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Vascular reactions in atopic dermatitis

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VASCULAR REACTIONS IN ATOPIC DERMATITIS

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I. Introduction

"Atopy" is defined as: "a form of allergy or hypersensitiveness occurring in man and characterized by: (1) immediate vascular, exudative reaction of the sensitive tissue following exposure to the specific exciting agent; (2) a tendency to acquire certain forms of familial idiosyncrasy such as hay fever, asthma, and atopic dermatitis; (3) the presence of Prausnitz-Kustner antibodies or atopic reagins."

The "specific exciting agents" cited in (1) of the above definition are most commonly heat, wool, or soap, although, of course, there are many others.

Approximately seventy percent of patients with atopic dermatitis have a family history of atopy (hay fever, asthma, and atopic dermatitis), thirty percent or more have asthma and/or hay fever themselves, and fifteen percent have allergic rhinitis and/or urticaria.

It used to be thought that diet played a significant role in atopic dermatitis. While atopic dermatitis can be exacerbated by certain foods, especially in infants, this is now thought to be a rather short-lived effect.

Skin tests with various extracts to determine individual causative factors in this disease have largely been abandoned and it is now felt that the atopic dermatitis patient may demonstrate a positive, immediate type of wheal response to a large number of proteins which often do not have any clinical significance. Essentially, the etiology and pathogenesis of atopic dermatitis is still unknown.

Atopic dermatitis follows a clinical course that has several distinct patterns.[1]

The age of onset of atopic dermatitis varies, but about four months appears to be the median. The typical clinical pattern of atopic dermatitis consists of the following stages:

1. Infantile atopic dermatitis occurring at approximately four months of age, followed by a tendency toward spontaneous clearing between the second and fourth years.

2. The appearance of the typical flexural type of eczema during the prepubertal and adolescent period.

3. The more localized or persistent regional patches of atopic dermatitis in adulthood.

A common thread throughout is the gradual clinical improvement that occurs with the passage of time. A large percentage of these patients are essentially free of symptoms by thirty years of age.

As stated in the definition of atopic dermatitis, it is " . . . . . characterized by an immediate, vascular reaction of the sensitive tissue . . . . ." Vascular reactions in the various dermatoses are intimately involved with the etiology, signs, and symptoms; and the case is no less for atopic dermatitis.

Some research workers have called atopic dermatitis "the cutaneous manifestation of a systemic disorder". But even when discussing the pathology of atopic dermatitis as regards the nervous, respiratory, gastro-intestinal, or other body organ systems, vascular phenomena must be considered. In each of the various clinical manifestations of atopic dermatitis,

vascular reactions play an important part in producing the predominating symptoms.

It is the intent of this thesis to examine a few of the peculiar vascular reactions occurring in atopic dermatitis to determine if, and to what extent, they contribute to the diagnosis and management of this disorder.

II. The Delayed Blanch Phenomenon

Among the most bizarre of the various vascular reactions in atopic dermatitis is the delayed blanch phenomenon first described by Lobitz and Campbell in 1953.[2]

Intradermal injection of acetylcholine in normal individuals results in an erythematous wheal and flare. In ten patients with atopic dermatitis, Lobitz and Campbell noted an unusual paradoxic delayed blanch occurring within the flare, three to five minutes after the intradermal injection of acetylcholine. This paradoxical blanching persisted for fifteen to thirty minutes. They stated the belief that this unusual reaction might be specific for patients with atopic dermatitis.

Lobitz and Campbell likened this paradoxic blanch phenomenon to the lymphatic spread of a vasoconstricting substance. They noted that when epinephrine in a 1:10,000 or a 1:100,000 dilution is introduced intradermally into normal skin, there is an immediate blanching (vasoconstriction) in the injection wheal due to the direct constrictor (motor) effect of epinephrine on the cutaneous blood vessels. This blanching then

spreads peripherally with the direct spread of epinephrine, even producing macular white pseudopods of vasoconstriction as the spread of epinephrine occurs via the lymphatics.

They contrasted the vasoconstrictor response of epinephrine to the vasodilator response of acetylcholine in normal skin. When acetylcholine in a 1:10,000 or 1:100,000 dilution is introduced into the skin of a normal person, two pharmacological effects take place to produce redness in or around the injection site.

The immediate response is the flare. This develops in five to ten seconds as a halo of arteriolar dilatation about the injection site and is of a short duration (about three minutes).

The second type of pharmacological effect is a slow, more prolonged redness that results from a direct action of the drug itself on the cutaneous blood vessels to produce a local vasodilation at the injection site. This slow, longer-acting response will increase in diameter as the acetylcholine diffuses laterally from the injection site.

They found that the responses of the skin of atopic persons to injection of epinephrine were the same "qualitatively and quantitatively" as those seen in normal persons.

They noted that the response to intradermally injected acetylcholine was the same in both atopics and normals with the exception that those people with atopic dermatitis developed the "delayed blanch phenomenon"; that is, vasoconstriction spreading peripherally and encroaching on the flare from within.

As noted above, the spread of the delayed blanch resembled the lymphatic spread of a vasoconstricting substance. It spread slowly from edge of the injection site and lasted 15-30 minutes. Adjacent skin sites did not show this "delayed blanch" phenomenon either after injections of isotonic saline as controls, or after similar injections with distilled water.

In later studies, other workers also noted the delayed blanch phenomenon.

In 15 patients with atopic dermatitis and white dermographism, Rothman and Bloom[3] found a blanching to intracutaneously injected acetylcholine in 7 cases.

Stuttgen and Krause[4], Reed and Kierland[5], Jillson et al.[6] and Rajka[7] found a blanching to acetylcholine in 60 to 70 percent of their patients.

Juhlin[8] noted that about 50 percent of his patients with atopic dermatitis showed a blanching of the skin after iontophoresis of either metacholine or the histamine liberator, compound 48/80.

Reed and Kierland[5] noted various gradations in the delayed blanch phenomenon in their patients with atopic dermatitis.

They used acetylcholine and methacholine in dilutions of 1:1000; 1:10,000; and 1:100,000 for their intradermal injections. The main areas they injected these solutions into were those which are usually more involved in atopic dermatitis; that is, the antecubital, popliteal, and nuchal zones.

They noted a delayed blanch phenomenon similar to that described by Lobitz and Campbell. It usually occurred within 2 to 3 minutes in most patients, although it did take as long

as 5 minutes in some of the patients. These latter patients were also noted to have weaker reactions which were preceded by a slight red response that faded into the white. Once established, however, the delayed blanch showed great persistence, some blanched zones lasting up to one and one half hours. Just as in the original findings of Lobitz and Campbell, the blanched site enlarged, showing small pseudopods of vasoconstriction similar in many ways to those produced by intradermally-injected epinephrine.

