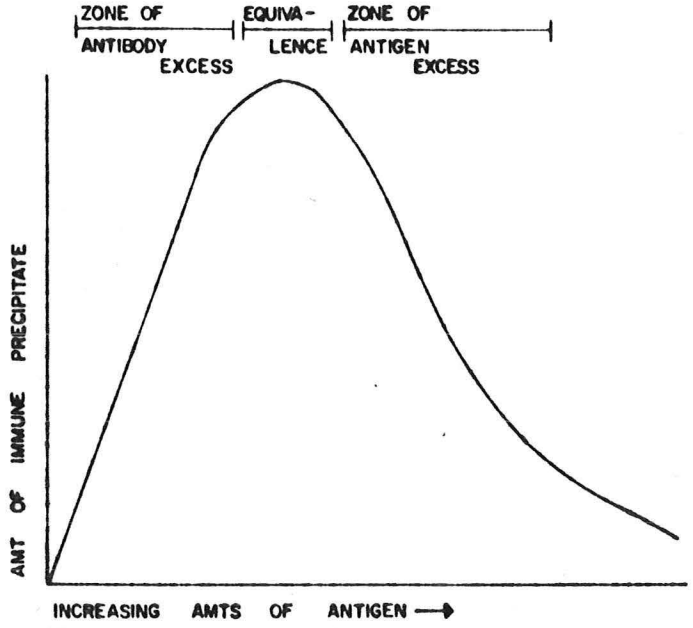
IMMUNE COMPLEX DISEASE

Marvin J. Stone, M.D.

April 17, 1979

Fig. 1.—Antigen-antibody precipitin curve. This curve is produced by weighing the precipitate formed when increasing amounts of antigen are added to a number of tubes, each containing a constant volume of antiserum. The zone of maximal precipitate formation is called the zone of equivalence. Soluble immune complexes are not found in significant quantity in the zone of antibody excess, but may be present in supernatants from the zone of equivalence or in higher concentrations in supernatants from the zone of antigen excess.



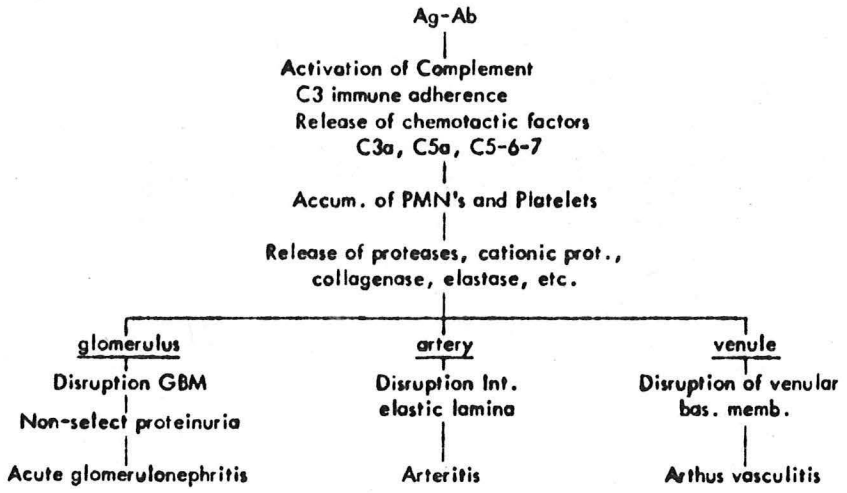
(55)

Table I Main Clinical Features of Immune Complex Disease

Fever		
Generalized lymphadenopathy		
Hypertension, Albuminuria, Oliguria, Haematuria, Oedema	-	Glomerulonephritis
Maculopapular rash, Leg ulcers, Purpura	-	Cutaneous vasculitis
Raynaud's phenomenon		
Arthritis		
Hepatitis		
Myositis and myocarditis		
Generalized urticaria		

(15)

Fig. 2. Summary of events taking place in immunological injury of tissues in which complement and neutrophils play an essential role.



