

MEDICAL GRAND ROUNDS
Parkland Memorial Hospital
January 18, 1968

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COMPLEMENT

1. General considerations
2. Chemistry and mechanism of action
3. Lysis of membranes (erythrocytes, nucleated cells, bacteria, glomerular basement membranes)
4. Functions related to host resistance and inflammation (phagocytosis, immune adherence, chemotaxis, histamine release, anaphylatoxin)
5. Hereditary deficiencies
 - (a) C'2 deficiency in man
 - (b) Hereditary angioneurotic edema (C'1 esterase inhibitor deficiency)
 - (c) C'6 deficiency in rabbits and C'5 deficiency in mice
6. Role in disease
 - (a) Myasthenia gravis, chronic active hepatitis, leprosy, cryoglobulinemia
 - (b) Hematologic disorders
 - (c) Renal disease
 - (d) Rheumatoid arthritis
 - (e) Systemic lupus erythematosus

Table I. *Properties of complement components*
(Müller-Eberhard)

Complement Component	Synonym	s-Rate	Electroph. Mobility	Serum Concentration (mg%)	Thermolability (56°C, 30 min.)
C'1 {	C'1q*	11S comp	γ_2	2-3	+
	C'1r	-	β	-	+
	C'1s*	C'1 esterase	α_2	-	+
	C'4*	β_{1E} -glob.	β_1	3-5	0
	C'2*	-	β_2	<1	+
	C'3*	β_{1C} -glob.	β_1	80-150	0
	C'5*	β_{1F} -glob.	β_1	3-5	+
	C'6	-	β_2	<1	0
	C'7	-	β_2	-	0
	C'8	-	γ_1	-	+
	C'9*	C'T	α_2 - α_1	-	+

*Highly purified active component isolated as a unique serum protein.

Fig. 1

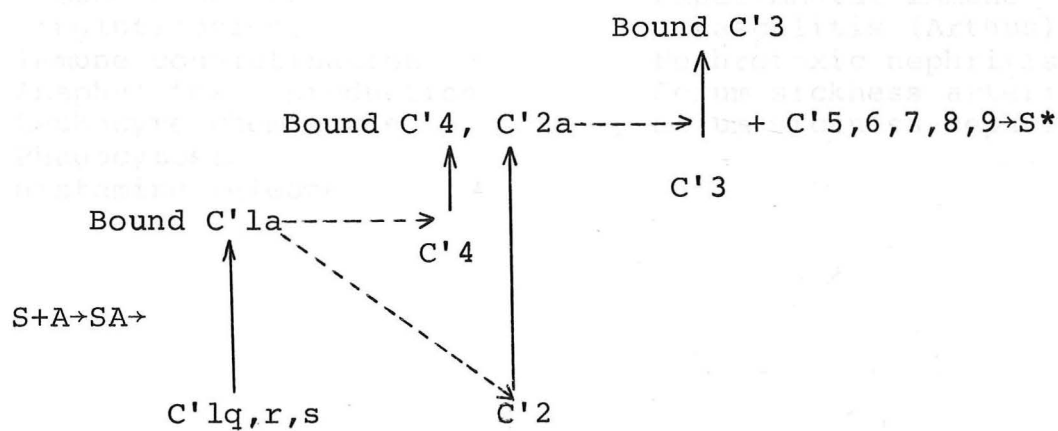


Table II. *Complement-dependent reactions in vitro and in vivo*

In vitro

Immune cytolysis
Bactericidal reaction
Immune adherence
Conglutination
Immune conglutination
Anaphylatoxin production
Leukocyte chemotaxis
Phagocytosis
Histamine release

In vivo

Phagocytosis
Immune hemolysis (AHA, PNH)
Experimental immune
 vasculitis (Arthus)
Nephrotoxic nephritis
Serum sickness arteritis
Serum sickness nephritis

