Immune Complexes and Disease

During the past few years immune complexes have been implicated in a growing number of different types of diseases. Clear evidence for a direct role has usually been absent. Now the picture has shifted, and new information indicates that complexes are involved directly in such diverse diseases as nephritis and rheumatoid arthritis.

Recent advances in this fast-growing field were reported in a symposium on immune complexes and disease, which was held in New York City, 19 to 20 February 1971, under the auspices of the New York Heart Association.

High-resolution techniques, and the development of new methods of analysis have begun to elucidate the processes involved in immune complex disease (ICD). In particular, it has been shown that the formation and deposition of an immune complex is a complicated chain reaction which involves not only the original interaction of the "antigen" and the "antibody," but also requires the participation of blood cells, complement, enzymes, chemical mediators, the cells of the affected organ, genetic makeup, and other factors.

The single most practical contribution of the symposium was that science is finally narrowing in on kidney disease. Immunofluorescent methods have been used in patients with primary glomerulonephritis, and in those who develop the disease in homografts (Robert McCluskey, SUNY, Buffalo). John Zabriskie (Rockefeller) presented a possible mechanism for acute and progressive nephritis. Observations in humans and animals indicate that progressive nephritis may be caused by a cross-reaction between the streptococcal membrane and the glomerular basement membrane. This interaction then initiates a continuous disease process. David Koffler (Mount Sinai) described the detailed studies that he and his associates have been carrying out in patients with systemic lupus erythematosus (SLE)—a disorder that may be considered the prototype of an immune complex nephritis. Clear evidence was presented that in patients with malignant renal disease, at least two systems are involved: complexes of DNA and antibody to DNA and complexes of γ-globulin and antibody to γ-globulin.

The role of viruses in New Zealand hybrid mice, which develop a disease that is remarkably similar to SLE, was discussed by Norman Talal (National Institute of Arthritis and Metabolic Diseases). The mice exhibit antibodies to RNA which were probably generated in response to a virus infection. Talal emphasizes the viral etiology of the disease in mice, although he recognized that development of the condition also requires a particular genetic makeup and various immunological factors, which as yet have not been elucidated.

Somewhat different results were obtained by F. J. Dixon (Scripps) in a study with the NZW hybrids. He found that superimposed viral infections of multiple type, such as lymphocytic choriomeningitis virus (LCM) and polyoma, hasten and intensify the DNA antibody responses and glomerulonephritis of these mice. On the other hand, lactate dehydrogenase virus (LDH) infections appear to protect against formation of antibody to DNA and against development of nephritis. Improvement with the "benign" virus was dramatic enough to suggest that viral superinfections might someday be of therapeutic value.

Whether or not viruses are the cause of some forms of human ICD was one of the most debated issues of the symposium. In any case, nature's ready-made cellular spies are an ideal tool for the study of ICD in experimental animals. Viruses not only provide a self-replicating foreign particle, but also set off a specific immune reaction in the host organism.

While circulating complexes of virus and its antibody are commonly found in chronic viral infections, they are not always associated with significant disease (B. A. Oldstone, Scripps). Infections of newborn animals with ten different viruses (including Coxsackie B, polyoma, Gross, Raider, and Friend, LDH, and LCM) affect the course of induced ICD. Some viruses have the ability to protect the animal against ICD, while others enhance the disease process.

Several speakers tried to determine the significance of various types of viruses in ICD. Carol Smith (Albert Einstein, New York) reported that a cell culture of synovial lining cells, obtained during open surgery from the joints of patients suffering from rheumatoid arthritis, showed increased resistance to infection with rubella and Newcastle disease viruses. Other cellular changes in the cultures also suggested the possibility of the existence of an occult virus infection present in the rheumatoid cell.

P. E. Phillips (Cornell) on the other hand, found no evidence of virus infections in 119 cell cultures. The specimen for the cultures had been derived from 142 subjects with rheumatoid arthritis (RA), SLE, and other connective tissue disease and controls.

Australia antigen was discussed by B. S. Blumberg (Institute of Cancer Research, Fox Chase, Philadelphia) who believes it to be related to one of the agents of viral hepatitis or at least to stem from one of the hepatitis viruses. David Gocke (Columbia) reported on the use of Australia antigen in a diagnostic test for the screening of transfusion blood. Dr. Gocke also has found circulating immune complexes consisting of Australia antigen and immunoglobulin in six patients with polyarteritis nodosa (proved by biopsy), thus implicating the first virus in ICD in humans.