(7)

Table 2. Potentially Injurious Constituents of PMN

Acid phosphatase
Lysozyme
Collagenase
Aryl sulfatases
Acid lipase
Endogenous pyrogen
Basic proteins
Mast cell-active
Permeability-inducing, independent of mast cells
Elastase
Neutral protease
Acid protease (cathepsins)
Fibrinolysin
Procoagulant
Tissue factor
Precipitation of fibrin monomers and antiheparin effect by basic proteins
Mononuclear cell chemotactic factor
Oxidizing substances
Superoxides, singlet oxygen, hydrogen peroxide

(7)

TABLE 3. MANIFESTATIONS OF CRYOGLOBULINEMIA

Weakness
Purpura (dependent)
Arthralgias
Raynaud's phenomenon
Acrocyanosis (occ. peripheral gangrene)
Livido reticularis
Cold urticaria
Cutaneous vasculitis with ulceration
Visual disturbances and retinal hemorrhages
Mucosal bleeding tendency
Cerebral thrombosis
Lymphadenopathy
Hepatosplenomegaly
Renal disease (proliferative glomerulonephritis, nephrotic syndrome, renal tubular acidosis)
None

(44)

TABLE 4. SOME DISORDERS ASSOCIATED WITH CRYOGLOBULINEMIA

Myeloma and macroglobulinemia
Diffuse lymphoma and chronic lymphocytic leukemia
Connective tissue diseases
  Systemic lupus erythematosus
  Polyarterities nodosa
  Sjögren's syndrome
  Rheumatoid arthritis
  Juvenile rheumatoid arthritis
  Ankylosing spondylitis
  Lyme arthritis
Renal disease (glomerulonephritis, nephrotic syndrome, renal tubular acidosis)
Cirrhosis & chronic active hepatitis
Sarcoidosis
Purpura-arthralgia syndrome
Infections
  Infectious mononucleosis
  Bacterial endocarditis
  Leprosy
  Cytomegalovirus
  Syphilis
  Hepatitis B
  Malaria
Status post-intestinal bypass surgery for obesity

TABLE 5. SOME RECENTLY DEVELOPED ASSAYS FOR IMMUNE COMPLEXES

Assay	*Property of Complex Required*	*Potential Interfering Substances**	*Approximate Sensitivity (AHG μg./ml.)†*
Raji cell [2]	C3b, d bound; Ig present	Antibodies reactive with Raji cells	10
Clq polyethylene glycol (PEG)[13]	Binds free Clq; insoluble in 2.5% PEG	Polyanions	10
Clq-solid phase[14, 15]	Binds free Clq; Ig present[14]	Polyanions	4
Clq-deviation[16]	Binds free Clq	Polyanions	4
Monoclonal rheumatoid factor (RF)[15, 17]	IgG Fc reactive with RF	RF	0.5–15
Polyclonal RF[18]	IgG Fc reactive with RF	RF	1–10
Platelet aggregation[19]	IgG Fc reactive with platelets	Platelet antibodies; RF	4
Macrophage uptake[20]	IgG Fc reactive with macrophages	RF; ?others	20–30

*All tests will detect Ig artifactually aggregated by improper storage. The Raji test seems rather insensitive to this phenomenon, perhaps because active complement components must also be present in the serum. The Clq-PEG test may be less sensitive to polyanions because macromolecular complexes are detected.

†The sensitivity is highly dependent on the nature of the complexes and is given as a very rough approximation in equivalent concentrations of heat aggregated IgG (AHG).

(6)

Table 6. Antigen non-specific methods for the detection of soluble immune complexes based on the biological properties of the complexes

Biological activity measured	Reactants used in the test
1. Reactivity with receptors on free molecules	
(a) Interaction with complement	
Complement and C1q deviation tests	
Measurement of anticomplementary activity	Fresh serum complement, sensitised sheep red cells
C1q deviation test	^{125}I-C1q, sensitised sheep red cells (or IgG-coated particles)
Inhibition of latex agglutination by C1q	Purified C1q, IgG-coated latex particles
Direct measurement of C1q–immune complex interaction	
C1q agarose precipitation test	Purified C1q
C1q binding test	^{125}I-C1q, polyethylene glycol
Solid-phase C1q binding test	C1q-coated polystyrene tubes, ^{125}I-antiglobulin or enzyme-linked antiglobulin is used in a second step
(b) Interaction with rheumatoid factor (RF)	
RF agarose precipitation test	Monoclonal RF
Radioassay using insolubilised monoclonal RF	Monoclonal RF coupled to microcristalline cellulose, ^{125}I-IgG aggregates
Radioisotope assay using soluble polyclonal RF	Polyclonal RF, ^{125}I-IgG aggregates, purified carrier human IgM, sheep antiserum anti-human IgM
Inhibition of latex agglutination by RF	Polyclonal RF, IgG-coated latex particles
2. Reactivity with cellular receptors	
(a) Interaction with Fc receptors on cells	
Platelet aggregation test	Human blood platelets
Inhibition of antibody-dependent cell-mediated cytotoxicity	Human blood lymphocytes, ^{51}Cr-labelled sensitised Chang liver cells
Radioassay using macrophages	Guinea-pig peritoneal exudate cells, ^{125}I-aggregates
(b) Interaction with complement receptors on cells	
Raji cell radioimmune assay	Cultured lymphoblastoid (Raji) cells, ^{125}I-antiglobulin
Inhibition of complement-dependent lymphocyte rosette formation	Lymphocytes from human adenoid, complement-coated sheep red cells

