

This Week's Citation Classic®

Cochrane C G & Koffler D. Immune complex disease in experimental animals and man. *Advan. Immunol.* 16:185-264, 1973.
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Studies about the pathogenetic importance of complement-fixing immune complexes during a 15-year period prior to 1973 were analyzed. These complexes were considered to play an important role in the pathogenesis of tissue injury in experimental models and humans. [The *SCI*® indicates that this paper has been cited in over 705 publications.]

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During the 15 years prior to 1973 significant advances were made in numerous laboratories in understanding the biology of antigen-antibody complexes. These complexes were in part composed of an autoantibody bound to either a polypeptide or a polynucleotide antigen. The demonstration of complement-fixing immune complexes within inflammatory lesions suggested that they were of pathogenetic importance for tissue injury in experimental models and human disease such as systemic lupus erythematosus.

Experimental acute serum sickness reaction was attributed to circulating immune complexes composed of an antigen and a specific antibody formed in response to administration of an antigen such as bovine serum albumin. The reaction was self-limiting if only a single immunization was given, but it developed into a chronic serum sickness syndrome when an animal was immunized by repeated doses of endogenous or exogenous antigen that maintained slight to moderate antigen excess. The appearance of vascular and renal lesions in animals with chronic serum sickness disease closely resembled the tissue changes found in vasculitis and glomerulonephritis in humans.

During the early years of the twentieth century, C.E. von Pirquet, P. Ehrlich, and other investigators first identified toxic bodies in the serum of animals and humans that were considered to cause serum sickness reactions. It was common to inadvertently immunize individuals with heterologous sera during the course of therapy designed to prevent tetanus and other diseases. Following a first injection of such a serum, toxic bodies appeared around day 9, virtually concomitant with the appearance of antibodies, but disappeared by day 14 or 15, whereas antibodies persisted. There was a 50-year hiatus between the original description of toxic bodies and the demonstration that these bodies were immune complexes containing antigens and antibodies.^{1,2} Localization of immune complexes in blood vessels, glomeruli, and other capillary plexi had important implications for causation of tissue damage in human disease.

In 1972, I was affiliated with Mt. Sinai School of Medicine and The Rockefeller University. Henry Kunkel, also at Rockefeller and an editor of *Advances in Immunology*, asked C.G. Cochrane and me to write a paper on immune complex disease for that journal. The result was the *Classic* article cited here.

Since 1973 methods for quantitation of immune complex levels using C1q globulin have been developed, knowledge about the alternative and classical complement pathways has been accrued, and local formation of *in situ* complement-activating immune complexes has been demonstrated. However, data obtained since 1973 have not provided new insights into the role of immune complexes in the pathogenesis of human disease. Therefore, the frequent citation of this review may in part reflect the paucity of new investigations about immune complexes during the past 15 years. Rather, a series of questions has been raised about the relative importance of circulating vs. *in situ* immune complex formation, the identification of the antigen component of immune complexes, and the role of complement, vasoactive amines, and prostaglandins as mediators of tissue injury.³ The answers to these questions await the emergence of sophisticated new ideas to augment the powerful new probes developed for study of the immune system.

1. von Pirquet C E. Allergy. *Arch. Intern. Med.* 7:258-88: 383-436, 1911. (Cited 85 times since 1955.)
 2. Dixon F J. The role of antigen-antibody complexes in disease. *Harvey Lect.* (58):21-52, 1963. (Cited 210 times.)
 3. Koffler D, ed. Symposium on the immunodiagnosis of rheumatic and related diseases. *Hum. Pathol.* 14:287-450, 1983.