Table III. *Biologic functions of complement components*

<u>Components</u>	<u>Function</u>
M—AC'1a-C'4	Immunoconglutination
M—C'4,2a-C'3	Opsonization, immune adherence, conglutination, immunoconglutination
M—————C'5	C' dependent histamine release (mast cells)
M—————C'5,6,7a	Leukocyte chemotaxis
M—————C'8,9	Membrane lesion: 80 Å hole

Table IV. *Hereditary complement deficiencies*

<u>Species</u>	<u>Deficient Component</u>
Man	C'2
Mouse	C'5
Rabbit	C'6

BIBLIOGRAPHY

General reviews on complement

1. Borsos, T., Dourmashkin, R.R. and Humphrey, J.H., Lesions in erythrocyte membranes caused by immune haemolysis. *Nature* 202:251, 1964.
2. Rosenberg, L.T., Complement. *Amer. Rev. Microbiol.* 19:285, 1965.
3. Nelson, R.A., Jr., The role of complement in immune phenomena. In *The Inflammatory Process*. B.W. Zweifach, L. Grant and R.T. McClusky, editors. Academic Press, Inc., New York, 1965, p. 819.
4. Muller-Eberhard, H.J., Nilesen, U.R., Dalmasso, A.P., Polley, M.J., and Calcott, M.A., A molecular concept of immune cytolysis. *Arch. Path.* 82:205, 1966.
5. Polley, M.J. and Muller-Eberhard, H.J., Chemistry and Mechanism of Action of Complement. *Progr. Hematol.* vol. 5, 1966.
6. Rapp, H.J. and Borsos, T., Complement research, fundamental and applied. *J.A.M.A.* 198:1347, 1966.

Synthesis and catabolism of complement components

7. Colten, H.R., Borsos, T., and Rapp, H.J., *In vitro* synthesis of the first component of complement by guinea pig small intestine. *Proc. Nat. Acad. Sci.* 56:1158, 1966.
8. Stecher, V. J., Morse, J.H. and Thorbecke, G.J., Sites of production of primate serum proteins associated with the complement system. *Proc. Soc. Exp. Biol. Med.* 124:433, 1967.
9. Alper, C.A. and Rosen, F.S., Studies of the *in vivo* behavior of human C'3 in normal subjects and patients. *J. Clin. Invest.* 46:2021, 1967.

Lysis of membranes

10. Ross, A. and Lepow, I.H., Studies on immune cellular injury. I. Cytotoxic effects of antibody and complement. *J. Exp. Med.* 112:1085, 1960.
11. Lepow, I.H. and Ross, A., Studies on immune cellular injury. II. Functional role of C'1 esterase in immune cytotoxicity. *J. Exp. Med.* 112:1107, 1960.
12. Bladen, H.A., Gewurz, H., and Mergenhagen, S.E., Interactions of the complement system with the surface and endotoxin lipopolysaccharide of *veillonella alcalescens*. *J. Exp. Med.* 125:767, 1967.

Host resistance and inflammation

13. Austen, K.F. and Cohn, Z.A., Contribution of serum and cellular factors in host defense reactions. I. Serum factors in host resistance. *New England J. Med.* 268:933, 944, 1963.
14. Spiegelberg, H.L., Miescher, P.A. and Benacerraf, B., Studies on the role of complement in the immune clearance of *Escherichia coli* and rat erythrocytes by the reticuloendothelial system in mice. *J. Immunol.* 90:751, 1963.
15. Ratnoff, O.D. and Lepow, I.H., Complement as mediator of inflammation: enhancement of vascular permeability by purified human C'1 esterase. *J. Exp. Med.* 118:681, 1963.
16. Ward, P.A., Cochrane, C.G. and Müller-Eberhard, H.J., The role of serum complement in chemotaxis of leukocytes in vitro. *J. Exp. Med.* 122:327, 1965.
17. Ciba Foundation Symposium on Complement. G.E.W. Wolstenholme and J. Knight, eds. Little, Brown, Boston, 1965.
18. Caren, L.D. and Rosenberg, L.T., The role of complement in resistance to endogenous and exogenous infection with a common mouse pathogen, corynebacterium kutscheri. *J. Exp. Med.* 124: 689, 1966.
19. Dias da Silva, W. and Lepow, I.H., Complement as a mediator of inflammation. II. Biological properties of anaphylatoxin prepared with purified components of human complement. *J. Exp. Med.* 125:921, 1967.
20. Ward, P.A., A plasmin-split fragment of C'3 as a new chemotactic factor. *J. Exp. Med.* 126:189, 1967.