(5)

Table 7. Raji Cell Radioimmune Assay for Immune Complexes in Human Sera

Diagnosis	No. Cases	No. Cases Positive	% Positive	μg AHG Equivalent/Ml	
				Mean	Range
Serum hepatitis (with or without HB_sAg)	34	18	52.9	65	(24–212)
Systemic Lupus Erythematosus	13	13	100	327	(24–1100)
Vasculitis	25	14	56	193	(25–1000)
SSPE	6	3	50	58	(24–100)
DHF	24	15	62	62	(25–225)
Malignancies	104	43	41	68	(20–383)
Hospitalized patients	60	5	8.3	39	(20–100)
Normal patients	120	4	3.3	21	(12–30)

(7)

Table 8. Generalizations About Glomerular Immunofluorescence in Common Histological Types of ICGN in Man

Histological Type	Glomerular Immunofluorescence
Proliferative GN	
Diffuse proliferative	Diffuse granular IgG, variable IgA, IgM, fibrin. C3 may predominate in poststreptococcal GN.
Diffuse proliferative with crescents	As above with striking fibrin deposits in crescents.
Focal proliferation	Focal granular IgG and C3, may be prominent IgA or IgM in segmental GBM and mesangial deposits. Fibrin variable.
Membranous GN	Diffuse heavy granular IgG and C3 with variable IgA, IgM, fibrin.
Membranoproliferative GN	
Subendothelial dense deposit type	Prominent granular C3, usually with IgG, IgM, variable IgA, fibrin.
Intramembranous dense deposit type	C3 in GBM, TBM, Bowman's capsule, without Ig.
Focal sclerosing GN	Granular IgG, IgM, C3 in sclerotic areas.
Chronic GN	Granular C3 may be prominent with or without IgG, IgA, IgM, fibrin.
GN of Systemic Disease	
SLE	Often striking granular IgG, IgA, IgM, C3 corresponding to histological findings with granular TBM and arteriolar deposits in 70%. Fibrin variable.
Henoch-Schönlein purpura	Granular IgG, IgM, C3, often prominent IgA and fibrin, especially in mesangium.

(45)

Table 9. Exogenous Antigens Involved in Human ICGN

Antigen	Clinical Condition
Pharmaceuticals	
Foreign serum, toxoids, drugs	Serum sickness
Infectious Agents	
Bacterial	
Nephritogenic streptococci	Poststreptococcal GN
Staphylococcus albus, Corynebacterium bovis	Infected atrioventricular shunts
Enterococcus	Bacterial endocarditis
Salmonella typhosa	Typhoid fever
Treponema pallidum	Syphilis
Diplococcus pneumoniae	Pneumonia
Parasitic	
Plasmodium malariae, P. falciparum	Malaria
Schistosoma mansoni	Schistosomiasis
Toxoplasma gondii	Toxoplasmosis
Viral	
Hepatitis B	Hepatitis
Oncornavirus-related antigen	Leukemia
Measles	Subacute sclerosing panencephalitis, SLE
Epstein-Barr virus	Burkitt's lymphoma

(45)

Table 10. Endogenous Antigens Involved in Human ICGN

Antigen	Clinical Condition
Nuclear antigens	SLE
Renal tubular brush border antigens	Membranous GN in Japan, sickle cell anemia, renal neoplasia
Thyroglobulin	Thyroiditis
Carcinoembryonic antigen	Colonic carcinoma
Tumor antigens	Neoplasms
Ig	Cryoglobulinemia

