COMPLEMENT PROTEINS AND RECEPTORS IN HUMAN DISEASE

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OUTLINE and INDEX

INTRODUCTION

The principal functions of the immune system are to recognize, destroy, and protect against reappearance of pathogenic agents and altered cells. Recent studies have unequivocally demonstrated that the complement system plays critical roles in humoral immunity, some forms of inflammation, immunoregulation, and in certain forms of disease susceptibiltiy (1-10). Complement is now regarded as, "... the essential effector mechanism in humoral immunity to infection" (R.R. Porter, 1).

Complement has not always been held in such high esteem by immunologists and clinicians. As recently as 30 years ago the Nobel laureate immunologist Burnet spoke for a majority of scientists when he commented that complement probably was an in vitro hemolytic artifact with an importance no greater than serum albumin allotypes. Continued studies have proven him wrong.

Knowledge of complement has come in three major phases (11, Table 1). Recognized because of the lytic property of the C5b-9 membrane attack complex, complement came to be seen as synonymous with in vitro hemolysis. Investigators were slow to recognize the biologic importance of complement 1.) because of this emphasis on the method of assay, 2.) because many stimuli can activate either or both of the two separate activation pathways, and 3.) because the first genetic deficiencies were detected in apparently healthy subjects.

Clinicians have been largely blind to the full importance of complement in host defense, disease susceptibility, tumor immunology, and some forms of inflammation. This has been the case largely because available methods for detecting complement activation and complement mediated tissue damage have been insensitive and because sophisticated clinical application of basic knowledge of complement often has had a glacial pace.

Serum complement and human disease has been the topic of these Grand Rounds three times over the past 18 years (7-9). Drs. Stastny (1968), Smiley (1973), and Jasin (1979) thoroughly updated advances in complement investigation and placed them in a clinical context. Two years ago at these rounds Dr. Jasin (10) reviewed immune complex diseases and the role of complement as they were understood at that time.

I have chosen to present a new vision of complement in a medical context. Clinically important insights have emerged recently that demand recognition and incorporation into clinical practice. This protocol is intended to illustrate the principal concepts involved and to act as a guide to the scattered literature on recent breakthroughs in concepts and technology. Clearly we have markedly improved our understanding of complement and our ability to monitor complement activation in vivo.

Table 1

HISTORICAL PHASES OF COMPLEMENT INVESTIGATION

1888-1900	Initial recognition	
	1888 Nuttall	Discovery of a heat labile serum activity that kills anthrax organisms
	1889 Buchner	Heat labile serum activity that kills typhoid organisms and lyses RBC
	1898 Bordet	Recognition of heat stable and heat labile serum factors that lyse cholera vibrios and RBC
	1899 Ehrlich	Recognition of the sequence of binding: Ligand bound by Heat stable specific serum factor then able to bind Heat labile nonspecific lytic factor
1900-1940	Gradual recognition and characterization of properites of C1, C2, C3, C4 using hemolytic assays	
1950-1970	Improved methods in protein chemistry permit isolation of principal complement proteins and initial quantitative estimates of reactions involved in sequential activation	
1970-Present	Increasingly diverse and sophisticated studies of the chemical, immunologic, phenotypic and molecular genetic, biologic and medical dimensions of the complement system.	

An appreciation of the roles of complement, diseases related to complement activation, diseases related to complement deficiencies, and the usefulness of new diagnostic methods can only follow a basic understanding of the complement system. After a brief review of the anatomy of the system, complement deficiency states will be reviewed. The surprisingly high incidence of autoimmune disease among patients with C' deficiencies will be reviewed from the perspective of the role of C' in nonpathogenic metabolism of immune complexes. The linkage of normal levels of specific complement allotypes to disease will discussed in a similar context. Newer assays for clinical monitoring of C' activation will be reviewed. My intent is to provide a path to

understanding and effective use of new knowledge of the medical aspects of complement.

Complement Activation (References 11-24)

