

Immunotherapy

The present issue of *Allergy* contains a competent review by Philip S. Norman on immunotherapy in allergic diseases. He correctly underlines the great gap between the widespread use of desensitization and the limited information on the clinical effects of this treatment. This lack of clinical knowledge obviously stems from the difficulties inherited in carrying out clinical trials which meet current standards, and the enormous number of antigens and antigen preparations which would be of potential value for the patients.

There is another gap in our present understanding of immunotherapy. This is the gap between the increasing knowledge of the immune-system obtained from basic immunological research and our limited knowledge of the mechanisms which lead to improvement, or lack of improvement, in the patients treated with desensitization.

The theoretical ways of interfering with the immune-response in allergic patients as deduced from the current understanding of the immune-system are numerous. It is known how antigenic stimulation leads to a complicated interaction between macrophages and the two main types of lymphocytes: T-lymphocytes and B-lymphocytes. Regarding antibody synthesis the production of IgE and IgG seems largely to follow the same rules (7). Macrophages and T-lymphocytes appear to play a major role in presenting antigen to B-lymphocytes in order to trigger antibody synthesis. So-called immune response (Ir) genes localized in the major histocompatibility complex influence the antibody response, but it remains to be seen whether this Ir gene effect operates on the level of the macrophage presentation of antigen or via the T-lymphocyte receptors for antigen (1).

The understanding of the complexity of the cell-cell interactions has greatly increased after the discovery that T-lymphocytes may have two functions in the antibody response. One subpopulation of T-lymphocytes acts as specific helper-cells (T_H) for B-lymphocytes in antibody production whereas other T-lymphocytes are suppressor cells (T_S) and reduce or abolish B-lymphocyte activation. This complicated scheme for antibody production obviously leads to several possible ways of abolishing an undesirable IgE antibody response. One is the induction of classical tolerance by repeated administration of antigen in a tolerogenic form which could lead to deletion of the corresponding T_H - or B-lymphocytes. Another possibility would be activation of T_S -lymphocytes leading to active suppression of the IgE response. Both mechanisms have been demonstrated in animal experiments (7), and the main difficulty in applying this knowledge in man is known species differences in responsiveness and lack of sophisticated methods for the evaluation of the function of the various lymphocyte subpopulations in man.

The ways of manipulating the immune system is in principle to stimulate with antigen with or without the addition of adjuvant according to a certain immunization schedule and via a certain route of administration. Since antigens are macromolecules which contain several epitopes (antigenic

determinants) it is possible to modify antigens chemically, which may result in deletion of epitopes responsible for the stimulation of B-lymphocytes without altering epitopes responsible for stimulation of T-lymphocytes. Antigens modified in this way may, after repeated administration, selectively stimulate T_s-lymphocytes leading to the induction of active suppression of the IgE response (2). Studies with haptene-carrier conjugates have shown that haptene coupled to an isologous carrier protein may be tolerogenic for B-lymphocytes predetermined to the production of IgE antibody to the haptene (3). This finding raises yet another possibility for the therapeutical use of modified antigens.

Specific activation of antigen-sensitive lymphocytes, however, may be carried out without the use of antigen itself. It has been shown that the antigen binding part of the lymphocyte receptors are complementary to the corresponding epitopes and therefore are unique structures in the same way as the epitopes themselves. It is thus possible to raise antibodies against these receptor structures (anti-idiotypic antibodies), and recent data suggest that stimulation of cells with such anti-idiotypic antibodies may lead to specific sensitization or suppression, depending on the class of antibody used (5). This principle is possibly far from clinical use, but represents a challenging field for future research.

Suppression of a certain IgE response may also be mediated through the administration of specific IgG antibody (6). Such antibody may act by capturing the antigen before it gets in contact with antigen-sensitive cells involved in the IgE synthesis. Another possibility is that IgG in combination with antigen preferentially activates T_s-lymphocytes.

The so-called blocking antibody which combines with antigen and thereby prevents contact between antigen and surface IgE on basophils and mast cells may regularly be demonstrated after desensitization (4). Since only a weak correlation can be demonstrated between titer of blocking antibody and symptom relief it seems unlikely that this mechanism solely should be responsible for the therapeutic response.

A first-line defence mechanism would be the production of IgA or IgG antibody in the mucous membranes of the body surfaces which could block the antigen before entering the organism. Such antibody has been demonstrated in man (4), and a promising way of exploring new techniques for desensitization would be to investigate the ways of enhancing the production of blocking antibody in the mucous membranes. It seems possible that the route of antigen administration might be important in this respect and it should be investigated whether application of antigen locally to the respiratory or gastrointestinal tract might lead to the desired therapeutic response.

Søren Freiesleben Sørensen

REFERENCES

1. Feldmann, M.: Are the Ir genes expressed by macrophages? *Nature* 267, 105, 1977.
2. Ishizaka, K., Okudaira, H. & King, T. P.: Immunogenic properties of modified antigens. II. Ability of urea-denatured antigen and α -polypeptide chain to prime T cells specific for antigen. *E. J. Immunol.* 114, 110-115, 1975.
3. Lee, W. Y. & Sehon, A. H.: Suppression of reaginic antibody formation. II. The use of adoptive transfer system for the study of immunological unresponsiveness. *J. Immunol.* 114, 837-842, 1975.

4. Norman, P. S.: A review of immunotherapy. *Allergy* *33*, 62-70, 1978.
5. Rajewsky, K. & Eichmann, K.: Induction of T and B cell immunity by anti-idiotypic antibody. *Eur. J. Immunol.* *5*, 661-666, 1975.
6. Strannegård, Ö. & Belin, L.: Suppression of reagin synthesis in rabbits by passively administered antibody. *Immunology* *18*, 775-785, 1970.
7. Tada, T.: Regulation of reaginic antibody formation in animals. *Prog. Allergy* *19*, 122-194, 1975.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.