The Present Status of Contact Allergy

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Allergic eczematous contact sensitization is the most unique cutaneous form of allergic sensitization and it is, therefore, of particular interest to dermatologists. No genetically conditioned tendency to allergic eczematous contact sensitization has thus far been established in man but it has been possible in guinea pigs to breed strains with an unusual tendency to allergic eczematous contact sensitization and so establish the existence of genetic factors.

There is no reliable statistical evidence to show differences in sensitizability in varying age groups in man. Clinical experience, however, strongly suggests a much lesser degree of sensitizability in infants and children and a somewhat diminished sensitizability in persons older than 60 years of age. Contact sensitization occurs as a rule when the allergen comes in contact with the skin, where it conjugates with epidermal and dermal proteins and forms one or more complete antigens. However, under actual clinical conditions, allergic eczematous contact sensitization may arise, although rarely, after introduction of the allergen via other routes of exposure, e.g. after oral or parenteral administration of the allergenic material. Under selected experimental conditions this form of sensitization can be readily induced by injecting the allergen with adjuvants into the subcutaneous tissues or the peritoneal cavity of guinea pigs.

Frey and Wenk described the important roles of the lymphatic pathways and the regional lymph nodes. Their studies show that sensitization may occur even after the local nervous supply has been deliberately cut. But if the local lymphatic pathways are cut or the regional lymph nodes are removed less than 48 hours after exposure to the sensitizing dose of allergen, allergic sensitization does not develop. The regional lymph nodes are necessary to initiate but not to maintain the sensitization. Perhaps their role is to afford an opportunity to a sufficient number of immunologically competent cells to be exposed to an adequate quantity of the sensitizing compound.

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During the phase of sensitization the regional lymph nodes undergo an increase in size and weight. Macher showed that at first there is a hyperplasia of the lymphatic reticulum cells (stem cells) and then an increase in the number of large lymphocytes. Cells from the regional lymph node get into the blood stream and seed other parts of the lymphatic system.

It is the mononuclear cells which carry the antibody-like factor. Nobody has reported the separation of this factor from these cells in allergic contact dermatitis, but in delayed tuberculin-type sensitivity in man where the transfer factor has been separated, it was shown to be a dialysable material of a molecular weight below 40,000. This indicates that it is neither a protein nor a globulin fragment and, therefore, not an antibody in the conventional sense. Thus there is nothing that we really know about the character of this factor in contact sensitivity. In guinea pigs passive transfer of contact sensitivity is possible with suspensions of mononuclear cells or lymph node cells. In man, in contradistinction to the ease with which delayed tuberculin-type sensitivity can be passively transferred with mononuclear peripheral blood cells, attempts to passively transfer contact sensitivity to simple chemicals have produced conflicting results. Our own findings in this area have been unconvincing.

The relationship between allergic eczematous contact sensitivity and delayed tuberculin-type sensitivity in man is of great interest. Since the early 1930's investigators in the field of immunology and immunochemistry have become increasingly interested in delayed skin reactions. Their concept generally is that allergic eczematous contact sensitization and delayed tuberculin-type hypersensitivity are practically the same and that both are based on the same immunologic mechanism. It is true that there are many identities and similarities between these two forms of delayed sensitization and it appears entirely possible that they are based on the same immunological process, being different only in minor respects. However, there are certain differences which are unexplained. For example, contact sensitivity can be engendered only in certain species of laboratory animals, namely guinea pigs, pigs and apes and cannot be induced in other species in which tuberculin-type sensitivity can be readily induced.

It must be remembered that practically all of the work on contact sensitization by immunologists in the past several decades has been done in guinea pigs and has involved sensitizing exposures by routes other than contact. Is it really immaterial whether on sensitizes by the normal route of exposure, namely contact, or whether one injects the simple chemical compound in Freund's emulsion into the foot pad or intraperitoneally? A high incidence and a strong degree of sensitization can be brought about by such artificial procedures. But is one justified in necessarily considering sensitization produced by these unphysiological means and routes of exposure identical with true contact sensitivity? Also, how can one overlook the very great anatomical differences that exist in guinea pig skin and human
skin and the fact that there is no such thing as an eczematous spongiotic response in the skin of guinea pigs?