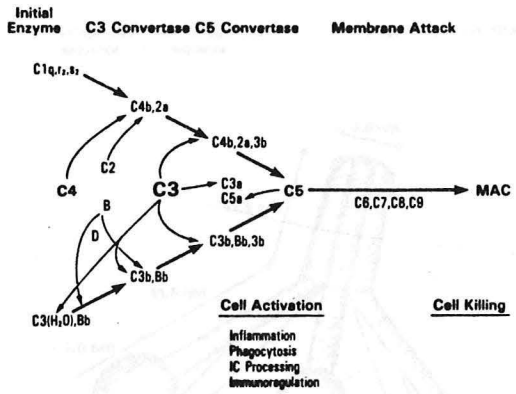


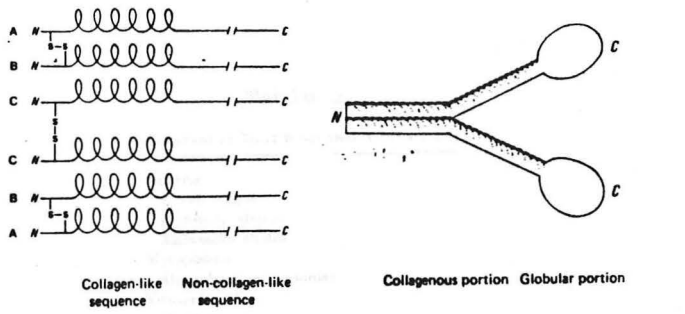
Figure 1

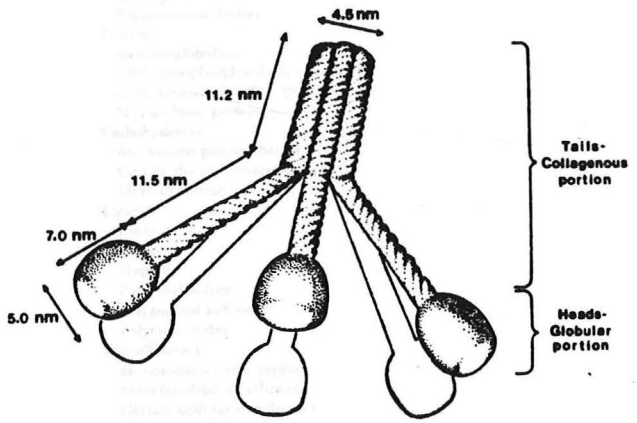
(From reference 6)

This depiction of the classical and alternative pathways visually stratifies the system in a useful manner. The system can be approached in blocks consisting of activation mechanisms, convertases, and membrane attack complex.

Classical Pathway Activation (references 11-17)

Activation of the classical pathway is accomplished by the binding of diverse activating molecules or surfaces to C1 (Figure 2). In addition to the well known ability of antibodies to activate the classical pathway, numerous microorganisms, parasites, membranes, proteins, lipids, and carbohydrates are now known to be able to activate this pathway (Table 2). Regulation of the pathway is exerted by the C1 esterase inhibitor (Table 3), intrinsic decay of the convertase (Figure 3), and by the actions of regulatory proteins I and the C4-binding protein. C1-INH binds to activated C1r (the basis for a new assay described below).





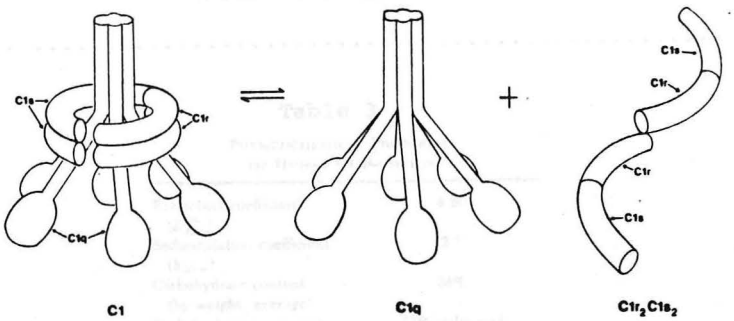


Figure 2

Structure and Organization of C1
(from reference 11)

Table 2

SUBSTANCES THAT BIND AND ACTIVATE C1

Bacteria
E. coli strains
Klebsiella strains
Salmonella strains
Mycoplasma
Mycoplasma pneumoniae
Viruses
Retroviruses
Parasite structures from
Schistosoma mansoni
Trypanosoma brucei
Proteins
Immunoglobulins
CRP (phosphorylcholine) complexes
p15E retroviral surface protein
Myelin basic protein
Carbohydrates
Ant venom polysaccharide
Certain di- and trisaccharides
Dextran sulfate
Lipids
Lipid A
Polyions
Heparin
Polyvinyl sulfate
Polyanethol sulfonate
Polynucleotides
Miscellaneous
Monosodium urate crystals
Mitochondrial membranes
Certain cellular membranes
Nitrophenylated molecules

(From reference 11)

