

Nonallergic factors in atopic dermatitis

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The nonallergic factors in atopic dermatitis are summarized. Atopic skin behaves as if it were in the state of "itchy skin." The inherited tendency to cutaneous vasoconstriction is apparent in the response to change of temperature, to pressure, and to pharmacologic vasodilating agents, such as nicotinic acid and Mecholyl. Vasoconstriction is demonstrable in children, as well as in adults, and in individuals with strong atopic family histories but with no personal atopic disease. Elevations of values for acetylcholine, histamine, and norepinephrine in the atopic skin are discussed. Studies with dermal perfusion confirm the ready release of histamine from the atopic skin and emphasize that a pharmacologic difference may underlie the vasoconstrictor and pruritic responses. Atopic dermatitis may be related to ichthyosis, cataract, alopecia areata, agammaglobulinemia, Aldrich syndrome, and phenylketonuria. Useful genetic markers for the inherited factors in atopic disease may be more readily found in the associated disease pattern than in the external physical characteristics of the patient, and the atopic skin may be a pharmacologically unique hyperreactive skin that responds to many types of physical, chemical, and immunologic stimuli with pruritus.

Atopic diathesis is a remarkable concurrence of genetically determined hyperreactive states. The allergic syndromes are the most dramatic and most frequently studied features of this complex, but numerous pharmacologic and physiologic findings now available offer an additional view of the whole problem. The nonallergic factors in atopic dermatitis are outlined in Table I. Although it is not the purpose of this paper to review the relation of allergy to atopy, the study of Peterson and associates,¹ demonstrating that typical atopic dermatitis occurs in agammaglobulinemia patients in the absence of wheal-and-flare reaction, natural or acquired, is so important that it must be emphasized as a preface to further inquiry into the unique reactivity of the atopic individual.

CUTANEOUS HYPERESTHESIA

Attempts to relate the nervous system to atopic dermatitis have been continuous but more noteworthy for theory than data. Two studies^{2, 3} have each demonstrated a general decrease in innervation of the skin altered by prolonged

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Table I. Nonallergic factors in atopic dermatitis

Genetic predisposition
Unique flexural, lichenoid dermatitis
Personality traits
Cutaneous hyperesthesia
Vasoactive reactions
Pharmacologic abnormalities of histamine, norepinephrine, and acetylcholine
Associated genetic traits: ichthyosis, cataract, phenylketonuria, agammaglobulinemia, Aldrich syndrome, alopecia arcata

scratching. Degenerative changes, such as those described by Cowan,⁴ occur in some of the deeper nerve fibers; these changes are seen in the host of inflammatory skin reactions and are not specific for itching skin. Illig⁵ reported a case in which dermatitis did not occur on an extremity affected with poliomyelitis although the area had been dermatitic prior to that time. Fregert and colleagues⁶ reported vitiligo in which atopic dermatitis did not involve the vitiliginous areas. The cold pressure test, consisting of measuring the blood pressure response to an ice-water stimulus, has been accepted as a test of pain sensitivity. Atopic individuals have a marked hyperresponse to this test, and, although it has been assumed that this is part of the vascular abnormality of the atopic person,⁷ it could just as easily be interpreted as a hyperesthetic phenomenon. Hypnosis^{8, 9} has been shown to affect the cutaneous vascular reactivity of patients with atopic dermatitis, emphasizing a cerebral-cutaneous relationship.

A simple sensory test consists of stroking the forehead with a cotton wisp, producing a tickle that adapts readily to touch. Kepecs and co-workers¹⁰ compared the irritability of atopic skin in 146 patients of all ages with that of 365 normal controls by this sensory test method. They hypothesized that atopic dermatitis is a disease of itching and scratching from the first month of life. Noting that a 6-month-old normal infant is as indifferent to the cotton wisp-induced tickle as are adults, they found by this test that atopic individuals had a peak irritability at 1 year of age, with a minimum at 4 years. This finding coincided with the known period of spontaneous remission. They viewed atopic dermatitis as an inability to adapt to irritative stimuli and noted that the incidence of irritation increased with the severity of the dermatitis. Their postulate that the central nervous system could reactivate dermatitis by re-establishing old patterns of dermal sensory irritation and pruritus is interesting and is attuned to the conception of "itchy skin." Itchy skin is hyperesthetic skin with a low threshold for pruritus, which surrounds a zone of cutaneous irritability.¹¹ Arthur and Shelley¹² stated that atopic skin behaved as if every point were "itchy." It has long been my belief that the atopic individual acts as if all of the skin were in the "itchy skin" state. Although the consideration of atopic dermatitis as a pruritic state is only descriptive, the causes of this pruritic state may lie in the factors to be described.

