases to which man has the misfortune to fall heir, none have remained more ill-defined than those cutaneous disorders which have been dubbed the "eczemas". The word "eczema" literally means "to boil over" or "burst out". It was originally employed to include all of the forms of acute and chronic inflammatory diseases of the skin whose etiology was obscure or unknown. This classification has then served no more useful purpose that to provide a dermatological scrap heap from which at intervals various clinical entities have been sorted and sifted on the basis of either etiology or clinical aspects. The term has become firmly rooted in the vocabulary and mind of the lay public and its scope and commentations are subject to even broader and looser interpretation than it enjoys among the medical profession. Nearly all of the European dermatologists employ the term "eczema" to indicate the clinical picture which Americans designate as "dermatitis venenata", "contact dermatitis", or "occupational dermatitis".

Hippocrates and Galen used the term eczema or a similar equivalent, but probably with a somewhat different set of clinical concepts than those of modern times.

The present conception dates from Willan, an English dermatologist of the Eighteenth Century, who first outlined the essential features of an "eczematous state". Roger described its multiformity and kaleidoscopic character. Devergie defined the four cardinal symptoms: Erythema, secretion, pruritus and porosity of the skin surface. Wilson differentiated the dry and moist forms and Anderson described the hyperaemic, scaly patch as an important type of lesion from which other morphologically different lesions developed.

The period of Anderson and Wilson devoted a large share of its attention to minute and detailed description of the appearance of the lesions. Later under Hebra's influence the histopathology received extensive study. Unna and Sabouraud investigated parasitic etiological factors. Ehrlich and his successors sought, but with meagre success, to explain many of the problems of the eczema group by biochemical investigation.

The advent of the field of allergy into the world of medicine opened another and somewhat fruitful approach to the classification and isolation of some of the conditions formerly relegated to the convenient and nebulous category of "eczema".

The publication of Schloss in 1915 stating that eczema in infancy was often due to allergy to certain foods stimulated interest and research in this direction and no year has since passed which has not brought some valuable contribution to our understanding of allergic or atopic eczema.

Coca first applied the term "atopy" to express the peculiar and often hereditary capacity of certain individuals to manifest untoward reactions toward common protein substances. These reactions include atopic dermatitis, hay fever, asthma, urticaria and possibly migraine.

A group of eczematous lesions appearing in the early months of life and persisting until the second year and at times into or throughout adolescence and even adulthood has been found to belong in this category. Atopic dermatitis of infancy is probably the best and the most proper designation for the disease formerly, and even the condition known as allergic infantile eczema as it serves to differentiate it clearly from the contact dermatitides

and the parasitic eczemas of the infantile period. It also implies the probable constitutional and hereditary aspects of the disease.

It is the purpose of this thesis to discuss some of the factors which have thus far been considered in the etiology of atopic infantile dermatitis and to in some measure evaluate them in the light of our present knowledge of the disease. The subject is considered primarily in relation to the etiological factors operative and of importance to the disease as it appears in infants, but the relation of the infantile disorder to childhood and adult forms of atopic dermatitis and to other atopic diseases is included to clarify and enlarge the understanding of the disease in infants.

THE MECHANISM OF ALLERGY

A thorough understanding of the present knowledge of the allergic antigen-antibody reaction is fundamental to a consideration of atopic disease. The necessary elements in the reaction consist of an allergic antigen of the nature of a water soluble protein and an antibody produced by tissue reaction and variously known as reagin, allergin or allergic antibody. The foreign protein injected into the body or invading it through the respiratory or gastro-intestinal tracts or through the placenta, for the first time stimulates the development of antibodies (in the tissues) which are digestive in character. These antibodies appear at the end of eight to twelve days, this time constituting the incubation period for the phenomenon. It is thought that the contact of antigen and antibody occurs in the cells of the sensitized tissue, and either of themselves or through toxic substances produced in the reaction, set up the symptoms which are clinically recognized as being characteristic of allergy. When the body is again invaded after the initial period of incubation, antibodies are present and in this case no incubation period is necessary and the reaction may manifest itself in a very few minutes.

There are two outstanding theories to explain the nature of anaphylaxis in animals and allergy in man. The first of these is the humoral theory which teaches that the reaction takes place in the blood and a toxin which Friedberger chose to call anaphylatoxin is formed by a fermentative process. This toxin in turn acts on the cells of the shock organ to produce the symptoms of the condition.

The second major theory is referred to as the cellular theory because

it holds that the reaction transpires in or on the cells of the shock tissue between antibodies already fixed there and the circulating antigens. It conceives the symptoms as being due to something in the nature of a physical shock similar to an electric shock and does not recognize the necessity for the formation of a toxic end-product.

The humoral theory has been virtually abandoned and the cellular theory is accepted by most allergists and immunologists.

Lewis and Dale have presented some experimental evidence which indicates that the release ofhistamine or a histamine-like substance (H-substance) may occur in the cells where the reaction occurs. It is known that histamine exists in loose combination in many of the body tissues and though it is inert while it is in the cells, when released into the tissue fluids it acts as a protein poison. The objections to this theory are that histamine fails to desensitize animals, it produces strong contractions in the smooth muscle of desensitized uterine horns, it has no affect on coagulability of blood as is seen in anaphylaxis, and it is difficult to see how one substance could cause such a wide variety of lesions of the same tissue as is seen in the cutaneous allergies.

Wells explains the first objection by stating that the process of desensitization implies an exhaustion of antibody and not an increased tolerance to histamine. If the antibody is exhausted, no reaction to antigen occurs and, therefore, no histamine is liberated.

It would seem that anaphylaxis in animals and the allergic states of man represent the same picture and perhaps they do, but certain differences are

to be noted in the two processes. Anaphylaxis is produced artificially and allergy is a spontaneous affair. Allergy has a strong hereditary factor which does not exist in anaphylaxis. Anaphylaxis may be congenital, but the sensitivity is very transitory, whereas in allergy it is of long duration. The shock organ may vary in different species in anaphylaxis,but is always the same in the same species (e.g. bronchial musculature of guinea pigs, pulmonary artery of rabbit, and liver of the dog). In allergy the shock organ may be not only different in different individuals but even in the same individual in response to the same antigen. The symptoms of allergy are most often due to edema whereas in anaphylaxis they are uniformly due to contraction of smooth muscles. Desensitization is rather easy in most experimental animals used in anaphylactic studies whereas it is difficult to produce and still harder to prove in allergic states. If antibody found in sensitized man can produce allergic manifestations in man and animal and vice versa, a basic relationship must exist between these antibodies. It is difficult to believe that allergy in man is entirely dependent on a special mechanism which is unique and unrelated to the mechanism which produces anaphylaxis in animals.

Marked individual variation is to be found in the degree of response of individuals of the same species in an allergic state. The energy of antibody production is never predictable in a given individual and the response with identical amounts of injected antigen cannot be foretold, except in a very general way, among individuals of the same species. Landsteiner has expressed a similar view.

Longscope and Mac Kenzie and later Mac Kenzie and Leake sought to

explain the wide individual range of reactivity to injected foreign proteins and the insusceptibility of certain individuals even when large amounts of serum were injected. They suggested that those who are relatively insusceptible may have some protective mechanism, either in their own blood serum or their tissue cells which prevents or delays the union of the antigen and antibody. Even in a thing like serum sickness, which is conceded to be devoid of hereditary influence, there is great variation in individual susceptibility.

The organism is provided with certain barriers (discussed more completely elsewhere) which prevent the invasion of allergins in their native state into the blood stream. These barriers are the relatively impermeable skin and mucous membrane covering the outer surfaces and body cavities and assisted by the respective tissue juices of these structures. Such foreign proteins as may gain entrance into the body may be promptly excreted in their original state through the kidneys. These barriers are not equally effective in all individuals nor to a like extent at all times in the same individual, for immaturity of the organism, pathologic states and disturbed physiology may alter them. Sensitization may occur at any age, but the periods of the greatest vulnerability are probably the ante-natal period, early childhood and during illness and convalescence.

Spontaneous immunity to a substance to which hypersensitivity formerly existed may occur, e.g. following an illness or a change in physiological activity, e.g. puberty.

PATHOLOGY AND PATHOGENESIS

The primary site of the pathological process involved in atopic eczema is the uppermost layer of the vascular cutis or corium. The blood vessel walls in this area are regarded as the shock tissue in which the allergic reaction occurs and therefore those substances which can be borne by the blood stream are the ones most likely to reach the shock tissue in sufficient quantity to produce a reaction. Only those allergins which are on the whole compatible with the blood fluids are likely to be carried in the blood stream and are usually water soluble and of the so-called "protein fractions" derived from ingested food or inhaled environmentals.

In exceptional instances, in adults but perhaps more frequently or even as a rule in infants, sensitizing substances may be able to pass through the epidermis and elicit allergic responses in the superficial cutis vessels. This mechanism is known as transepidermal penetration.

