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PASSIVE TRANSFER OF ALLERGIC ECZEMATOUS CONTACT-TYPE SENSITIVITY^{1, 2}

By

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Until recently allergic eczematous contact-type (AEC-T) dermatitis was classified in the immunologic group of delayed reactions based on sensitizations, mainly because of the time required for the process to appear, that reaction time being about the same as that of tuberculin reactivity (24 to 96 hours). Nowadays, AEC-T dermatitis is considered to be an immunologic process of the delayed-type based on sensitization for more cogent reason, namely:

1. The development of sensitization of the AEC-T process depends on the integrity of the lymphatic system. Ablation of lymphatics of the site at which induction of sensitization is attempted prevents that induction.

2. The clinical and histologic changes of the reaction end point are similar to the general ones of delayed-type sensitization in the form of perivascular infiltration of lymphocytes and histiocytes and a certain amount of destruction of parenchymal cells in the area of infiltration.

3. AEC-T dermatitis, like the process of delayed-type sensitivity in general, appears to be correlated with the functional properties of circulating "immunologically competent" cells, probably lymphocytes.

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4. The sensitization in the AEC-T process is directed primarily against the protein fraction of specific protein-haptene conjugates.

5. Circulating antibodies do not appear to be present or operative in AEC-T dermatitis. No such entities can be detected by any known in vivo or laboratory technique. Moreover, sensitization of this delayed-type can be induced in patients with hypogammaglobulinemia who are notably incapable of producing adequate circulating antibodies.

Study of the immunologic nature of AEC-T dermatitis has been pursued by many investigators. The working hypothesis has always been that the time elapsing between the first contact and the challenge was the sensitization time or incubation period. As sensitization in the immunological sense implies to many investigators the production of specific antibodies, efforts have been made to prove the existence of such specific antibodies. The passive transfer technic has long been considered a most sensitive and reliable technic for this purpose.

The first attempts to transfer AEC-T sensitivity to simple chemicals were made by *Urbach* (1, 2) in 1925. He used blister fluids obtained from reaction sites, injected them into the skin of non-sensitive recipients and challenged the local site with corresponding test material. The principle was employed by *Fellner* who, in 1919, accomplished transfer of delayed tuberculin sensitivity in man by using a mixture of tuberculin and material obtained from the papules of a positive tuberculin reaction.

Many workers reported successful transfers employing this Urbach-Koenigstein technique in experimental animals as well as in man, to with toward iodoform, arsphenamine, ammonium persulphate, 2,4 dinitrochlorobenzene by *Perutz* (4), *Fuhs & Riehl* (5), *Riehl* (6), *Brandt & Konrad* (7). *Bissozero & Ferrari* (8), *Musger* (9), *Von Dishoeck & Roux* (10), *Ballestero & Mom* (11) and others.

In contrast to these successful transfers came the negative results of the attempts by *Jadassohn* (12), *Silzberger* (13), *Leider & Baer* (14), and others which put in doubt the reliabi-

lity of the Urbach-Koenigstein technique. Parallel with the people who tried to transfer passively delayed sensitivity using *Fellner's* principle, *Landsteiner & Chase* worked to establish another technic, namely that of cellular passive transfer. *Bail* has been the first in 1910 (15) to transfer tuberculin sensitivity in guinea pigs after intraperitoneal injection of lymph node and splenic cells obtained from tuberculin sensitive guinea pigs. But it was *Landsteiner & Chase* (16) and *Chase* (17, 18) who established a consistently reproducible technic, that of a passive transfer by means of cells. The suggestion of *Chase* (19, 20) that chiefly lymphocytes and monocytes carry the capacity to transfer delayed sensitivity has been confirmed particularly by *Wesslén* (21), who transferred tuberculin sensitivity using almost pure suspensions of lymphocytes obtained from the thoracic duct of rabbits and by *Kirchheimer, Hess & Spears* (22) who have reported that guinea pig peritoneal exudates composed almost exclusively of granulocytes, do not transfer tuberculin sensitivity. Recently, the use of lymph node antiserum in guinea pigs by *Waksman* (23) and monocyte antiserum by *Wielhem, Fisher & Cooke* (24) supports the suggestion that lymphocytes and monocytes are the essential cells involved in the delayed-type of sensitization.

This reliable technic introduced by *Landsteiner & Chase* in 1942 has been utilized by many investigators to study delayed sensitivity. The results have been strikingly successful in guinea pigs for the passive transfer of tuberculin sensitivity (17, 25, 26), as well as of the contact sensitivity to simple chemicals (16, 17, 27, 28, 29, 30, 30, 31, 32). They were consistently reproduced by the different investigators using peritoneal exudates from blood leucocytes, spleen cells, lymph node cells and generally cells from organs rich in reticulo-endothelial cells (32).