VASCULAR REACTIVITY

White dermographism is the best known of the atopic cutaneous vascular abnormalities (Table II). Described by Ebbecke,¹³ and popularized by Whit-

field,¹⁴ it is the white-line response to pressure that contrasts sharply with the red line seen in normal skin. It can be observed also in other dermatoses, as described by Reed and colleagues.¹⁵⁻¹⁷ A well-recognized consequence of this phenomenon is the typical pale well-rubbed face of atopic patients.

Table II. *Vasoactive changes in atopy*

White dermographism
Delayed blanch to acetylcholine, methacholine, and nicotinic acid esters
Reduction of histamine flare
Marked vasoconstriction in the cold and slow vasodilation on warming

Another paradoxical vascular response is the white reaction that follows iontophoresis or intradermal injection of acetylcholine or methacholine. Originally described by Lobitz and Campbell,¹⁸ it is a spreading white reaction that occurs 5 to 30 minutes after injection and lasts 10 to 60 minutes. Such injections produce vasodilation in normal skin and in the mucous membranes of atopic patients.¹⁹ This reaction occurs in 70 per cent of patients with atopic dermatitis as observed by Lobitz and Campbell,¹⁸ Reed and associates,¹⁵⁻¹⁷ Champion,²⁰ and West and co-workers.²¹ Fifty per cent of atopic patients without dermatitis were found to have positive reactions to this skin test, and it was postulated that a different but closely related gene might relate atopy to vasoconstriction.²¹ A similar white and paradoxical response occurs to applications or injections of nicotinic acid esters and nicotinamide. Documented by Callaway,²² it was observed in 70 per cent of the atopic population. Engelhardt²³ stated that a white reaction is equivalent to the diagnosis of neurodermatitis.

All present studies indicate that the white paradoxical reaction of atopic skin represents vasoconstriction. Rothman and Bloom⁷ stated that it was an inherent vasoconstrictor responsiveness of the blood vessels. Vasoconstriction is reflected in the response of atopic skin to hot and cold environment in the studies of Eyster, Roth, and Kierland,²⁴ and Weber, Roth, and Kierland.²⁵ The atopic skin of the fingers and toes usually was colder at room temperature, constricted more in the cold, and dilated more slowly in the warm environment. Atopic patients have been described as having circulatory vagotonia with increased peripheral resistance and diminished cardiac function.²⁶ Abrams and Farber²⁷ studied the digital flow in atopic dermatitis with the plethysmograph and corroborated the vasoconstrictor tendency with environmental temperature change. They correlated the vasomotor response with the severity of the disease, thus raising the question: "Are the vasoconstrictor effects the result of the dermatitis or are they genetically determined changes related to the cause of the dermatitis?" A study²⁸ of 21 patients between the ages of 1 and 6 years with atopic dermatitis revealed that 16 demonstrated delayed blanch with methacholine. The atopic children had a lower digital temperature than did the normal controls of the same age and demonstrated the same vasoconstriction seen in adults with cold exposure. Skin temperature of the forehead and of the antecubital fossae was comparable to control values at all temperatures. These

studies indicate that vasoconstrictor effects are present in the skin long before the establishment of a protracted, severe dermatitis. Hinrichs and associates²⁹ demonstrated the delayed blanch in 30 of 100 newborn children but could not correlate the blanch with family history of atopy. The adjustment to a new thermal environment is assumed to be a significant factor, but observations of these children through childhood and retests of their skin should be a most interesting demonstration of the relationship of paradoxical blanching to atopic disease.

PHARMACOLOGIC ABNORMALITIES

Since the vascular changes and hyperesthesia of atopic skin must have some fundamental physiologic basis, it has been proposed that unique changes in skin acetylcholine, norepinephrine, and histamine concentrations or reactivity are important in atopic disease and are a basis for these alterations.

Acetylcholine

Scott³⁰ utilized a fluorometric method for determining acetylcholine on biopsied skin specimens and found that the amount of acetylcholine was fifteen times greater in atopic skin than in the normal. In banal eczema, the acetylcholine content was five times more than the normal values but became normal with remission of the disease. The atopic skin maintained a high level of acetylcholine content in remission. Scott noted that acetylcholine repeatedly injected into normal skin caused a paradoxical vasoconstrictive response. Acetylcholinesterase is prominent in the blood vessels in atopic skin, as described by Scott,³¹ and confirmed in my laboratory. However, I see no significance in this, since red blood cells contain acetylcholinesterase and inflammatory skin disease shows many esterase reactions. Epinephrine in anesthetic agents will also change the cholinesterase content of human dermis.