However, Reed and Kierland noted that this reaction was not the same in all patients with atopic dermatitis. Of the 41 such patients they tested with acetylcholine, 27 had pronounced to moderate responses, 10 had slight responses, and 4 gave normal (red) reactions. Thus, they found that one-third of their patients had a poor delayed blanch to acetylcholine despite the presence of atopic dermatitis. Patients who reacted greatly to 1:1000 dilutions of acetylcholine were also reactive to dilutions of 1:10,000 and 1:100,000. However, patients who reacted poorly to dilutions of 1:1000 showed no reaction to a dilution of 1:10,000 or 1:100,000.

Reed and Kierland further noted that similar results were obtained after the intradermal injection of methacholine. Although methacholine is more stable than epinephrine, the persistence of the delayed blanch with acetylcholine was similar in every respect to that with methacholine.

There are many theories as to the etiology of the delayed blanch phenomenon.

Lobitz and Campbell[2] suggested that it might be due to paradoxic arteriolar vasoconstriction spreading peripherally from the intradermal wheal. This, they supposed, was due to either (1) acetylcholine itself acting to give a motor (constrictor) response rather than the usual inhibitor (dilator) response; or (2) some other vasoconstricting substance being released after acetylcholine had been injected.

Davis and Lawler[9] and Scott[10] thought that it was due to edema. Using a technique of direct microscopy, Davis and Lawler studied the blood vessels in the skin of patients with atopic dermatitis. They found dilated vessels which caused them to believe that the phenomenon was due to edema. However, it has subsequently pointed out by various authors that Davis and Lawler were looking at skin where the superficial layers to the stratum corneum had been removed by repeated application of adhesive tape. Such a procedure per se might be traumatizing enough to cause edema.

Kalz and Fekete[11] in studies using Coomassie blue were unable to demonstrate edema in the region of the delayed blanch. In their 20 patients whose skin was normal, the intradermal injection of methacholine resulted in small wheals that did not develop bluing. In 12 patients with atopic dermatitis, the injection of methacholine produced larger flat wheals with some bluing, but the peripheral blanched zones which occurred in all of them did not exhibit bluing. Therefore, Kalz and Fekete surmised that the blanch phenomenon was not caused by the leakage of plasma from dilated capillaries.

As Champion[12] stated, "There can be little doubt that the typical delayed blanch is due to vasoconstriction--the white area is not raised, the color is slightly different from edema . . . . . .

Using the same method that Moeller and Rorsman[13] used in their studies on capillary leakage in atopic dermatitis, Juhlin[8] used intravenously injected flourescein in order to try to detect edema. Juhlin produced blanched areas in atopic skin by using iontophoretically or intracutaneously introduced methacholine or compound 48/80, a histamine liberator. He found no flourescence in the blanched areas, in contrast to the surrounding affected skin. Thus, he concluded that the blanching in the delayed blanch phenomenon was due to vasoconstriction and not to edema. "If any edema had been present," he states, "the blanched areas should have had a yellow flourescence with this sensitive method."[8]

The fact that there appeared to be a paradoxic vasoconstriction in atopic dermatitis patients as compared to the vasodilation in normal patients when both were injected with vasodilating agents such as methacholine and compound 48/80 interested Juhlin.

It had been postulated that there was an increased tendency toward vasoconstriction in patients with atopic dermatitis. In an earlier work Juhlin[14] had shown that lower doses of iontophoretically introduced epinephrine and norepinephrine are needed to produce a blanching in atopic patients

than in normals. This led him to believe that the blanching reaction in atopic dermatitis might be due to an increased release of catecholamines or an increased sensitivity to them.

To test this hypothesis, Juhlin studied the reactions in skin pretreated with guanethidine. Guanethidine interferes with the appearance of norepinephrine at sympathetic nerve endings, either by blocking its synthesis or preventing its release. It may also release amines from nerve endings and alter sensitivity of the receptor substance. However, guanethidine treatment does not suppress the response of the effector organ to injected norepinephrine. On the contrary, it augments it (Maxwell, et al.[15]).

Juhlin noted that guanethidine pretreatment of the skin in normal subjects and in those with atopic dermatitis increased the response to epinephrine and norepinephrine. He also found that the blanching caused by metacholine and compound 48/80 in atopic dermatitis patients was replaced by a normal reddening when tested in areas pretreated with guanethidine. Thus, Juhlin theorized, the normal reddening is due to a depletion of the catecholamine stores by guanethidine pretreatment and there is therefore less norepinephrine present to be released by metacholine or compound 48/80. "The explanation of the blanching in atopic dermatitis should then be the increased release of norepinephrine caused by metacholine and compound 48/80," Juhlin summarized[8].

The mechanism for the above effect might well be similar to the sympathetic stimulating effect of acetylcholine and

nicotine found by Kottegoda[16] and Burn and Rand[17].

In studies performed on the rabbit-ear, Kottegoda found that the acetylcholine and nicotine induced vasoconstriction was turned to vasodilation when a sympatholytic agent was added.

Burn and Rand[17], in studies on the cat and rabbit, showed that acetylcholine and nicotine probably acted by liberating norepinephrine and epinephrine from the chromaffin cells. An excellent review on this subject has recently been published by Burn[18]. Here he presents evidence that all sympathetic postganglionic fibers release acetylcholine, which in turn releases norepinephrine. This substantiates the second proposal by Lobitz and Campbell (see above) that the delayed blanch is due to some other vasoconstricting agent being released by acetylcholine and is in contrast to Burn's earlier work[19] in which he found that when acetylcholine is leached from an isolated rabbit ear preparation by prolonged continuous perfusion so that the tissue then contains less than physiologic amounts of acetylcholine, the addition of acetylcholine produces vasoconstriction rather than the expected vasodilation. These earlier findings by Burn lend credence to the first proposal by Lobitz and Campbell (see above) that the delayed blanch is due to acetylcholine itself acting to give a motor (constrictor) response rather than the usual inhibitor (dilator) response.

Juhlin[14] noted that he could increase the amount of catecholamines in the skin of normal subjects by iontophoresis of epinephrine and norepinephrine. In such pretreated skin, a blanching was produced by iontophoretic administration of meta-

choline or compound 48/80. These findings substantiate his theory that the blanching in atopic dermatitis is due to an increased release of norepinephrine.

Juhlin[8] also found that guanethidine pretreatment did not change the red reaction produced by iontophoresis of metacholine in normals and some atopics. This is in agreement with the findings of Maxwell et al.[15] that guanethidine does not suppress the parasympathetic efferent transmission.

Juhlin noted that the blanching reaction was obtained at an intermediate dose. Higher doses of metacholine or compound 48/80 caused reddening, indicating that here their vasodilatory properties prevail over the vasoconstriction caused by released norepinephrine. This might explain why delayed blanch produced by intracutaneous injection is seen only in the periphery of the wheals where the concentration is less.