It is my belief that it is risky to draw conclusions in respect to allergic contact sensitization in man on the basis of experiments using unphysiologic means of exposure in guinea pigs. The incidence of allergic contact sensitization in man after oral or parenteral administration of the sensitizes is very low. However, using the artificial methods mentioned, a substantial incidence of contact sensitization to simple chemical compounds in guinea pigs has been produced which otherwise would not occur. This would suggest that when these artificial methods are used the mechanism of sensitization involves factors which are not part of ordinary contact sensitization in man. One possible link is the accumulation of macrophages in the area in which the antigen is concentrated after its administration in Freund's adjuvant. This is very important since Fishman showed that it is RNA-antigen complexes from stimulated macrophages which engender antibody formation by the lymphocytic cells.

What are the roles of the hapten and of the carrier protein in determining the specificity of the resulting antigenic complex in allergic contact sensitization? Newer evidence indicates that the carrier protein component in such conjugated materials is not only an inactive carrier but plays an important role as an antigenic determinant. The concept that the protein carrier is important in determining antigenic specificity logically leads to the conclusion that allergic eczematous contact sensitization is a form of autosensitization. If the carrier protein is of such importance as an antigenic determinant it appears likely that the route of exposure during the sensitization process and during elicitation of contact allergic reactions is of great significance, since this route determines those proteins which are available for conjugation and consequently as carriers and their structures in turn must determine the nature of the antigenic complexes which are formed.

In this connection it is important to know what happens when the sensitizing exposure to the unconjugated simple chemical compound takes place directly in the lymph node, thus depriving the allergen of the opportunity to conjugate with the fibrous proteins of the epidermis and dermis. Experiments in guinea pigs have had contradictory results. If the findings of those who reported that contact sensitization can readily be engendered by injection of the simple chemical compound directly into the lymph node are correct, then one can consider the following possible explanations for the development of contact sensitivity: 1) There is constant drainage of epidermal and dermal proteins from the skin into the regional lymph nodes, providing an opportunity for conjugation of the simple chemical with these cutaneous proteins. 2) There is leakage of simple chemicals from the injected lymph nodes back into the skin despite the efforts of the investigators to prevent this. 3) There is leakage from the injected site in the lymph node into the bloodstream and from there unconjugated or loosely conjugated hapten reaches the skin.
4) The characteristics of the carrier protein are not as important in determining specificity as has been concluded on the basis of evidence developed in recent years.

Histologically the appearance of perivascular accumulation of small round cells and histiocytes in the upper dermis within 6 hours is the first visible change under the light microscope. These cells then migrate through the disturbed basal cell layer into the epidermis. Subsequently, intra-and intercellular edema develops in the epidermis leading to the spongiosis which is so characteristic of eczema in man. From the immunologic viewpoint it is significant that even in normal epidermis one out of every 200 cells is a small round cell, perhaps a lymphocyte.

Recent studies with electron microscopy by Flax and Caulfield have shown that at 5 to 6 hours after exposure to the contact allergen mononuclear inflammatory cells accumulate in the upper dermis and in the epidermis and that there is increased permeability of venules in the upper dermis. At 8 to 10 hours extracellular edema is noted in the epidermis adjacent to intraepidermal mononuclear cells. Tonofilaments become disrupted and desmosomes become damaged in such areas. The resultant loss of cohesion leads to blister formation. At 10 to 15 hours there is progressive intracellular alteration with focal cytoplasmic degeneration.

Another problem which has been the subject of extensive discussions in recent years is the differentiation between “dermal” contact sensitivity and “epidermal” or eczematous contact sensitivity. By dermal contact sensitivity is meant an allergic reaction elicited by contact but taking place in the dermis, corresponding to the dermal delayed tuberculin-type of reaction to microbial agents. By eczematous contact sensitivity is meant the allergic reaction elicited by contact but taking place in the epidermis in the form of papulovesiculation and histologically showing spongiosis. According to St. Epstein pure eczematous sensitivity could be delayed sensitivity based on a reaction of cellular antibodies with epidermal conjugates of contact allergens in the epidermis. Pure dermal sensitivity could be delayed sensitivity based on a reaction of cellular antibodies with dermal conjugates of contact allergens in the dermis. There can be no question that most cases of allergic contact dermatitis seen clinically have components of eczematous and dermal reaction, usually with predominance of the epidermal component. But do these two forms of sensitivity also exist separately and independently?

