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The mechanism of sensitization in allergic dermatitis

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THE MECHANISM OF SENSITIZATION IN ALLERGIC DERMATITIS

Submitted by:

George J. Kacoyanis

COPY

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Grade 95

To: Dr. F. J. Ingelfinger

From: Dr. Herbert Mescon

Subject: Thesis of George J. Kacoyanis

This is an excellent, thorough critical review of the literature written in a mature, concise manner.

I think this should be filed in the school library as an outstanding thesis to be available to interested physicians.

Signed H. Mescon

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Introduction

Allergic dermatitis is a disorder of the skin manifested by an inflammation upon exposure to a specific antigenic substance for which the individual has acquired an hypersensitivity. This type of reaction has been described in the literature under various names such as eczematous sensitization, contact dermatitis of the allergic type, contact allergy, dermatitis venenata, allergic sensitization, and allergic eczematous hypersensitivity. Nevertheless, the names all refer to one condition (hereafter called allergic dermatitis in this paper) which has several distinguishing characteristics. There must be a period of time after exposure of the skin to a specific allergen during which the individual becomes sensitized (usually ten to fourteen days). After sensitization, the individual may be made to react upon application of the specific allergen (or, in some instances, a chemically related material). The entire area of the skin is hypersensitive although sensitization may have occurred by application of the allergen to a defined area. The reaction is of the delayed hypersensitive type with the appearance of lesions on a previously sensitized individual occurring several hours, usually between twenty-four and forty-eight, after exposure to the allergen. There is no evidence that this type of sensitivity is inherited as in atopy. The lesion consists of a marked inflammation of the skin usually with vesicle formation.

Apparently, the main shock tissue is the skin.

Extensive research has been carried out in an effort to discover the mechanism of sensitization in allergic dermatitis. The literature reveals a large volume of information gained from these investigations. Yet, a great deal is still to be proven in order to gain a comprehensive insight of the cause, method of spread and the reaction presented by this type of hypersensitivity. Experimentation of this type is very important because a complete understanding of the mechanism of sensitization is a basis for formulating methods of prophylaxis and treatment. At the present time, little can be done to prevent immunologically the sensitization of an individual, and treatment, for the most part, consists of alleviation of the distress of the inflamed, vesiculated tissue. With the industrial production of large numbers of synthetic products, the number of cases of allergic dermatitis increases. As a result, there is an increasing necessity for full understanding of the problems associated with the sensitive state. Indeed, it has been said that allergic dermatitis is a disease of civilization.

The purpose of this paper is to present the various aspects of allergic dermatitis which are associated with the mechanism of sensitization.

Factors Influencing the Incidence of Sensitization

In 1895, Jadassohn (1) was the first to recognize that certain drugs were capable of producing allergic reactions

of the skin. Following this, in 1920, one of the first to recognize the patch test as a specific diagnostic tool was Markley (2) who demonstrated a marked reaction to guinea pig hair taped to the side of the neck of an hypersensitive subject. Since this time, the patch test has been used widely to detect sensitivity of the skin to specific allergens in populations.

Spain (3) utilized the patch test to a great extent, actually bringing the term "patch test" into common usage, in demonstrating that an hypersensitive reaction did not occur on first exposure to the antigen. He tested eighteen infants and found that none of them showed positive patch tests to poison ivy extract, yet 65 per cent of patients over eight years old were sensitive to the extract. Furthermore, he pointed out that sensitive individuals reacted at a delayed time after exposure to the allergen. This led him to suggest that the reactions from patch tests should be sought for a period of at least ten days after the test was done. In 1929, Bloch (4) recognized that individuals sensitive to specific agents had a history of previous exposure. Classical proof that prior sensitization was necessary before an hypersensitive reaction occurred on contact with the antigen was offered in 1931 by Straus (5). He found that of 119 newborn infants, none were sensitive to poison ivy extract when patch tested. Later, 48 of the same infants

were retested and 72.9 per cent showed positive patch tests. Control studies were done on 41 normal adults which resulted in 75.6 per cent positive reactors to the same patch tests. His work also pointed out the fact that this type of hypersensitivity is not an inherited one since all of the newborn infants were not sensitive.

Of the population tested by Spain, Newell and Meeker (6) in 1934, twenty-seven per cent showed positive skin tests to a 1:100 dilution of an extract of poison ivy and twenty-four per cent showed a positive reaction to poison oak extract. Further population studies were carried out by Knowles et al (7) who tested 104 and 119 male medical students at two different times and found 40.4 per cent and 49.6 per cent positive reactors to a five per cent extract of poison ivy leaves, respectively. Grolnick (8) was able to sensitize 86.3 per cent of 37 patients by placing one or several applications of krameria to the skin. Later, Kanof and Rostenberg (9) reported an incidence of twenty-five per cent positive skin reactors to a dilution of 1:100 of poison ivy extract in a group of 48 people.

The various figures of incidence of skin reactivity to allergens were not consistent because of many factors (such as the nature of the allergen, the concentration of the allergen, the patient, the age of the patient, etc.). Some of these factors have undergone extensive investigation since an understanding of why people react differently to

specific substances would be a major advance toward a complete knowledge of the mechanism of the sensitization.