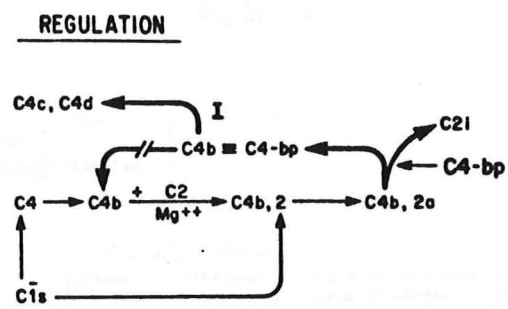
Table 3

PHYSICOCHEMICAL PROPERTIES OF HUMAN C1 INHIBITOR[a]

Extinction coefficient ($E^{1\%}_{1cm}$)	4.50
Sedimentation coefficient ($S_{20,w}$)	3.7
Carbohydrate content (by weight, average)	34%
Carbohydrate types and amounts	17% sialic acid 12% hexose
Molecular composition and subunits	Single polypeptide chain
Relative charge	α
Concentration in serum	137 μg/ml

From reference 11

Figure 3



From reference 16

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Alternative Pathway Activation (References 18-24)

Table 4

Proteins of the alternative pathway

Symbol	Name	Functions	Molecular weight	Serum concentration µg/ml
C3	C3	Initiation as $C3(H_2O)$; after enzymatic activation covalent attachment via thioester as C3b, which is nonenzymatic subunit of C3/C5 convertase	185 000	1300 (1050–1650)
B	Factor B	Zymogen of Bb (M_r = 60 000) which is a serine protease that forms C3/C5 convertase with $C3(H_2O)$ or C3b; activated by Factor D	93 000	210 (170–260)
D	Factor D	Serine protease which activates Factor B when in complex with C3b or $C3(H_2O)$	24 000	1
H	Factor H	Negative regulator which accelerates decay-dissociation of C3/C5 convertase; cofactor of Factor I	150 000	475 (360–550)
I	Factor I	Serine protease regulating C3b by conversion to C3bi and C3bi by fragmentation to C3c and C3dg; requires Factor H or CR1 as cofactor	88 000	35 (30–40)
P	Properdin	Positive regulator stabilizing C3/C5 convertase by binding to the complex	220 000	26 (20–30)

(From reference 19)

Figure 4

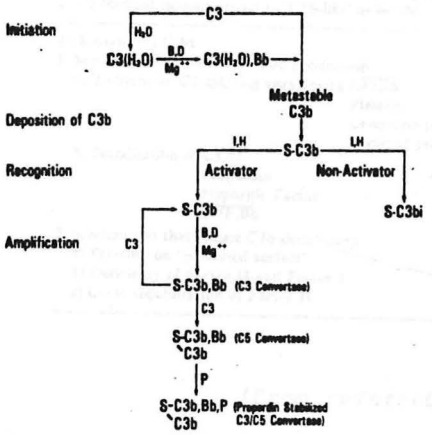


Fig. 1. Proposed molecular reaction mechanism of alternative pathway activation. Initiation results from spontaneous hydrolysis of the putative thioester in native C3, which produces a C3 molecule with C3b-like functional properties. The resulting C3 convertase $C3(H_2O)$,Bb generates metastable C3b. Deposition of metastable C3b occurs randomly from the fluid phase, but only on activators does the bound C3b escape control sufficiently to cause C3 convertase formation which then mediates positive feedback amplification, progressive C3b deposition, properdin recruitment, and C5 convertase formation

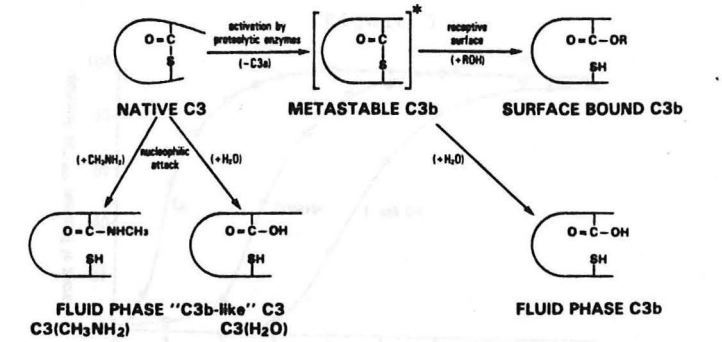


Fig. 2. Proposed chemical reactions at the activated carbonyl site of C3. Current evidence suggests that an intramolecular thioester bond in the α-chain of C3 becomes the reactive group of the metastable binding site of proteolytically produced C3b. C3 altered by nucleophilic attack or hydrolysis of the thioester becomes functionally C3b-like without proteolytic release of C3a

Mechanisms of Alternative Pathway Activation

(From reference 19)