There are reports of purely eczematous sensitivity with positive patch tests and with absence of dermal type reaction as evidenced by a negative intracutaneous test. Purely dermal contact sensitivity also has been reported to neomycin, nickel and other materials. However, in our Department we have not seen any cases where an allergic contact dermatitis was found to be associated only with a positive intracutaneous test and a negative patch test to the causal allergen.

The concept of an eczematous contact sensitivity as an entity separate from dermal contact sensitivity could explain the differences which have been reported in the
results of cellular passive transfer tests of contact sensitivity in man and also the
differences in cellular passive transfer of contact sensitivity between man and
guinea pigs. Perhaps those cases of contact allergy in which cellular passive
transfer is successful are cases with a strong dermal component and those which
cannot be passively transferred are cases of pure eczematous contact allergy or
eczematous contact allergy associated with a very weak component of dermal
sensitivity.

Again, I would like to call attention to the very marked differences between
the structures of the skin of guinea pigs and man. What is called contact sensi-
tivity in the guinea pig, grossly and histologically has many of the earmarks of
dermal contact sensitivity in man. Papulovesicular eczematous lesions, the hallmark
of eczematous contact sensitivity in man, are not seen in the skin of guinea pigs.
Histologically also there are no true eczematous changes with spongiosis in the
skin of guinea pigs except under unusual conditions such as application of the
allergen to the nipple or to skin which deliberately has been made acanthotic.

Much has been learned during the past few decades about those factors which
either interfere with the establishment of allergic contact sensitization or which
may abolish such sensitization once it is established. It has been known for some
time that intravenous administration of the contact allergen or feeding of the
allergen before the sensitizing exposure often induces specific immunologic unre-
sponsiveness. More recently we showed that a slight degree of specific immunologic
tolerance could be induced in guinea pigs born to mothers who either had been
fed the homologous allergen during gestation or who had been injected intra-
peritoneally with the homologous allergen during gestation. Furthermore, de Weck
and Frey were able to completely abolish contact sensitivity in already sensitized
guinea pigs for a very short period of time by intravenous administration of con-
siderable doses of the homologous allergen. Recent experiments of our group show
that thymectomy in newborn guinea pigs does not diminish their capacity to subse-
quently undergo sensitization to dinitrochlorobenzene.

It has been accepted for many years that an incubation period of sensitization,
usually a minimum of 120 hours, elapses between the first exposure to the contact
allergen and the development of clinical sensitivity. However, Golay and Brun
some years ago showed that histologically there is reactivity to the contact allergen
in guinea pigs 48 hours after the first exposure to the allergen. Recent work by
Uhr indicated that in other forms of allergic sensitization which are mediated by
humoral antibodies there is evidence of allergic reactivity within only a few hours
after first exposure to the allergen. This, together with the findings of Golay and
Brun, makes it necessary to reconsider the question of the incubation period in
eczematous contact allergy. Perhaps our conventional concepts of the incubation
period of sensitization in contact allergy are not entirely correct.

Finally, I would like to say something about changes in the incidence of allergic
sensitivity to various contact allergens which have occurred in our patient material and apparently also in other localities where this has been studied. The incidence of sensitivity to contact allergens depends on a number of factors, principally the sensitizing potential ("sensitizing index") of the allergen; 2) the susceptibility to allergic contact sensitization; 3) the persistence of the sensitivity once it has been established; and 4) the frequency and intensity of the opportunities for exposure to the allergen. We undertook a comparison of the incidence of allergic contact sensitivity to nickel sulphate, potassium dichromate, mercury bichloride, paraphenylenediamine and formaldehyde in 1937 and in 1961-62 in a selected patient population consisting mostly of patients with contact dermatitis. No significant changes in the incidence of contact sensitivity to nickel sulphate and potassium dichromate were found. However, the incidence of allergic contact sensitivity to mercury bichloride, paraphenylenediamine and formaldehyde had increased considerably. It appears likely that these changes are attributable to increased opportunities to exposure to the substances.

There is no particular reason to assume that there would be marked alterations in the susceptibility of a whole population to undergo contact sensitization. Marcussen showed that in Denmark the percentage of reactions to a given series of test substances remained quite constant between 1938 and 1955. Allergic contact sensitivity once established often persists for many years. However, loss of sensitivity after a few years does occur although the figures reported vary considerably in different localities and for different allergens. It appears very likely therefore that the increased incidence of contact sensitivity observed in our studies to these particular allergens is due to changes in the opportunities for exposure. The figures show the profound effects of civilization with all its synthetics, improvers and additives on the incidence of contact sensitization.