Hereditary deficiencies

21. Rother, V. and Rother, G., Ueber einen angeborenen komplement-defekt bei kaninchen. *Z. Immunitätsforsch* 121:224, 1961.
22. Donaldson, V.H. and Evans, R.R., A biochemical abnormality in hereditary angioneurotic edema. *Am. J. Med.* 35:37, 1963.
23. Carew, L.D. and Rosenberg, L.T., Complement in skin grafting in mice. *Immunology* 9:359, 1965.
24. Austen, K.F. and Sheffer, A.L., Detection of hereditary antioneurotic edema by demonstration of a reduction in the second component of human complement. *New Eng. J. Med.* 272: 649, 1965.
25. Gewurz, H., Pickering, R.J., Muschel, L.H., Mergenhagen, S.E. and Good, R.A., Complement-dependent biological functions in complement deficiency in man. *The Lancet*, Aug. 13, 1966, p. 356.

26. Klemperer, M.R., Woodworth, H.C., Rosen, F.S. and Austen, K.F., Hereditary deficiency of second component of complement C'2 in man. J. Clin. Invest. 45:880, 1966.
27. Nilsson, V.R. and Müller-Eberhard, H.J., Deficiency of the fifth component of complement in mice with an inherited complement defect. J. Exp. Med. 124:1, 1967.

Role in disease

28. Townes, A.S., Complement levels in disease. Johns Hopkins Med. J. 120:337, 1967.

Myasthenia gravis

29. Nastuk, W.L., Plescia, O.J. and Osserman, K.E., Changes in serum complement activity in patients with myasthenia gravis. Proc. Soc. Exp. Biol. Med. 105:177, 1960.
30. Plescia, O.J., Segovia, J. and Strampp, A., An assessment of changes in the complement levels of myasthenic sera. Ann. N.Y. Acad. Sci. 135:589, 1966.
31. Nastuk, W.L., Kessler, H.J., Grynbaum, A., Smith, M., and Herrmann, C., Immunological changes following thymectomy in myasthenia gravis. Arch. Neurol. 15:1, 1966.

Chronic active hepatitis

32. MacLachlan, M.J., Rodnan, G.P., Cooper, W.M., and Fennell, Jr., R.H., Chronic active ("lupoid") hepatitis. A clinical serological and pathological study of 20 patients. Ann. Int. Med. 62:425, 1965.

Leprosy

33. Paca de Azevedo, M. and Homem de Melo, P., A comparative study of the complementary activity of serum in the polar forms of leprosy and in the leprosy reaction. Int. J. Leprosy 34:34, 1966.

Cryoglobulinemia

34. Riethmüller, G., Meltzer, M., Franklin, E. and Miescher, P.A., Serum complement levels in patients with mixed (IgM-IgG) cryoglobulinemia. Clin. Exp. Immunol. 1:337, 1966.

Rheumatic fever

35. Küpper, K., Langer, E. and Klein, Nachweis komplementbindenden strukturen in aschoffschen knötchen operativ eut fernter herzhoren. Virchows Arch. Path. Anat. 334:342, 1961.

36. Kaplan, M.H., Bolande, R., Rakita, L. and Blair, J., Presence of bound immunoglobulins and complement in the myocardium in acute rheumatic fever. *New Eng. J. Med.* 271:637, 1964.

