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Etiology of atopic dermatitis

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INTRODUCTION

Of all the dermatoses, atopic dermatitis is one of the more common, and moreover, is one which usually provokes or stimulates a lively debate, or even an argument, since many of its facets are only slowly becoming understood. Some, in the past and present, have dogmatically felt it was a simple problem. Others, the majority, feel that the problem of its etiology, in particular, is not at all or at least only partially understood. This is evidenced by the fact that there are almost as many ideas and theories about its etiology as there are writers upon the subject. It is the purpose of this paper to gather some of the old and new beliefs regarding the etiopathogenesis of this disease, to attempt to evaluate various theories and suppositions, and, finally, to arrive at a conclusion which seems logical in the face of present-day knowledge concerning the etiology of atopic dermatitis. It is not the purpose of this paper to discuss other aspects of this condition. The literature dealing with atopic dermatitis is bountiful, consequently anyone desiring to learn of other points (therapy, clinical course, etc.) of the disease may easily refer to one or more of the sources listed in the Bibliography. The references used in preparation of this papaer are, I feel, representative of all schools of thought. Since there is such a vast amount of material available, a summary of the entire

literature would be confusing, redundant, and, frankly, a tremendous task.

THE TERM "ATOPIC DERMATITIS"

History

In the past there have been literally hundreds of names for what we now call atopic dermatitis; it is neither practical or helpful to list them. However, a brief history of the development of the term "atopic dermatitis" may prove useful. Brocq and Jacquet (5) in 1891, presented the concept of "neurodermatitis", divided into two forms: localized and disseminated. "Disseminated neurodermatitis" became the most accepted name until Coca (6) and Sulzberger (29, 30) introduced the designation "atopic dermatitis". Before one attempts to define "atopic dermatitis", one must first sift through some of the confusion regarding "neurodermatitis" as characterized by Brocq and Jacquet. (5)

They felt that seven features were essential. One: nervousness, including above normal impressionability, the tendency towards furious rages, the predisposition to weep easily without adequate cause, depression, paresthesias and hyperesthesias, alcoholism, arthritism, globus hystericus, hemianesthesias and attacks of hysteroepilepsy. Two: constant itching which always preceded the appearance of visible skin changes. Three: sharp demarcation of the plaque which was precisely limited to the area of prior itching. Four: concentrically arranged zones of skin changes resembling

other nervous dermatoses such as scleroderma en plaques. Five: absolutely dry lesions. Six: Hypertrophy at the papillae of the cutis which resulted in visibly raised papules and pigmentations. Seven: chronicity.

Following their (Brocq and Jacquet) presentation of the concept of neurodermatitis, the term was greatly misused. Many did not feel that dryness, sharp demarcation or chronicity were essential to the diagnosis. New terms were coined which were in direct contrast to the original criteria for diagnosis, some of which were "acute neurodermatitis", "wet neurodermatitis", and later, "neurodermatitic reaction". These terms and the indifference shown to the original definition of neurodermatitis confused the picture considerably, but even greater confusion was precipitated by physicians and laymen who felt that the term implied the "nervous" causation of the eruption, in a sense of psychiatric etiology for the disorder.

Dermatologists, due to the above cited misunderstandings, felt that the term "disseminated neurodermatitis" was unwanted, but there were also additional reasons why the term was felt to be unsatisfactory. Many men had been aware that the condition often appeared in persons who had, at one time, suffered from asthma and allergic rhinitis, and in those families where there seemed to be a higher than average incidence of these allergic diseases. It had also been noted that cases of infantile eczema often progressed to typical "disseminated neurodermatitis", indicating that at various ages the disease fell into a spectrum-like pattern. Many of the

infantile cases displayed food allergy more commonly than did other dermatoses. (2)

Due to these various observations, new names were coined for the disease. Besnier (3) referred to it as "prurigo diathesique", Rost (20) called it "exudative eczematoid" and differentiated between infantile eczema (the early form) and the later adult form. Stokes (26) called the disease "hay-fever-asthma eczema", while Blumenthal and Jaffe (4) referred to it as "allergic neurodermatitis".