In summary I would like to quote from an article which Dr. Sulzberger and I wrote in 1936:

"...The eczematous contact type of reaction of the human skin is a form of allergy with special and peculiar characteristics which are not necessarily identical with the cutaneous hypersensitivity demonstrated in guinea pigs by means of intracutaneous injection or even external application of allergens...".

I think that the evidence that has been developed since 1936 supports the opinion that while eczematous contact sensitization shares many features with other forms of delayed sensitivity it remains a form of delayed allergic sensitization which is unique to the skin of man.
接触アレルギーの現状

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アレルギー性接触皮膚炎においてはアレルゲンが表皮、真皮の蛋白と結合し、リンパ腺に運ばれて抗体が産生され、感作が成立すると考えられているが、モルモットにおいてはアレルゲンをadjuvantと混じて注射することによっても感作を起こし得る。しかし、局所のリンパ流を障害したり、リンパ腺を切除すると感作は起こり得ない。感作の導入に際して所属リンパ腺は先ず腫大し、細胞細胞（核幹細胞）、ついで大リンパ球の増加があり、リンパ腺から流出する細胞は他のリンパ系に定着する。

ヒトのツ反型遅延性アレルギーでは、末梢血単核球による受動感作が可能であり、分子量40,000以下の透析可能な抗体類似物質が分離されている。

モルモットでは接触アレルギーにおいても単核球やリンパ腺組織浮遊液による受動感作が可能である。しかしヒトの接触アレルギーでは一定のデータがない。

接触アレルギーとツ反型遅延性アレルギーとは似た点が多く、1930年代には同一免疫機構によるものと考えられていた。しかし、動物の種類によっては接触アレルギーが起こり難く、かつ、例えばモルモットの接触アレルギーにおいてはヒトにおける湿疹様病状や組織学的な海綿状変性がみられない点で、全く同一の機構によるとは考えられない。

接触アレルギーの抗原特異性にはhaptenのみならずこれと結合する蛋白も関与するとされる。従って、アレルギー性接触皮膚炎は一種の自己感作とも考えられる。

しかしhaptenと結合して完全抗原を形成する自己蛋白が何かということに関しては論議が多く、それが皮膚蛋白でなくとも接触アレルギーが成立し得ることを示す実験もある。例えば、リンパ腺中に注入したhaptenによって感作の成立したという報告などである。

最近、真皮性接触アレルギー（dermal contact sensi-

ivity）と表皮性接触アレルギー（epidermal or eczem-
atous contact sensitivity）とが区別され、通常の接触皮膚炎においては両方が共存しうるが、主変化は前者によるものと考えられる。その結果、最近反応性、皮内反応陰性となる。また、neomycine, Niなどは純真皮性アレルギーと考えられるものがあり、真皮性接触アレルギーの強いものでは細胞反応が成功し、純表皮性接触アレルギーでは成功しないと考えてよい。そこで、モルモットの接触アレルギーが真皮性アレルギーに当たると考えられる。

接触アレルギーの成立以前にアレルゲンを静注、経口投与すると特異的免疫学的不応状態を招来することができる。また、妊娠中の母体に非経皮的にアレルゲン投与したモルモットの仔は、軽度ではあるが、特異的免疫学的応答を一時的に獲得する。更に、アレルゲンを大量に静注すれば脱感作を行えない物など、感作の成立を障害、除去する方法も種々知られていたが、胸腺摘出を行なってもモルモット新生児のDNCB感作能力は変化したことも知られた。

従来、感作の成立には120時間以上の潜伏期が必要であると考えられていたが、最近、モルモットで最初の接触後48時間以内に組織学的反応性のあることが観察され、潜伏期に関する考え方も改めることが必要となった。

最後にNi, Cr, Hg, P. P. D., フォルマリンなどに対する感受性の推移を1937年の患者におけるデーターと1961〜62年の患者におけるものとについて比較した成績について述べると、Hg, P. P. D., フォルマリンに対する感受性のあまるものの増加をみた。文明化の上昇を反映する現象と考えられる。

（三木吉治抄録）