Hematologic disorders

37. Shulman, N.R., Immunoreactions involving platelets. I. A steric and kinetic model for formation of a complex from a human antibody, guinidine as a haptene and platelets; and for fixation of complement by the complex. *J. Exp. Med.* 107:665, 1958.
38. Hinz, C.F., Jr., Picken, M.E. and Lepow, I.H., Studies on immune human hemolysis. I. The kinetics of the Donath-Landsteiner reaction and the requirement for complement in the reaction.; II. The Donath-Landsteiner reaction as a model system for studying the mechanism of action of complement and the role of C'1 and C'1 esterase. *J. Exp. Med.* 113:177, 193, 1961.
39. Hinz, C.F., Jr., and Mollner, A.M., Studies on immune hemolysis. III. Role of 11S component in initiating Donath-Landsteiner reaction. *J. Immunol.* 91:512, 1963.
40. Harboe, M., Müller-Eberhard, H.J., Fudenberg, H., Polley, H. J. and Mollison, P.L., Identification of the components of complement participating in the antiglobulin reaction. *Immunology* 6:412, 1963.
41. Rosenfield, R.E., Hader, G.V., and Gilbert, H.S., Complement and the antiglobulin test. *Vox Sang.* 5:182, 1960.
42. Leddy, J.P., Hill, R.W., Swisher, S.N. and Vaughan, J.H., Observations on the immunochemical nature of red cell auto-sensitization. In *IIIrd Int. Symposium on Immunopathology*, P. Grabar and P. Miescher, Eds., Schwabe, Basel, 1963, p. 318.

Renal disease

43. Gunn, W.C., Variation in amount of complement in blood in some acute infectious diseases and its relation to clinical features. *J. Path. Bact.* 19:155, 1914-1915.
44. Fischel, E.E. and Gajdusek, D.C., Serum complement in acute glomerulonephritis and other renal diseases. *Am. J. Med.* 12:190, 1952.
45. Lange, K. and Wenk, E.J., Complement component in the sera and urines of patients with severe proteinuria. *Am. J. Med. Sci.* 228:448, 1954.
46. Lange, K., Wassermann, E. and Slobody, L.B., The significance of serum complement levels for the diagnosis and prognosis of acute and subacute glomerulonephritis and lupus erythematosus disseminatus. *Ann. Int. Med.* 53:636, 1960.

47. Freedman, P. and Markowitz, A.S., Gamma globulin and complement in the diseased kidney. J. Clin. Invest. 41:328, 1962.
48. Michael, A.F., Drummond, K.N., Vernier, R.L. and Good, R.A., Immunologic basis of renal disease. Pediat. Clin. North Amer. 11:685, 1964.
49. Drummond, K.N., Michael, A.F., Good, R.A. and Vernier, R.L., Immunopathologic studies in nephrotic syndrome. J. Pediat. 65:1114, 1964.
50. West, C.D., Northway, J.D. and Davis, N.C., Serum levels of Beta_{1C} globulin a complement component, in the nephritides, lipoid nephrosis, and other conditions. J. Clin. Invest. 43:1507, 1964.
51. Unanue, E. and Dixon, F.J., Experimental glomerulonephritis. IV. Participation of complement in nephrotoxic nephritis. J. Exp. Med. 119:965, 1964.
52. Koffler, D. and Paronetto, F., Immunofluorescent localization of immunoglobulins, complement, and fibrinogen in human diseases. II. Acute, subacute and chronic glomerulonephritis. J. Clin. Invest. 44:1665, 1965.
53. West, C.D., McAdams, A.J., McConville, J.M., Davis, N.C. and Holland, N.H., Hypocomplementemic and normocomplementemic persistent (chronic) glomerulonephritis; clinical and pathologic characteristics. Pediatrics 67:1089, 1965.
54. West, C.D., Holland, N.H., McConville, J.M., McAdams, A.J., glomerulonephritis and in lupus nephritis. Pediatrics 67:1113, 1965.
55. Gotoff, S.P., Fellers, F.X., Vawter, G.F., Janeway, C.A. and Rosen, F.S., The Beta_{1C} globulin in childhood nephrotic syndrome. Laboratory diagnosis of progressive glomerulonephritis. New England J. Med. 273:524, 1965.
56. Cochrane, C.G., Unanue, E.R. and Dixon, F.J., A role of polymorphonuclear leukocytes and complement in nephrotoxic nephritis. J. Exp. Med. 122:99, 1965.
57. McCluskey, R.T., Vassalli, P., Gallo, G. and Baldwin, D.S., An immunofluorescent study of pathogenic mechanisms in glomerular diseases. New England J. Med. 274:695, 1966.
58. Michael, A.F., Drummond, K.N., Good, R.A. and Vernier, R.L., Acute poststreptococcal glomerulonephritis: immune deposit disease. J. Clin. Invest. 45:237, 1966.
59. Klemperer, M.R., Gotoff, S.P., Alper, C.A. and Rosen, F.S., Beta_{1C}-globulin in glomerular nephritis. Pediatrics 37:529, 1966.