It has been shown that the incidence of sensitive individuals to allergic dermatitis increases with age to adulthood and then decreases as age increases. As stated above, the incidence of sensitivity of newborn infants is zero. Coca (10) tested twelve people under six years of age for sensitivity to poison ivy and found that only one individual was sensitive. He also patch tested twelve people over twenty years old with the same extract and found that eleven of them were sensitive. In the group of people tested by Kanof and Rostenberg (9), the average age was 44.5 years and the incidence of sensitivity to a dilution of 1:100 poison ivy extract was twenty-five per cent. Kligman (11) has reported studies of sensitivity to poison ivy and recorded the incidence according to age group as follows:

<u>Age of person</u>	<u>Per cent of people sensitive</u>
21-30	58
31-40	47
41-50	41
51-60	32
61-70	14

It was his opinion that this decline in sensitivity was not coincident with a decline in exposure. Evidently, people who had received repeated exposures to the specific allergens did not demonstrate a lower threshold of sensitivity. In Kligman's words, there was no "booster effect" to sensitivity by increased exposure to the allergen.

In early years of experimental investigation, the impression was gained that there was a difference in skin sensitivity among various races. Deibert, Menger and Wigglesworth (12) set out to prove this by simultaneously patch testing full-blooded American Indians and people of the White race to poison ivy extract. They found that in 227 indians (between the ages of fourteen and twenty-four years) and in 46 white people tested that the incidence of sensitivity was 56 and 58.8 per cent respectively. Thus, there was no significant difference in sensitivity to poison ivy between the races tested. This was substantiated by later work (9) demonstrating no significant difference between the reactivity of White and Negro races.

It has been mentioned above that allergic dermatitis was not an hereditary disease and sensitivity to allergens of this type could not be demonstrated in newborn infants. It has been recorded (13) that a history of familial allergy was just as prevalent among normal individuals as among those with allergic dermatitis. Furthermore, in studies conducted by Knowles et al (7) on the incidence of susceptibility to poison ivy, there was no significant difference among the sensitive subjects whether there was a personal or family history of allergy or not. However, Chase (14) was able to breed strains of guinea pigs of high and low susceptibility to skin sensitization with 2-4 dinitrochlorobenzene.

Guinea pigs have been widely used as experimental animals in sensitivity studies since it was shown (15) that they could be made sensitive to poison ivy extract. However, the typical lesion of allergic dermatitis in humans was not the same as that which appears in guinea pigs. For this reason, Straus (16) sensitized monkeys and found that lesions on this animal were more like the lesions on humans. Fortunately, allergic dermatitis is a type of disease in which experimentation on human beings is easily done and not extremely uncomfortable for the patient.

Another factor which has been found to influence the ability of the animal to become sensitized was a vitamin C deficient diet. It has been shown by Simon (17) and confirmed and extended by Kile and Pepple (18) that guinea pigs on a vitamin C deficient diet did not become sensitized to poison ivy extract to as great an extent as other animals on an adequate diet.

Rostenberg (19) reported on the factors which interrelate to produce skin sensitivity. It was his opinion that the nature of the allergen, its quantitative factors, and the host, the environmental influences on the host, and the genetic constitution of the host, determine whether or not a particular individual possesses the capacity to demonstrate allergic dermatitis in any given situation.

Nature of the Allergen

A great many different substances have been found to be sensitizing agents in experimental animals and in man.

Landsteiner's and Jacobs' (20)(21)(22) classical experiments with guinea pigs contributed to the understanding of the nature of substances capable of sensitizing individuals. They showed that the allergens capable of producing allergic dermatitis could be simple chemical compounds. These simple chemical compounds in vivo combined firmly with proteins and as a result, acted as antigens. They sensitized guinea pigs to 1:2:4 chlor-dinitrobenzene, paranitrosodimethylaniline, 1:2:4 trinitrobenzene, picryl chloride and four dichloro-dinitrobenzenes. Landsteiner and Jacobs, and Landsteiner (23) noted that there appeared to be a correlation between the sensitizing ability of a substance and its chemical structure. These authors observed that the structures which commonly induced sensitivity in animals were compounds with labile Cl^- and NO_2^- ions which were easily displaced. Thus, the free bonds were able to conjugate with the protein producing an antigen. On the other hand, they noted that compounds with stable ions were not freely displaceable and, therefore, the conjugation with protein was not possible. Landsteiner and his colleagues formulated the following conclusions to these studies: 1. simple compounds could combine or conjugate with proteins in vivo to form sensitizing agents,

2. other groups of chemical compounds required alteration in structure by metabolic processes in vivo prior to combining with the protein. Specifically, they showed that paraphenylenediamine was oxidized then combined in firm chemical union with the protein. These conclusions were supported with additional experimentation by Landsteiner and DiSomma (24).