Due to the successful results of the cell transfer in experimental animals, attempts were made in man. The delayed tuberculin sensitivity (DTS) has always been passively transferred with success (33, 34, 35, 36). Passive transfer of AEC-T sensitivity though, gave inconsistent results. *Baer & Sulzberger*

(37), *Haxthausen* (38), *Baer, Serri & Kirman* (39), *Curtis* (40), *Serri* (41), *Meneghini & Levi* (42), *Harber & Baer* (46) reported negative results in all their attempts. On the contrary, *Good* (43,44), and *Epstein & Kligman* (45) reported successful results.

Discussing the results of these two groups we recall that *Epstein & Kligman* reported effective transfer to pentadecyl catechol (P.D.C.) by intact isolated peripheral blood leucocytes, by whole blood transfusion, by blister fluids containing leucocytes and by blister fluids from which most or all of the leucocytes had been removed by centrifugation. But their effort to transfer the sensitivity to P.D.C. to children who had never been exposed previously to poison ivy, had been unsuccessful. This observation supports the suggestion of *Sulzberger & Medawar* that the passive transfer of delayed sensitivity may be a booster effect or an anamnestic response in a latent pre-existing sensitivity. *Epstein & Kligman* suggested also that quantitative variables like degree of donor sensitivity, volume of leucocytes, shown to be critical for transfer of bacterial hypersensitivity, become even more important for the transfer of AEC-T sensitivity to simple chemicals. The recent attempt, though, of *Harber & Baer* (46) in which all the quantitative variables and the nature of simple chemical used as antigen (avoidance of previous exposure) were taken into consideration, was unsuccessful. It seems that previous exposure is important. If this exposure produces a flare of a latent sensitization or simply alters the subject's immunologic reactivity remains in the realm of speculation. It is evident, though, that some allergens are superior to others in their ability to reveal the successful transfer of sensitivity. Another important variable is the individual response of the recipient. *Epstein & Kligman* (45) have shown in relation to the passive transfer of P.D.C. sensitivity, that each recipient reacted to the leucocyte injection in a way characteristic of himself, and that difference existed among recipients. They showed that leucocyte injections from the same donor evoked different reactions in different recipients and leucocytes from different donors induced a reaction char-

acteristic of that recipient. Their study divides the recipients into three groups. In group A, the majority of subjects became positive and returned to a permanently negative state within one to three weeks. In Group B the passively acquired sensitivity increased to level where it remained for several months, and in Group C, the sensitivity appeared early, became negative or nearly so, and then showed a persistent secondary rise. If these curves have to be ascribed to passive transfer, we have to admit that the second group shows rather a type of an "active" mechanism of sensitization. The first group exhibits a reaction which could be ascribed to acquired antibody. The third group showed a bimodal response. The initial rise and fall of curve in this bimodal pattern fits into a true passive sensitization and is compatible with that of the first group. The second rise, though, is difficult to explain. It might be suggested, as *Baer & Sulzberger* (37), and *Baer, Serri & Kirman* (39) have done, that the injection of lymphocytes releases a substance which increases the capacity of the recipient to get actively sensitized to the particular challenged antigen, or even what *Metaxas & Metaxas-Bühler* (26) would support that lymphocytes might carry even traces of potent antigen responsible for an active sensitization. Whatever the possible explanations could be, no definite conclusions can be drawn from the work done up to now. It remains still an unsettled question what role the lymphocytes play in the mechanism of delayed sensitization.

Lawrence (47) has shown in man that a specific factor migrating with alpha-globulin is released from lymphocytes in bacterial hypersensitivity. This factor: 1) is not dependent upon highly polymerized D.N.A. of the donor cells; 2) probably is not dependent upon highly polymerized R.N.A. of the donor cells; 3) and probably is not dependent upon the integrity of donor cells proteins susceptible to tryptic digestion. This transfer factor, reports *Lawrence*, shows a paradox behaviour namely, the simultaneous capacity of a specific interaction with the antigen and the incapacity to neutralize properties of the antigen ordinarily neutralized by antibody. If

this factor is an antibody precursor, or an antibody capable of producing widespread effect in such a minute amount that is not detectable by the most sensitive test, remains to be disclosed. This factor is not demonstrated in the mechanism of AEC-T sensitivity in man.

In the guinea pigs the existence of such a transfer factor could not be proven in leucocytes taken from guinea-pigs sensitive to tubereulin or simple chemicals (17, 48, 49). The successful transfer of D.N.C.B. sensitivity in guinea-pigs by means of cells lysed by sonic vibration, reported by *Jeter, Tremaine & Seeborn* (50) awaits confirmation. They attribute the negative results of *Chase* and others to the technic used (heat, freezing and thawing), which, in destroying the cells, destroyed the transfer factor too.

Although in AEC-T sensitivity to simple chemicals, in experimental animals, the presence of the "transfer factor" is not proven, the cellular passive transfer resembles absolutely that of the delayed bacterial sensitivity. In man, the passive transfer of delayed tuberculin sensitivity is consistently reproducible, while neither the presence of "transfer factor" nor a consistent success of cellular passive transfer is proven in AEC-T sensitivity.