60. Drummond, K.N., Michael, A.F., Good, R.A., and Vernier, R.L., The nephrotic syndrome of childhood: immunologic, clinical and pathologic correlations. J. Clin. Invest. 45: 620, 1966.
61. West, C.D., Winter, S., Forristal, J., McConville, J.M. and Davis, N.C., Evidence for in vivo breakdown of Beta_{1c}-globulin in hypocomplementemic glomerulonephritis. J. Clin. Invest. 46:539, 1967.
62. Soothill, J.F., Altered complement component C'_{3A} ($\beta_{1c}-\beta_{1a}$) in patients with glomerulonephritis. Clin. Exp. Immunol. 2: 83, 1967.
63. Soothill, J.F. and Hendrickse, R.G., Some immunological studies of the nephrotic syndrome of Nigerian children. The Lancet Sept. 23, 1967, p. 629.
64. Hadley, W.K. and Rosenau, W., Study of human renal disease by immunofluorescent methods. Arch. Path. 83:342, 1967.
65. Austen, K.F. and Russell, P.S., Detection of renal allograft rejection in man by demonstration of a reduction in the serum concentration of the second component of complement. Ann. N.Y. Acad. Sci. 129:657, 1966.
66. Carpenter, C.B., Gill, T.J. III, Merrill, J.P. and Dammin, G.J., Instability of the complement system in patients with renal allografts. Transplantation 5:864, 1967.

Rheumatoid arthritis

67. Laurell, A.B. and Grubb, R., Complement, complement components, properdin and agglutination promoting factors in rheumatoid arthritis. Acta path. microbiol. scand. 43:310, 1958.
68. Heimer, R., Levin, F.M. and Kahn, M.F., Inhibition of complement fixation by human serum. II. The activity of γ_{1M} -globulin and rheumatoid factor in complement fixation reactions. J. Immunol. 91:866, 1963.
69. Hedberg, H., Studies on the depressed hemolytic complement activity of synovial fluid in adult rheumatoid arthritis. Acta Rheum. Scand. 9:165, 1963.
70. Hedberg, H., Norden, A., Lundquist, A. and Afzelius, B., Depression of hemolytic complement of synovial fluid in adult rheumatoid arthritis. Acta Med. Scand. 175:347, 1964.
71. Pekin, T.J. and Zvaifler, N.J., Hemolytic complement in synovial fluid. J. Clin. Invest. 43:1372, 1964.
72. Schmid, F.R. and Roitt, I. M., Inhibition of complement action by rheumatoid factor. J. Lab. Clin. Med. 66:1019, 1965.

73. Fostiropoulos, G., Austen, K.F. and Bloch, K.J., Total hemolytic complement (CH50) and second component of complement (C²_{hu}) activity in serum and synovial fluid. *Arthritis & Rheum.* 8:219, 1965.
74. Barnett, E.V., Bieneustock, J., and Bloch, K.J., Antinuclear factors in synovia. Possible participants in the rheumatoid inclusion body. *J. Amer. Med. Asn.* 198:143, 1966.
75. Fish, A.J., Michael, A.F., Gewurz, H., and Good, R.A., Immunopathologic changes in rheumatoid arthritis synovium. *Arthritis & Rheum.* 9:267, 1966.
76. Rodman, W.S., Williams, R.C., Jr., Bilka, P.J. and Müller-Eberhard, H.J., Immunofluorescent localization of the third and the fourth component of complement in synovial tissue from patients with rheumatoid arthritis. *J. Lab. Clin. Med.* 69:141, 1967.
77. Pekin, J., T. J., Malinin, T. I. and Zvaifler, H.J., Unusual synovial fluid findings in Reiter's syndrome. *Ann. Int. Med.* 66:677, 1967.
78. Kissmeyer-Nielsen, F., Svejgaard, A., Kjerbye, K.E. and Christensen, T., Blocking effect of rheumatoid factor on complement fixation by thrombocyte isoantibodies. *Vox sang.* 12:199, 1967.

