

Nydegger U E, Lambert P H, Gerber H & Miescher P A. Circulating immune complexes in the serum in systemic lupus erythematosus and in carriers of hepatitis B antigen: quantitation by binding to radiolabeled C1q.
J. Clin. Invest. 54:297-309, 1974.
[WHO Research Unit, Geneva Blood Ctr., and Dept. Medicine, Univ. Geneva, Switzerland]

The work exploits privileged binding of radiolabeled first component of complement (C1q) to antigen-complexed immunoglobulin (Ig) but not to monomeric Ig, and it applies this reaction to the study of clinical serum or extravascular fluid samples. The reaction product between ¹²⁵I-C1q and complexed Ig found in precipitates reflects the amount of antigen-complexed Ig in the reaction mixture. [The SC7® indicates that this paper has been cited in over 520 publications.]

Urs E. Nydegger
Central Laboratory of Haematology
Inselspital
CH 3010 Bern
Switzerland

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Circulating or extravascular-fluid-suspended antigen-antibody complexes (so-called soluble immune complexes or SICs) may occur during the course of a number of idiopathic inflammatory, infectious, renal, hematological, or neoplastic diseases. The conditions under which SICs are found in these diseases are based on widespread, fast, and easy screening tests for SICs, introduced into clinical medicine at the beginning of the last decade.

This paper on the radiolabeled C1q binding test (which was subsequently published in a modified version¹) remains the leading SIC-detection assay in many laboratories worldwide. For its original development a number of favourable circumstances coincided: P.H. Lambert's basic idea to convert V. Agnello's discovery of agar-gel precipitation between C1q and immunoglobulin aggregates² into a radioimmunoassay met with H. Gerber's and my perseverance to make the system work in fluid phase; and P.A. Miescher's clinical expertise was essential to obtain blood samples from patients with active disease.

The publication of our paper sparked the development of many other test systems for the detection of SICs, so that today numerous different procedures are available, some in the form of commercial test kits. SIC reactants other than C1q have been used (for example, conglutinins, rheumatoid factors, IC-receptor-bearing cells, and monoclonal antibodies) against SIC-bound complement components, but C1q remains the most widely used.

It is remarkable that most knowledge on the pathogenetic properties of SICs was obtained from SIC monitoring of chronic inflammatory diseases characterized by chronically circulating SICs, rather than from laboratory animal studies of mechanisms of physiological removal of antigens by antibodies, of which the formation of SICs is a transient physiological consequence. A large body of literature has now accumulated on SICs, but perhaps some of it is occasionally too enthusiastic (the SIC issue in cancer, leukemia, and kidney diseases is not settled); however, sometimes it points to new clinical involvement of SICs.

Thus, SICs are useful clinical parameters to follow in monitoring such diseases as active systemic lupus erythematosus, rheumatoid arthritis, necrotising vasculitis, and some forms of bacterial or viral diseases (for example, endocarditis or AIDS, especially pediatric AIDS). The levels of the complexes may correlate with clinical activity of the disease, and their disappearance upon therapy or removal after plasmapheresis may mean clinical improvement. Research into the molecular composition of SICs may give additional information about the nature of the antigen that chronically affects the host, eluding efficient neutralization and removal by antibodies. It may also provide information about the cause of reticuloendothelial system insufficiency to remove the SICs from circulation and inflammatory sites.

Three recent papers are recommended for further reading.³⁻⁵ Our work was awarded the Prize of the Swiss Society for Internal Medicine in 1975.

1. Zubler R H, Lange G, Lambert P H & Miescher P A. Detection of immune complexes in unheated sera by a modified ¹²⁵I-C1q binding test. Effect of heating on the binding of C1q by immune complexes and application of the test to systemic lupus erythematosus. *J. Immunology* 116:232-5, 1976. (Cited 850 times.)
2. Agnello V, Winchester R J & Kunkel H G. Precipitation reactions of the C1q component of complement with aggregated gamma globulin and immune complexes in gel diffusion. *Immunology* 19:909-19, 1970. (Cited 440 times.)
3. Nydegger U E & Sveithg S-E. Improved standardization in the quantitative estimation of soluble immune complexes making use of an international reference preparation. Results of a collaborative multicenter study. *Clin. Exp. Immunol.* 58:502-9, 1984.
4. Nydegger U E. A place for soluble immune complexes in clinical immunology. *Immunol. Today* 6:80-2, 1985.
5. Nydegger U E & Kazatchkine M D. Modulation by complement of immune complex processing in health and disease in man. *Prog. Allergy* 39:361-92, 1986.