Champion[12] proposed that it is the muscarinic action of acetylcholine that is responsible for the delayed blanch. Acetylcholine has both a muscarinic and a nicotinic effect. The delayed blanch can be inhibited by atropine but not by local anesthetics. He tested 5 patients with pure muscarine and found that at a concentration of 1:10,000 it would elicite a delayed blanch whereas he could not elicite a delayed blanch using nicotine in any concentration. "This therefore," he concludes, "is a paradoxic vasoconstriction caused by a drug which usually causes vasodilation. It may be due to a para-

doxical response of the vessels or because some vasoconstrictor substance has been released."

Champion also states, "It has not been possible to demonstrate an increase in catecholamines in the skin in atopic eczema and most workers have failed to show any abnormal reactions to adrenalin, although Juhlin (1961) has recently claimed to do so."[12]

Much experimental work has been done to determine what factors influence the delayed blanch phenomenon. Lobitz et al.[20] employed various methods of denervating the skin in attempting to alter the delayed blanch. Among the methods used were: (1) local intradermal infiltration of the skin with 1% procaine hydrochloride solution; (2) a "field block" of the skin with 1% procaine hydrochloride solution; (3) the injection of a 1% procaine hydrochloride solution intravenously; (4) a brachial plexus nerve block; and (5) a unilateral lumbar sympathectomy. They noted a complete failure of any of the above methods to affect the blanch. Hence, they concluded that some local tissue factor in the skin of persons with atopic dermatitis is responsible for the delayed blanch. This agrees with their second theory proposed earlier, that "acetylcholine may stimulate the release of some vasoconstrictor substance present in the skin of persons with atopic dermatitis."[2]

In studies of patients with atopic dermatitis, Reed and Kierland[5] failed to inhibit the delayed blanch after intradermal injection of phentolamine, diphenhydramine or procaine. However,

they did note that atropine produced various degrees of inhibition. At dilutions of 1:1000 and 1:10,000, atropine caused a definite wheal and an axon reflex similar in every way to those produced by an injection of histamine. Thus, injection of atropine at these concentrations may release histamine in the skin. After this response to atropine lessened, they injected acetylcholine at the same site. They noted that the effect of acetylcholine was inhibited completely in persons who reacted weakly to acetylcholine, whereas the inhibition in most cases was moderate to poor if the reaction was pronounced.

The inhibition by atropine of the delayed blanch led Reed and Kierland to propose the same thoughts that Champion[12] did later. That is, they believed that the blanch may be caused by the muscarinic action of acetylcholine. Also, they felt that the failure of procaine to inhibit the blanch indicated that the nicotinic action was probably not in operation.

The failure of diphenhydramine (benadryl) to inhibit the reaction suggested to Reed and Kierland that histamine was not released by acetylcholine. They also believed that the failure of Phentolamine (1:1000) to inhibit the delayed blanch indicated that acetylcholine does not release any epinephrine-like substance.

The usefullness of the delayed blanch phenomenon in predicting and/or diagnosing atopic dermatitis is still being argued. If it could be used to predict atopic disease, it could enable physicians to begin prophylactic care early in the patient's life with the hope that the later development of atopic disease might be prevented.

In 1962, as a result of their study of 29 patients with hayfever or asthma or both, but without atopic dermatitis, West and associates[21] suggested that the delayed blanch reaction was found not only in patients with atopic dermatitis, but also in those with other forms of atopy as well. One of the children studied and found to have a delayed blanch reaction was a 4½ year old girl who had no atopic illness, but had a definite familial history of atopy. Therefore, they considered that this test might have value in predicting the subsequent development of atopic disease.

Recently, W. L. Hinrichs et al.[22] studied a random sample of 100 healthy, full-term, newborn infants to see if the delayed blanch phenomenon was of any value in predicting the probability of future atopic disease in them.

Their study group was comprised of an equal number of boys and girls, all of whom were 3-4 days of age. They found no apparent correlation between a family history of allergic disease and a positive delayed blanch reaction. They concluded that it could not be determined whether or not the delayed blanch reaction in this group of infants would be of value in predicting future atopic disease until their study group had been followed for 10 years or longer.

L. A. Johnson et al.[23] are somewhat more definite in their statements regarding the value of the delayed blanch in predicting the presence or possible presence of the atopic state. They state, "The repeated concurrence of the delayed blanch pheno-

menon and the atopic state must be significant." Even though they found the delayed blanch reaction to be neither a constant finding nor specific for atopic dermatitis or the atopic state in general, they found it to be of value in demonstrating that children who have atopic dermatitis have an altered vascular reactivity, probably from birth. They were led to postulate that the delayed blanch was genetically determined by the fact that it occurred in the normal children of atopic parents and hence might be of some value in the case of various skin conditions to determine whether or not atopic factors should be given added consideration. Examples of some of the above skin conditions are eczema of the hand, chronic urticaria, and nummular eczema.

R. H. Champion[12] points out various difficulties in assaying the delayed blanch. One of the difficulties he mentions is distinguishing edema of the skin from the delayed blanch. Superficially, edematous skin may be mistaken for the delayed blanch. Edema of the skin is not uncommon and may occur in both normal and atopic subjects. He suggests careful inspection of the skin site, even employing the capillary microscope if necessary, to confirm the edema. Note here that he is not arguing whether or not the delayed blanch is caused by edema; he readily ascertains it is not edema, but rather a vasoconstrictive phenomenon which must be carefully distinguished from edema.

Another difficulty Champion mentions is the fact that the delayed blanch reaction may be equivocal and there is often not a clear all-or-none response.

The test site is another important factor in assaying the delayed blanch. "I have usually tested both abnormal and clinically normal skin of the forearm and back," Champion states, "and often the back has given the most clear-cut responses." He also found that abnormal skin which showed bright red erythema or edema may give a negative response, although sometimes it is only these areas which give a delayed blanch.

In tests on 50 patients with typical lichenified atopic eczema, Champion found 36 which gave a definite delayed blanch. He concluded that although the delayed blanch phenomenon may be specific enough to suggest its use as a diagnostic test, it was of little or no use in the final analysis. When there was any doubt clinically, he found the delayed blanch to be negative or equivocal.

Thomsen, et al.[24] seem to agree with Champion. They agree that the delayed blanch is highly characteristic of atopic dermatitis, but their results confirmed those of West[21] and others that the phenomenon may be found in many atopics without atopic dermatitis. They also found an equally high frequency of the delayed blanch in nonatopics as well. They postulate that the delayed blanch reaction is "neither specific of atopic dermatitis nor of the atopic state". They interpret the delayed blanch reaction as a secondary phenomenon which gives no definite information concerning the pathogenesis of atopic dermatitis.

It should be noted that the delayed blanch phenomenon is not to be confused with the so-called "white line reaction" or

white dermographism that is seen when the skin of the atopic person is firmly stroked with a pointed instrument.