Sulzberger's conception of the type of pathological process involved is probably the best explanation that has thus far appeared. He regards the fundamental pathological manifestation to be a "submanifest, subclinical" wheal type of reaction, whether seen in infant, child or adult. The whealing which is produced and the trauma inflicted by the patient because of the accompanying pruritus eventually lead to epidermal involvement and ultimately to the eczematoid and lichenified appearance seen in a typical case. He believes that the infant's skin is more permeable, both from within and without and therefore both transepidermal penetration of allergens and transepidermal penetration of extravasated fluids with resultant weeping, oozing, crusting and spongiosus occurs. With the atopic

dermatitis seen as a subclinical urticarial reaction, the epidermal changes are therefore secondary in nature in contrast to eczematous contact hypersensitivities where the epidermis is primarily involved and the vascular changes are secondary.

The fact that the blood vessels are the shock tissue in the wheal type reactions indicate not only the nature of the allergens but also the time which may be expected to elapse between the exposure of the shock tissue to its specific allergen and the first appearance of clinical symptoms, as the blood vessels are capable of rapid contraction, dilatation and change in permeability and the time required for reaction may be only a question of minutes. The consideration of the vascular site of the hypersensitivity in atopic dermatitis helps us to understand the frequent association of positive specific reactions (skin tests manifested as a wheal) which are so often found in other types of atopy. The pathogenesis of asthma and hay fever is closely akin to whealing. In all, the superficial blood vessels are hypersensitive and contact with the specific excitant produces extravasation of fluid and of eosinophiles. In the lung the phenomanon is followed by contraction of the bronchioles and other manifestations of asthma, in the conjunctivae by epiphora and in the nasal mucous membrane by rhinorrhea. In the skin the extravasated fluid cannot escape but remains confined by overlying impermeable epidermis and whealing, either manifest or subclinical, ensues.

It is apparent from a consideration of the probable pathogenesis of atopic conditions that in order to do proper skin testing, the allergen must be brought in contact with the shock tissue in the corium. Either the scratch test or the intracutaneous injection method is suitable.

THE EVOLUTION OF ATOPY

Hill and Sulzberger have recently traced the evolution of atopic eczema from its first appearance in infancy to its adult manifestations and haveshown the transitions that exist in the stages of the disease. They point out that although the clinical picture differs greatly in the atopic dermatitis of infants and the "neurodermatitis" of childhood and adult life, the underlying basis of atopic dermatitis is the same in all stages. Frequently these stages may be traced in the same person from year to year.

The infant is not merely a small man, he is a different sort of small man. He reacts differently to many diseases than does the adult. His skin differs greatly in anatomy, physiology (heat regulatory mechanism and metabolic processes) from that of the adult. The capacity for sensitiveness probably begins with the embryo and in many runs through infancy and childhood and persists well into adult life. There is a distinct hereditary aspect seen in the atopic dermatitis-hay fever-asthma group and is different from other types of allergy, e.g. hypersensitive states to metals, drugs, infection. In the latter group, as far as is known, there is no reaginic mechanism. The atopic individual may lose his hypersensitivity to one substance and develop one to another. This may be due to the increased frequency of use and excessive amount of the substitute substance.

The first stage of clinical atopic dermatitis is that of infantile dermatitis. The atopic symptoms usually do not develop under three to four months of age. One of the most striking features of this period is the prominence of egg albumen as shown by cutaneous testing, eighty-five per cent of all infants reacting to any substance react to egg, if they react to anything. Since egg albumen has one of the lowest coefficients of

digestibility of all food stuffs and is most easily absorbed into the blood stream in its native state and since, as Ratner has shown, the placenta is permeable to such foreign substances, the possibility of the fetus coming in contact with an atopen in sensitization-producing quantity is probably good. If there is no prenatal sensitization, the infant is likely to become sensitized relatively early in postnatal life because of the ease of its absorption through the gastro-intestinal tract wall. It is thought that the gastro-intestinal tract of the infant has a higher degree of permeability to foreign protein than that of the child or the adult. It is certain that in babies who are sensitive to egg alone and who do not eat egg, this food is not producing the dermatitis unless the thesis of the excretion of allergens by the breast milk be subscribed to. It is known, however, that hypersensitivity to egg white may exist in an infant who has never been breast fed and so we have the paradox of an atopic baby with eczema who does not come in contact with the only atopen to which in the present state of knowledge he can be proved to be sensitive. He is prepared for eczema by his atopy and his sensitivity to egg white but the actual dermatitis seems to have developed from causes still not clearly understood.

The development of sensitivity usually depends on frequent and adequate exposure, to the atopen in question. In this connection it is interesting to note the abrupt rise in the incidence of wheat sensitivity after the sixth month, about which time most infants begin to eat cereal. The incidence of sensitivity to wheat nearly doubles between the sixth and twelfth months. There are relatively few reactions to exogenous atopens (inhalents) before the first year and among these silk is found to be the

worst offender at the infantile period (under one year) in the evolution of atopic dermatitis, the ratio between ingestants (foods) and inhalents (silk, cat hair) is found to be twenty to one. It will be seen that as the atopic state changes with the age of the individual, the foods become less important and the non-ingested environmentals become more significant.

Many infants outgrow their atopy and have no symptoms throughout the remainder of their lives, but it is probable that they may be able to pass on the predisposition to atopy to their offspring.

The second stage in atopic evolution occurs between the ages of two and twelve and is characterized by varying degrees of change in the character of the lesion, their distribution and also in the nature of and relative incidence of the atopic agents. In this group about sixty per cent have had their dermatitis since early infancy. Two-thirds as many react to egg albumen in this group as compared with the infantile group and only half as many react to wheat and milk. The reactions to non-ingested atopens are about two and one-half times as frequent at this stage. The onset of puberty sees a cessation of symptoms of atopic dermatitis in a rather appreciable percentage of patients.

The third or adult stage begins with puberty. Most of the individuals included in this group have had either continuous or intermittent dermatitis since either infancy or early childhood, but some cases date the onset of their first symptoms to the period of puberty. Morphological changes occur in the lesions at this period and a further increase in the importance of environments as atopic agents occurs. The ratio is approxi-

mately 13:15 (.87:1) between food and environmentals. The onset of atopic dermatitis is very rare and there is a tendency toward the subsidence of symptoms in some cases as the individual becomes older.

HEREDITY

That heredity played a prominent role in allergic disease was suspected and mentioned by many of the early workers in allergy. Cooke and Vander Veer published evidence in 1916 which brought to this factor more careful attention than had previously been accorded it. Rockemann, Spain, Adkinson, Balyeat, Elrod, Rowe and many others confirmed these observations and built up our present knowledge of the relationship. The literature shows a relatively early recognition in clinical circles of the heredity factor by the use of terms such as "exudative diathesis", "allergic diathesis", "allergic constitution" and "allergic predisposition".

Coca included heredity when he first defined the nature of atopy. He stated that the incidence of atopy is highest among persons with a bilateral family history of some atopic manifestation and that in these individuals the symptoms appear earlier than in those having a unilateral or a negative family history. He further declared that heredity influences the clinical form and the shock organ to be involved and also to what group of atogens the individual will become sensitive.

Statistics on the subject reveal that in normal non-allergic people the incidence of a positive family history is rather low, ranging from 3.5 to 8.7 per cent, whereas in individuals suffering with some form of allergic disease, the family history was positive in 49 per cent of adults and 58 per cent of children. O'Keefe's and Rockeman's report shows only a 28 per cent family history in their series of 212 cases of atopic dermatitis. Balyeat, however, obtained a positive family history in 76 per cent of 181 cases and Bwings 69 per cent in 157 and 220 cases respectively.

Cooke and Vander Veer in 1916 produced evidence suggesting that

allergy was inherited and that furthermore it was probably transmitted as a Mendelian dominant character. Spain and Cooke were able to confirm and elaborate these observations on the basis of studies of the incidence of allergic disease in the children of families wherein one or both parents had some form of allergy. It was estimated that where both parents were affected, 75 to 100 per cent of the offspring would have some form of allergy. If only one parent was an allergic individual, 50 to 75 per cent of the offspring would inherit a predisposition to the disease and if both parents were negative, 0 to 10 per cent. The really disturbing element in the picture is the high incidence of allergy in families with a negative family background (41 per cent). Adkinson's studies led him to the conclusion that the nature of the transmission was of the order of a recessive rather than a dominant character. Whatever the more intricate details may be, it is probable that one is justified in concluding that the greater the hereditary background of allergy the more certain is the potentiality for the development of hypersensitivity in the offspring.

Heredity is related to the age at which the onset of symptoms of allergy may be expected as the greater the degree of allergic heritage, the earlier the symptoms appear. If the inheritance be bilateral one may expect about 36.3% of the individuals to exhibit some type of allergy before the fifth year; if unilateral 14.3 % and if negative 5%. In the tenth year the percentages in these groups run about 62, 32 and 18 per cent.

There is some evidence that the transmission of allergic predisposition is type specific, i.e. hay fever parents are more apt to confer hay fever than asthma or eczema to their offspring. This point is greatly

disputed and there is as good evidence on the basis of clinical observation to indicate that such specificity is absent and allergy may display a different element in its personality in each of the offspring of an allergic parent.