The filtration function of the kidney appears to be involved in making this organ the prime target of ICD. C. B. Wilson (Scripps) has charted the fate of immune complexes in rabbits in which acute and chronic serum sickness was induced with isotopically labeled bovine serum albumin (BSA). In animals with acute serum sickness and severe glomerulonephritis, more than 99 percent of the circulating labeled BSA was deposited in the kidney where it became rapidly covered by deposits of circulating complexes of host antibody to BSA and complement. In chronic serum sickness, produced by daily injection of BSA, the daily deposition of labeled BSA increased as the disease progressed (from 0.04 percent of the daily dose of BSA to 0.5 percent).

Using rhesus monkeys and rabbits, Mart Mannik (University of Washington) demonstrated the role of complement for uptake of injected, soluble, already-formed immune complexes. The relative rate of uptake by the kidney and by the hepatic reticuloendothelial system depended in part on the structure of the complex itself.

The deposition of circulating immune complexes in various tissues was discussed by C. G. Cochrane (Scripps).

The release of vasoactive materials (histamine and serotonin) from mast cells and platelets is an important factor for deposition. These vasoactive amines increase the permeability of the blood vessels, which then permit the passage of soluble complexes. Whether or not the latter become entrapped depends on their size: complexes smaller than 19*S* "pass," while larger ones are deposited. Administration of antihistamines or vasoactive material affects complex deposition in the expected manner: antihistamines decrease deposition, vasoactive material enhances the process.

P. M. Henson, also from Scripps, investigated the interaction of neutrophils and immune complexes in experimental animals. Here ICD falls into two classes: (i) those like arteritis which require large numbers of neutrophils and (ii) those like glomerulonephritis in which the role of the neutrophils is less clear. Henson simulated the in vivo situation in models in which (i) the immune complex was anchored to a Micropore filter, which represented a surface that could not undergo phagocytosis, and (ii) the immune complex was either "free" or fixed to antibody and complement. In model (i), the degranulation was observed toward the exterior of the cell. In model (ii), however, when the complexes were phagocytized, degranulation was observed into the phagocytic vacoula, and enzymes appeared in the surrounding medium.

According to H. J. Muller-Eberhard (Scripps), complement participates in ICD via two different mechanisms. In the first, the complement products accumulate on the surface of the target cell and cause its destruction, either directly, by cytolysis, or indirectly, by phagocytosis. The second mechanism involves freely circulating complement components (anaphylatoxins and leukotactic factors) which act on effector cells such as granulocytes.

Leukotactic factors consisting of complement-related products were found by P. A. Ward (Armed Forces Institute of Pathology) in soluble tissue extracts of vasculitis lesions and in synovial fluid from patients with RA. Similar materials were, however, also found in synovial fluids from patients with inflammatory, nonrheumatic arthritis and in extracts of experimentally infarcted myocardium. Chemotactic factors—mostly related to the C5 and C6 components of human complement—were also found in RA joints by N. J. Zvaifler (University of California, San Diego) who showed that these were produced locally by an enzyme found in more than half of the rheumatic fluids examined.

The role of chemical mediators (K. F. Austen, Robert B. Brigham Hospital, Boston) is also undergoing revision. Recent evidence (infusion of large amounts of mast cells which did not induce a massive allergic reaction, and failure of antihistamines to affect all symptoms in such a well-defined allergic disease as asthma) indicates that histamine is by no means the only chemical mediator involved. One of the factors that is currently being considered is the cellular level of cyclic AMP which seems to control the antigen-induced release of both histamine and the slow-reacting substance of anaphylaxis (SRS-A). β-Adrenergic agents and methylxanthines, which increase the level of cyclic AMP, are inhibitory, whereas β-adrenergic blocking agents, like propanol, which decrease the cellular levels of cyclic AMP, enhance the antigen-induced release of the mediators.

The localized acute inflammatory reaction noted in ICD has long been associated with the appearance of large numbers of polymorphonuclear leukocytes at the site of inflammation (N. J. Zvaifler and Gerald Weissmann, New York University). Weissmann showed that the immune complexes themselves trigger the release of enzymes from human polymorphonuclear leukocytes. The release is selective: lysosomal enzymes (β-glucuronidase, acid phosphatase) are released, cyctoplasmic lactate dehydrogenase is not. (Such a selective release was confirmed by Henson with human and rabbit neutrophils.)

R. J. Winchester (Rockefeller) described unusual complexes containing γ-globulin which were found in the serum and joint fluid of patients with rheumatoid arthritis. The exact nature of these complexes remains unknown, but those in the joint fluid can activate and fix complement, and they appear to play a role in initiating the characteristic inflammation of the joints. Zvaifler presented related observations on the local synthesis of γ-globulin by synovial tissue. There was considerable discussion of the possible stimulus involved in this local production of antibodies and the local formation of immune complexes.

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