When the skin of a normal person is firmly stroked with a pointed instrument, the "triple response" (1. red line, 2. flare, 3. wheal) of Lewis and Grant[25] is obtained. The "red line" (or red reaction) develops in 3 to 15 seconds, is limited to the line of stroke, is due to direct dilatation of the capillaries, and is not dependent upon nervous mechanisms for its occurrence. The "flare" (or spreading flush) develops in a few seconds after the red line, is due to an axon-reflex dilation of the arterioles and is dependent upon local nervous mechanisms (axon reflex). The "wheal" (or local edema) is preceded by and completely replaces the red line (red reaction), develops in 1 to 3 minutes after injury, is surrounded by the flare, and is due to transudation of fluid from the minute vessels (capillaries) involved previously in the production of the red line (red reaction).

When the skin of the patient with atopic dermatitis is stroked with a pointed (dull) instrument, the red line of the first stage of the triple response of Lewis and Grant appears in the usual 15 seconds, but then 5-15 seconds later (15 to 30 seconds after stroking), vasoconstriction occurs, producing a blanch that replaces the red line, thus producing the well-known "white line". This blanching persists for 2 to 5 minutes and does not have any whealing component.

The delayed blanch phenomenon is due to the injection of some substance such as acetylcholine or compound 48/80,

develops at 3-5 minutes, spreads slowly peripherally beyond the injection site and lasts 15-30 minutes.

The white line reaction is due to focal trauma, develops in 15-30 seconds, is localized to the trauma site, and is of 3-5 minutes duration.

Although Thomsen et al.[24] have claimed that the delayed blanch is found in patients who have no atopic disease, it is generally held to be most often seen in atopics. This is in contrast to the white line reaction which is found in many different skin diseases. Whitfield[26] mentions just a few of these. They are pityriasis rubra, psoriasis, seborrheic dermatitis, pityriasis rosea, and erysipelas. The patient will often find it produced by pressure of clothing, brassiere straps, belts, garters, girdles, etc.

III. Relation of Vasodilation and Vasoconstriction to the Pruritus in atopic dermatitis

A recent textbook states "The cardinal treatment principle in the management of atopic dermatitis is control of pruritus."[1] Before treatment of any disease process is begun, it is quite helpful to know the etiology. It is interesting to note the trend in various authors' consideration as to the pathology of pruritus in atopic dermatitis. The older authors tended to believe it was due to increased vasodilation, while more recent authors tend to believe it is due to increased vasoconstriction, although this question is still not settled.

D. T. Graham et al.[27] ran various tests on patients with atopic dermatitis. They measured skin temperature with the Hardy radiometer and the "reactive hyperemia threshold" using the method of DiPalma, Reynolds, and Foster.

They concluded that the first step in the pathogenesis of atopic dermatitis is cutaneous vasodilatation, associated with itching and followed by scratching. They suggest that the lesions are the result of scratching or otherwise irritating a skin which is the site of vasodilatation, and that the lesions would not occur otherwise. They further state that the amount of trauma necessary to produce a fairly stable lesion varies according to certain characteristics of the skin, among which is the state of the blood vessels.

They disagree with the studies of Eyster, Roth, and Kierland[28] who reported that individuals with atopic dermatitis show more rapid skin cooling than do "normal" persons and that their skins rewarm more slowly in warm environments.

Graham et al. conceded to Eyster, Roth, and Kierland that atopic dermatitis patients develop vasoconstriction more readily under certain conditions than do other persons, but maintained that this does not necessarily indicate that vasoconstriction is important in the pathogenesis of the disease, since Eyster, et al. did not report evidence that the symptoms and signs were increased by or during the vasoconstriction. Graham, et al. also mention the fact that patients with atopic eczema usually state that they feel better while they are in cool environments, or when local vasoconstricting agents such as ice or pledgets soaked with epinephrine are applied.

Graham, et al. conclude that itching in atopic dermatitis occurs at times of vasodilatation because "itching is the result of low intensity stimulation of pain endings in the skin and vasodilation (at least of the arterioles) lowers the pain threshold and presumably the itch threshold." This concept of the importance of vascular changes in itching was also arrived at by Gaul and Underwood on the basis of their clinical observations.[29]

Further evidence that it is the vasodilation in atopic dermatitis which causes the pruritus comes from Cormia[30]. In investigations of histamine-induced pruritus, he found that the threshold for itching was decreased when histamine was injected into the involved skin of patients with various types of eczema such as atopic dermatitis, pruritus of the anus and scrotum, and nummular eczema.

In a later study, Cormia and Kuykendall[31] further found that the injection of epinephrine before histamine was given reduced the flare response and also diminished the induced pruritus, probably because of epinephrine-caused vasoconstriction off-setting the histamine-caused vasodilation.

Reed and Kierland[5], in studies on patients with various dermatoses including atopic dermatitis, noted that upon injection of histamine or the histamine-liberating compound 48/80 into inflammed skin, the patients immediately complained bitterly of burning and itching in the affected parts, and had a desire to scratch these areas. The scratching produced white dermographism and reduced the pruritus. When the white

dermographism lessened, the pruritus returned, causing more scratching. Reed and Kierland propose that the white dermographism, in bringing forth vasoconstriction, is one of the mechanisms in the reduction of pruritus in a patient.

Gaul and Underwood[29] also implicate vasodilation in atopic pruritus. They noted that some of their patients, when seen long after their dermatitis had healed, complained of itching, burning, and transitory rashes whenever they became warm enough to perspire.

They proposed that during the fall and winter a person becomes subjected to much greater extremes of both temperature and humidity, and that at these extremes, moisture is removed from the skin by evaporation so rapidly that there is excessive cooling and hence persistent vasodilation results. They give examples of various patients with atopic dermatitis who noted an exacerbation of their pruritus whenever they encountered extremes in temperature. These patients noted a remission of the pruritus with the arrival of summer and relatively stable temperatures.

It has been found that there is an oscillation between vasodilation and vasoconstriction in skin exposed to cold temperatures. The demarcation point, as cited by Gaul and Underwood, seems to be 52° F. They implicate the vasodilation aspect of this oscillation as the main factor in atopic pruritus caused by temperature extremes. They cite cases where infants are seen with only their faces involved, the covered areas on the infants appeared normal. They note that the areas of distribution of the pruritus seem to follow the mode of dressing

the child. That is, the distribution of atopic dermatitis occurs in areas of the body having the greatest heat loss. They give the face and flexor surface of the extremities as examples of these areas.

When the extremities are flexed, the temperature of the opposed skin builds up to body temperature and some moisture usually accumulates. Extending the extremities causes sudden cooling, and flexion, sudden heating. An excess of heat produced by the body is first dissipated by vasodilation in the upper extremities, and if this is not sufficient, by vasodilation in the lower extremities. Gaul and Underwood noted that atopic lesions are seen in the areas where these temperature shifts occur and imply that there is sufficient vasodilation in these areas to cause edema and produce itching and burning which is eventually followed by lichenification and pigmentation.