Norepinephrine

Catecholamines have been measured and studied in human and animal skin chemically and also studied by fluorescent microscopy by Möller.³² Norepinephrine constitutes 95 per cent of such materials and is restricted to the nerves about the vessels and the arrectores pilorum muscles. The presence of dopa decarboxylase, catechol-O-methyl transferase, and monamine oxidase implies that the skin can synthesize and degrade norepinephrine; this has been confirmed by norepinephrine-¹⁴C tracer studies. Sympathectomy and treatment with reserpine abolish almost all catecholamines from the skin, but small residual amounts raised the question of extraneural location. Both mast cells and special chromaffin cells in the skin have been suggested as possible sites. Solomon and Wentzel³³ demonstrated that the plasma of four atopic patients had less than the usual amount of norepinephrine and, in studying the distribution of intravenously and intradermally injected norepinephrine-¹⁴C, they found an increased binding of this substance in atopic skin.³⁴ Quantitative studies of norepinephrine in atopic skin have not been made. Möller³⁵ demonstrated that increased binding does occur in inflammatory skin disease, but whether it is due to permeability or other factors

is not clear. Guanethidine has been proposed as a means of suppressing pruritus in atopic dermatitis³⁶ but, in my clinical experience, patients may have a blood pressure of 80 mm. of mercury systolic and 60 mm. diastolic and may experience dizziness without having symptomatic relief from the dermatitis or pruritus. Juhlin³⁷ noted that guanethidine induced blanching of the skin with methacholine and, as a theory of the pharmacology of atopic skin, proposed that sympathetic postganglionic fibers release acetylcholine, which in turn releases norepinephrine, and that methacholine releases increased amounts of norepinephrine in atopic skin. No explanation of the white-line phenomenon was given on this basis, but one would assume that norepinephrine should be released by trauma in atopic skin if this theory is correct. It is recognized that release of catecholamine from the ganglion cell requires binding of the unoccupied beta carbon of acetylcholine, and for this reason Mecholyl is less acceptable as a catecholamine releaser.³⁸ It may be better to postulate direct vasodilation by Mecholyl with secondary catecholamine release. Since nicotinic acid produced the same change in atopic patients, this nonganglionic vasodilating activity of Mecholyl seems reasonable. Rothman and Bloom⁷ stated that the threshold response to epinephrine was normal in atopic individuals, confirming the normal responses obtained by Lobitz and Campbell¹⁸ and Reed and Kierland.¹⁶ Juhlin³⁹ measured the cutaneous response to iontophoretically applied epinephrine and norepinephrine. A lower threshold for blanching in atopic skin was suggestive of a hypersensitivity to catecholamine but might be interpreted as a further expression of enhanced vasoactivity. Hingerty and Meenan⁴⁰ reported normal twenty-four-hour urinary values of catecholamines in 22 children with eczema.

Histamine

Johnson and associates⁴¹ described a significantly elevated histamine level in skin from the antecubital fossae of patients with atopic dermatitis. They were reluctant to ascribe to this a role in the production of the disease process. Skin histamine was elevated in studies of eczema by Levi and co-workers⁴² and seemed grossly related to mast cell population. A recent study⁴³ demonstrated, in an atopic patient, a quantitative increase in mast cells in the skin. Rorsman⁴⁴ found that the number of basophilic leukocytes in the blood is decreased in urticaria but not in atopic dermatitis, and VanArsdel and colleagues⁴⁵ demonstrated that histamine release from the blood by antigen-antibody interaction in the atopic individuals was not related to the degree of skin reactivity. Preliminary studies with the dermal perfusion technique in our clinical research unit have demonstrated a ready histamine release from the atopic skin. This method involves perfusing the dermal subcutaneous compartment with saline and sampling the perfusate periodically.⁴⁶ When a histamine liberator, such as 48:80, is injected into the skin overlying the area of perfusion, histamine release can be detected by assaying the perfusate directly in the guinea pig ileum bioassay. It is similarly possible to study kinins by this method by means of the rat uterus bioassay with bradykinin as a standard. Most atopic individuals studied to date release detectable histamine in this system, and such histamine release does not appear to be correlated with the degree of skin disease. Such preliminary studies

confirm the data mentioned previously showing an increase in mast cells and histamine in atopic skin. Since these findings can be demonstrated even in remission, it may reflect a fundamental pharmacologic difference between the atopic and the normal skin.