The original findings of Landsteiner et al, were confirmed and extended by several investigators. Sulzberger and Baer (25) used several chlor-nitro substituted benzenes as sensitizing agents on human subjects. They found that the capacity to produce allergy paralleled the ability of the allergen to form conjugates with larger molecules of protein. More recently, Gell (26) found that sensitization to trinitrophenylmethylnitramine occurred by conjugation with body protein to form the antigenic "picrylprotein". Further substantiation of the findings of Landsteiner and Jacobs was the work of Zeligman (27) who found that oxidation products of paraphenylenediamine were the cause of sensitization to paraphenylenediamine. But, compounds structurally related to paraphenylenediamine and not oxidized to quinhydrone were not sensitizing agents.

It may be concluded that sensitizing agents react in the body in one of three ways: 1. by combination with protein as the nitrobenzenes, 2. by conjugation with protein only after being altered in some way by metabolism

as paraphenylenediamine, or 3. by formation of an adsorbed complex with the protein instead of actual chemical union. Thus, simple chemical compounds which combine with body protein become antigenic.

It has been shown (28) that these simple chemicals when injected are not, themselves, antigens which provoke the normal antibody response. Many investigators have studied the routes of inoculation of the sensitizing agent in order to effect sensitivity. Substances have been injected by the intravenous, intraperitoneal (15)(17), oral (29) and intramuscular (17) route with no developing sensitivity.

One report has been made by Landsteiner and Chase (30) indicating that it was possible to sensitize animals by intraperitoneal injection of the allergen. Although others have reported this finding, these experiments included careful controls to prevent contamination of the skin. In this work, sensitization of the skin occurred following intraperitoneal injection of picryl chloride in an adjuvant of killed tubercle bacilli in paraffin oil.

Following this, Landsteiner and Chase (31) successfully sensitized the skin of guinea pigs by intraperitoneal injection of either picryl chloride or 2:4 dinitro-fluorobenzene conjugated in vitro with homologous erythrocyte stromata.

Haxthausen (32) was able to sensitize the skin of humans by intramuscular injection. This was possible

only when he mixed serum from the experimental subject with the sensitizing agent (dinitrochlorobenzene). Because of this, he concluded that sensitizing agents must be coupled to proteins before injection in order for routes of inoculation other than the cutaneous application of the sensitizing agent to be effective in causing skin sensitivity.

Most workers agree that sensitization of the skin occurs most readily by application of the allergen to the skin or by intradermal inoculation, although it has been established that sensitization by routes other than the cutaneous route is possible. In all experiments in which sensitization of the skin was effected by inoculation of the allergen by routes other than cutaneous, the allergen was combined with a protein before injection.

Method of Absorption of Allergen from the Skin

Once the allergen has formed a complex with proteins of the skin, the means by which it is absorbed from the skin has been one of the major problems in the mechanism of sensitization in allergic dermatitis. Several investigators conducted experiments in an effort to determine whether the complex remained in the skin or was transported to other sites within the body. It was thought that this information would give an insight into the means by which the skin sensitization becomes generalized over the total area of the body. Rostenberg (33)

reviewed and summarized this work. He set down and discussed three possible means by which the allergen may be absorbed from the skin. First, it was proposed that the allergen may be absorbed in the same chemical state in which it was applied to the skin. By this means, the protein complexed with the allergen would merely act as a transport mechanism to get the allergen across the skin barrier and then release the allergen in its original chemical state for absorption. This was shown not to be the case because, based on work cited previously, allergens injected directly into the body by the intramuscular or intravenous route were not capable of causing skin sensitization to develop. The second possibility was that the allergen was not absorbed from the skin at all but remained in the localized skin area where it was applied. Also, this has been proven not to be true because, removal of the sensitized skin area twenty-four hours after application of the allergen did not prevent development of generalized skin sensitivity (17). The third proposal of a means in which the allergen is absorbed from the skin is the one which is generally accepted (28) and is consistent with experimental evidence at the present time. This is that the allergen is absorbed from the skin in its conjugated form with protein. This is supported by work of Landsteiner and Chase (30)(31) and Haxthausen (32),

who successfully sensitized skin of animals and humans by intraperitoneal or intramuscular injections of the allergen coupled to a protein.

It was thought by Witten and March (34) that perhaps something in the skin of sensitive individuals differed from the skin of nonsensitive people. This difference might be in the manner of absorption of the allergen from the skin and, thus, account for the development of sensitivity. In order to test this hypothesis, they carried out isotope studies with C^{14} labeled dinitrochlorobenzene as an allergen in guinea pigs. By measuring the radioactivity, they found that the allergen localized in the epidermis and occasionally in hair follicles and sweat ducts of the skin. They also showed that the allergen disappeared from the skin faster in sensitive than in nonsensitive animals. These investigators found a greater quantity of radioactivity in the buffy coat of the blood in sensitive animals than in nonsensitive animals. The results of this report were in contrast to results obtained in previous studies carried out by Witten et al (35) using radioactive Mercury as an allergen. However, it was noted that the techniques employed in this earlier study were in error. It was the conclusion of these investigators that, since absorption is increased in sensitized animals, the skin on preliminary exposure to allergens are altered in some manner to render the individual allergic to the compound in question. However, this concept as a phase in the mechanism of

sensitization is yet to be challenged or confirmed by other investigators.