Tuft states that recent studies have revealed that the hereditary factor in allergy may be sex-linked. Bray found that the hypersensitivity factors were transmitted twice as frequently through the female than the male and that double the number of offspring are likely to be affected. Sex is further involved in the picture in that male children show a much greater tendency to recover at puberty and also the female is more apt to develop an allergic disease after puberty.

The kind of allergen to which the offspring is sensitive is not transmitted by the germ plasm and is usually different from that of the parent. The nature of the factor which is transmitted is a most unsettled question. Coca considers that "shock organ" tissue abnormality is passed on and that these tissues are predestined to develop hypersensitivity of a certain type and at a certain age. Kolmer is somewhat more general in his concept as he reasons that since vascular reactions comprise the major tissue reactions in human allergy, the inherited factor is some instability in the vasomotor system. This problem has been approached from the standpoint of endocrinology, biochemistry and other avenues, but is still wide open for a thoroughly satisfactory explanation.

Congenital, i.e. not transmitted via the germ plasm, sensitization undoubtedly exists as will be discussed below. It may be either active or passive, the former being the more common in man, the latter in lower

animals. If heredity is a pre-requisite for an atopic state it will be rather difficult to reconcile the fact that many individuals have typical atopic disease without any traceable familial element, unless it be through a combination of recessives which may be potent enough to produce the atopy in the individual. It does not explain the congenital type of transmission and its relationship, if any, to heredity.

The relationship of heredity to the diseases of the skin is summarized by Osborne and Walker as follows: "There is no experimental evidence that a person inherits any specific epidermal sensitivity, although he may inherit an ease of sensitization, or a susceptibility to sensitization."

PLACENTAL TRANSMISSION

Sensitization in utero proceeds by two mechanisms, active and passive transfer through the placenta. In the active mechanism the antigen passes through the placenta and thereby gains entrance into the blood stream of the fetus. The passive transfer method implies the passage of antibodies of some antigen to which the mother is sensitive. This mechanism is probably of much less importance than is that of the active transfer.

Ratner and his associates have done a large amount of original work on the subject of placental permeability and have collected the literature on the subject rather completely. They make a distinction as to the permeability of the placenta to heterologous substances by dividing the types of placental groups according to the number of cell layers present in them. The group to which the ruminants belong has a placental type characterized by the interposition of several cellular layers between the fetal and maternal circulations. This type has been found to be generally impermeable to the passage of heterologous substances. The group to which man and the guineapig belong has but a single cell layer separating the two circulations and these placentae are extremely permeable to many forms of heterologous substances.

Ratner sensitized a large number of adult female guinea pigs to horse serum. These animals were then tested and it was found that in all cases the offspring were born with a sensitivity to horse serum and showed a severe anaphylactic reaction or anaphylactic death when it was given to them intravenously. Subsequent litters born from these guinea pigs were also found to be sensitized and the transmission persisted throughout the lives of these animals. The passive sensitization in the offspring persisted up to

the age of three months and then gradually diminished. It was impossible to pass the sensitivity farther than the second generation due to its transitory character.

Guinea pig mothers injected with horse serum a few days before parturition gave birth to litters which did not show anaphylaxis until the age of one month.

Ratner feels that the results of his animal experimentation may be applied to man due to the histologic similarity of the placentae of man and his experimental animals and because he has been able to find rather convincing clinical evidence to support his contention. He believes that the overindulgence in certain foods on the part of the mother (e.g. eggs and nuts) during the gestational period is a causal factor in the subsequent development of allergy in the offspring. He cites the case of a pregnant mother who had a marked craving for nuts and ate a pound a day of them during pregnancy and her child developed asthma (allergic) at the age of four when nuts were first added to his diet. The child had positive skin tests to all varieties of common nuts and was free of clinical symptoms when he avoided them. Several similar cases are cited wherein egg and egg foods were the offending agent and one case of wheat allergy attributed to this phenomenon. Ascoli has been able to show that proteins may pass the placenta. Ratner feels that the passage of heterologous substances through the placenta should not be regarded as pathological but as physiological.

It should be recalled that the placenta is permeable to other sub-

stances of a protein nature besides antigens, as the passage of antitoxins, precipitins and bacteriolysins have also been demonstrated in studies done on man, guinea pigs and rabbits.

SENSITIZATION

Through the Gastro-intestinal Tract:

An increasing amount of evidence is accumulating in the literature showing the importance of the gastro-intestinal tract as a portal of entry of sensitizing agents into the blood stream. Rosenan and Anderson, Richet and Mohecamt are among those who have demonstrated in experimental animals that native protein may enter the blood stream and thereby give rise to sensitizing antibodies. Schloss and Worthen and Anderson and Schloss and Dubois have demonstrated this relationship clearly in children.

The importance of the passage of sensitizing bodies through the intact gastro-intestinal wall is exemplified by the reports of French investigators, who found that the ingestion of horse meat so sensitized certain individuals that when they received primary injections of antitoxin derived from horse serum, severe anaphylactic reactions and even death ensued.

Hutinel observed that after severe gastro-intestinal disturbances a child may manifest sensitivity to a food where previously he had had complete tolerance to it. This is explained on the basis of increased permeability (see also the discussion of milk and its relationship to infantile dermatitis) engendered by the irritation existing in the gastro-intestinal tract and thereby permitting the ready entrance of unchanged protein into the blood stream. Before carrying the conclusions of this observation too far, one must consider that the gastro-intestinal upset might well be the first manifestation of an allergic state. Increased permeability has also been noted on the part of the gastro-intestinal tract during convalescence from other forms of disease than those previously affecting the gastro-

intestinal tract in conditions where weight loss and cachexia are evident and even following surgical operations. Uncooked foods (see milk) are particularly prone to initiate a sensitivity. It is readily appreciated that raw eggs (as egg nog,etc.) and raw milk are frequent articles in the dietary of convalescents.

Walzer and Strauss have recently conducted experiments on the Rhesus monkey demonstrating the absorption of undigested protein. The skin of the animals was sensitized with serum from humans which contained definite reagins to peanuts and cottonseed. In all cases positive cutaneous reactions developed at the site of sensitization following the ingestion of peanuts or cottonseed.

Mellanby and Twart showed that certain strains of B. coli can form histamine from histidine. Davis suggested that the absorption of this product from the intestinal wall into the circulation may neutralize the action of adrenalin on the walls of the blood vessels.

Through the Respiratory Tract:

The passage of native proteins through the wall of the respiratory tract has given rise to much controversy. The exact point at which antigens pass the wall and enter the blood stream has been variously thought to be in the upper respiratory tract, the trachea, and the lung alveoli. Nearly all of the experimentation in this direction has been carried out by employing liquid spray inhalents and it has been demonstrated that by this means the lower animals can be sensitized. Ratner, Gmehl and Jackson employed dry antigens (horse dander and castor bean) and exposed guinea pigs to an environment in which this dry dust was circulated. The animals with-

stood the initial contact without any untoward reaction but when they were exposed again after two to three weeks, they evidenced manifestations which in all respects resembled human asthma. When animals were exposed to dry dander for one-half hour, few were affected but as this exposure was increased up to five or six hours, a majority became sensitized. Animals sensitized to horse dander died in anaphylactic shock from a primary injection of horse serum.

Among the more common environmentals which may have etiological significance in infantile eczema are silk, horse, dog and cat danders, goose feathers, rabbit skin, cottonseed, orris powder, wool, timothy and ragweed pollens. These allergens as inhalents are regarded as being relatively unimportant as related to infantile atopic dermatitis according to Tuft, but Hill feels that they may be of far greater importance than is realized at the present time.

BREAST MILK

It has been a long and well established tradition in the minds of the laity that the infant may be affected by substances transmitted to it through the milk of the mother. The medical profession relegated this idea to the realm of superstition and it was the concensus of opinion that the breast milk played no part in initiating or influencing pathological states in the infant. More recently further investigation and an evaluation of this factor have been initiated by various workers and clinical and experimental evidence accumulated to prove it worthy of consideration.

O'Keefe and Shannon working in the early part of the last decade were struck by the fact that many entirely breast fed infants gave very definitely positive intracutaneous tests to a wide variety of food allergens. They tried eliminating these foods from the dietaries of the nursing mothers and were able to get very encouraging clinical results in a large number of the cases so treated. O'Keefe found 40% of babies sensitive to some allergen of food origin were cured by the omission of these elements in the mother's diet and more were definitely benefitted.

Shannon demonstrated the presence of egg and veal protein in the breast milk after the ingestion of these foods by the mother. Donally showed by use of the passive transfer reaction that the protein of egg eaten by lactating women may be eliminated in their milk in small but detectable quantities. Smyth injected egg sensitive serum into the skins of 36 newborn, breast fed infants and then fed the mothers large amounts of egg. In no case was there a positive reaction at the site of injection, which Smyth interpre ted as indicating that the amount of egg present in breast milk was not sufficient to cause a reaction in the baby.

Dill found no evidence in the guinea pig to substantiate the explanation of sensitization through breast milk. Stuart expressed a similar view. Ratner, Jackson and Gmehl concluded that in the human and in animals with the exception of the mouse, milk plays a neglible role in the transfer of heterologous substances to the suckling. In another article, however, Ratner expressed the view that despite more recent work to the contrary his clinical experience has made him feel that Shannon's premise,i.e. that a mother partaking of an excess of a particular food during the nursing period may pass this food in an unchanged state through the breast milk and thus affect the baby. Ehrlich was the first to voice the impression that a nursing mother may definitely confer immunity to her offspring through breast milk. He worked with mice and drew his conclusions therefrom.

