

Immune Complexes and Disease

The pathogenetic role of immune complexes (IC) has been studied in a variety of disorders, including infectious, and autoimmune diseases as well as malignancies. Most data concerning the immunopathology associated with IC occurrence, however, have been obtained by experimental model studies, while the immunopathogenetic potential of circulating IC in human diseases is generally poorly understood, although in some types of nephritis, arthritis and vasculitis, there is good reason to believe that IC produces disease.

Currently, a large number of methods to detect IC in biological fluids or tissues have been presented. The majority of these techniques is based on the biological properties of IC, such as their interaction with complement components, antiglobulins, conglutinins or their interaction with complement—or Fc receptors. The emergence of this large variety of techniques is mainly due to the lack of one single test system which can detect IC of all sizes and properties. The variability of IC lies within class of immunoglobulin, nature of antigen, ability to fix complement as well as size. The small IC bear particular interest due to their persistence in the circulation. In consequence of this IC heterogeneity it has been difficult to find a common IC standard. This again has made direct interlaboratory comparison of test results impossible. Optimal conditions require selection of limited numbers of techniques as well as standard reagents suitable for exchange on a large scale. Therefore a trial in standardization of IC assays is under investigation by WHO.

In this issue of ALLERGY a review article by Steensgard & Johansen discusses biochemical aspects of IC formation. Among the problems drawn to attention are the factors influencing the properties and fate of IC, especially the concentration of antigen molecules and the number of antigen determinants. Antibody, class, subclass, heterogeneity and affinity are other factors of importance for the molecular distribution of IC. In the *in vitro* study presented with the review, the sedimentation pictures of preformed IC were studied by an ultracentrifugation technique. For the sake of simplicity only IC formed between bivalent antibody molecules and corresponding antigen were analysed. The results illustrate the complexity of the IC distribution pattern at different antigen/antibody ratios and point to the number of problems existing *in vivo* in respect to IC quantitation as well as characterization. The heterogeneity of antibody involved is only one of several factors affecting the IC pattern as shown in the Sips plot. Other factors of importance include the genetically and environmentally determined immunological response capacity of the host, e.g. the route of antigen administration, or the capacity of the mononuclear phagocytic system to remove the IC material.

The formation of IC is an integral part of the immune response, and the fate of IC depends on a dynamic equilibration between their formation and elimination. Complexes are formed when an antibody reacts with its corresponding antigen. A temporary IC formation is therefore a normal event, being responsible for the elimination of antigens from the organism. The antigens involved can be proteins,

hapten-carrier compounds, nucleoproteins, polysaccharides, DNA and RNA derived from viruses, bacteria, parasites and food products. Auto- and tumor-antigens represent possible endogenous components involved in complex formation. Attempts to identify suspected antigens in IC have until now been disappointing, primarily for technical reasons. The need for experimental models is therefore considerable. Zonal distribution models parallel to the experiments by Steensgaard & Johansen may be a promising tool for studying the complexity of IC systems in human autoimmune disorders. Characterization of thyroglobulin/anti-thyroglobulin complexes in autoimmune thyroid diseases, or DNA/anti-DNA complexes in systemic lupus erythematosus (SLE) are human models of potential interest.

IC, which is insufficiently cleared from the circulation, may recirculate for variable periods of time, and thereby becomes a pathogenic factor if extravascular accumulation takes place. First-line of target are the vessels of glomeruli, choroid plexus, synovial membranes and skin. Deposition of IC may result in local activation of biological effector mechanisms such as the complement system, the coagulation system or lymphoid cells, resulting in an acute or chronic inflammatory response. In several connective tissue disorders—SLE, rheumatoid arthritis, sclerodermia, periarteritis and ankylosing spondylitis—where IC has been demonstrated in the circulation, extravascular deposition of complexes seems responsible for a variety of disseminated organ disorders.

The current knowledge on the pathogenetic effect of IC in a number of chronic and acute diseases has led to an increasing interest in principles to prevent these injurious effects. If the identity of the antigen components is known (e.g. glutenin enteropathy or microbiological components) suitable therapy may be offered which can interrupt and prevent IC formation. Unfortunately, however, the antigens involved in IC formation leading to IC syndromes have so far seldom been identified, and unspecific therapy, such as anti-phlogistics and/or immunosuppression is used to decrease the damaging effects of the non-specific mediating systems (complement activation, etc.). In some situations of acute IC-associated disease (e.g. in patients with SLE) plasmapheresis has been used and a short-time reduction of plasma IC concentration has been observed. The benefit of this therapeutic measure, however, has not yet been clarified. Removing IC from the circulation would seem logical in prophylaxis of IC damage. But serious questions are raised due to possible unintentional stimulation of autoantibodies in patients with autoimmune disorders, depletion of plasma proteins, as well as unexpected dangerous reactions due to the plasma substitute used. These complications increase the demand of a specific IC immunoabsorbent technique.

Conclusively, a practical approach to IC in clinical situations depends on continued and renewed efforts with methodological, biochemical and basic theoretical considerations as exemplified in the review in this issue.

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