Table 5

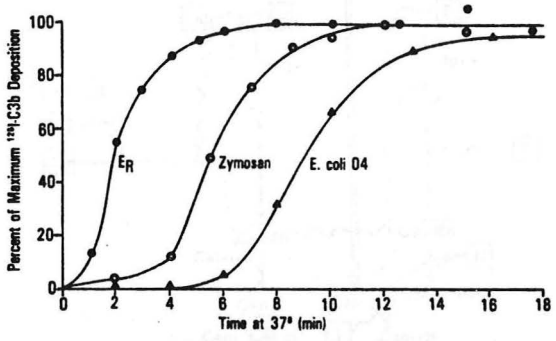
Initiation of alternative complement pathway. Tick-over maintained by spontaneous hydrolysis of C3 internal thioester bond to 'C3b-like' molecule

Tick-over "fired" by

1. Mechanisms that increase C3b production
   a) 'Exogenous' C3 splitting enzymes eg $\overline{C4b,2b}$
      Plasmin
      Leucocyte proteases eg elastase
      Bacterial proteases
   b) Stabilisation of $\overline{C3,Bb}$
      Properdin
      Nephritic Factor
      $\overline{CVF,Bb}$
2. Mechanisms that reduce C3b destruction
   a) Fixation on "protected surface"
   b) Deficiency of Factor H and Factor I
   c) Local sequestration of Factor H

(From reference 19)

Figure 5



Time course of C3b deposition on alternative pathway activators. Deposition on rabbit erythrocytes (E_R) was measured by incubating a mixture of 300 µl C7 depleted human serum containing 2 µg ^{125}I-labeled C3, 100 µl GVB, 25 µl 0.1 M MgEGTA, and 125 µl E_R (4×10^9/ml in GVB). Samples were removed at the indicated times and layered on 300 µl of 20% sucrose in a Beckman microfuge tube. The cells were sedimented by centrifugation at 8000 *xg* for 30 s. The pellet and supernatant were separated by cutting the tube just above the pellet and the percent bound radioactivity was determined. Zymosan and *E. coli* 04 (5×10^9 particles/ml) were treated similarly. The C3 bound by E_R, zymosan, and *E. coli* at the plateau were 7.0%, 4.1%, and 2.3% of input, respectively

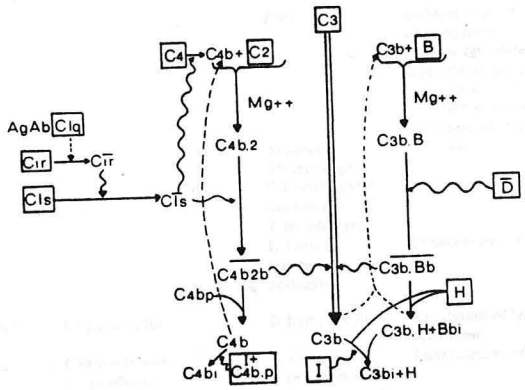
(From reference 19)

Table 6

Summary of Initial Mechanisms of Complement Activation

I.	Zymogen Cleavage (Classical)
II.	"Tickover" (Alternative)
III.	Exogenous Proteases
	Coagulation, Kinin, Fibrinolytic Systems
	Microorganisms
	Neutrophils

Figure 6



A Summary of Complement Activation and Regulation of Activation

(From reference 19)

Biological Effector Systems (References 25-57)

Receptors for Complement Proteins:

Table 7

Summary of specificity, cellular distribution, and biological activities of the complement receptors

Receptor	Ligand	Cell type	Biologic response
C1q	Collagen-like region on C1q exposed after dissociation of C1 complex	PMN	Increases oxidative metabolism
		Monocytes Lymphocytes Lymphoblastoid cells	Enhancement of ADCC Induction of cytolytic activity toward chicken E
C3a	C3a, C4a requires C-terminal arginine	Mast cells	Secretion of vasoactive amines
		Macrophages	Secretion of IL-1, stimulation of prostaglandin and thromboxane production
		T Lymphocytes	Inhibition of antibody response
CR1	C3b C3bi and C3c bind with lower affinity	Erythrocytes	Acts as Factor I cofactor to produce C3d,g from C3bi Clearance of immune complexes
		PMN	Enhances IgG dependent phagocytosis Induces IgG independent ingestion under certain conditions Secretion reactions Induction of respiratory burst
		Monocyte/ Macrophage B Lymphocytes Subsets of T lymphocytes	As PMN
		K Cells Glomerular podocytes	Enhancement of ADCC
CR2	C3d,g or C3bi C3d binds with lower affinity	B Lymphocyte	Regulation of lymphocyte activation
		K Cells with T cell markers Lymphoblastoid cells	Enhancement of ADCC
CR3	C3bi	Like CR1 except not on erythrocytes	Enhancement or induction of phagocytosis Induction of respiratory burst Secretion reactions Enhancement of ADCC Genetic deficiency of CR3 linked to severe, recurrent bacterial infections