Talbot in 1918 cited a case wherein a nursling with infantile dermatitis cleared up promptly when the mother, who was in the habit of consuming a pound of chocolate candy per day, stopped eating chocolate. Two weeks later she took some cocoa and the infant's dermatitis recurred. Rinkel studied the relationship of the ingestion of a specific food by the mother to the onset of pruritus and exacerbations of eczematous lesions in a breast fed infant. He took a typical case of a three months old female infant which had been entirely breast fed, except for orange juice started at five weeks. The infant was scratch tested with fifty different foods common to the mother's dietary and those giving positive reactions were diminished or eliminated from the mother's diet. The mother was put on a basic diet and the baby improved sufficiently to permit the addition of test foods to the mother's diet. The mother made an accurate record of the time of ingestion

of each new food, the time of each nursing and the appearance of an aggravation of symptoms in the infant. Breast milk taken up to an hour after the ingestion of the new food had no specific effect but that taken in two to three hours brought forth a definite reaction in the child within an hour of the nursing. One food (bananas) produced a reaction eleven hours after nursing.

Shannon thinks that some of O'Keefe's failures to obtain a clinical cure were due to the limited number and variety of skin tests employed by him. It is obvious that this method of approach necessitates a thorough familiarity with an understanding of allergy and experience in the techniques and their proper interpretation in order to use it with any degree of success. Many obstacles present themselves, among them being the lack of clinical significance in many positive skin tests and also the failure of some individuals to give a positive reaction to an allergen to which they can be shown by clinical trial to be sensitive. These difficulties are multiplied in the infant because it is known that the younger the individual the less likely it is for a positive test to be obtained.

There appears to be a very definite quantitative as well as a qualitative factor involved in the excretion of heterologous protein substances by the breast milk. In cases in which all the food sensitizing agents cannot be eliminated from the diet of the mother, a decrease in the amount of these foods is of help because there appears to be a threshold in the mother up to which the food may be eaten without appearing in the breast milk. Shannon states that eggs in particular should be limited. He feels that it is safe for the nursing mother to resume her normal diet after a period of

three months and that in six months the baby may be fed the foods to which he was previously shown to be sensitive.

Many workers have advanced the idea that it was the colostrum which was responsible for the transmission of allergens and not the breast milk proper. Ratner, basing his conclusions on experimental and clinical evidence, stated that colostrum plays no role in the transmission of protein hypersensitivity.

Sprenkel recently published an article wherein he reveals that infantile eczema may be treated through the breast milk through the employment of parenteral injections of normal saline, Ringer's solution or distilled water given in 5 cc doses intravenously, subcutaneously or intramuscularly. The idea seems most fantastic, especially in the light of the nearly homeopathic doses of the very simple agents employed but he claims such excellent results that one cannot be justified in dismissing the form of therapy without further investigation and clinical trial.

COW'S MILK

In as much as cow's milk is the only food that many infants with atopic dermatitis are ingesting it is apparent that the place of this food in relationship to the disease is of great importance. Hill states that sensitivity to cows milk is the most important single cause of atopic dermatitis in children. Casein and lactalbumin are the milk proteins which have the greatest allergenic qualities and of these the lactalbumin is the more important. An intimate biologic relationship exists among the caseins obtained from the three major sources of milk, i.e. human, cow and goat and

so little is gained by substituting one milk for another if the sensitivity is to the casein fraction. Since casein is unchanged by heating it is immediately obvious that the employment of evaporated cow or goat milk will not circumvent the problem of casein sensitivity. They whey fraction, containing lactalbumin, leaves the stomach in a highly soluble liquid state and has a far better chance of being absorbed unchanged than has the casein fraction.

Ratner divides the pathogenic factors of milk sensitization into the congenital and those acquired by sensitization through the gastro-intestinal tract. Congenital sensitization may be passive occurring in utero and occurs only when the mother is sensitive to milk and the fetus is sensitized by the passage of milk antibodies through the placenta. This mechanism probably plays a relatively minor role. The fetus may be actively sensitized in utero by placental transmission of milk antigens and the development of antibodies to these antigens post-natally. Rosenan, Anderson, Ratner and other workers have shown that proteins administered orally may pass the intact intestinal wall and enter the blood stream. Ratner concludes that although the intestinal wall is normally impermeable to proteins, abnormal conditions may account for sensitization in the following conditions. (a) Occasional feedings of raw milk during the newborn period, when the intestinal wall is naturally more permeable, may give rise to a state of hypersensitiveness when the child is later given cow's milk either to supplement breast feeding or when it is weaned. (b) Periods of excessive ingestion of raw cow's milk followed by periods of complete abstinence may also result in sensitization. (c) In Patients who are fed raw milk during convalescence from some disease or after severe gastro-intestinal disturbances, hypersensitiveness may develop.

In Hill's series, 37 of 200 patients tested gave positive skin reactions to proteins of cow's milk. Six of these reacted to casein alone, nine to lactalbumin and twenty-two to both. Nineteen of these 37 also gave a positive reaction to egg, although most had never eaten.egg. Schloss, in his earlier work, found precipitins for milk in the serum of many infants with negative skin tests. He has more recently obtained both positive precipitin and passive transfer tests under the same conditions. Hill found only 17% of a series of 153 eczematous infants under one year to be scratch positive. In 63 of the negative individuals in this series, 56% gave a positive intracutaneous test* most of which were etiologic. It is therefore seen that if one relies solely on the scratch test he will frequently miss milk sensitivity.

Mendel and Lewis showed that in man raw egg white is digested to only a slight extent whereas coagulated egg white is much more extensively digested. It was later found that evaporated freshly boiled and acidified evaporated milk when fed by mouth showed a marked reduction in sensitizing ability.

The loss of antigenic properties of heated milk is presumably due to coagulation of the whey fraction proteins and it is thought that coagulation delays the passage of these proteins through the gastro-intestinal tract, thus making for more complete digestion and diminishing the probability of their absorption as native antigens. Boiling of milk also removes other antigens transferred through milk.

In 1911 Varrot began to write about the use of superheated milk in

*Crude whey used for intracutaneous testing.

the treatment of infantile eczema. He used milk heated at 108°C and homogenized. This was no more than evaporated milk. Kerley advocated prolonged boiling (six hours) in 1926 and in 1931 the S.M.A. Corporation introduced their "hypoallergic" milk which was treated in a somewhat similar manner. Besiedka, working with guinea pigs sensitized to whole milk, found the antigenic properties of milk to be unchanged when heated to 120°C for fifteen minutes, when heated to above 120°C it lost some of its potency and when heated to 130°C it was only slightly antigenically potent. Cutler found that in evaporated milk, which is heated to 116°C for twenty minutes there is no change in the antigenic properties of the casein, but that the coagulable proteins of the whey fraction lost some of their antigenic power.

As a sensitizing agent given by injection, Ratner and Gmehl point out that milk which is evaporated, freshly boiled for several hours, or superheated shows practically no loss in antigenic character of the lactalbumin.As a shock agent given by injection evaporated milk or superheated milk shows an unmistakable loss of antigenic properties of the whey fraction. This is more marked with evaporated milk than with superheated milk.

Drying does not influence the antigenic properties of milk because the exposure to heat in the drying process is too short. Acidification renders the milk more antigenic because it is more prone to release the whey proteins and thereby increase the possibility of sensitization. However, it has been found that acidified evaporated milk is less antigenic.

In clinical characteristics the amount of benefit derived from the use of superheated milk is dependent on the degree of sensitivity and whether the sensitivity is due to lactalbumin or to casein. Hill states that

he has seldom seen evaporated milk do much good in cases of infantile eczema and regards a milk-free diet as preferable.

Blockfan in 1916 and Schloss in 1920 recognized the significance of cow's milk in infantile eczemas and devised a milk-free diet upon which the skin of the patients improved but which produced untoward gastro-intestinal effects.

Finkelstein removed the cow's milk whey and fed cow casein with human whey to eczematous infants twenty-five years ago.

OTHER COMMON FOOD ALLERGENS

Egg and milk (cow or goat) are admittedly the most frequent offenders in producing atopic dermatitis. They are discussed more extensively elsewhere in this thesis. The cereals, particularly wheat, stand next to egg and milk among the food allergens important in the infantile age group. It is possibly due to the fact that most babies take a large amount of wheat in the second half of their first year or it may be that wheat is an unusually good sensitizing agent.

Spinach and peas are the most likely to cause trouble among the vegetables. Beans, the potato-tomato family, and carrots are also of importance. Among the fruits, orange juice is probably most important because it is fed to so many infants to provide a good and cheap source of vitamin C. Positive scratch tests for orange are not common, but intracutaneous tests are not infrequently positive. The place of oranges in the infant diet can be readily taken care of by giving cevitanic acid. Apple is probably next most important, followed by banana, strawberry and melon. Apple sensitization is frequently mentioned in the literature and specific hereditary transmission in families has been reported.