Finally in 1931, Arthur F. Coca (6) published his concept of "atopy", described as "certain clinical forms of human hypersensitiveness that do not occur, so far as is known, in the lower animals, and which are subject to hereditary influence. In this category have been included thus far only asthma and hay fever, but it is generally thought that eczema and certain forms of drug and food idiosyncrasy will eventually be placed with these".

In 1933, Wise and Sulzberger (31), while classifying various forms of allergic sk n eruptions, suggested replacing "disseminated neurodermatitis" with "atopic dermatitis". They felt that "atopic dermatitis" was preferable to "atopic eczema" because the term would allow inclusion of forms from infantile eczema to the adult form, wherein the lesion is no longer truly an "eczema" because it is lichenified and thickened. Additionally, the term would help avoid confusion with allergic and non-allergic true eczemas, and

especially with allergic eczematous contact-type dermatitis, a dermatitis which is often clinically and/or always histologically, eczematous in all stages. Thus we follow the development of the term "atopic dermatitis".

Concepts and Definitions

A straightforward, concise definition of the term "atopic dermatitis" is not available, due to the very nature of the disease. Baer (2) says: "By using the name atopic dermatitis we recognize a definite clinical entity which undergoes the clinical and histologic evolution from atopic infantile eczema, to the typical lichenified eruption in older children, adolescents and adults. By using the name atopic dermatitis we denote that patients with the disease are likely to present certain immunologic stigmata, certain abnormalities in the responses of the vascular tree, an unusual susceptibility to certain infections as well as other characteristic stigmata. However, the clinical significance of many of these stigmata still awaits further elucidation. By using the name atopic dermatitis we recognize that we are dealing with a dermatosis that has as much of a characteristic prognosis and response to certain therapeutic measures as any other common dermatosis."

Sulzberger's definition (30) states that atopic dermatitis includes those inflammatory dermatoses which are in the majority of cases intimately and characteristically associated with other atopic stigmata in the affected person and/or his family. The

atopic stigmata in the affected person include tendencies to develop: asthma; hay fever; sensitization by so-called "protein" allergens, and urticarial reactions to skin tests with these; Prausnitz-Kuestner antibodies (i.e. circulating antibodies permitting passive transfer of the specific sensitivities); and eosinophilia.

Stoughton (27) in 1956, discussed the role of atopy in the disease. He stated that people with neurodermatitis, hay fever, and asthma as well as urticaria, frequently carry circulating antibodies (demonstrated by the Prausnitz-Kuestner test), as do many members of the family. These persons are known as "atopic types" and the characteristic skin disease which they manifest is frequently called atopic eczema. "What role this atopy actually plays in their skin disease is at best a matter of speculation".

Coca, cited by several authors, first used the term "atopy" to describe a type of hypersensitivity which shows the following pattern: 1) Hereditary influences, 2) specific immediate whealing type of skin reaction, 3) circulating antibody reagins, 4) clinical demonstration of a symptom complex which includes atopic dermatitis, hay fever, and asthma.

It is now probably evident that the term is most often defined in a manner describing the patient, his family, various physical characteristics, and certain allergic characteristics. This is of necessity due to the complexity of the situation; to attempt a "dictionary-type" definition would be to oversimplify the problem and omit important features for the sake of brevity.

BRIEF CLINICAL PICTURE

In order to renew our picture of the clinical case of atopic dermatitis, a brief description as outlined by Hill and Sulzberger (11) is now presented. As has been previously stated, the condition falls into a spectrum-like pattern, with respect to both age and severity. The earliest form is that of infantile eczema, from age 2 months to 2 years. This stage is characterized by highly pruritic, oozing, weeping, crusting lesions of the face and scalp; also seen are scattered patches of eczematous and eczematoid changes on the extremities and trunk.

The next stage, childhood, is seen from age 4 to 10 years. The lesions have a greater tendency to be dry; the prurigolike elements are more pronounced; and extensor surface involvement is seen to become more definite. The classic third or adolescent and young adult phase usually appears between ages 12 and 23 years. At this time flexural lichenification and thickening become marked. There are seen the "great itch crises" with resultant linear excoriations due to scratching.