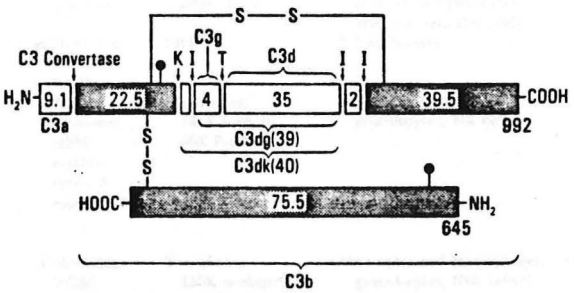
Table 7 (continued)

C3e	C3e or C3d-K	Neutrophils	Mobilization of leukocytes from bone marrow Secretion of granule-associated enzymes
H	Multimeric forms of Factor H	B Lymphocytes	Factor I secretion, blastogenesis
		Monocytes	Induction of respiratory burst
		PMN	Factor I secretion
C5a	C5a C5a desArg binds with lower affinity	Mast cells	Secretion of vasoactive amines Leukotriene production including SRS-A
		PMN	Chemotaxis, enzyme secretion, aggregation
		Monocytes	Chemotaxis, leukotriene production including SRS-A, enhancement of immune response

From reference 27

C3 and C3 cleavage products:

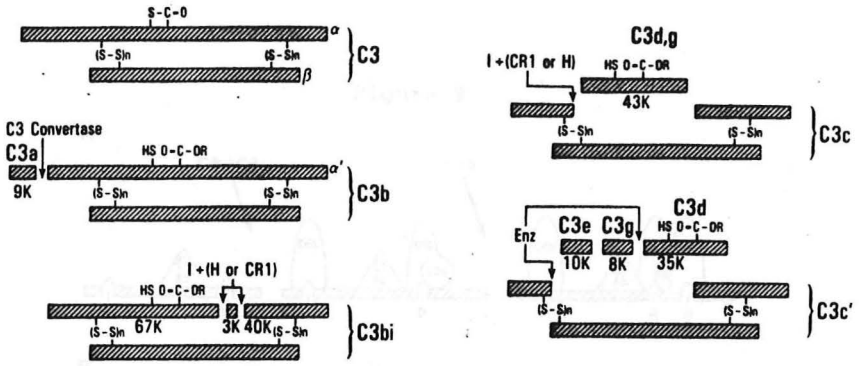
Figure 7



Schematic representation of the human C3 molecule. The *numbers* indicate molecular weights in kilodaltons (except 992 at the C-terminus of the α-chain and 645 at the N-terminus of the β-chain, which indicate the number of amino acid residues in each chain). The information is derived from cDNA sequence analysis [4]. The shaded areas together represent C3c. *I*, Factor I cleavages; *K*, kallikrein cleavage point

(From reference 6)

Figure 8



From reference 17

Table 8

MEMBRANE RECEPTORS FOR BOUND FRAGMENTS OF C3: CR_1, CR_2, CR_3, AND CR_4 STRUCTURE, SPECIFICITY, CELL TYPE DISTRIBUTION, AND DISTINGUISHING MONOCLONAL ANTIBODIES

Receptor type	Specificity	Structure	Cell type distribution	Monoclonal antibodies
CR_1	C3b>C4b >iC3b C3i, C3c	Four allotypes: 160K, 190K, 220K, 250K	Erythrocytes, granulocytes, monocytes, B and some T cells, kidney podocytes, dendritic reticulum cells	44D[a], 57F[a], 57H, 31D, C3RTo5, E11
CR_2	iC3b=C3dg >C3d ⩾C3b	140K	B lymphocytes	Anti-B2[b], HB-5[a]
CR_3	iC3b, *S. cerivisiae*, rabbit erythrocytes, *S. epidermidis*	Two chains: 165K α-chain 95K β-chain	Monocytes and macrophages, granulocytes, NK cells	Anti-Mac-1[c], OKM1[d], OKM9[d], OKM10[d], MN-41, anti-Mol, anti-Leu-15[a]
CR_4	iC3b=C3dg >C3d	Two chains: 150K α-chain[e] 95K β-chain[e]	Monocytes and macrophages, granulocytes, (NK cells?)	Anti-Leu-M5[a,e]