It appears that sensitivity to one fruit or vegetable allergen often means that the individual is sensitive to some degree to the rest of the members of the particular botanic family to which the food belongs (e.g. sensitivity may exist to all of the citrus fruits, all of the legumes, to apples and pears). The part of the fruit eaten is often of significance as a patient may be sensitive to the rind or akin and yet be able to consume the more edible portion with impunity. Fish oils rarely produce or aggravate an allergic process but are not unknown to do so.

Sensitization to more than one food is more common that to a single food and as the infant becomes older this tendency displays itself more frequently. Hill reports the obtaining of positive skin reactions to protein split products, e.g. egg peptone, milk peptone, wheat peptone, and casein aninoids, in cases where a negative reaction to the whole protein occurred. The study is not extensive enoughto draw any definite conclusions from it.

THE ENVIRONMENTAL ALLERGENS

The environmental allergens include the inhalents and contactants. The importance of environmentals in the age group included under infantile atopic dermatitis is relatively far less than that of the food allergens, but it should not be forgotten in the consideration of any case of atopic dermatitis of infancy.

It is probable that contactants play little or no primary role in infantile dermatitis, but they may be of secondary importance. The skin of the average atopic infant is much more resistant to contact irritants than would be expected. This is shown particularly in the very few positive patch tests that occur in atopic infantile dermatitis. Contact with wool and silk may produce an urticarial reaction but it is believed that these materials act in the same manner as samples used in percutaneous testing, i.e. the irritant penetrates the epidermis and evokes a vascular response in the cutis.

The inhalants are very definite factors with which to be reckoned in this disease. The common inhalants include silk, wool, dog, cat and horse dander and hair, orris root, cotton, rayon and house dust. Silk is probably

the worst offender of this type of allergen in the infant age group. It may be necessary to merely eliminate silk in the clothing of the infant to effect a clinical remission in some cases, whereas in others a completely silk-free environment must be established. The latter is very difficult if not impossible to effect in many cases.

An improvement in a case of atopic dermatitis which ensues when the child begins to spend more time out of doors in the summer may lead one to suspect an environmental allergen in the etiology of the particular case.

Hill found scratch tests to be positive to environmental allergens in ten per cent of thirty-eight eczematous infants under one year of age; thirty-seven per cent of fourteen infants between one and two years of age and fifty per cent of forty-nine children between two and twelve. Twenty-one cases which gave positive scratch tests to an environmental allergen were patch tested and only one positive, atypical in nature, was found.

AGE

The recently developed concept that the atopic dermatitis of infancy represents the initial stage in what may be a life-long disease and not a separate clinical entity places the relationship of the age of the eczematous individual in a somewhat different light than it was formerly. Goodman and Burr's series of 206 cases showed that 46% developed atopic dermatitis the first month of life and 80% within the first three months. Bamber's cases were on an average of eight months of age on admission and had had an average duration of symptoms of five months prior to admission. The early age of initial symptoms would appear to indicate a fundamental rather than an acquired disposition to the disease, though if we accept Ratner's views

and work on transplacental sensitization, it is not unlikely that the same mechanism is operative in the acquisition of allergy at one month as at a much later period.

The majority of infants developing dermatitis (atopic) after the sixth month are found to date the onset of their disease shortly after the addition of a new food to the diet, e.g. wheat, raw milk, egg, etc.

THE NUTRITIONAL STATE

The literature on the eczemas of infancy constantly bears out the oft repeated observation that overfed and fat babies are more often found to have an eczema than their less well nourished contemporaries. This seems to be particularly true among breast-fed infants. Bamber, Hill and Talbot have rather extensive series which bear out this point very well.

The eczema of many of these infants improves with a reduction in their food intake. This may be due to the fact that the amount of the particular sensitizing protein is reduced to a minimum or that large amounts of food in general influence the eczematous process unfavorably. Fat infants have a tendency toward a moister type of dermatitis with much crusting, whereas less well nourished babies have a dryer type with a greater tendency toward lichenification. Some have claimed that the commonest food component to cause atopic dermatitis when given in excess is fat. They claim that large amounts of fat are found in the stools of these patients in the form of soaps. Some cases show considerable improvement with a reduction of fat in the dietary. This may be due to some remote influence on the general nutrition of the skin or by the direct influence of toxic products from

decomposition or incomplete digestion of food in the presence of excess fat or to the excessive fat itself. The mechanism may be due to the relationship of fat to casein and in the stomach is intimately amalgamated with fat, its digestion becomes more difficult and the possibility of undigested protein being absorbed in the intestine thereby enhanced.

It is very probable that the atopic dermatitis of infancy has not been clearly distinguished from seborrheic eczema and that the observations above are applicable only to the latter type.

CLIMATE AND SEASON

It is not unexpected that an organ so intimately related to the thermal regulatory mechanism of the body would be particularly prone to disturbance when its function is impaired by disease. Vidal mentioned the tendency for the eczemas to show exacerbation and increase in severity during the autumn and winter. Bamber considers that of the external contributory factors, cold weather and marked variation in temperature are the most important. He regards low temperature and cold wind as being important precipitating factors. Tumica states that this type of eczema is relatively rare in Australia and quotes Picards observation that in Louisiana it is seen only in the infrequent cold spells. Bamber has seen some cases which first appeared in the winter to show exacerbations with the advent of hot weather. Talbot includes cold, dry winds as being among the common precipitating factors of infantile eczema. Goodman and Burr have recently studied the relation of climate to the eczemas of infancy and have concluded that cold aggravates the condition in most cases.

ENDOCRINES AND ATOPY

The answer to the enigma of atopy has been sought in the intricate and until recently equally mystifying endocrine system. Every gland of internal secretion has been charged with at least a share in the etiology of atopy. That they may well be very important in relation to allergic disease can not be denied but the exact nature of their role is still nebulous and elusive.

The thyroid, the pituitary and the gonads, especially the ovaries, have been studied from the clinical standpoint and some clinical observations tend to support the feeling that some entertain in regard to their relationship to allergy. The effect that changes in the physiologic state of the individual which occur concomitant with puberty, pregnancy, menstruation and the menopause have an allergic condition are perhaps the most outstanding. We may see an atopic dermatitis which has existed since infancy clear up spontaneously at puberty in a boy or it may become aggravated or flare up anew or even appear for the first time at this period in a girl. An atopic disease may increase greatly or disappear during a pregnancy whereas menstruation is often seen to increase the symptoms. There is a tendency for scantiness of the menstrual flow in atopic individuals. The urine shows normal values for the gonadotropic hormone. An initiation or an exacerbation of symptoms is sometime seen during the first few years of married life.

It has been found that cretinoid infants exhibiting an atopic dermatitis have cleared rapidly when thyroid extract was administered. A hypoadrenia has been suggested as a possible factor on the basis of hypotension, hypoglycemia and the tendency for improvement of symptoms of some forms of allergy when adrenalin is injected. It has been shown that adrenalectomized

rats are more susceptible to anaphylactic sensitization than normal animals. Organic diseases of the adrenals do not show evidence of allergic phenomenon, but the possibility exists that a functional suprarenal disturbance may be operative.

The thymus gland which is at the peak of its activity at the period wherein atopic dermatitis of infancy occurs has been indicted but never convicted of being instrumental in certain cases of the disease. The sudden death which sometimes occurs in these patients has been explained on the basis of status thymic lymphaticus and some claim to have discovered definite thymic enlargement in some of these cases.

SOME ACCESSORY FACTORS

A. Infection.

1. Bacterial. The role of low grade infection is probably of considerable importance in some phases of atopic infantile dermatitis, but it is difficult to properly evaluate. The sodden, thickened fissured, broken skin covered with exudative debris presents an ideal opportunity for the growth of bacterial organisms. Sometimes frankly pustular or furuncular lesions are seen associated with and secondary to the dermatitis. Infection may often be the factor which keeps the eczematous process active and many of these cases respond well to simple boric acid or ammoniated mercury ointments. Infection is a far more frequent complication in atopic dermatitis of infants and children than in adults.

The Morococcus of Unna was described as being a possible etiological factor but more recently was found to be identical with staphylococcus epidermis albus. Whiting described a peculiar diplococcus isolated from lesions on the cheeks of small children. It is certain that though pathogenic micro-organisms are not primarily concerned in the production of atopic infantile dermatitis, they add to the symptoms and often serve to perpetuate the process by their growth and toxins.

The element of focal infection must be ruled out in all cases. Bacterial foci may influence the eczematous process directly through toxins thrown into the circulation or through allergy to bacteria and their products.

2. Fungus. White isolated a yeast-like organism (cryptococcus) from a number of cases of infantile atopic dermatitis and was able to produce characteristic lesions a number of times on healthy portions of the skin by

inoculation from the original lesion. In some cases he was able to produce improvement or even clinical cure by employing fungicidal therapy. He is not certain whether the fungi are parasitic or sapraphytic in nature. The finding of fungi in these lesions means little but their disappearance and subsequent clinical improvement of the lesions cannot be overlooked. Hill has seen cases where the mothers of eczematoused babies developed a typical epidermophytosis of the hands after caring for their infants. He thinks that fungus infection is more often found in allergic than in non-allergic patients.