Taking into account the similarity of DTS and AEC-T sensitivity in experimental properties, we have to try to find an explanation through some speculations and few facts for the discrepancies in cellular passive transfer. Of course, we cannot draw any definite conclusion as we do not know the exact role of the lymphoid cells. If the presence of a specific transfer factor will be repeatedly proven in DTS, the lack of it in the cells from subjects sensitized with simple chemicals would mean one of the following:

- a) that this transfer factor had been released in the sensitized organism previous to the cell transfer, or that
 - b) it does not exist in the mechanism of AEC-T sensitivity.
- In the latter case, the inconstant positive results of passive transfer could be explained as a "booster" effect or as "active sensitization" and that would mean the presence of even traces

of antigen in the transferred cells or the presence of a non-specific factor enhancing the capacity of the recipient to become sensitized toward the challenging antigen. Concerning the hypothesis that transfer factor could have been released from the cells before the cellular passive transfer, implies the presence of antigen in the donor. *Benacerraf* (51) and *Salvin* (52) working recently on the mechanism and relation existing between the DTS and the AEC-T sensitivity, have shown that AEC-T dermatitis is the result of sensitization to an altered skin or serum protein, the whole process being a kind of auto-sensitization. *Gell* (53) has shown that cross reactivity exists between a delayed sensitization to an altered protein and the native protein. If we accept that AEC-T sensitivity is an auto-sensitization process we suggest that the specific or a cross-reacting antigen is constantly present and could interact with the sensitized cells, resulting in the release of transfer factor in vivo. *Lawrence & Pappenheimer* suggest that transfer factor is released from human leucocyte suspensions without much cell damage. The hypothesis of in vivo release of transfer factor is supported by the observations of *Cole & Favour* (54) who reported to have transferred DTS in guinea pigs by means of a factor present in a subfraction (IV-10) of serum alpha globulin. It is of particular interest that the donor animals must be tested 48 hours before being bled or the passive transfer does not occur. *Favour* points out the possibility that lysis of certain hosts cells by the antigen in vivo, with liberation of antibody into plasma may occur. Having in mind the above mentioned probable constant presence of an autoantigen and the interaction of it with the sensitized cells, we cannot exclude the possibility that the negative results of the cellular passive transfer is due to the absence of the transfer factor from the cells because of a previous release. Whether this hypothetical release takes place in the serum or in the tissues we cannot know. The negative results of the passive transfer with whole blood (41, 46) and the unsuccessful attempts of *Meneghini & Levi* (55) to disclose probably incomplete antibodies in the serum by the sensitive hemagglutination technic, may suggest

that the difficulty of detecting the transfer factor or the specific antibody in the serum is due to a masking effect and an appropriate separation of serum protein would disclose it (specific factor or antibody in the serum). He observed that the successful passive transfer by means of the subfraction (IV-10) of alpha-globulin was counteracted if it was injected mixed with gamma-globulin. If the observation of *Cole & Favour* will be confirmed, the question of the mechanism of AEC-T sensitivity will take on other aspects. The unsuccessful attempts of passive transfer by means of proteins extracted from the skin, reported by *Curtis* (40) are not satisfying. The number of donors and recipients used in this study was so small that the interference with the results of the individual reaction of the recipient cannot be excluded as *Sulzberger* suggested. So the unsuccessful attempts of passive transfer by means of skin proteins and the negative results of Urbach-Konigstein technic is not enough to exclude the possibility of the release of transfer factor in the tissues. Recently, *Joan Raskin* (56) showed by fluorescent technic that in AEC-T sensitivity there is an increase of skin globulin. Further study and more controls are needed toward this direction.

SUMMARY AND CONCLUSIONS

In summary, many investigators tried to prove the immunologic nature of AEC-T sensitivity using the passive transfer technic. Attempts have been made by means of serum, of blister fluid containing or not containing cells, (i.e., Urbach-Konigstein technic) and by cell transfer.

Up to this time the results show that (1) passive transfer of AEC-T sensitivity by means of serum is unsuccessful; (2) passive transfer of AEC-T sensitivity by Urbach-Konigstein technic, i.e., by means of blister fluid with or without cells, gave inconsistent results both in guinea pigs and in man; (3) passive transfer of AEC-T sensitivity by means of cells is definitively successful in guinea pigs but doubtful in man.

In closing our review, we suggest that the question of the

immunologic base of AEC-T sensitivity needs further study and effort toward the proof of the existence of the transfer factor. We do not believe there is a species difference determining the unsuccessful passive transfer. We suggest that as man is more sensitive than guinea pigs, the interaction of antigen and sensitized cells may be easier and quicker in the organism, so that the transferred cells do not carry the transfer factor which may be released in the tissues.

If the AEC-T sensitivity is definitely a kind of autosensitization, the transfer factor is released in the site of antigen in a disproportionate amount to the body surface. The negative results of the Urbach-Königstein technic may be due then to small amounts of transfer factor contained in the blister fluid. Speaking of transfer factor, we like to think of a kind of specific antibody carried on the cell surface.

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