The route of absorption of the complexed allergen with protein has been the subject of numerous experimentations. As early as 1927, Spain and Cook (36) postulated the passage of allergens through the blood and lymph channels in order to effect generalized skin sensitivity. Then in 1934, Straus (29) performed experiments which Coca stated were consistent with the point of view that sensitivity was limited to the epidermis and generalized skin reactions occurred after local application of poison ivy extract by diffusion of the allergen through oily substances normally present in the skin. This was confirmed later by Straus and Coca (37) who made an incision around the upper part of the arm of the Rhesus monkey and peeled the skin of the arm down toward the elbow forming a cuff and, thus, separating the epidermis of the lower part of the arm from the rest of the skin. Sensitization of the skin of the lower part of the arm to poison ivy extract did not cause generalized skin sensitization over the rest of the body. These workers stated that since sensitivity did not cross the area where there was no epidermis, sensitivity was not due to transportation of the allergen by internal body fluids but was due probably to diffusion through oily substances normally present in the skin.

In contrast to these studies, Simon (17) performed experiments of the same nature and his results indicated

that the route of distribution of the allergen was not confined to the epidermis. He destroyed an area of skin, by application of nitric acid, circling the middle of a guinea pig and found that sensitization of the skin of the hind end of the guinea pig resulted in sensitivity of the front end of the guinea pig as well as the hind end. Furthermore, he added that it took eighteen to twenty-four hours for the allergen to be absorbed from the skin because removal of the entire thickness of skin, to which the allergen had been applied, before eighteen to twenty-four hours prevented the development of sensitization.

In basically similar experiments, these investigators (cited above) obtained contradictory results as to how the allergen complex is transported. However, Haxthausen (32) presented evidence that generalized sensitization occurred because of systemic distribution of the allergen and not by extension through the epidermis. He transplanted sensitive skin of one identical twin to the other non-sensitive member of the pair and vice versa. He found that sensitive skin in the nonsensitive individual soon lost its sensitivity and the nonsensitive individual did not produce generalized skin sensitivity from the transplant. Conversely, the nonsensitive graft in the sensitive individual soon acquired sensitivity. He concluded that sensitivity was not spread through the skin but by some other internal route.

Evidence in support of the systemic distribution of

allergen as a means of obtaining generalized skin sensitivity also was presented by Landsteiner and Chase (38). They sensitized an area of skin of guinea pigs with poison ivy extract and then cut around this area leaving a sensitized island. They found that cutting the skin did not interfere with development of generalized skin sensitivity. However, they extended their experiments by cutting away skin and muscle around the sensitized area. This prevented sensitization from occurring on other areas of the body. They attributed this to destruction of lymphatics which were a pathway for distribution of the allergen.

Rostenberg (39) conducted a number of studies to determine the route the allergen takes after leaving the skin. In a review of the subject he stated that the lymph was the probable means of transfer of the allergen. Later, in 1947, he (33) reported experiments from which he concluded that there were many routes of passage of the allergen from the skin leading to generalization of sensitization. The lymph was probably the main means of transmission of the allergen but that generalized sensitization could occur even though lymph channels were severed and that this was due to transfer of the allergen by the prickle cell bridges of epidermal cells and blood. This view was supported by others (28).

Presence of Antibodies

It has been proposed that the allergen is absorbed from the skin and transported in the body by means of the lymph, blood and prickle cell bridges of the epidermis.

The place to which the allergen is transported is not known, however, it is generally assumed that this is the site of antibody production in the body and here the allergen provokes the formation of antibodies (40)(17). The antibodies produced are not of the conventional circulating type which react in vitro in serological tests, and these antibodies have been very difficult to detect (41). Because of this elusive nature of the antibody involved in allergic dermatitis, investigators have turned to use of the Prausnitz-Kuestner Reaction which has become a powerful tool in diagnosis and study of atopic allergy. These experimenters have attempted to passively sensitize nonsensitive subjects by injecting them with various tissues and fluids from sensitive persons. The classical method of performing the passive transfer test by injection of serum or plasma from a sensitive individual into a nonsensitive subject has been unsuccessful in numerous attempts to transfer sensitivity in allergic dermatitis.

*successful if large amounts
used unpublished in humans*

One of the basic studies of passive transfer was conducted by Grolnick (42) who set out to determine whether or not the antibodies in allergic dermatitis were passively transferred through the placenta. He sensitized seven pregnant women to krameria and found that none of the babies born of these women reacted to krameria in a patch test. Therefore, he concluded that antibodies of allergic dermatitis were not passed through the placenta to the fetus. This finding was confirmed by the work of Straus (5) who showed that all newborn

infants tested were nonsensitive to poison ivy extract.

In 1942, Landsteiner and Chase (43) reported the first successful transfer of cutaneous sensitivity to picryl chloride in guinea pigs. This was done by intraperitoneal injection of peritoneal exudates from sensitized animals into nonsensitive animals. These guinea pigs developed sensitivity to picryl chloride in two days following injection. This sensitivity lasted a few days then faded indicating passive not active sensitization. In addition, they discovered that the cells of the exudate were necessary for this transfer because neither serum nor clarified supernatant fluid of the exudate were capable of transmitting the sensitivity. However, heating the exudate abolished the capability of passive sensitization.