However, it should be noted here that this pruritus could be caused by sweating. That is, perspiration occurring during various temperature shifts could irritate mildly inflammed skin enough to cause severe itching.

Gaul and Underwood cite an example of vasodilation causing pruritus in a patient with atopic dermatitis who experienced burning and itching of his face whenever he entered a warm room from a cold environment. They state that vasodilation occurs in everyone under these circumstances in order to further dissipate heat which has been built up outdoors to meet the particular temperature. The vasodilation (a natural physiologic reaction here) was enough in this case to cause pruritus.

They further postulate that excessive washing with soap and water can produce a chronic vasodilation. When this injury from excessive washing is coupled with vasodilation from cold weather, the total stress is sufficient enough to produce eczematization and pruritus. They state that persisting vasodilation can disturb normal keratinization and, in turn, may affect the integrity of the epithelieal mantle and its ducts, thereby predisposing to pruritus.

Other systemic factors causing peripheral vasodilation such as psychic stimuli, exercise, and food ingestion can also cause pruritus in atopic dermatitis, according to Gaul and Underwood.

In contrast to the above opinions that the primary pathology in the pruritus of atopic dermatitis is vasodilation, are those which hold that the primary pathology in atopic dermatitis is vasoconstriction and that this is also the etiology of the pruritus. There is much disagreement about both these theories, however.

Many authors have noted that atopic skin has an unusual vasoconstrictive capacity. The pale face, white dermographism[26], vasoconstrictions in response to acetylcholine, methacholine[20], and nicotinic acid esters, diminished histamine axon flare[28], and vasoconstriction in a cold environment as demonstrated by skin temperature[32], all attest to the increased vasoreactive capacity of atopic skin.

Cutaneous abnormalities in the metabolism of norepinephrine and epinephrine in atopic dermatitis are suggested by Juhlin[14]

who found that extremely low concentrations of norepinephrine or epinephrine produces blanching in the skin of patients with atopic eczema. He interprets this difference to be an expression of increased sensitivity of the cutaneous blood vessels to catecholamines. Juhlin also found that norepinephrine, when introduced into the skin by iontophoresis, remains in situ longer in patients with atopic dermatitis than in patients with other dermatoses[33]. Both these findings imply an increased tendency to vasoconstriction in atopic dermatitis.

Solomon et al.[34] hypothesized that, under stress, patients with atopic dermatitis bind norepinephrine excessively at the major site of its production (the skin), so that the normally small quantity of norepinephrine which should escape into the circulation does not, and results in a local bound accumulation as well as a circulating deficit of this catecholamine. This is in agreement with the above-mentioned findings of Juhlin. Solomon et al. also demonstrated that in a small number of patients with atopic dermatitis, there will be no measurable circulating norepinephrine during a flare-up of the disease; and that in remission the plasma levels become normal once more.

In a later investigation[35], Solomon et al. made studies to determine whether there is any difference in the metabolic fate of intravenously and intracutaneously administered norepinephrine in patients with atopic dermatitis and patients with other dermatoses. They studied norepinephrine metabolism by measuring the residue of intravenously and intracutaneously injected isotopically labeled dl-norepinephrine acetate in the

serum, the amount excreted in the urine, and the uptake of this material by the skin.

They found that the urinary excretion of norepinephrine is less in atopic dermatitis than in normal controls, that norepinephrine disappears from the plasma in a different fashion in atopic dermatitis than in controls and that the concentration in the skin was 2 to 50 times higher in the skin of atopics as compared to controls after intracutaneous injection of norepinephrine. The degree of cutaneous C-14 labeled norepinephrine roughly correlated with the clinical severity of the dermatitis. They conclude that their results indicate that norepinephrine, in excess of normal, appears to be bound tightly in the skin in acute atopic dermatitis. They end, however, by warily citing previous findings of Montagna[36] and Mercanti[37] who found that histochemical evidence for the presence of catecholamines in human skin is equivocal.

Moeller[38] had shown that there was, in fact, a cutaneous epinephrine store in man, although its exact location was elusive (Mercanti[37]). In 1962 Viglioglia[39] reported the antipruritic effect of guanethidine (a norepinephrine blocking agent) in atopic dermatitis.

Solomon et al.[40] studied the effect of orally administered guanethidine on the vasoconstriction produced by a 0.1% triamcinolone acetonide cream (a corticosteroid preparation) applied under an occlusive dressing. They found that guanethidine inhibited partially or completely the vasoconstrictive response in the skin to topically applied triamcinolone acetonide. This

inhibition was seen in patients with acute and chronic atopic dermatitis as well as with other dermatoses. After 2 weeks of guanethidine therapy by mouth, 8 of the 10 patients with acute atopic dermatitis were greatly improved. The patients with chronic atopic dermatitis had considerable reduction in pruritus.

Since guanethidine decreases vasoconstriction and decreases pruritus, vasoconstriction is heavily implicated as the cause of the pruritus in the above cases.

The pharmacological effect of guanethidine, like that of reserpine, is a specific suppression of sympathetic impulses in the nerve endings, and moreover, depletion of the norepinephrine depots in organs receiving sympathetic innervation. Accordingly, Moeller[41] found reserpine therapy or postganglionic denervation to make the norepinephrine disappear from the skin and the ability of the skin to take up circulating norepinephrine to be reduced or abolished. Unlike reserpine, guanethidine has no cerebral effect.

Thomsen et al.[24] ran tests on 13 patients with severe atopic dermatitis. They were only able to report that 6 of the 13 had experienced a favorable effect upon the pruritus after guanethidine therapy. This is no better than the effect which would be expected with a placebo. They discontinued the trial therapy with guanethidine after a short period of time because they felt that it was not justified to continue longer without supportive treatment in this series of patients suffering from such intense itching. The dosage of guanethidine used was maximal, as all developed side effects.

Thomsen's results are at variance with those of Viglioglia[39] mentioned above. He and his workers cite several reasons why this might be so. First of all, Viglioglia does not state the severity of the disease in his patients or whether they received other supportive treatment at the same time. Secondly, his treatment period (three months) was considerably longer than that of Thomsen's group.

Thus, the Thomsen group was unable to demonstrate a definite anti-pruritic effect of guanethidine on atopic dermatitis. They postulate that this could mean either that the increased norepinephrine activity in the skin is of no significance to the itching, or that it cannot be influenced by guanethidine in clinically applicable doses.