From reference 26

Figure 9

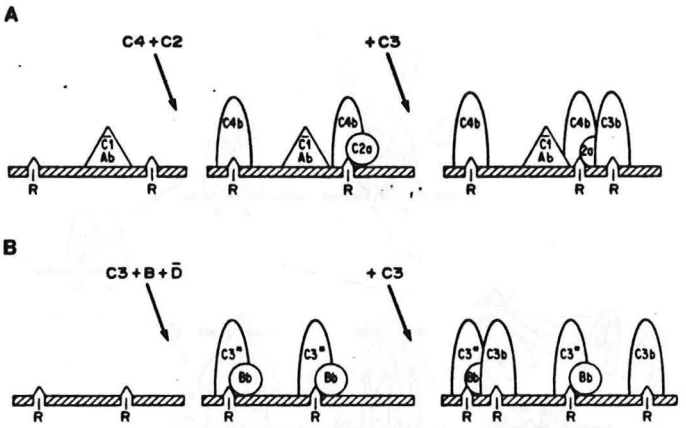


FIG. 1. Assembly of C3-convertase and deposition of C3b on substrates. (A) Classical pathway: Interaction of C4 with activated C1-antibody complexes (C1-Ab) generates nascent C4b. The nascent C4b fragments form hydroxylester and amidoester bonds with nucleophilic acceptor groups (R) in the antibody or on the substrate surface in close proximity to their site of generation. The bound C4b provide the required binding sites for C2. The same C1-esterase that cleaves C4 also cleaves C2. Cleavage of C2 to C2a and formation of the classical pathway C3-convertase C4b2a complex can only occur on bound C4b fragments that are positioned such that C2 is in close proximity to Ab-C1 complexes. The C2a portion of the C4b2a complex is a serine esterase, but it is only active when complexed with C4b. The C4b2a complex spontaneously and irreversibly dissociates with a half-life of 5 minutes at 37°C, and this dissociation is accelerated by C4bp and DAF. Interaction of C3 with the substrate-bound C3-convertase complex (C4b2a) generates nascent C3b. The nascent C3b fragments, in turn, form covalent bonds with substrate acceptor groups (R) in the immediate vicinity of their site of formation adjacent to C4b2a, but do not bind to C4b2a. R groups for C3 (or C4) may be carboxyl groups of carbohydrates or amino groups of proteins, and are *not* specific C3 receptors. (B) Alternative pathway: The inherent instability of the internal thiolester in the native C3 molecule spontaneously and continously generates small amounts of fluid-phase and bound C3* (C3i). This C3* forms a magnesium-dependent complex with factor B (B), such that the B in the complex becomes labile to cleavage by the serine protease factor D (D). Cleavage of B in the complex generates bound C3*Bb complexes that form the initial C3-convertase of the alternative pathway. Interaction of additional C3 with C3*Bb leads to cleavage of C3 into C3a fragments and nascent C3b, followed by covalent attachment of a proportion of the nascent C3b to substrate acceptor groups (R) in the immediate vicinity of the C3-convertase. These bound C3b then form C3bBb C3-convertase sites that cleave more C3. As with the C4b2a complex, spontaneous decay dissociation of C3bBb (half-life 2 minutes at 37°C) is accelerated by a control protein, in this case H rather than C4bp. However, properdin (not shown) associates with C3bBb bound to activating surfaces, generating a C3bBbP complex with extended half-life of 20 minutes at 37°C. This action of properdin that stabilizes bound C3-convertase, as well as the action of H that rapidly dissociates both fluid-phase C3bBb and C3bBb bound to host membranes (see text), works to focus the C3-convertase on the substrate surface rather than in the fluid phase. Further interaction of B and more C3 with these complexes extends C3b deposition outward to acceptor sites progressively more distant from the site of the initial C3-convertase formation.