This work was extended by Chase (44) who stated that he had passively transferred sensitivity to picryl chloride, 2:4 dinitrochlorobenzene and o-chlorobenzene by cells from exudates, splenic pulp or lymph nodes of sensitized guinea pigs. He, too, mentioned that cells subjected to freezing or heating were not effective in the passive transfer of the sensitivity.

Later, Haxthausen (32) reported passive transfer of sensitivity to dinitrochlorobenzene by transfer of ground thymus gland of sensitive guinea pigs. He concluded that lymphocytes were carriers of the sensitizing antibody since most cells of the thymus gland were lymphocytes and since granulocytes were not capable of transmitting sensitization. This conclusion also accounts for results of previous

investigators.

This antibody seemed different from the preformed circulating antibodies usually found in the blood serum because freezing or heating to such a degree that would not destroy preformed antibody did, in fact, destroy the passive sensitizing effect of these lymphocytes. The sensitizing effect of these lymphocytes was destroyed by any treatment which was not compatible with the viability of the lymphocytes. Haxthausen (32) was unsuccessful in his studies to determine the way in which this sensitizing effect was transmitted from the lymphocytes to the cells of the skin. He found that local passive transfer was not successful. He concluded his work by posing the question of whether the lymphocytes themselves have this effect or whether they act only as carriers.

Following successful passive transfer of sensitivity in experimental animals, experiments were done in the hope of accomplishing the same thing in man. In 1952, Haxthausen (45) tried intracutaneous injections of leukocytes from sensitized individuals into nonsensitive persons. In his words, "The results of sixty-six passive transfer experiments turned out perfectly negative."

In similar studies, Baer, Serri, and Kirman (46) attempted passive transfer by injecting plasma suspensions of viable white cells from sixty-six sensitive donors into sixty-six nonsensitive individuals. Of the recipients,

sixty-two of the sixty-six people tested produced negative patch tests to the specific sensitizing agent.

Baer and Sulzberger (47) found essentially the same results when they took the white blood cells from 120 milliliters of blood from sensitive patients and injected them into the skin of twenty-seven nonsensitive persons. Twenty-three of these people, upon subsequent patch tests to the area where the white blood cells had been injected, showed no evidence of having received passive sensitization. It was noted that the four people who did show sensitivity to the patch tests retained their sensitivity for a long period of time indicating active sensitization rather than a passive sensitivity.

Furthermore, passive transfer of sensitivity from sensitive humans to nonsensitive guinea pigs was unsuccessful. This was attempted by Rosenthal, Litt and Baer (48) by intraperitoneal injection into guinea pigs of white blood cells from sensitive persons.

Then, in 1957, Epstein and Kligman (49) reported successful transfer of sensitivity from man to man. They stated that transfer of sensitivity in humans depended upon the extreme sensitivity of the donor, the large number of cells required, the nature of the allergen, and the recipient. It was noteworthy that at least 170 million lymphocytes, equivalent to 150 to 200 milliliters of blood, were required for transfer of dinitrochlorobenzene sensitivity in man.

Experiments of passive transfer produced by intra-

cutaneous injection of fluid from the blisters of the lesions of allergic dermatitis have been attempted many times. In the past, this procedure (50), called the Urbach-Koenigstein Technique, has been used and results obtained were very irregular. It is now recognized that the fluids of these blisters contain a great many leukocytes which were responsible for the positive results obtained on passive transfer of the blister fluid. It appeared entirely possible that one of the principle reasons for positive or negative results obtained with this test may have been due to the presence or absence of viable leukocytes retained in the injection into the nonsensitive animal.

Since all the work on passive transfer of sensitivity of allergic dermatitis indicated that the lymphocytes played a major role in transport of the antibody, it seemed reasonable to assume that interference with the functioning of lymphoid tissue would directly affect the sensitive state of allergic dermatitis. This hypothesis was tested in 1951 by Cohen, Mayer and Crieep (51). These investigators sensitized guinea pigs to paraphenylenediamine and then x-rayed each animal with 175 r. This dose of irradiation did not completely destroy the lymphoid tissue. Subsequent testing by external application of ten per cent paraphenylenediamine ointment to the skin demonstrated an attenuation of the degree of skin sensitivity in the irradiated animals as compared to non-irradiated controls. However, in another group of guinea pigs

treated in the same manner, subsequent testing was done by intradermal injection of the sensitizing substance and the results were no different between irradiated and non-irradiated animals. The variation of results among these experimental groups was unexplained.

Further work along the same lines was carried out by Rostenberg, McCrarey and Bluefarle (52) in 1956. They found that patients with a lymphoma-leukemia disease did not possess the ability to develop sensitivity to simple chemicals as readily as control groups of patients with other chronic illnesses. These workers believed that this impairment occurred as a direct result of the lymphoblastomatous disease process on the cells of the lymphoreticular system which are concerned with production of antibody. They proposed further investigation into these reactions.