RELATED DISEASES

The genetic nature of the atopic state is apparent in the fundamental cutaneous reactions just summarized, but equally significant are the less well-documented relationships to other clinical diseases. Discussing these clinical and laboratory observations together is justified for they all reinforce the inherited nature of the atopic reactions. The clinical states of note that have been related to atopy are: ichthyosis, cataract, alopecia areata, agammaglobulinemia, phenylketonuria, and Aldrich syndrome. I have added several personal clinical observations to enlarge clinical interest in these relationships. Paradoxical vascular abnormalities are present in a significant number of patients with these conditions, and other atopic stigmas would be expected to be found often. It has been accepted that ichthyosis and dry skin are dermadromes of atopy and, if one performs a skin test with methacholine on patients who have ichthyosis, one finds that many of the patients have the delayed blanch reaction. The occurrence of ichthyosis or cataract or both in patients with atopic dermatitis has led some authors to conclude that atopic dermatitis is a genetically determined ectodermal nevroid syndrome.⁴⁷ A study by Muller and me⁴⁸ of skin tests on many patients with alopecia areata (since our study demonstrating the significant incidence of atopy in alopecia areata) revealed that a large percentage of such patients show cutaneous atopic reactivity. The coincidence of atopic dermatitis and alopecia areata is frequently accompanied by cataract. My colleagues and I⁴⁹ were interested in the incidence of positive delayed blanch skin tests to methacholine in phenylketonuria patients at the Faribault State Hospital, Faribault, Minnesota. All of those who were being given the phenylalanine-restricted diet showed the paradoxical test. Reasoning from this that the delayed blanch reaction might be related to aminoaciduria, we checked the urinary amino excretion of 11 patients with atopic dermatitis and found no significant patterns. In the few cases of agammaglobulinemia with atopy at our clinic, the vascular reactivity has been atopic in type, indicating that such reactivity is not immunologically determined.

The relation of the intestinal malabsorption syndrome and colitis to dermatitis was summarized in the excellent study by Wells.⁵⁰ My colleagues and I have seen only one patient who had sprue with atopic dermatitis, but, for years, I have determined quantitative stool fat and serum carotene values in such patients. Many of them have had low values of serum carotene, some of which remained low when the disease was in remission. Gastrointestinal intolerance of fat would help explain the relationship of atopic disease to milk, a relationship recognized by the experience of generations of physicians. The response of eczema to a gluten-free diet was noted by Friedman and Hare.⁵¹ Bogdanovich⁵² found decreased gastric acids in 21 patients with a chronic course of atopic dermatitis. Recently, thyroid disease⁵³ was added to the diseases for study in

relation to atopy. Two hundred patients with constitutional eczema had a 21 per cent incidence of all types of thyroid disease, and 33 per cent of 146 patients with thyrotoxicosis had eczema. My colleagues and I have been impressed with the incidence of thyrotoxicosis and Hashimoto's thyroiditis in our patients with alopecia areata and plan to study this recently reported clinical correlation.

The high incidence of atopic disease in a number of distinct, genetically determined, disease patterns indicates that the atopic gene or genes possibly may be related directly to the disease patterns mentioned. Efforts have been made to study the physical body types of atopic persons⁵⁴ and their eye color⁵⁵ without finding distinctive markers for genetic work. These related diseases may be more useful in determining the inherited factors in atopic disease.

SUMMARY

The nonallergic factors in atopic dermatitis are summarized. Atopic skin behaves as if it were in the state of "itchy skin." The inherited cutaneous vasoconstriction is apparent in the response to change of temperature, to pressure, and to pharmacologic vasodilating agents such as nicotinic acid and Mecholyl. Vasoconstriction is demonstrable in children, as well as in adults, and in individuals with family histories of frequent atopy but with no personal atopic disease. Elevations of values for acetylcholine, histamine, and norepinephrine in the atopic skin are discussed. Studies with dermal perfusion confirm the ready release of histamine from the atopic skin and emphasize that a pharmacologic difference may underlie the vasoconstrictor and pruritic responses. Atopic dermatitis may be related to ichthyosis, cataract, alopecia areata, agammaglobulinemia, Aldrich syndrome, and phenylketonuria. Useful genetic markers for the inherited factors in atopic disease may be more readily found in the associated disease pattern than in the external physical characteristics of the patient. The atopic skin appears to be a pharmacologically unique hyperreactive skin that responds to many types of physical, chemical, and immunologic stimuli with pruritus and may be discovered in genetic association with other diseases.

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