From reference 26

Figure 10

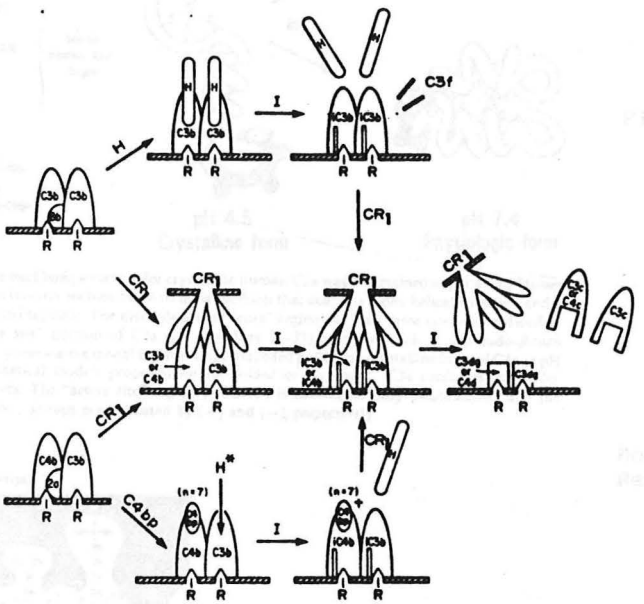


FIG. 3. Formation of C3 receptor ligands. C3b clusters can either interact with H or with CR_1, displacing Bb. Interaction of C3b3b with H results in I-mediated conversion to iC3bi3b (releasing 3K M_r C3f fragments), but does not permit further iC3b breakdown, probably because of the low affinity of H for fixed iC3b (Ross *et al.*, 1983a). Interaction of C3b3b with CR_1 also results in conversion of the C3b3b to iC3bi3b, but can additionally lead to further I-mediated breakdown of the iC3bi3b to C3dg3dg. This latter cleavage releases C3c fragments into the fluid phase. The subsequent interaction of I and H-generated iC3bi3b with CR_1 can similarly result in production of C3dg3dg and C3c. The ability of CR_1 to support iC3b fragmentation may be a consequence of its capacity to cluster in the membrane and form multipoint bonds with the iC3b. C4b3b clusters can interact with C4bp and H, or with CR_1, releasing C2a, and permiting I-mediated cleavage to iC4bi3b.

*C4bp alone may be able to support this reaction, because C4bp may serve as an I-cofactor with both C3b and C4b to iC3b and iC4b, both in the fluid-phase (Fugita and Nussenzweig, 1979) and bound (Gottlieb and Medof, unpublished observation). Interaction with CR_1 results in I-mediated conversion of iC4bi3b to C4d3dg. At high C4b densities, C4bp can also support cleavage of iC4b to C4d, perhaps because it exists as a multimer of 7 covalently bonded subunits (Dahlback *et al.*, 1983). that may be able to mediate multipoint binding.

From reference 26

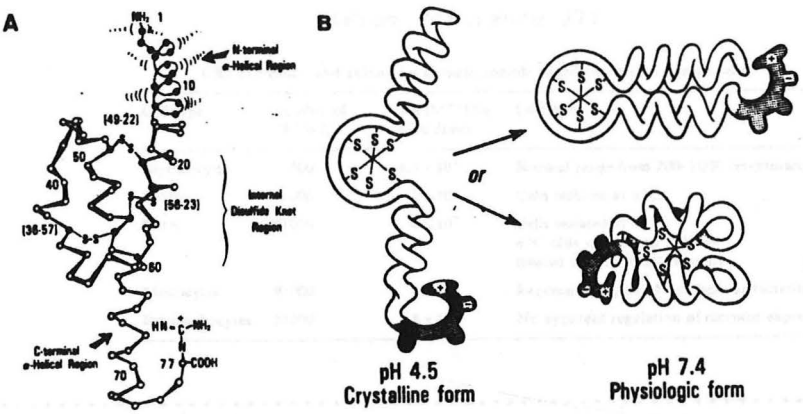


Figure 11

Fig. 3. A The peptide backbone structure for crystalline human C3a was determined at pH 4.5 by Huber et al. [28]. The main features include an N-terminal portion that suggests alpha helical structure and a long C-terminal helical segment. The disulfide-linked "core" region contains three intra-chain disulfide bridges. The "active site" portion of C3a (e.g., residues 73–77) is folded back in a pseudo-β-turn conformation. **B** A representative model is given of the extended or "open" crystalline form of C3a at pH 4.5 with two hypothetical models proposed for the folded or "compact" C3a conformation under physiologic conditions. The "active site" region (LGLAR) is shaded for easy identification and the guanidino and carboxy groups are indicated by (+) and (−), respectively