Baer (2) lists several additional features that are commonly seen, namely white dermagraphism, abnormal responses to heat, cold and other stresses. There is sometimes a lower than normal resistance to skin infections with virus such as those of vaccinia and herpes simplex. In some cases there is perhaps a greater than normal resistance to pyodermic infections and to contact type

allergic eczematous dermatitis. There are sometimes sudden, shock-like fatal reactions upon exposure to certain foreign agents (e.g. foreign sera, medicaments, etc.). There may be seen certain forms of juvenile cataract and other ophthalmic changes. There is no conclusive evidence proving increased incidence of potentially allergic conditions such as urticaria, angioneurotic edema, urticarial dermographism, photosensitivity or other physical allergy, or drug eruptions (e.g. those of acneform, morbilliform, scarlatinaform, eczematous or fixed types).

THEORIES OF ETIOLOGY

Allergy

Having dealt briefly with introductory items essential to understanding the fundamental process of the disease and its clinical course, we may now proceed to the main question contemplated, the etiopathogenesis of this disease. The first aspect to be reviewed is that of allergy.

Rostenberg (21) states that there are two major arguments as evidence supporting the atopic hypothesis as to the causation of the skin lesions of atopic dermatitis. First, that patients with this condition have a relatively high incidence of associated atopic allergies, either within themselves, within their families, or both. Second, that these patients often display multiple positive immediate wheal reactions to a variety of protein allergens.

They may also have passive transference antibodies to some or all of the substances which yield wheals upon direct testing. Strauss and Kligman (28) favor an allergic etiology because of the definite "flare-up" that exposure to the specific allergen produces in a few persons; and because exacerbations are localized to pre-existing lesions or healed sites (sensitized areas), not to absolutely normal skin. They further state: "In susceptible persons the intranasal, subcutaneous and surface application of specific protein allergens may cause a flare-up of an existing area of contact dermatitis due to fixation of the protein antigens in the site of inflammation. This patch of dermatitis may even be transformed into an area of neurodermatitis after prolonged scratching."

Simon (23) also favors the allergic theory, stating that atopic dermatitis is primarily a sensitization reaction to autogenous epidermis, rather than other protein allergens as mentioned above. He bases his opinion on work he has done with dander extracts. Cormia (7) also feels this way, stating that patients with "autoeczematization" have become sensitized to a water soluble fraction of their own epidermal cells.

There are, as would be expected, arguments against the allergic etiology. Rostenberg (21), while stating above two factors for the allergic pathogenesis, further states two main reasons against it. 1) Occasionally, but rarely, the lesions have exacerbated when the person was exposed to certain allergens. 2) Again occasionally, but rarely, the lesions are improved by avoidance of

or desensitization to the specific known allergens. Strauss and Kligman (20), like Rostenberg, state: "Allergists tend to suspect that the dermatitic skin of patients with atopic dermatitis may be a specific allergic manifestation of the atopic state. Yet it must be admitted that specific therapy directed against an allergic cause (hyposensitization and avoidance of exposure) is unusually unrewarding." Stoughton (27) states that many authorities include atopic eczema or neurodermatitis as an allergic skin disease, but others do not. There are many characteristics of atopic dermatitis or neurodermatitis which suggest an allergic basis but practically never is a specific antigen found which can be shown to be responsible for the disease.

Finally, also disputing the allergic theory, is Hill (12), who feels that atopic dermatitis is at least 75% of the eczema of infancy and childhood. He frankly states that he does not know the mechanisms, but that even if the allergens giving positive skin tests are removed, the course of the disease is not changed. A possibility, however, is that not enough skin testing was done, and that one or more allergens may still be present, enabling sensitization to continue.

Psychogenic

The possibility of a psychogenic basis for atopic dermatitis has been widely studied. Kierland (15) feels this factor is controversial. He relates the so-called "atopic personality" in which the

children are precocious, restive, active and aggressive. With age they become leaders, both scholastically and extracurricularly. Then a vicious cycle begins: as the dermatitis becomes worse, the child is spoiled, whereupon he develops into a dominating and selfish member of the household. In doing so, he loses his leadership qualifications and consequently becomes a frustrated, depressed person with numerous emotional complexes. He has suppressed resentment, tension and high intelligence. He may show suppressed and repressed hostility towards his mother, sometimes towards his father.