(45)

REFERENCES

IMMUNE COMPLEX DISEASE

I. Reviews & Mechanisms

* 1. Cochrane CG, Koffler D: Immune complex disease in experimental animals and man. Adv Immunol 16:185, 1973

2. Andrews BS, Penny R: The role of immune complexes in the pathogenesis of disease. Aust NZ J Med 6:591, 1976

3. WHO Scientific Group: The role of immune complexes in disease. WHO Tech Rep Ser (606):1-58, 1977

4. Editorial: Immune complexes in health and disease. Lancet 1:580, 1977

* 5. Zubler RH, Lambert PH: Immune complexes in clinical investigation. Recent Adv Immunol 1:125, 1977

* 6. McCluskey RT, Hall CL, Colvin RB: Immune complex mediated diseases. Human Pathol 9:71, 1978

* 7. Cochrane CG, Dixon FJ: Immune complex injury. In Immunological Diseases, ed 3 (Samter M, ed). Boston: Little, Brown, 1978, ch 11

8. Wells JV: Immune mechanisms in tissue damage. In Basic and Clinical Immunology, ed 2 (Fudenberg HH, Stites DP, Caldwell JL, Wells JV, eds). Los Altos: Lange, 1978, ch 23

9. Whittingham S, Irwin J, Mackay IR, Marsh S, Cowling DC: Autoantibodies in healthy subjects. Aust Ann Med 18:130, 1969

10. McDuffie FC: Autoantibodies in healthy subjects. Ann Int Med 72:596, 1970

11. Wilson CB, Dixon FJ: Quantitation of acute and chronic serum sickness in the rabbit. J Exp Med 134:7s, 1971

12. Cochrane CG: Mechanisms involved in the deposition of immune complexes in tissues. J Exp Med 134:75s, 1971

13. Roy LP, Fish AJ, Michael AF, Vernier RL: Etiologic agents of immune-deposit diseases. Progr Clin Immunol 1:1, 1972

14. Cochrane CG, Wuepper KD, Aiken BS, Revak SD, Spiegelberg HL: The interaction of Hageman factor and immune complexes. J Clin Invest 51:2736, 1972

15. Carter PM: Occasional survey. Immune complex disease. Ann Rheum Dis 32:265, 1973

16. Miller GW, Nussenzweig V: A new complement function: Solubilization of antigen-antibody aggregates. Proc Nat Acad Sci 72:418, 1975

17. Miller GW, Steinberg AD, Green I, Nussenzweig V: Complement-dependent alterations in the handling of immune complexes by NZB/W mice. J Immunol 114:1166, 1975

18. Takahaski M, Takahaski S, Brade V, Nussenzweig V: Requirements for the solubilization of immune aggregates by complement. The role of the classical pathway. J Clin Invest 62:349, 1978

II. Methods

19. Johnson AH, Mowbray JF, Porter KA: Detection of circulating immune complexes in pathological human sera. Lancet 1:762, 1975

20. Agnello V: Detection of immune complexes. In Manual of Clinical Immunology (Rose NR, Friedman H, eds). Washington: Am Soc for Microbiol, 1976, ch 90

* 21. Schur PH: Immune-complex assays: The state of the art. New Eng J Med 298:161, 1978

22. Pussell BA, Lockwood CM, Scott DM, Pinching AJ, Peters DK: Value of immune-complex assays in diagnostic and management. Lancet 2:358, 1978

23. Rossen RD: Measuring serum immune complexes in cancer. Ann Int Med 88:570, 1978

24. Franklin EC, Holman HR, Muller-Eberhard HJ, Kunkel HG: An unusual protein component of high molecular weight in the serum of certain patients with rheumatoid arthritis. J Exp Med 105:425, 1957

25. Allen JC, Kunkel HG: Antibodies against γ-globulin after repeated blood transfusions in man. J Clin Invest 45:29, 1966

26. Creighton WD, Lambert PH, Miescher PA: Detection of antibodies and soluble antigen-antibody complexes by precipitation with polyethylene glycol. J Immunol 111:1219, 1973

27. Nydegger UE, Lambert PH. Gerber H, Miescher PA: Circulating immune complexes in the serum in systemic lupus erythematosus and in carriers of hepatitis B antigens. Quantitation by binding to radiolabeled C1q. J Clin Invest 54:297, 1974