Systemic lupus erythematosus

79. Vaughan, J.N., Bayles, T.B. and Favour, C.B., The response of serum gamma globulin level and complement titer to adrenocorticotrophic hormone (ACTH) therapy in lupus erythematosus disseminatus. *J. Lab. Clin. Med.* 37:698, 1951.
80. Elliot, J.A. and Mathieson, D.R., Complement in disseminated (systemic) lupus erythematosus. *Arch. Derm.* 68:119, 1953.
81. Wedgewood, R.J. and Janeway, C.A., Serum complement in children with "collagen diseases." *Pediatrics* 11:569, 1953.
82. Williams, R.C. and Law, D.M., Serum complement in connective tissue disorders. *J. Lab. Clin. Med.* 52:273, 1958.
83. Ellis, H.A. and Felix-Davis, D., Serum complement, rheumatoid factor and other serum proteins in rheumatoid disease and systemic lupus erythematosus. *Ann. Rheum. Dis.* 18:215, 1959.
84. Asherson, G.L., Serum complement in systemic lupus erythematosus and other diseases. *Aust. Ann. Med.* 9:57, 1960.
85. Morse, J.H., Muller-Eberhard, H.J. and Kunkel, H.J., Anti-nuclear factors and serum complement in systemic lupus erythematosus. *Bull. N.Y. Acad. Med.* 38:641, 1962.

86. Lachmann, P.J., Müller-Eberhard, H.J., Kunkel, H.J., and Paronetto, A., The localization of in vivo bound complement in tissue sections. J. Exp. Med. 115:63, 1962.
87. Townes, A.J., Stewart, C.R., Jr., and Osler, A.G., Immunologic studies of systemic lupus erythematosus. Bull. Hopkins Hosp. 112:202, 1963.
88. Burnham, T.K., Neblett, T.R. and Fine, G., The application of the fluorescent antibody technique to the investigation of lupus erythematosus and various dermatoses. J. Invest. Dermat. 41:431, 1963.
89. Burkholder, P.M., Complement fixation in diseased tissues. II. Fixation of guinea pig complement in renal lesions of systemic lupus erythematosus. Am. J. Path. 42:201, 1963.
90. Kalsbeck, G.L. and Cormane, R.H., "Bound" complement in the skin of patients with chronic discoid lupus erythematosus and systemic lupus erythematosus. Lancet 2:178, 1964.
91. Miyasato, F., Pollak, V.E. and Barcello, R., Serum β_1A (β_1C) globulin levels in systemic lupus erythematosus: their relationship to clinical and renal histologic findings. Arthritis & Rheum. 9:308, 1966.
92. Bahgat, N. and Rothfield, N., Relation of changes in serum complement to renal, skin and joint lesions in patients with systemic lupus erythematosus. Egypt. Rheum. 3:1, 1966.
93. Tan, E. and Kunkel, H.G., An immunofluorescent study of the skin lesions in systemic lupus erythematosus. Arthritis & Rheum. 9:37, 1966.
94. Hanauer, L.B. and Christian, C.L., Clinical studies of hemolytic complement and the 11S component. Am. J. Med. 42:882, 1967.
95. Castanedo, J.P. and Williams, Jr., R.C., Anticomplementary activity of sera from patients with connective tissue disease and normal subjects. J. Lab. Clin. Med. 69:217, 1967.