B. Trauma.

The importance of trauma cannot be overestimated. It is probably seldom important as a primary cause but as a secondary factor its significance is paramount. The soil is prepared by the individuals atopic state wherein he is hypersensitive to irritants, either internal or external. If the skin of a normal person is rubbed, abraded, scratched or otherwise irritated it soon shows a tendency if left alone to return to a normal state. The eczematous skin shows this tendency to a much lesser degree and furthermore is not often left undisturbed. The decided benefit derived from restraining eczematoused infants from scratching is excellent clinical proof of the importance of this factor. Some dermatologists have argued that without scratching and other frictional irritation eczematization would not occur whereas others, including Hill, do not agree with this view.

Other forms of trauma, especially cold and exposure to wind and marked drying, must not be forgotten as being contributory to the development of the clinical picture of the disease.

C. External Irritants.

Contact sensitization to external irritants is relatively unimportant in relationship to atopic infantile dermatitis but may sometimes coexist, the more common irritants being wool, dog and cat hair and silk. Contact dermatitis due to drugs employed in the treatment of the atopic dermatitis or for other conditions should not be forgotten.

D. Teething.

The laymans feeling that eczema is related to teething directly and etiologically is quite certainly without foundation but many cases of exacerbations and aggravations of the skin lesions are seen during difficult dentition. The explanation may be due to nutritional disturbances, occasioned by the infant's refusal to eat, to general metabolic changes incident to dentition or to effects on the sympathetic nervous system which are reflected by the capillaries and small arterioles, as it is felt by some that atopic individuals have an unusual lability of their sympathetic nervous systems.

E. Constipation.

Changes in intestinal activity are often reflected in the intensity of an eczematous process. Clinical improvement is often seen following a diarrhea and conversely constipation appears to aggravate an atopic eczema. Constipation in varying degrees is seen in 85% of all cases of atopic dermatitis according to Goodman and Burr. Pusey expressed a similar view and adds that breast fed infants whose mothers are chronically constipated do not improve if kept at the breast.

F. Vaccination.

There is probably no basis for the belief entertained by some and rather frequently alluded to, especially in European literature, that small pox vaccinations may produce infantile eczema. Vaccinia may be superimposed upon eczema and the lesions may occur at the sites of the pre-existing eczema. In some cases this may produce a most serious complication with a marked elevation in temperature and evidences of severe intoxication and a fatal termination under these conditions is not infrequent.

G. Splenic Deficiency.

The French literature recently reported the use of splenic extract in the treatment of infantile eczema. The series of cases was very small and the type of eczema treated was not clearly defined by the author. A dosage of 40 drops of splenic extract was employed and almost complete disappearance of the lesions was accomplished in a week of this therapy. Treatment was discontinued and prompt exacerbations of the eczema took place.

BIOCHEMICAL FACTORS

The subject of allergy has been extensively studied from the standpoint of the biochemistry of allergic individuals but unfortunately relatively little of practical significance has emerged from these efforts.

Calcium studies have shown the allergic individual to be rather constantly deficient in this element according to Burgess and other workers. Burgess worked with eczema patients and found a low precipitable and total serum calcium. Feldman feels that the primary fault in this direction more probably lies not in the total calcium but rather in a disturbance in the calcium-potassium balance. He states that hypersensitive skins have a higher ratio of potassium as compared with the calcium present. Klander demon-

strated this fact in the experimental animal. It will be recalled that the action of calcium in relation to the nervous system is to stimulate the sympathetics, whereas potassium exerts its action on the parasympathetics. Calcium decreases the permeability of cell membranes and that of blood vessel walls and thereby limits exudation.

The relative decrease in calcium concentration may be due to the fixation of calcium by its antagonists, sodium and potassium or to the presence of disturbances in the uric acid, mineral acid, cholesterol and other metabolic factors. Although calcium has long been used, rather empirically, in the treatment of allergic disease and despite considerable data on the role of calcium, Tuft states that because of the lack of convincing and consistent evidence in its relationship to allergy it cannot be regarded as being an important, if even a, significant factor.

Changes in carbohydrate metabolism, particularly the presence of low blood sugar in these individuals are considered more extensively elsewhere in this review. Bray found slight hepatic insufficiency and has offered this as evidence that allergy may be related to hepatic dysfunction. Beldman has observed that some eczema patients thrive on low carbohydrate diets.

A slight shift to the lakaline side is present rather uniformly in all forms of allergy. The plasma bicarbonate is distinctly on the alkaline side. Beckman revived the use of acid therapy in 1930 for the treatment of allergic conditions. He claims as evidence in support of this therapy the clinical observation that conditions tending toward the production of acidosis, e.g. starvation (infectious, pregnancy and high altitudes with loss of alkali) are known to produce improvement in many cases of allergic disease.

Walzer considers that the benefit of acid therapy is due to the fact that in many allergic individuals there is a deficiency or absence of gastric acidity and therewith a diminution in the digestion of proteins, increasing the possibility for the absorption of native protein.

It is evident that the nature of the relationship of changes in the acid-base equilibrium to allergy is not known and it is probable that these changes may represent effect rather than cause.

Feldman mentions a high blood cholesterol in many allergic patients and also high values for blood uric acid. He cites the case of a fourteen year old patient suffering with a scrotal eczema who cleared completely on a purine-free diet and cincophen (which reduces uric acid).

Ribadean, Dumas and Levy reported a hypoprotanemia with a special diminution of the albumin fraction in the blood of eczematous infants.

THE SERUM LIPIDS AND INFANTILE ECZEMA

The observation of the Burr's that marked cutaneous changes occurred in rats fed on a diet deficient in unsaturated fatty acids suggested the possibility of such a deficiency being related to the eczemas of man and especially infantile eczema. Early studies in this direction on the serum of human subjects revealed that the serum cholesterol and total fatty acid was somewhat less in eczematous infants as compared with normal infants, of the same age. The total iodine absorption of the normal infant was found to average 539 mgs. of I 2/100 cc. whereas in the infant with eczema, the figure averaged 383 mg. /100. The iodine number of the serum fatty acids in the normal was found to be 111 whereas in the eczematous it was 84.

Faber and Roberts investigated the serum lipids of thirty-one infants and young children, fifteen of whom had atopic dermatitis and sixteen who did not. The serum of the eczema group showed (a) a very slightly higher average cholesterol, (b) considerably higher average total fatty acids, (c) considerably higher average total lipids, and (d) a moderately lower iodine number for fatty acids. These writers do not agree with the conclusions of Hansen that the above facts indicate that the lipids are the factors of primary importance as etiological agents in eczema.

The following table compares the findings of Hansen as compared with Faber and Roberts. Hansen's cases were on fasting bloods, Faber's were not. Faber used the Myers and Wordell method of cholesterol determination. Hansen used Bloor's method.

*	No. Cases		Cholesterol		Total Fatty Acids		Total Lipids		Iodine Number	
	F & R	H	F & R	H	F & R	H	F & R	H	F & R	H
Average:										
Normal	16	6	161	185	290	361	451	546	117	111
Eczema	15	7	168	147	351	342	516	488	107	84
Range:										
Normal			121-346	142-232	181-340	292-411	336-674	434-643	86-152	100-136
Eczema			342-223	118-160	254-473	261-443	401-657	409-586	80-140	69-104

Hansen's cases were treated over a seven months period.

Cornbleet and Pace treated a group of eighty-seven patients with maize oil. These patients were all over five years of age and most of them had had eczema of a severe degree since infancy. These cases ran an uneven clinical course but showed steady improvement. The skin first became lighter until it was a dead white, then it became thinner and more supple. The pruritus was the last symptom to disappear. The face was the first region to show clearing and the hands and feet the last. Cornbleet considers that twelve to eighteen months of continuous therapy are required to secure a clinical cure. In his series he has some cases having over three years of cure.

Domianovich and Cardiviola have recently reported a number of cases of infantile eczema which were fed milk with a high fat content and have concluded that a high fat diet is deleterious to only a very small percentage of these infants, whereas many babies are definitely improved or even cured on such feeding.

A group of Hansen's patients were treated locally with crude coal tar ointment and the iodine numbers of their serum fatty acids were determined before the tar was applied and throughout the course of treatment until clinical improvement took place. He found that the Iodine number went up following clinical improvement and that when coal tar treatment was stopped the iodine number dropped and the lesions reappeared.

Laub and Zakon report uniformly poor results with the use of linseed oil as recommended by Hansen and further declare that they believe that a real danger of producing a still greater hypersensitivity by setting up allergic reactions to linseed and cottonseed exists. Marshall administered unsat-

urated fat in the form of corn oil without securing any clinical benefit.

THE CARBOHYDRATES AND ATOPY

The possibility of the existence of some relationship between carbohydrates and their metabolism to dermatitis and other forms of atopy has been studied and as might be expected the observations and conclusions are very conflicting and show a need for further investigation before any positive statement can be made. The existing studies were done on a group of eczemas which were not at all closely related and it is therefore impossible to do more than present the findings as such and to make little attempt to evaluate the etiological possibilities as refer to atopic dermatitis alone.