28. Sobel AT, Bokisch VA, Muller-Eberhard HJ: C1q deviation test for the detection of immune complexes, aggregates of IgG, and bacterial products in human serum. J Exp Med 142:139, 1975

29. Luthra HS, McDuffie FC, Hunder GG, Samayoa EA: Immune complexes in sera and synovial fluids of patients with rheumatoid arthritis. Radioimmunoassay with monoclonal rheumatoid factor. J Clin Invest 56:458, 1975

30. Svehag S-E: A solid-phase radioimmunoassay for C1q-binding immune complexes. I. ΔIgG as indicator molecule. Scand J Immunol 4:687, 1975

31. Zubler RH, Lange G, Lambert P, Miescher PA: Detection of immune complexes in unheated sera by a modified ^{125}I-C1q binding test. Effect of heating on the binding of C1q by immune complexes and application of the test to systemic lupus erythematosus. J Immunol 116:232, 1976

32. Theofilopoulos AN, Wilson CB, Dixon FJ: The Raji cell radioimmune assay for detecting immune complexes in human sera. J Clin Invest 57:169, 1976

33. Hay FC, Nineham LJ, Roitt IM: Routine assay for the detection of immune complexes of known immunoglobulin class using solid phase C1q. Clin Exp Immunol 24:396, 1976

34. Theofilopoulos A, Eisenberg RA, Dixon FJ: Isolation of circulating immune complexes using Raji cells. Separation of antigens from immune complexes and production of antiserum. J Clin Invest 61:1570, 1978

35. Tung KSK, Woodroffe AJ, Ahlin TD, Williams RC, Wilson CB: Application of the solid phase C1q and Raji cell radioimmune assays for the detection of circulating immune complexes in glomerulonephritis. J Clin Invest 62:61, 1978

36. Kano K, Nishimaki T, Palosuo T, Loza U, Milgrom F: Detection of circulating immune complexes by the inhibition of anti-antibody. Clin Immunol Immunopathol 9:425, 1978

37. McDougal JS, Redecha PB, Inman RD, Christian CL: Binding of immunoglobulin G aggregates and immune complexes in human sera to staphylococci containing protein A. J Clin Invest 63:627, 1979

III. Cryoglobulins

* 38. Grey HM, Kohler PF: Cryoimmunoglobulins. Sem Hematol 10:87, 1973

39. Stone MJ, Metzger H: The valence of a Waldenstrom macroglobulin antibody and further thoughts on the significance of paraprotein antibodies. Cold Spring Harbor Sympos Quant Biol 32:83, 1967

40. Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M: Biologic and clinical significance of cryoglobulins. A report of 86 cases. Am J Med 57:775, 1974

41. Waldmann TA, Johnson JS, Talal N: Hypogammaglobulinemia associated with accelerated catabolism of IgG secondary to its interaction with an IgG-reactive monoclonal IgM. J Clin Invest 50:951, 1971

42. Stone MJ: Studies on monoclonal antibodies. I. The Specificity and binding properties of a Waldenstrom macroglobulin with anti-γG activity. J Lab Clin Med 81:393, 1973

43. Stone MJ, Fedak JE: Studies on monoclonal antibodies II. Immune complex (IgM-IgG) cryoglobulinemia: The mechanism of cryoprecipitation. J Immunol 113:1377, 1974

44. Stone MJ: Multiple myeloma, macroglobulinemia, and related plasma cell dyscrasias. In Laboratory Medicine (Race, GJ, ed). Hagerstown: Harper & Row, vol 4, ch 24, 1979 (in press)

IV. Renal

* 45. Wilson CB, Dixon FJ: Glomerulonephritis. In Immunological Diseases, ed 3 (Samter M, ed). Boston: Little, Brown, 1978, ch 79

46. Rossen RD, Reisberg MA, Sharp JT, Suki WN, Schloeder FX, Hill LL, Eknoyan G: Antiglobulins and glomerulonephritis. Classification of patients by the reactivity of their sera and renal tissue with aggregated and native human IgG. J Clin Invest 56:427, 1975