In a double-blind study, Robinson et al.[42] tested the effect of guanethidine on the pruritus of 21 patients with atopic dermatitis. The dosage was 20 mg. daily for 2 weeks. Ten preferred guanethidine, 6 preferred a placebo, and 5 had no preference. These differences do not approach statistical significance. Owing to great individual variation in the pattern of symptoms, Robinson and his workers concluded that a longer trial with more patients would be necessary if more definite conclusions were to be reached. Thus, there was no conclusive evidence of any benefit with guanethidine in this study.

The question of increased vasoconstriction in atopic dermatitis is generally agreed upon by many authors; its significance, however, is not. As Champion[12] stated, "In the present state of our knowledge it is not possible to decide

whether the tendency to vasoconstriction is one of the factors which predisposes the patient to develop skin changes or whether it in some way reflects the basic etiology of atopic eczema or whether it is an interesting, but unimportant secondary phenomenon."

IV. Histamine and Histamine liberators (their effect in cases of atopic dermatitis)

The effect of histamine or of compounds causing release of histamine has been noted to be different from normal in patients with atopic dermatitis.

Histamine, when introduced into the normal skin, produces the well-known triple response. The three components of this response are local reddening from local vasodilation of minute vessels, the so-called "flare" or widespread dilation of neighboring arterioles caused by a local neural response, and the local enlarging wheal produced by increased vascular permeability. This reaction to histamine is similar to that seen after mechanical stroking of the skin.

The response to histamine in atopic dermatitis was studied by Eyster and associates[28]; the flare portion of the triple response was missing in all six patients examined. Kalz and associates[43] noted that only 14 of 32 patients with atopic dermatitis had flares after injection of histamine. The patients were given psychiatric examinations and Kalz and associates hypothesized that the absence of flare corresponded to the suppression of feelings of resentment and anger in the patient.

Reed and Kierland[5] injected histamine into the skin of patients with various skin inflammations including atopic dermatitis. They also injected compound 48/80 to determine if the normal triple response would be elicited from any released histamine. Compound 48/80 has been widely used as a histamine liberator in animals. In man it has been injected intravenously in the treatment of allergic disorders and in studies on headache. All sites selected for injection showed varying degrees of white dermographism to a strong mechanical stimulus, and studies were performed on the effect of white dermographism on the reaction to histamine. Observations by Reed and Kierland also were made on the pruritus induced by histamine. The 48/80 was given only once to each person because of the possibility of sensitization, as noted by some investigators, if repeated injections of 48/80 are given.

Reed and Kierland found that the flare response to histamine depends on the acuteness of the inflammation present. It was decreased in the more acute inflammatory processes, the flare being marked partly or completely by the already dilated minute vessels of the skin.

Injection of 48/80 into normal skin produced a strong flare. Inflammation of the skin reduced the size of the flare produced by 48/80, the reduction paralleling the acuteness of the cutaneous disease. The size of the wheal was also reduced noticeably in the more acute inflammatory conditions, the reduction being more pronounced with 48/80 than in the case of histamine.

Reed and Kierland also discovered that the preparation of the skin for the injection is important, for rubbing the skin produces white dermographism. When histamine was injected into a zone of vasoconstriction (white dermographism), the usual flare was absent or reduced, in contrast to the flare produced by histamine injected into adjacent skin that was not rubbed. As the vasoconstriction of the skin dminished, the flare slowly appeared, first around the wheal and then in more peripheral regions. The vasoconstriction from the white dermographism was thus a more powerful effect than was the dilatation from the axon reflex.

Juhlin[8] found that the threshold dose of iontophoretically injected 48/80 was decreased in urticaria and atopic dermatitis. He then set out to ascertain whether patients with urticaria or atopic dermatitis differ in sensitivity and/or reaction to a histamine liberator injected intravenously[44].

Juhlin found that in blood studies on the patients tested, the eosinophiles were usually disrupted with extrusion of granules. This was especially marked in patients with atopic dermatitis who sustained more than a 50% decrease in their number of eosinophiles. Among the other patients, no significant decrease in eosinophiles took place.

The role of the eosinophile leukocyte remains obscure. By some, it is regarded as the antihistamine cell of the body. In that case, release of histamine should provoke increased release of antihistamines, which in turn might be explained morphologically by the explosive destruction of the eosinophiles.

The patients with atopic dermatitis and massive eosinophilolysis seemed, however, to derive no clinical benefit from this supposed antihistamine release. It is, of course, possible that a markedly increased release of histamine had taken place in these patients so that the amount of antihistamine was insufficient. However, since no histamine determinations were done, Juhlin concludes by stating that "nothing can be said with certainty in this matter." Graham and associates[45], however, believe that a significant elevation of skin histamine levels may be possible due to an inflammatory infiltrate of eosinophil or basophil leukocytes. They found that polymorphonuclear leukocytes contain about 7 micrograms histamine per gram, eosinophil leukocytes about 360 micrograms per gram, and basophil leukocytes about 2,400 micrograms per gram.

Johnson et al.[46] were also interested in the role of histamine in allergic reactions in the skin. Although it has been repeatedly demonstrated that histamine is released from various tissues, including the skin, as a result of antigen-antibody reactions in sensitized skin, a direct causal relationship between histamine content in the skin and the degree of allergic response of the skin has not been established. Johnson and his group decided to investigate the skin histamine levels in chronic atopic dermatitis, since this condition may approximate the clinical prototype of chronic cutaneous allergy.

They found that what they thought was a significant difference in the skin histamine levels of normal skin and skin inflammed with atopic dermatitis was actually a non-conclusive

bit of evidence. They were led to this viewpoint by the fact that there are considerable regional variations in the histamine levels of normal skin. They state, "One would not be justified in concluding that the increase in histamine content in skin from individuals with atopic dermatitis was a significant factor in the production of this disease."

Juhlin[8] noted that the whealing produced by 48/80 was decreased in his patients who exhibited the delayed blanch phenomenon. He surmised that this was probably because the increased vasoconstriction found in the delayed blanch prevented the formation of edema. This was in accordance with earlier findings that the tendency to edema formation is decreased in atopic dermatitis. However, in atopic patients where metacholine produced a red reaction, Juhlin found an increased whealing reaction to 48/80. The increase in whealing here was of the same magnitude as found earlier in patients with eczema (Juhlin and Rune[47]).

Williams[48] showed that the intramuscular administration of histamine to patients with atopic dermatitis produces an increase of skin temperature at the sites of predilection for this condition (antecubital and popliteal areas, hands, feet, face).

V. Effect of Various Irritants on atopic skin

The effect of various irritants on atopic skin has been noted to be different from that seen on normal skin. The two main skin irritants which have been investigated are the Cantharides and Nicotinic acid esters.

Allison and Bettley[49] compared the response of normal and eczematous subjects to applications of cantharidin. Cantharidin is the active principle of cantharis $C_{10}H_{12}O_4$, an anhydride of cantharidic acid. Allison and Bettley acquired the following results:

1. Patients with atopic eczema produce larger blisters containing more protein, both absolutely and relative to their own plasma, than do normals or other types of eczema of comparable severity.