Osman noted that asthmatics appeared to be definitely benefitted and recurrences prevented by the use of increased sugar in their dietary. He then tried the effect of a similar measure on patients with infantile eczema and reported good response in seven severe cases on this treatment alone. He remarked that the series was too small, the duration of cure too short and the capriciousness of the disease too great to attach any very definite significance to his observations.

Campbell studied the sugar tolerance of a group of eczematous patients at the Montreal General Hospital and found that they exhibited a lowered tolerance for sugar and a delay in its assimilation. Restriction of sugar and other forms of carbohydrates was followed by decided improvement and in some cases complete cure. He states that changes in sugar metabolism are most apt to be found in older patients but have also appeared in younger ones. In evaluating this circumstance, Campbell feels that an abnormal per-

centage of sugar in the blood is only a contributory factor and may possibly serve to lower the resistance of the skin to irritants. Dietary alone does not often result in a clinical cure and local treatment must be instituted simultaneously.

Usher compared blood sugar curves in a series of adult patients with eczema with a series of normal controls and found alterations in 54.7% of the former group and 38% in the latter. He does not think that disturbed carbohydrate metabolism increases the sensitivity of the skin to chemical irritants and considers that dextrose is not a dermal irritant.

Finkelstein recommends a decided reduction of milk and only a limited amount of carbohydrate for the infantile eczema dietary. Ratner and Gmehl studied the anaphylactogenic properties of malted sugars and corn syrup which furnish a common carbohydrate source in the infant diet. They believe that corn syrups are non-anaphylactogenic because the corn starch from which they are made is heated in an autoclave in the presence of pure hydrochloric acid, resulting in complete hydrolysis. They were able to produce experimental evidence to bear out their contention. Barley malt, malt extracts and malt sugar owe their anaphylactogenic properties to hodein, a protein derived from barley. These workers conclude that allergy to carbohydrate foods can be ascribed only to their protein constituents and therefore pure dextrimaltose, corn syrup and crystalline sugars play no role in allergy.

THE NERVOUS ELEMENT

A constitutional instability, inadequacy or hyperirritability of the nervous system is considered by many to be an integral part of atopic derma-

titis. It has accordingly been variously designated as generalized or disseminated neurodermatitis, neurodermite diffuse and neuropathatic exudative diathesis, i. e. a constitutional state predisposing to any disease or group of diseases, the term employed by the Germans to include the factor of nervous irritability.

It has long been recognized that some individuals with atopic dermatitis or eczema are nervous, irritable, emotionally unstable, suffer from gastro-intestinal instability, present evidence of vasomotor instability and experience an exacerbation of their eruption following fatigue or undue emotional strain. Hazen cites a case wherein it appears that the nervous element alone was responsible for the precipitation of an eczematous state. In this case an eight year old child of a nervous and highly emotional temperament developed eczema following scoldings by his father when he thought himself not to blame.

It is very probable that Besmer's prurigo which is preceded either immediately or more remotely by infantile facial eczema in more than half of the cases is not to be considered a separate entity, but rather a variant or even identical with atopic dermatitis. Transitions from one to the other are often seen and frequently blend so thoroughly into one another that it is difficult to establish the point of transition. The infantile and family history of children with Besmer's prurigo are similar to those of eczematous infants and it is probable that the same constitutional factors underly both. Besmer regards the "allergic diathesis" as being transmitted by a Mendelian dominant. Berend investigated the role of the sympathetic nervous system by administering amyl nitrite and noted that after a preliminary flushing of the face there ensued a striking pallor in children with the "exudative

diathesis", a phenomenon which was absent in normal infants. He further found that eczematous infants cleared rapidly after the administration of amyl nitrite and he assumed that the pallor was due to hypersensitivity, either centrally or peripherally, of the splanchmic, the vagotonia of Eppinger and Hebra.

There are many who feel that the nervous element is a manifestation rather than an etiological element in this disease and should therefore be considered of secondary rather than primary significance. Sulzberger, Talbot, Spain, Somm and Shakow hold this view.

THE BLOOD PICTURE

In 1934 Vaughan reported studies of a leukopenic response after the ingestion of allergenic foods and suggested that the resulting leukopenia might be a helpful adjunct in the study of food allergy. He found 62% agreement with skin tests and also noted that there were cases where a leukopenia response was obtained with foods clinically responsible for allergy where skin tests showed negative reactions. The principle of the leukopenic response as a diagnostic aid is similar to that of Widal,Iancanesco and Abram's proposed haemoclastic or colloidoclastic crisis test for liver function. The value of the leukopenia in the latter case has not proven to be significant. A series of fasting white counts are taken at ten minute intervals, the suspected food is fed and then white counts are taken at fifteen minute intervals for an hour and then a final count at the end of an hour and a half. A normal range of 1,000 is allowed in either direction. A drop of less than a thousand is considered borderline. A test of this sort requires a lot of time and technical work and is, therefore, employed only when other diagnostic

measures are not satisfactory. Rinkel regards the test to be 84 per cent accurate.

Madison and Squier recently studied changes in the eosinophile count along with the leukopenic response. The counts were made directly in the usual counting chamber using Camara and Alvarez modification of the acetone eosine diluting fluid. In their series of two hundred test on eighty-four allergic patients the response was positive in 102, questionable in 4 and negative in 94. Fourteen of the patients were under five years of age. In 74 tests showing a fall in leukocytes of 1000 or more, definite eosinophilia occurred in 95.9%.

Cooke stated that he felt that there was a local production of eosinophiles in the tissues and that secondary eosinophilia follows in the blood if the stimulus is sufficient to affect bone marrow. He points out that patients with bacterial and atopic asthma may show abundant eosinophiles in the bronchial secretions though differential counts may be normal. Madison and Squier feel that the blood eosinophilia precedes local tissue eosinophilia and that the local tissue increases are the result of migration from the blood stream. Knott and Pearson found the percentage of eosinophiles in wheals increases with increase in blood eosinophilia. Madison and Squier had a patient suffering from migraine who showed a positive blood response to potato and who developed a typical migraine headache a half hour after eating potato. This patient showed an eosinophilia, which rose from an initial level of 200 cells to 300 cell/cubic mm. and within a half hour reached 400 cells/cubic mm.

Campbell, Drennan and Rettie showed that in the guinea pig eosinophilia occurs only after repeated injections of foreign protein and only

after the latent period usually necessary for the development of hypersensitivity. They interpret this fact as meaning that the allergic reaction and not foreign protein per se is responsible for the eosinophilia.

THE GOLD SOL CURVE IN ALLERGY

A consideration of the phenomena of allergy with accompanying edema and discharge of serum and mucous lead Anderson to study the mechanism from the standpoint of the physico-chemical changes in the gold sol. He interpreted the clinical manifestations seen in allergy as being due to disturbances in water balance or in the combination of water with the protein molecule or groups of molecules. He postulated that instead of an abnormal substance being responsible that the fault might lie in the direction of the absence of some factor which maintains complete solution of the body proteins in the water of the living cell.

The protection of colloidal mixtures against electrolytes by the presence of protein solutions is commonly known. However, if the serum is diluted sufficiently, a point is reached where it loses its ability to protect the colloidal system from precipitation by electrolytes.

A control of normal serum diluted 500,000 times and in the amount of .02 cc per tube was used in a series of tube set up as follows: .02 cc, .05 cc. .1 cc, .15 cc, .2 cc and .25 cc of 1% salt solution. Color changes began in tube three, increasing to tube five, tube five and six showing complete precipitation. An identical set up was then applied using serum obtained from an allergic patient. The color change made its appearance in tube one and was complete in the fourth tube. This shows a very definite and apparent loss of protection to the gold solution by the allergic serum. The procedure was

repeated with more gradual steps in dilution and the resulting changes were more gradual but definitely present and in relative proportion.

An interesting observation which appeared rather by accident in these experiments was that when allergic serum was "aged" (i.e. one hour or more), it gave more protection than correspondingly aged normal serum. With more rapid dilution methods, the color change with allergic serum begins one tube ahead of normal serum.

ATOPIC DERMATITIS AND JUVENILE CATARACT.

A peculiar and very interesting syndrome has been observed in a number of atopic individuals consisting of the coexistence of atopic dermatitis and juvenile cataract. Reports of this curious combination have appeared in the literature from time to time but as yet no thoroughly satisfactory explanation has been advanced to account for it. The common embryological origin of the skin and the lens were thought by Davis to correlate the phenomenon. Attempts have been made to establish an endocrine factor in the condition, especially a possible relationship between one of the endocrine glands and the sympathetic nervous system, but these lines of research have proven fruitless. Daniel pointed out that the ectodermal epithelium of the ciliary body is responsible for the formation of the aqueous fluid which in turn nourishes the lens and carries away its waste products. It has been suggested that some process, possibly allergic in origin, affects the ectodermal structures of the body and that the lens may be affected indirectly by changes arising in the epithelium of the ciliary body and affecting the lens through the secretion produced in the ciliary body.