47. Howell SB, Epstein WV: Circulating immunoglobulin complexes in Wegener's granulomatosis. Am J Med 60:259, 1976

48. McPhaul JJ: IgA-associated glomerulonephritis. Ann Rev Med 28:37, 1977

49. Ahlin, TD, Tung KSK, Walker LC, Leonard CD, Williams RC: Decrease in circulating immune complexes during hemodialysis. Am J Med 64:672, 1978

50. Levinsky RJ, Malleson PN, Barratt TM, Soothill JF: Circulating immune complexes in steroid-responsive nephrotic syndrome. New Eng J Med 298:126, 1978

51. Gamble CN, Ruggles SW: The immunopathogenesis of glomerulonephritis associated with mixed cryoglobulinemia. New Eng J Med 299:81, 1978

52. Rossen RD, Reisberg MA, Singer D, Suki WN, Duffy J, Hersh EM, Schloeder FX, Hill LL, Ecknoyan G: The effect of age on the character of immune complex disease: A comparison of the incidence and relative size of materials reactive with C1q in sera of patients with glomerulonephritis and cancer. Medicine 58:65, 1979

53. Striker GE, Mannik M, Tung MY: Role of marrow-derived monocytes and mesangial cells in removal of immune complexes from renal glomerulo. J Exp Med 149:127, 1979

54. Lockwood CM, Worlledge S, Nicholas A, Cotton C, Peters DK: Reversal of impaired splenic function in patients with nephritis or vasculitis (or both) by plasma exchange. New Eng J Med 300:524, 1979

V. Infectious Diseases

* 55. Reed WP, Williams RC: Immune complexes in infectious diseases. Adv Int Med 22:49, 1977

56. Abruzzo JL, Christian CL: The induction of a rheumatoid factor-like substance in rabbits. J Exp Med 114:791, 1961

57. Moran CJ, Ryder G, Turk JL, Waters MFR: Evidence for circulating immune complexes in lepromatous leprosy. Lancet 2:572, 1972

58. Dobrin RS, Day NK, Quie PG, Moore HL, Vernier RL, Michael AF, Fish AJ: The role of complement, immunoglobulin and bacterial antigen is coagulase-negative staphylococcal shunt nephritis. Am J Med 59:660, 1975

59. Perez GO, Rothfield N, Williams RC: Immune-complex nephritis in bacterial endocarditis. Arch Int Med 136:334, 1976

60. Beeler BA, Crowder JG, Smith JW, White A: Propionibacterium acnes: Pathogen in central nervous system shunt infection. Report of three cases including immune complex glomerulonephritis. Am J Med 61:935, 1976

61. Bayer AS, Theofilopoulos AN, Eisenberg R, Dixon FJ, Guze LB: Circulating immune complexes in infective endocarditis. New Eng J Med 295:1500, 1976

62. Petersdorf RG: Immune complexes in infective endocarditis. New Eng J Med 295:1534, 1976

63. Moss SW, Gary NE, Eisinger RP: Nephritis associated with a diphtheroid-infected cerebrospinal fluid shunt. Am J Med 63:318, 1977

64. Conn DL: Immune deposits in normal skin in infective endocarditis. JAMA 238:1182, 1977

65. Stagno S, Volanakis JE, Reynolds DW, Stroud R, Alford CA: Immune complexes in congenital and natal cytomegalovirus infections of man. J Clin Invest 60:838, 1977

66. Walker LC, Ahlin TD, Tung KSK, Williams RC: Circulating immune complexes in disseminated gonorrheal infection. Ann Int Med 89:28, 1978

67. Cabane J, Godeau P, Herreman G, Acar J, Digeon M, Bach J-F: Fate of circulating immune complexes in infective endocarditis. Am J Med 66:277, 1979

68. Kelton JG, Neame PB, Gauldie J, Hirsh J: Elevated platelet-associated IgG in the thrombocytopenia of septicemia. New Eng J Med 300:760, 1979

VI. Oncology

* 69. Robins RA, Baldwin RW: Immune complexes in cancer. Cancer Immunol Immunotherapy 4:1, 1978

70. Costanza ME, Pinn V, Schwartz RS et al: Carcinoembryonic antigen-antibody complexes in a patient with colonic carcinoma and nephrotic syndrome. New Eng J Med 289:520, 1973

71. Couser WG, Wagonfield JB, Spargo BH, Lewis EJ: Glomerular deposition of tumor antigen in membranous nephropathy associated with colonic carcinoma. Am J Med 57:962, 1974