Function of Allergen in the Body

The role of the allergen in the body presumably is to stimulate the production of antibodies, although there is no demonstrable antibody in sensitized subjects by conventional serological tests. Nevertheless, the ability to passively transfer sensitization indicates that a substance similar to antibody must be present. Furthermore, primary exposure of an individual to an allergen requires a period of ten to fourteen days for sensitivity to develop and the same allergen is required to evoke the allergic reaction. These conditions are the same requirements for the conventional antigen antibody reactions. Few investigators question that the mechanism involved in allergic dermatitis has an antigen antibody basis.

As with all other antigen antibody systems, neither the site nor the mechanism of antibody production is definitely established. A few investigators have advanced theories to account for the formation of antibody in allergic dermatitis.

Rostenberg (53), Rostenberg and Brunner (54) and Rostenberg and Best (55) proposed that the antigen complexed with protein is picked up by macrophages. The antigen is transported by way of lymphatics and blood to the hemato-poietic and reticulo-endothelial systems. Here, it causes enzymatic adaptation to occur in the primitive reticulum cells. The enzymes of the primitive reticulum cells become adapted to the antigen and the result is a specific alteration in the product produced by these enzymes. This adaptation is believed to be passed on to descendants of the primitive reticulum cells. The cells in which this adaptation has occurred respond differently, from the normal, upon subsequent encounters with the antigen.

Epstein (56) has set forth another hypothesis of the antigen antibody reaction in allergic dermatitis. The usual concept of the antigen in allergic dermatitis is that the simple chemical (hapten) portion of the complex confers specificity upon the allergen while the protein portion of the complex merely acts as a carrier. Epstein has suggested that the protein portion, normally from the skin, by its action with the hapten is altered in such a way as to have an antigenic effect itself.

He has called this protein portion a "protigen". Both the hapten and the "protigen" possibly provoke antibody production which is believed to take place in lymphatic tissue. Therefore, the allergic reaction might be elicited not only by exposure to the simple chemical substance but also by substances which might be liberated from the skin. This theory explains several observations characteristic of allergic dermatitis.

Still another theory was published by Everall and Truter (57). This approach is based upon an assumption that there are "neutralizers" present in the body which function to remove foreign substances. When the foreign substances reach such proportions as to outnumber the "neutralizers", the threshold is lowered and sensitivity develops. "Neutralizers" are said not to be found in plasma or serum but may be associated with lymphocytes.

Protection against Sensitizing Agents

Many efforts have been made to establish some means by which people could develop protection against sensitizing agents. Epstein and Claiborne (58) observed that people of the oriental race who were born in the orient but subsequently came to this country were less sensitive to poison ivy than persons of the same race born in this country. They proposed that this decreased sensitivity was due to a developed immunity arising from environmental factors. It had been thought that early exposure to plants (Rhus) related to the poison ivy plant in childhood developed this lasting immunity.

With such a protective mechanism in mind, numerous attempts have been made to prevent sensitization or to desensitize by a long continuous exposure to the sensitizing agent. In 1946, Chase (59) found that feeding a one per cent solution of 2:4 dinitrochlorobenzene to guinea pigs inhibited the development of sensitivity. This inhibition was specific and did not affect the capacity of the animal to become sensitive to other allergens. In these experiments, the duration of protection was measured only to the twenty-seventh week after exposure. Shelmire (60) hyposensitized an individual to poison ivy by massive oral doses of the oleoresin over a period of ten months. On the other hand, he was not able to desensitize several individuals sensitized to krameria by feeding them the antigen. Grolnick (61) was equally unsuccessful in desensitizing humans by oral administration of tincture of krameria. Kligman (11) fed an alcoholic extract of poison ivy to children and noted no protection against sensitization to the specific agent. He proposed that success of such studies depended upon whether experimental animals or human subjects were used. Results in animals were more favorable than with human subjects. It was his opinion that the successful prevention of sensitization could only be explained either by an immunological mechanism or a blocking pharmacological

property which interfered with the sensitizing process. Recently, such a mechanism has been described by Epstein and Kligman (62). These investigators applied two unrelated sensitizing substances simultaneously to separate skin sites. It was noted that sensitization occurred to only one agent and not to both. Sensitivity did not develop to the other allergen for about two weeks after the initial application of the substance to the skin. Apparently, the more potent allergen was capable of blocking sensitivity to the weaker agent. This interference phenomenon has yet to be explained, although similar experiments have been reported long ago with the influenza virus and related viruses.

Oral, topical and parenteral (63)(11) routes of administration of sensitizing agents have been used repeatedly in an effort to protect against sensitization in humans. Although these attempts have been unsuccessful, occasional spontaneous loss of sensitivity has been reported (12). Kanof and Rostenberg (9) conducted a study on 66 people (average age of 47.8 years) who were incarcerated for an average period of eleven years. Fifteen and one-half per cent of these people were shown to be sensitive to a 1:100 dilution of poison ivy extract as opposed to twenty-five per cent of a control group (average age of 44.5 years) of 48 people. This indicated that, although sensitivity did persist, there was a decrease in the incidence of sensitivity among people who were not

in contact with the plant for a number of years.