A study by Rush, Storkan and Obermayer (22) dealt with five adult patients with chronic disseminated neurodermatitis. They found that exacerbations of neurodermatitis were precipitated by emotional tension, and that a decrease of inflammation occurs when tension is relieved. They feel that their study strengthens the impression that attacks of neurodermatitis arising out of emotional causes thus serve as a vehicle for a highly specialized reaction resembling psychosis but less serious in its damage to the personality in that the focus of attention is limited to the integumentary system. "The patient with neurodermatitis reacts to certain situations both emotionally and somatically in the primitive fashion of infancy".

Levin and Behrman (16) feel that the onset of symptoms is markedly influenced by environmental factors, for the psychosoma-

tic individual reacts more actively than others do to changes in social, economic, fami y, and sexual relationships. Stokes (25) lists the characterist cs of those patients with "eczema-asthma-hay fever personality": 1) deep-seated feeling of insecurity, 2) easily developed feeling of inferiority, 3) aggressiveness, with a tendency to dominate and command attention, 4) an intense "I-sensitiveness" or self-consciousness, 5) a marked lability of physical and mental reaction, 6) an intrinsic kinetic drive, 7) an "all-or-none" type of reactivity to all stimuli and problems, 8) an I.Q. greater than average, 9) tension, expressed or repressed, 10) restlessness, due to rapid exploration and exhaustion of a subject, leading to boredom, 11) a deep-seated overdependence, and 12) over-reactiveness to all kinds of competition.

Allerhand, Gough and Grais (1) studied 30 cases of atopic dermatitis and found the following to be common in all: 1) restlessness, need for activity, difficulty relaxing, 2) impatience with others, 3) moderate dominance and brusqueness of manner, 4) emphasis on inner strength and resourcefulness, 5) declared confidence in own health and ability. Cormia (7) states: "The influence of psychosomatic predispositions on the development of the dermatitis is seen very frequently, and must be accepted even though the exact role has not yet been determined".

Others supporting the psychogenic role in the development of atopic dermatitis are Lynch, Hinckley and Cowan (17). These men studied 13 patients with atopic dermatitis and found that a definite

psychosomatic relationship seemed apparent. They state, however, that their results do not permit a generalized concept of personality type. All of their patients presented certain personality factors in common: 1) suppression of resentment, 2) tension, 3) more than average intelligence and self-assertiveness, 4) an almost uniform absence of anxiety and hypochondriasis. These authors report that in almost all of their cases the onset of the eruption or its exacerbations was influenced by environmental factors. In patients who had atopic dermatitis and neurotic manifestations, the psychic factors were of great importance. In these cases, almost any environment would provide the dynamic stress necessary to engender the resentment and the cutaneous reaction.

Rogerson (19), studying 30 children with eczema-asthma-neurodermatitis syndrome, found that: 1) children were high-strung and overactive, 2) overanxious, 3) aggressive and dominating, and 4) most were far above the average I.Q. He also noted that many were quite likely to be overprotected. Ten percent of the group were only children and six others were only sons. He also found that in 18 of the 30 cases the parents were obviously overanxious and overprotective.

From the above data one feels that certain personality patterns are apparently "atopic dermatitis-prone", but we will see that there are those who look upon this with varying degrees of hesitancy of acceptance, and outright disagreement. Of the latter group, Sulzberger (30) is outstanding; in contrast to what others

say, there is no personality or psychiatric change in patients with atopic dermatitis except that caused by the disease. He further states (29) that he is unable to find any preponderance of manifest psychic or neurologic disturbances in a large series of patients with atopic dermatitis. He feels that patients in his series impressed him as being no more "nervous", irritable or psychopathologic than any other group of patients suffering from other chronic, distressing, and sometimes disfiguring dermatoses. He reports that, on the whole, these patients showed fewer psychoneurotic tendencies than were found in a group of patients with acne vulgaris. His opinion is that the "nervousness" encountered in patients with atopic dermatitis is 1) purely coincidental, 2) caused by the same factor that caused the dermatologic condition, or 3) the result of the dermatitis.

Hubler (13) states that localized neurodermatitis is an external manifestation of chronic emotional tension and is characterized by one or more chronic, lichenified plaques located on areas easily reached. However, he, like Sulzberger, also feels that these patients are relatively "normal" people, with only a few having severe compulsions or other neuroses. He feels the method of production is that the itching is irritated by emotional tension. It is a very severe, paroxysmal itching. A habit pattern of itching and scratching is established, and the breaking of this habit pattern is ineffectual when done locally because the fundamental cause remains.