72. Jose DG, Seshadri R: Circulating immune complexes in human neuroblastoma: Direct assay and role in blocking specific cellular immunity. Int J Cancer 13:824, 1974

73. Sutherland JC, Markham RV, Mardiney MR: Subclinical immune complexes in the glomeruli of kidneys postmortem. Am J Med 57:536, 1974

74. Jones LW, Levin A, Fudenberg HH: Clomerular antigen complexes associated with transitional cell carcinoma. Surg Gynecol Obstet 140:896, 1975

75. Jerry LM, Rowden G, Cano PO, Phillips TM, Deutsch GF, Capek A, Hartmann D, Lewis MG: Immune complexes in human melanoma: A consequence of deranged immune regulation. Scand J Immunol 5:845, 1976

76. Carpentier NA, Lange GT, Fiere DM, Fournie GJ, Lambert P-H, Miescher PA: Clinical relevance of circulating immune complexes in human leukemia. Associated in acute leukemia of the presence of immune complexes with unfavorable prognosis. J Clin Invest 60:874, 1977

77. Theofilopoulos AN, Andrews BS, Urist MM, Morton DL, Dixon FJ: The nature of immune complexes in human cancer sera. J Immunol 119:657, 1977

78. Noonan FP, Halliday WJ, Wall DR, Chinie JA: Cell-mediated immunity and serum blocking factors in cancer patients during chemotherapy and immunotherapy. Cancer Res 37:2473, 1977

79. Poulton TA, Crowther ME, Hay FC, Nineham LJ: Immune complexes in ovarian cancer. Lancet 2:72, 1978

80. Brown CA, Hall CL, Long JC, Carey K, Weitzman SA, Aisenberg AC: Circulating immune complexes in Hodgkin's disease. Am J Med 64:289, 1978

VII. Rheumatology

* 81. Editorial: Immune complexes in rheumatic disease. Lancet 2:79, 1976

82. Weisman M, Zvaifler N: Cryoimmunoglobulinemia in rheumatoid arthritis. Significance in serum of patients with rheumatoid vasculitis. J Clin Invest 56:725, 1975

83. Conn DL, Schroeter AL, McDuffie FC: Cutaneous vessel immune deposits in rheumatoid arthritis. Arth Rheum 19:15, 1976

84. Steere AC, Malawista SE, Hardin JA, Ruddy S, Askenase PW, Andiman WA: Erythema chronicum migrans and Lyme arthritis. The enlarging clinical spectrum. Ann Int Med 86:685, 1977

85. Brentjens J, Ossi E, Albini B et al. Disseminated immune depostis in lupus erythematosus. Arth Rheum 20:962, 1977

86. Hill GS, Hinglais N, Tron F, Bach J-F: Systemic lupus erythematosus. Morphologic correlations with immunologic and clinical data at the time of biopsy. Am J Med 64:61, 1978

87. Nishimaki T, Kano K, Milgrom F: Studies on immune complexes in rheumatoid arthritis. Arth Rheum 21:639, 1978

88. Fuller TJ, Richman AV, Auerbach D, Alexander RW, Lottenberg R, Longley S: Immune-complex glomerulonephritis in a patient with mixed connective tissue disease. Am J Med 62:761, 1977

89. Bennett RM, Spargo BH: Immune complex nephropathy in mixed connective tissue disease. Am J Med 63: 534, 1977

90. Frank MM, Hamburger MI, Lawley TJ, Kimberly RP, Plotz PH: Defective reticuloendothelial system Fc-receptor function in systemic lupus erythematosus. New Eng J Med 300:518, 1979

91. Hardin JA, Walker LC, Steere AC et al. Circulating immune complexes in Lyme arthritis. Detection by the ^{125}I-C1q binding, C1q solid phase, and Raji cell assays. J Clin Invest 63:468, 1979

VIII. Liver - G-I

92. Almeida JD, Waterson AP: Immune complexes in hepatitis. Lancet 2:983, 1969

93. Alpert E, Isselbacher KJ, Schur PH: The pathogenesis of arthritis associated with viral hepatitis. Complement-component studies. New Eng J Med 285:185, 1971

94. Combes B, Stastny P, Shorey J, Eigenbrodt EH, Barrera A, Hull AR, Carter NW: Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. Lancet 2:234, 1971