In contrast, desensitization of persons with allergic dermatitis has been encountered frequently in industry. Continually, people in industry have become sensitized to industrial products. A large number of these individuals have been known to become desensitized by the process commonly referred to as "hardening" (28). This process is merely a repeated exposure to the agent which has induced the sensitization. There develops a resultant lessening of the sensitive reaction. The aforementioned experimental studies of topical and parenteral administration of allergen did not shed light as to the nature of this reaction. At present, it is not known how this "hardening" process takes place.

Substances Capable of Provoking the Reaction

The reaction of allergic dermatitis in sensitive individuals can be brought about by application to the skin of the specific substance which caused the sensitivity to develop. This fact is one of the basic characteristics of allergic dermatitis and one of the main reasons why it is generally felt that this is an antigen antibody reaction.

Besides provocation of the reaction by the specific allergen, it has been found that the reaction, in some instances, could be elicited by chemically related substances to the sensitizing agent. This has come to be known as cross-sensitization. A great many studies have been conducted on the nature and action of substances involved

in cross-sensitization. It was felt by Epstein (56) that cross-sensitivity was due to the presence of a particular chemical group or grouping of the sensitizing substance. Sensitization then, brought about the production of antibodies which would react with various chemicals having the same chemical grouping. Rostenberg and Kanof (64) proposed three possible requirements for cross-sensitivity. These were: 1. structural similarity of the compounds, 2. conjugation of the cross-sensitizing compound with protein in the same way as the original sensitizing agent, 3. breaking down of the sensitizing allergen by the body so that sensitization occurred to some degradation product and the cross-sensitizing substance was metabolized to yield the same product. In experiments performed with halo benzenes, Rostenberg and Kanof found that the ability of a substance to conjugate with the protein was not the prime factor in determining whether or not a substituted halo benzene was capable of causing a cross reaction in a sensitive individual to another halo benzene. But, moreover, in tests of six structural isomers of substituted benzenes, they concluded that the order of reactions seemed to parallel the order of closeness of geometric resemblance to the original compound.

Numerous chemicals have been tested for their ability to elicit the allergic dermatitis reaction by cross-sensitization. This subject has been adequately reviewed by Baer (65) and Wagner (66). Cross-sensitization has been found to occur frequently among certain local

anesthetics and sulfonamide drugs, local anesthetics and paraphenylenediamine, certain derivatives of nitrobenzene and of aniline, paraphenylenediamine and azodyes, and many more.

It has been found that substances which cause the state of delayed hypersensitivity by sensitization through the skin could also cause an immediate type of hypersensitivity if the agent were injected intravenously in an already sensitized animal. This has been found to occur (67) among certain substances giving rise to the typical allergic dermatitis. The importance of this finding lies in the administration of drugs, particularly sulfonamides or local anesthetics, to sensitive individuals (68). Even more important is the apparent reactivity to the substances on seemingly first contact which is truly a cross-sensitization. Fatalities have been reported (69)(70) due to glomerulonephritis which occurred in persons with poison ivy sensitivity who were given injections of extracts of poison ivy in an effort to desensitize the individuals.

The spontaneous flare-up phenomenon has been referred to numerous times in the literature. It consists (71) of the reaction of allergic dermatitis occurring about seven to twenty-four days after application of the allergen to the skin of a nonsensitive individual. Grolnick (72) has found this to be due to remaining antigen fixed to the skin. Persons who had several patch tests before the flare-up occurred were found to react to the most

recent site of application of the allergen, then reactions occurred at sites of other applications in order of the most recent to the oldest test site. This was found to be due to the concentration of antigen which remained at the test sites. It was noticed by White and Baer (73) that of 124 patients who received subsensitizing doses of dinitrochlorobenzene, 70 developed a flare up reaction at these test sites when they subsequently were subjected to sensitizing doses of this allergen.

Furthermore, Grolnick (74) reported his observations that healed sites of the reaction of allergic dermatitis were more reactive and responsive to another unrelated allergen than was the normal skin of the same person. This was also found by Sulzberger and Rostenberg (75) who stated that people with allergic dermatitis were twice as susceptible to sensitization with another specific substance than were people with normal skin who had never had allergic dermatitis.

Nature of Action Between Sensitized Cells and Allergen

The process of sensitization, by some unknown mechanism, imparts to the skin the capacity to react upon exposure to the specific allergen. It has been shown by Shel mire (76) that this exposure of the allergen to the skin need occur for only one minute for the reaction to manifest itself. Apparently the allergen unites with the sensitive cell, or some part of it, immediately upon contact. The lesion appears usually between twenty-four and forty-eight hours later.

Dienes (77) studied the response of the sensitive tissue to the allergen and stated that the process affects the epidermis mainly and the immediate underlying layer of the derma. Although most investigators (71) believe the reaction is limited to the skin, some evidence has appeared (18) that the mucous membrane adjacent to skin is also reactive.