The term juvenile cataract has been applied to this condition be-

cause it appears in young adult or late adolescent life. The age range is 16 to 35 with the average age of 23.1 for first symptoms of cataract. A great many of these patients have had typical cutaneous manifestations of atopic dermatitis for some time previously and in some the history of dermatitis goes back to infancy. No evidences of congenital disturbance, endocrine dysfunction, avitaminosis nor any of the usual causes of pre-senile cataract are to be found in these patients. The attempts to attribute the lens changes to x-ray therapy, ultra-violet therapy and medication are ruled out because the syndrome is seen to develop in many cases in whom no therapy had previously been given.

The lens, according to Kirby, is characterized by a fragile and easily ruptured capsule, scanty cortex and a very firm amber nucleus. In Brunstring's series, six of the ten cases were in female patients. It is felt that in a large series that no sex difference in incidence would be found to exist.

Kugelberg reported two cases of neurodermatitis and cataract and abstracted the records of eighteen more from the records of nearby European clinics. Gault reported similar findings recently. Daniel reported three cases seen at the Mayo Clinic in 1935 and Brunstring has since reported four additional cases seen there since Daniel's report was published. These cases all had well defined symptoms of "neurodermatitis" with associated eosinophilia and very frequently a history of personal and familial allergy in the form of infantile dermatitis, asthma, hay fever and other allergic manifestations. These patients gave positive reactions to cutaneous tests with both food and environmental allergens.

A typical case is that presented by Davis. A fifteen year old white

girl began to rapidly develop cataracts in both lenses which were mature in less than a year. She had a previously existing disseminated "neurodermatitis" and a long history of asthma and recurring dermatitis since infancy.

DEATH IN INFANTILE ECZEMAS

The rapidity and unexpectedness of death which occurs in some cases of infantile eczema has long been known to both the layman and the medical profession. The mysterious blanching of the skin which sometimes occurs prior to death brought about the lay tradition that it is dangerous to "drive" in the eruption. The significance of the blanching remains as obscure today as when it was first commented on over three hundred years ago.

Many have regarded these cases as being due to status thymicolymphaticus and have written up series of cases with post mortem findings of thymic hypertrophy to support their contention. Von Ranke found only five out of sixteen cases over a ten year period, which had no thymic hyperplasia.

Septicemia as a cause of rapid exodus in eczematous infants was first mentioned by Dutinel and Rivet in 1909. They studied cases which were hospitalized and concluded that since these infants have a diminished defense mechanism to infection, the hospital often provides an unfavorable background because of the increased possibility of being exposed to infection.

Infantile dermatitis appears to confer a definite susceptibility to respiratory infection and death is often the result of a massive infection of the respiratory tract following generalized sepsis. It is curious to note that of fifteen cases of sudden death in this disease collected by Moro, thirteen occurred during February, March and April, the peak of the

upper respiratory infection season.

Koch and Schwartz recently published an interesting series of 103 cases of infantile eczema which were hospitalized in the Milwaukee Children's Hospital between August 1922 and April 1931. Fifty-six of these cases were uncomplicated on admission and of these twenty-three had an uneventful stay in the hospital, thirty-three developed complications, a morbidity of 58.9%. There were ten deaths in this group, giving a mortality of 17.9%. Forty-seven of the infants were admitted with already existing complications. Thirty-three of these had an uneventful course and twelve developed additional symptoms, a hospital morbidity of 25.5%. In this group there were five deaths, a mortality of 10.6%. Schwartz found that in the ten cases that died in theseries admitted without complications four showed septicemia, four had a fulminating type of broncho-pneumonia and two died with intestinal intoxication. Toxemia in all cases was uniform and severe and was associated with rapid weight loss and dehydration. In a few cases a sudden collapse was the only clinical evidence of impending disaster. Bacteriological studies of the septicemias revealed streptococcic in two, streptococci and pneumococci in one and pure pneumococcus in one. Six of the ten cases were autopsied and in none of these was any thymus pathology evident.

Curiously enough, the severity of the eczema did not seem to be the deciding factor in the development of complications. Food was ruled out as a factor. Sudden weight loss often served as a premonitory sign in developing complications. Some showed a clearing of the skin concomitant with the development of severe infection, others did not. Some of the cases

were in open wards and some in private rooms.

Schwartz feels that the increased exposure to infection, no matter how good the precautions, makes it wise to think before hospitalizing these babies.

SUMMARY AND CONCLUSIONS

The development of the field of allergy has made possible the separation of the atopic dermatitis of infancy from the ill-defined category of the "eczemas" and established it as a definite clinical entity. The etiology of the disease is shown to be allergic and since the factor of heredity is so closely associated, it is designated as "atopic" i.e. an allergic disease with a hereditary predisposition.

The pathology of the disease is characterized by a wheal type of reaction with the "shock tissue" wherein the allergic reaction takes place being the vessels of the upper layer of the corium. Epidermal involvement is considered to be secondary to the sub-clinical, submanifest wheal and is produced by trauma inflicted on the pruritic skin.

Atopic dermatitis in infancy is seen as a stage in what may be a lifelong disease process and its evolution is traced according to its three principle age periods: Infancy, childhood and adulthood. It becomes evident that the type of lesion and the clinical course of the disease are conditioned by differences in the physiological response of the individual according to his age. It is also interesting to note the marked changes that occur as to the type of allergen most predominantly involved in these age periods.

Heredity, while it cannot at present be proven to be an absolute prerequisite, is so intimately related that its influence must be considered and appraised. It is known that only 3.5% to 8.5% of non-allergic people have a family history of allergy whereas in individuals suffering with some form of allergic disease, the figures reported by various workers range between 28 to 75%, with the average being well over 50%. A bilateral family

background of allergy is known to be more certain to produce a hypersensitive offspring and with an earlier development of symptoms of allergic disease than is a unilateral one. The hereditary factor is now considered to be a recessive and is thought by some to be sex-limited with double the number of offspring being affected through the female than through the male line. The kind of allergen is not transmitted through the germ plasm, but the capacity to develop allergy probably is.

The modes of transmission, beginning with Ratner's work on transmission of heterologous proteins through the placenta and including sensitization through the gastro-intestinal tract, through the breast milk and through the respiratory tract are discussed.

The more common allergens and the factors regarding them and their relation to the disease process and the particular age group of the patient are considered. Cow's milk, which is the most important food source in the period of infancy is seen to be also a common allergenic substance. Its various physical states and chemical properties are evaluated in relation to allergy. Other allergens discussed include egg albumen, cereals, vegetables, fruits and environmentals.

The average age of onset of symptoms averages about three months. The early age of initial symptoms would appear to indicate a fundamental rather than an acquired disposition to the disease.

Fat infants, especially those who are breast fed have a higher incidence of atopic dermatitis and tend to have a moister and more crusted type of lesion whereas thin infants more often have lichenified lesions. Some

attribute much of the disease process to a fault in fat metabolism.

The disease appears to be worse and more subject to exacerbation during the autumn and winter months, though extremes of heat may also affect the disease process unfavorably.

The endocrines cannot as yet be proven to have any direct relationship to atopy, although some have attempted to associate changes in the clinical state of atopic individuals at puberty, in pregnancy and at menstruation with them.

Infection seems to be the factor which serves to perpetuate or intensify a previously existing atopic dermatitis. The possibility of a fungus being responsible either directly or indirectly in some of these cases is considered. It is believed that atopic individuals are more inclined to develop a fungus infection of the skin than the non-atopic.

Trauma e.g. scratching and rubbing is of importance, because it serves to perpetuate and intensify the process and also because the skin in atopic dermatitis does not show as good a tendency to heal as does the normal skin. Some go so far as to say that without trauma, eczematization would not occur.

External irritants, vaccination and teething are to be regarded as of relatively little importance. Constipation found in 85% of infants with atopic dermatitis and this is considered to aggravate the disease. A case of improvement with splenic extract is reported.

Biochemical investigation indicates that there may be a disturbance

in the calcium-potassium balance and that there is a slightly greater shift to the alkaline side in atopic conditions. High blood cholesterol and uric acid values have been found in many of these patients. The work of Hansen on the serum lipids in relation to the disease is reviewed. very conflicting reports concerning the effect of the carbohydrates are to be found in the literature.

A constitutional instability, inadequacy or hyperirritability of the nervous system is to be found in many individuals who have had infantile atopic dermatitis. There is still considerable dispute as to whether this element is primary or secondary. The relationship between Besmier's prurigo and atopic dermatitis is noted.

The blood picture in atopic dermatitis is seen to be characterized by eosinophilia and a leukopenia following exposure to the allergen responsible. It is believed that the allergenic reaction and not the foreign protein reaction per se is responsible for these findings.

The recently reported and highly interesting changes in the gold sol curve produced by the serum of allergic individuals is reviewed.

The relationship and sometimes coexistance of atopic dermatitis and juvenile cataract is discussed and a review of the cases in the literature is presented.

The infant with atopic dermatitis seems to be more susceptible to infection, especially upper respiratory infection and may develop a fulminating process with septicemia. It is thought inadvisable by some to hospitalize

these infants due to the increased possibility of contact with infection. The sudden death which has been frequently observed in these cases is probably not due to status thymicolymphaticus.

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