95. Florin-Christensen A, Roux MEB, Arana RM: Cryoglobulins in acute and chronic liver diseases. Clin Exp Immunol 16:599, 1974

96. Sergent JS, Lockshin MD, Christian CL, Gocke DJ: Vasculitis with hepatitis B antigenemia: Long-term observations in nine patients. Medicine 55:1, 1976

97. Wands JR, LaMont JT, Mann E, Isselbacher KJ: Arthritis associated with intestinal-bypass procedure for morbid obesity. Complement activation and characterization of circulating cryoproteins. New Eng J Med 294:121, 1976

98. Gerber MA, Sarno E, Vernace SJ: Immune complexes in hepatocytic nuclei of HB Ag-positive chronic hepatitis. New Eng J Med 294:922, 1976

99. Thomas HC, Potter BJ, Sherlock S: Is primary biliary cirrhosis an immune complex disease? Lancet 2:1261, 1977

100. Walker WA, Wu M, Bloch KJ: Stimulation by immune complexes of mucus release from goblet cells of the rat small intestine. Science 197:370, 1977

101. Levo Y, Gorevic PD, Kassab HJ, Zucker-Franklin D, Franklin EC: Association between hepatitis B virus and essential mixed cryoglobulinemia. New Eng J Med 296:1501, 1977

102. Wands JR, Dienstag JL, Bhan AK, Feller ER, Isselbacher KJ: Circulating immune complexes and complement activation in primary biliary cirrhosis. New Eng J Med 298:233, 1978

IX. Miscellaneous

103. Matthews JD, Whittingham S, Mackay IR: Autoimmune mechanisms in human vascular diseases. Lancet 2:1423, 1974

* 104. Christian CL, Sergent JS: Vasculitis syndromes: Clinical and experimental models. Am J Med 61:385, 1976

105. Dreisin RB, Schwartz MI, Theofilopoulos AN, Stanford RE: Circulating immune complexes in the idiopathic interstitial pneumonias. New Eng J Med 298:353, 1978

106. Editorial: Immune complexes in cryptogenic fibrosing alveolitis. Lancet 1:1192, 1978

107. Schwartz MI, Dreisin RB, Pratt DS, Stanford RE: Immunofluorescent patterns in the idiopathic interstitial pneumonia. J Lab Clin Med 91:929, 1978

108. Versey JMB, Gabriel R: Soluble-complex formation after myocardial infarction. Lancet 2:493, 1974

109. Lessof MH: Postcardiotomy syndrome: Pathogenesis and management. Hosp Pract Sept, 1976

110. Lampert PW, Oldstone MBA: Host immunoglobulin G and complement deposits in the choroid plexus during spontaneous immune complex disease. Science 180:408, 1973

111. Tachovsky TG, Lisak RP, Koprowski H, Theofilopoulos AN, Dixon FJ: Circulating immune complexes in multiple sclerosis and other neurological diseases. Lancet 2:997, 1976

112. Ryan LM, Kozin F, Eiferman R: Immune complex uveitis: A case. Ann Int Med 88:62, 1978

113. Volpe R: The role of autoimmunity in hypoendocrine and hyperendocrine function. With special emphasis on autoimmune thyroid disease. Ann Int Med 87:86, 1977

114. Kalderon AE, Bogaars HA: Immune complex deposits in Graves' disease and Hashimoto's thyroiditis. Am J Med 63:729, 1977

115. Mowbray JF, Hoffbrand AV, Holborow EJ, Seah PP, Fry L: Circulating immune complexes in dermatitis herpetiformis. Lancet 1:400, 1973

116. Mohammed I, Holborow EJ, Fry L, Thompson BR, Hoffbrand AV, Stewart JS: Multiple immune complexes and hypocomplementemia in dermatitis herpetiformis and celiac disease. Lancet 2:487, 1976

117. Moorthy AV, Zimmerman SW, Maxim PE: Dermatitis herpetiformis and celiac disease. Association with glomerulonephritis, hypocomplementemia and circulating immune complexes. JAMA 239:2019, 1978

118. Mihas AA, Goldenberg DJ, Slaughter RL: Sulfasalazine toxic reactions. Hepatitis, fever & skin rash with hypocomplementemia and immune complexes. JAMA 239: 2590, 1978