2. Patients with more than 15% of their skin affected by atopic dermatitis had a significantly raised blister fluid white cell count. This was related to the excessive volume of blister fluid formation.

3. Patients with less than 15% of their skin affected by atopic dermatitis had a significantly lower blister fluid white cell count than the other groups tested.

4. The volume of blister fluid formed was greater in the atopic group than in the other groups tested.

They believed that if the blister protein came mainly from the capillaries, then cantharidin must have produced a greater degree of vascular permeability in atopic and eczematous subjects than in normals.

The fact that the urticaria group they tested had normal results although vascular permeability is likely to be more easily produced in that group, suggested to Allison and Bettley

that the increased permeability in eczema and atopy is due to the action of the cantharidin on the vessels being modified by an altered epidermis. They concluded that in atopic dermatitis the epidermis of apparently normal skin is more readily damaged by cantharidin than the skin of a normal person, and that this fragility is very much greater in subjects with atopic eczema than in those suffering from other types of dermatitis.

Nicotinic acid is one of the essential vitamins. It is related chemically to nicotine, but possesses none of the pharmacologic properties of the latter. It functions in the body in the form of the amide, which is as active as the acid.

Nicotinic acid given orally causes flushing of the face and a feeling of warmth, due to vasodilatation from a direct effect on blood vessels. This blush effect may last for two hours and sometimes is accompanied by itching and burning. This vascular reaction is not shared by nicotinamide. In order to achieve this flush reaction, nicotinic acid must be given in unphysiologically large amounts, indicating that the action is pharmacologic rather than physiologic.

Illig[50] reported an "anemic reaction" to the percutaneous absorption of esters of nicotinic acid in 33 of 47 patients who had atopic dermatitis. However, he rubbed the oinement into the skin of these patients and probably produced white dermographism (see below).

Reed and Kierland[5] injected doses of 0.1 ml of 1:1000 monoethanolamine nicotinate (Abbott) intradermally into 10

patients who had atopic dermatitis and 5 patients with normal skin. The above solution is a mixture of nicotinic acid and monoethanolamine. They compared the reaction with that induced by injection of 0.1 ml of an isotonic solution of sodium chloride. In normal skin, a red wheal appeared, with a flare similar to that caused by the saline. In inflammed skin, the reaction was little different from that produced by saline, with "perhaps somewhat more of a flare being present".

Thus, monoethanolamine nicotinate, which breaks down in the skin into nicotinic acid, does not have the paradoxic action of acetylcholine, namely, the delayed blanch. Illig was apparently dealing with white dermographism in his above-mentioned work, for he found the "anemic reaction" only when the ointment was rubbed into the skin of patients who had atopic dermatitis. The normal controls showed the hyperemic reaction that occurs when any ointment is rubbed into normal skin.

Any study of percutaneous absorption in patients who have white dermographism will be influenced by the strong tendency toward vasoconstriction when the skin is traumatized.

This fact seems to be ignored by Rovensky and Preis[51] who rubbed Trafuril ointment into the skin of their test subjects. Trafuril is an ointment containing 5% nicotinic acid tetrahydrofurfurylester. They consider the blanch observed after the application of Trafuril to be similar to the delayed blanch phenomenon observed with acetylcholine (see above) differing from it only in quantity, not in quality. It is interesting to note that they, like Davis and Lawler[9], consider

the delayed blanch phenomenon (and also the blanching reaction to nicotinic acid esters) to be due to edema and not increased vasoconstriction. They, like David and Lawler, based their findings on microscopic studies of the capillaries. They considered that the atypical Trafuril phenomenon in atopy is more than an empirical test considering the altered susceptibility of the hemato-parenchymatoris barrier to various mediators.

Rovensky and Preis followed the Trafuril reaction in 3 groups of children with atopy. Thirty-five mg. of Trafuril ointment were rubbed in on the volar surface of the forearm, and the reaction was read in 20 to 30 minutes. It was evaluated as typical on the appearance of vivid erythema, sometimes with a pomphus, reaching 2-3 cm beyond the treated area. The reaction was considered as atypical, or pathological, when no erythema or a blanch appeared within 20 to 30 minutes. Hardly visible erythema encircling the treated spot with a narrow line, or its reticulation or a feeble rosy reaction were considered "uncertain" reactions.

The results of the Trafuril test in atopy were atypical. Rovensky and Preis felt that the Trafuril test was a valuable diagnostic aid and a good indicator of what they termed "the endogenous eczematous constitution," basing this opinion on the high rate of agreement between the atypical Trafuril test and the obvious clinical picture of atopic dermatitis in toddlers. They state that the Trafuril test is constant during the course of atopic dermatitis and is not influenced by cortisone or salicylate therapy.

VI. Conclusion

While it has been established that vascular reactions to various agents are often atypical in atopic dermatitis, the exact nature and extent of these atypical reactions is still controversial. The vascular reactions discussed above certainly do not constitute the entire field. They merely represent the type of work which is currently going on. In the opinion of many authors and researchers, the above vascular reactions, and others like them, will play a significant role in the eventual determination of the exact etiology, diagnosis, and treatment of the atopic state including atopic dermatitis.

BIBLIOGRAPHY

1. Stewart, W. D., Danto, J. L., Maddin S.: Synopsis of Dermatology: The C. V. Mosby Company, St. Louis, Mo.: 1966.

2. Lobitz, W. et al.: Physiologic studies in atopic dermatitis, Arch Derm and Syph 67:575-84, 1953.

3. Rothman, S. and Bloom, R. E.: The increased vasoconstrictor tendency in atopic dermatitis, Arch Belg Derm Syph 13:300-309, 1958.

4. Stuettgen, G. and Krause, H.: Zur Bewertung abnormen Hautgefaessreaktionen beim endogenen Ekzem und Asthma, Allerg Asthma 3:206-212, 1957.

5. Reed, W. B. and Kierland, R. R.: Vascular reactions in chronically inflammed skin, Arch Derm 77:91-96, 181-90, 263-8, 1958.

6. Jillson, D. F. et al.: Problems of Contact Dermatitis in the Atopic Individual, Ann Allerg 17:215-23, 1959.

7. Rajka, G.: Prurigo Besnier (atopic dermatitis), with special reference to the role of allergic factors, Acta Dermatovener (Stockholm) 40:285-306, 1960.

8. Juhlin, L.: Vascular reactions in atopic dermatitis, Acta Dermatovener (Stockholm) 42:218-29, 1962.

9. Davis, M. J. et al.: Observations on the delayed blanch phenomenon in atopic subjects, J Invest Derm 30:127-31, 1958.

10. Scott, A.: The Distribution and behavior of Cutaneous Nerves in Normal and Abnormal Skin, Brit J Derm 70:1-21, 1958.

11. Kalz, R. and Fekete, Z.: Studies on the mechanism of the white response and of the delayed blanch phenomenon in atopic subjects by means of Coomassie blue, J Invest Derm 35:135-40, Sept '60.