Histology of the lesions of allergic dermatitis has been studied and described many times (17)(71)(78)(79)(80). Within one or two hours after contact with the allergen, there appears vasodilatation and edema of the corium. There is some dispute as to whether this reaction is initiated in the epidermis or the corium. Nevertheless, the first discernible changes are alteration of individual prickle cells and epidermal edema. This leads to spongiosis and formation of the "primordial vesicle" when the damaged cell is dissolved. Following this, the overstretched intercellular bridges rupture and intra-epidermal vesicles result. There is a regenerative effort of basal cells forming new cells. Because of this, the epidermis is hyperplastic and the damaged tissue is pushed outward. The edematous strata undergo an accelerated process of faulty keratinization in which there is no disappearance of nuclei. At this time, inflammatory cells, leukocytes, and lymphocytes invade the epidermis in great numbers. The upper corium is edematous and from dilated blood capillaries many lymphocytes infiltrate the area and into the epidermis. Eosinophils are present.

The reaction of allergic dermatitis has been described many times as being indistinguishable from lesions of the skin caused by primary irritants. However, histologically, the lesions differ (80) in that the main infiltrating cell in primary irritant lesions is the polymorphonuclear neutrophil, whereas, the infiltrating cell of allergic dermatitis is the lymphocyte. Smears of exudates from the lesions of allergic dermatitis have been found to contain (81)(63) an abundance of mononuclear cells. In contrast, the lesions of primary irritants are filled with polymorphonuclear neutrophils.

Rostenberg (19)(53) has made studies on the lesion of allergic dermatitis and from the type of lesion produced he concluded that the mechanism of action of the specific antigen antibody system is to interfere with the pyruvate oxidase enzyme system of the cells and to inhibit hexokinase activity at the epidermal-dermal junction. It was shown that chemical agents which inhibit these enzyme activities are vesiculating agents.

Generalized physical findings (82) in patients with allergic dermatitis are usually normal with exception of the skin lesions just described. It, therefore, appears that the shock tissue in this type of hypersensitivity is the skin.

Conclusions

Up to the present time, researchers have contributed a great deal to the understanding of the immunological mechanism of allergic dermatitis. Yet, many aspects of this reaction remain obscure. The conclusions that can be drawn portray the process of sensitization, and its related factors, in the following sequence.

Throughout the years, many studies have been conducted on various groups of people in order to determine the per cent of normal populations possessing the capacity to become sensitive to various allergenic substances. The outcome of these studies was that the incidence of sensitization of a given population varied with the nature of the allergen, the concentration of the allergen, the species of the host, the environmental influences on the host, the age of the host, and finally, the genetic make-up of the host. Apparently, all of these factors interact to determine the capacity of an individual to become sensitized.

Numerous substances have been shown to be capable of sensitizing the skin of man or experimental animals. These substances can be simple chemical compounds which by themselves are not antigenic when introduced into the body by means other than the cutaneous route. However, when these simple chemical agents are applied to the skin, they combine chemically with proteins of

the epidermis and are absorbed from the skin in this form.

The route of absorption of the allergen combined to the protein has been the subject of many ingenious investigations and the topic of heated debates because different experimenters arrived at different conclusions from their investigations. The most widely accepted view today is that the combined allergen is absorbed from the skin by the lymph, blood, and prickle cell bridges of the epidermal cells. This manifold means of transmission of the allergen probably accounts for the differing reports in the literature of various investigators.

It is generally accepted that the allergen is transported to the portion of the body concerned with antibody production. Here, specific antibodies are produced which are not of the normal circulating type. Several theories have been proposed to account for this particular type of antibody production but no direct proof is available at the present time.

The antibody, once formed, in some way is transported and released to the epidermal cells, since reactions of allergic dermatitis take place almost exclusively in the skin. There is indirect evidence in the literature that this means of transport of the antibody is the lymphocyte since passive transfer of the sensitivity can be effected by transfer of large numbers of lymphocytes from a sensitized individual.

Efforts have been made to immunologically block the process of sensitization. Most of these attempts have been unsuccessful. However, an interference phenomenon has recently been observed in which sensitization to an allergen is inhibited by simultaneous application of another potent allergen.

Once sensitivity is established, an individual manifests the allergic reaction upon subsequent exposure to the same substance which caused the sensitivity to develop. This specificity accounts for the general belief that allergic dermatitis is based upon an antigen antibody interaction. It has been noted that chemical agents possessing structural formulas very similar to the structure of the allergen which caused sensitivity to develop may elicit the allergic reaction in that individual upon first exposure. This is called cross-sensitization and because of the similarity of structural formulas of many synthetic chemicals used in industry, this cross-sensitization has become a real problem.

Provocation of the sensitive reaction in an allergic person is accompanied by definite histologic changes of the epidermis and underlying corium. This reaction is manifested by marked inflammation of the skin with formation of vesicles.

Research in the field of allergic dermatitis appears inviting and challenging. There is still a great deal

needed to be done to uncover the basic mechanisms of antigen antibody interaction. A full understanding of this reaction is needed in order to control the increasing occurrence of sensitivity to synthetic chemicals. It is the author's opinion that investigations into the nature and action of the antibody by means of the flourescin labeled antibody technique might prove rewarding. This approach has not been used, to the knowledge of the author, in studies of allergic dermatitis.

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