Familial

As has been indicated elsewhere previously in this discussion, various authors indicate the importance of family history in this disease. Cormia (7), feels that a definite hereditary predisposition may be noted, especially with regard to family history of pyogenic infections, hay fever and asthma. Likewise, Wright (32) stresses the importance of a history of atopy in the family, feeling that atopy is usually manifest as hay fever, asthma, atopic dermatitis and possibly some cases of allergic rhinitis. Levin and Behrman (16) believe that neurodermatitis may be hereditary and atopic, or may be acquired. They feel that the predisposition to the development of the cutaneous lesions is inherent and dependent upon a hypersens tive constitution.

None of the references consulted thought that familial history was non-contributory to the development of atopic dermatitis. The only disagreement which may arise would be upon the grounds of the importance of a positive (or negative) family history. Almost all authors state that familial tendencies to atopic disease are noted.

Non-classified

There are other factors reported by various writers as being important either in the development of the disease or the production of exacerbations in atopic dermatitis. Sulzberger (30) lists several factors which he thinks are contributory to exacer-

bations of atopic dermatitis: 1) heat, 2) cold, 3) rapid changes of environment of temperature, 4) perspiration, 5) certain foods (notably fish, eggs, "acid foods"), 6) specific articles of clothing such as silk, wool or satin garments, 7) almost all greasy ointments or greases, 8) work, worry, strain and nervous upsets. He has also found a difference among patients regarding susceptibility to moist or dry heat; some patients are better adjusted to dry rather than moist heat, and vice-versa.

Kierland (15) states that patients with atopic dermatitis have a tendency to have hypotension and a glucose tolerance test with a flat type curve. Concerning cataracts, he feels that less than ten percent of patients with atopic dermatitis develop them. The cataracts which are seen are usually central, capsular, either anterior or posterior polar; develop earlier than senile cataracts, and mature more rapidly than do senile cataracts. Kierland (15) further states that the fall and/or winter months are the worst periods in most patients' lives, and that they usually feel best in the summer months. As Sulzberger (30) indicated, Kierland (15) feels that rapid changes of environmental temperature (cold out-doors, into a hot room) often produce an intense pruritis.

Strauss and Kligman (28) state that recurrence or worsening of atopic dermatitis is often seen in the presence of intercurrent respiratory infections. Smith and Hughes (24) believe that atopic dermatitis is neither purely atopic nor purely neurogenic in origin, but rather it appears in the person who is hypersensitive

both in his emotions and in his cutaneous vascular system. Deutsch and Nadell (8) state that the following components are recognized as being synergistic in the production of atopic dermatitis: 1) a pathological cutaneous process in early childhood, 2) involvement of instinctual drives in the skin disease, 3) development of neurotic traits on the basis of the cutaneous disorder, 4) the contribution of the family constellation with its complimentary neurotic traits, and 5) the final fusion between the physiological system and the personality pattern.

SUMMARY

In summary, the history and definition of the term "atopic dermatitis", plus a brief clinical picture, have been presented. An attempt has been made to present representative samples of literature concerning the etiology of atopic dermatitis, the major theories dealing with 1) allergy, and 2) psychiatry. Within these two camps one finds much disagreement. It has been shown that both camps agree upon the mportance of a familial tendency towards atopic diseases (atopic dermatitis, hay fever, and asthma). Environmental, infectious and other factors have also been briefly touched upon.

CONCLUSIONS

It is difficult to draw any concrete conclusions as to the true etiology of atopic dermatitis when proponents of some theories

have become so dogmatic. Other authors are a bit more broadminded, and I believe that this is the course to choose at this time. do not feel that one can conclude that either allergic or neurogenic (psychogenic) factors may, by themselves, cause the disease, rather that a combination is probably, involving 1) familial history of atopy, 2) certain unknown, as yet, allergic factors, and 3) certain psychogenic elements. Hill (10) states: "Atopic dermatitis is one of the most complicated and obscure situations in all medicine; it is very common and it causes a great amount of suffering. It needs zealous and concentrated research of the same type that is now applied to cancer." Strauss and Kligman (28) state: "In our opinion the basic cause of atopic dermatitis is unknown."

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