12. Champion, R. H.: Abnormal vascular reactions in atopic eczema, Brit J Derm 75:12-15, Jan '63.

13. Moeller, H. and Rorsman, H.: Studies on Vascular Permeability Factors with Sodium Fluorescein: II. The effect of intracutaneously injected histamine and serum in patients with atopic dermatitis, Acta Dermatovener (Stockholm) 38:243-250, 1958.

14. Juhlin, L.: Skin reactions to iontophoretically administered epinephrine and norepinephrine in atopic dermatitis, J Invest Derm 37:201-5, 1961.

15. Maxwell, R. A. et al.: Pharmacology of 2-(Octahydro-I-azocinyl)-ethyl-guanidine sulfate (SU-5864), J Pharmacol Exp Ther 128:22-29, 1960.

16. Kottegoda, S. R.: The Action of Nicotine and Acetylcholine on the Vessels of the Rabbit's Ear, Brit J Pharmacol 8:156-161, 1953.

17. Burn, J. H. and Rand, M. J.: The Relation of Circulating Noradrenaline to the Effect of Sympathetic Stimulation, J Physiol (London) 150:295-305, 1960.

18. Burn, J. H.: A New View of Adrenergic Nerve Fibers, Explaining the Action of Reserpine, Bretylium, and Guanethidine, Brit Med J I:1623-28, 1961.

19. Burn, J. H.: Relation of Motor and Inhibitor Effects of Local Hormones, Physiol Rev 30:177, 1950.

20. Lobitz, W. C. et al.: Effect of denervation on the delayed blanch phenomenon, Arch Derm 75:228-29, Feb '57.

21. West, J. R. et al.: Delayed blanch phenomenon in atopic individuals without dermatitis, Arch Derm 85:227-28, Feb '62.

22. Hinrichs, W. L. et al.: Delayed blanch phenomenon as an indication of atopy in newborn infants, J Invest Derm 46:189-92, Feb '66.

23. Johnson, L. A. et al.: Cutaneous vascular reactivity in atopic children, Arch Derm 92:621-4, Dec '65.

24. Thomsen, K. et al.: Guanethidine in the treatment of atopic dermatitis. Delayed blanch phenomenon in atopic and nonatopic individuals, Arch Derm 92:418-21, Oct '65.

25. Lewis, T. and Grant, R. T.: Vascular Reactions of the Skin to Injury: The Liberation of a Histamine-Like Substance in Injured Skin; The Underlying Cause of Factitious Urticaria and of Wheals produced by Burning; and Observation upon the Nervous Control of Certain Skin Reactions, Heart 11:209-65, 1924.

26. Whitfield, A.: On the white reaction (white line) in dermatology, Brit J Derm 50:71-82, 1938.

27. Graham, D. T. et al.: The relation of eczema to attitude and to vascular reactions of the human skin, J Lab Clin Med 42: 238-54, 1953.

28. Eyster, W. et al.: Studies on the peripheral vascular physiology in patients with atopic dermatitis, J Invest Derm 18:37-45, 1952.

29. Gaul, L. E. and Underwood, G. B.: Infantile and atopic eczema from injury to the skin by overcare and overtreatment, Am J Dis Child 80:739-52, 1950.

30. Cormia, F. E.: Experimental histamine pruritus: I. Influence of physical and psychological factors on threshold activity, J Invest Derm 19:21-34, 1952.

31. Cormia, F. E. and Kuykendall, V.: Experimental Histamine Pruritus: III. Influence of Drugs on the Itch Threshold, Arch Derm and Syph 69:206-218, 1954.

32. Weber, R. et al.: Further contributions to the vascular physiology of atopic dermatitis, J Invest Derm 24:19-29, 1955.

33. Juhlin, L.: The fate of iontophoretically introduced epinephrine and norepinephrine in patients with atopic dermatitis and in normal skin, J Invest Derm 37:257-61, Oct '61.

34. Solomon, L. M. et al.: Plasma catecholamines in atopic dermatitis, J Invest Derm 41:401-4, Dec '63.

35. Solomon, L. M. et al.: Physiologic disposition of C14 norepinephrine in patients with atopic dermatitis and other dermatoses, J Invest Derm 43:193-200, Sep '64.

36. Montagna, W.: The Structure and Function of the Skin: Academic Press Inc., New York, N. Y.: 1956.

37. Mercanti, E. C.: Failure to show the presence of a chromaffin system of cells in the human skin, J Invest Derm 34:317, 1962.

38. Moeller, H.: The catechol amines of the skin, Acta Dermatovener (Stockholm) 42:386-92, 1962.

39. Viglioglia, P. A.: Guanethidine as an Antipruritic, Arch Derm 85:472-475, 1962.

40. Solomon, L. M. et al.: Studies in the mechanism of steroid vasoconstriction, J Invest Derm 44:129-31, Feb '65.

41. Moeller, H.: On Catechol Amines of the Skin, Acta Dermatovener (Stockholm) suppl 55:1-16, 1964.

42. Robinson, T. W. et al.: Trial of guanethidine in atopic eczema, Brit J Derm 78:645-8, Dec '66.

43. Kalz, F. et al.: Studies on vascular skin responses in atopic dermatitis. The influence of psychological factors, J Invest Derm 29:67-78, 1957.

44. Juhlin, L.: Reactions to infusion of a histamine liberator. Effects of Compound 48/80 on eosinophil and basophil leukocytes in patients with atopic dermatitis, urticaria, and alopecia areata, Arch Derm 88:771-8, Dec '63.

45. Graham, H. T. et al.: Distribution of histamine among leukocytes and platelets, Blood 10:467-81, 1955.

46. Johnson, H. H. et al.: Skin histamine levels in chronic atopic dermatitis, J Invest Derm 34:237-8, 1960.

47. Juhlin, L. and Rune, C.: Skin Reactions to Compound 48/80 in Normal Subjects and Patients with Urticaria and Eczema, Acta Dermatovener (Stockholm) 42:11-16, 1962.

48. Williams, D. H.: Skin temperature reaction to histamine in atopic dermatitis (disseminated neurodermatitis), J Invest Derm 119-129, April '38.

49. Allison, J. H. and Bettley, F. R.: Investigations into cantharidin blisters raised on apparently normal skin in normal and abnormal subjects, Brit J Derm 70:331-9, 1958.

50. Illig, L.: Die Reaktion der Haut des Neurodermitikers auf zwei nikotinsaeureesterhaltige Reizstoffe, Derm Wschr 126:753-63, 1952.

51. Rovensky, J. and Preis, A.: The significance of the Trafuril test, with special reference to atopy and rheumatic fever, Ann Pediat 193:289-303, 1959.