Both from
Ref #46

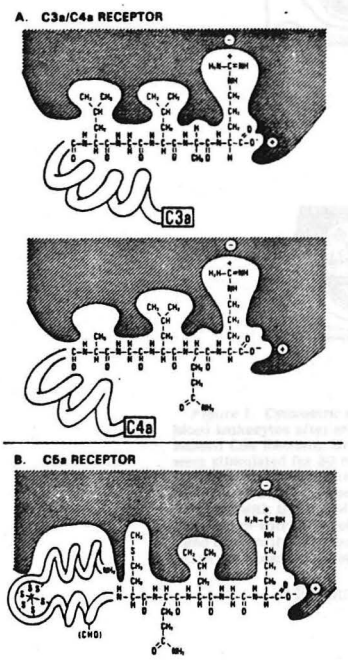


Fig. 4. A Features of the molecular interactions between the C3a "active site" and the C3a/C4a receptor are illustrated. Binding subsites are indicated for the leucyl side chains at positions 73 and 75, and for the charged guanidino- and carboxy-groups of arginine 77. Similar interactions are proposed for human C4a except that substitution of alanine at position 73 and glutamine at position 75 causes the proteins to bind less effectively to the receptor. **B** The molecular interactions between C5a and C5a receptor are more complex than those proposed for C3a. Binding subsites for the methionyl side chain at position 70, the leucine at position 72, and the guanidino and carboxy groups of arginine 74 are believed quite similar to those in the C3a receptor. However, a separate and essential interaction with a site somewhere in the N-terminal portion of C5a molecule is presumed to also occur based on the experimental results

Figure 12

Table 9

(From reference 27)

CR1 expression and affinity for dimeric, soluble ligand on various human cells

Cell type	Number of CR1/cell	Ka (M^{-1}) for C3b dimer	Comments
Erythrocyte	500	6.5×10^7	Normal range from 200–1 000 receptors/cell
PMN	5000	2×10^7	Cells isolated at 4 °C
PMN	30000	4×10^7	Cells isolated at 23 °C. 4 °C cells warmed to 37 °C or treated with chemoattractants
Monocytes	30000	4×10^7	Expression regulated by chemoattractants
B Lymphocytes	20000	6×10^7	No apparent regulation of receptor expression

Figure 13

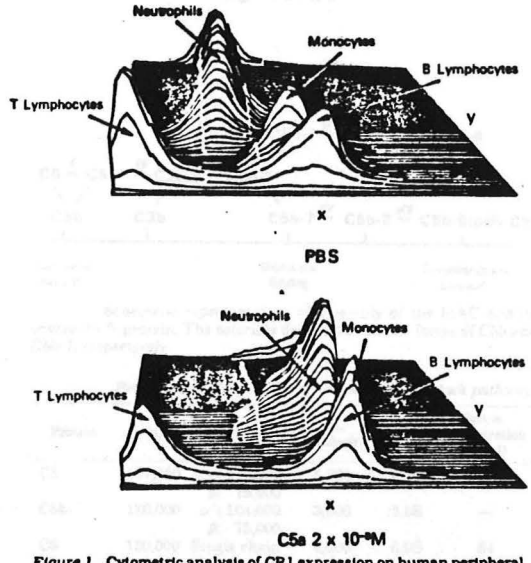


Figure 1. Cytometric analysis of CR1 expression on human peripheral blood leukocytes after stimulation with PBS control (top) or 2×10^{-9} M human C5a (bottom). Unprocessed leukocytes in citrated venous blood were stimulated for 30 min at 37°C, were placed on ice, and were then stained with unconjugated 3D9 followed by FITC-goat $F(ab')_2$ anti-mouse IgG. The x axis in these figures represents CR1 expression with data collected with the use of logarithmic amplification; the y axis presents side scatter with data collected by using linear amplification. The right-hand shift in the distribution of monocytes and neutrophils after stimulation with human C5a signifies increased CR1 expression on these cells.

(From reference 37)

Table 10

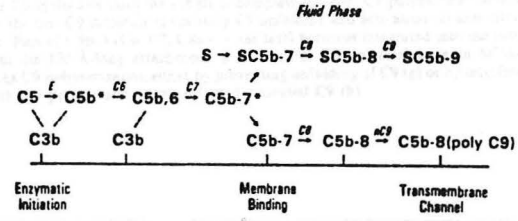
(From reference 37)

CR3 expression on human peripheral blood monocytes stimulated with human C5a, FMLP, or PBS control (N = 2)

Stimulant	MCF	Mean % Increase Above Control[a]
PBS control	28.65 ± 1.75	—
C5a 2×10^{-8} M	63.25 ± 6.55	123 ± 36
C5a 5×10^{-9} M	57.00 ± 6.20	101 ± 34
C5a 2×10^{-9} M	50.85 ± 0.35	78 ± 10
FMLP 2×10^{-8} M	58.50 ± 0.50	105 ± 14
FMLP 2×10^{-9} M	49.15 ± 5.45	71 ± 9
FMLP 2×10^{-9} M	43.45 ± 5.85	54 ± 30

[a] The mean percent increase above control was calculated for each experiment as follows: [(MCF of monocytes treated with test reagent/MCF of monocytes treated with PBS) − 1] × 100. The results of replicate experiments were then averaged to determine the mean percent increase in CR3 expression at various concentrations of test reagents.

Figure 14



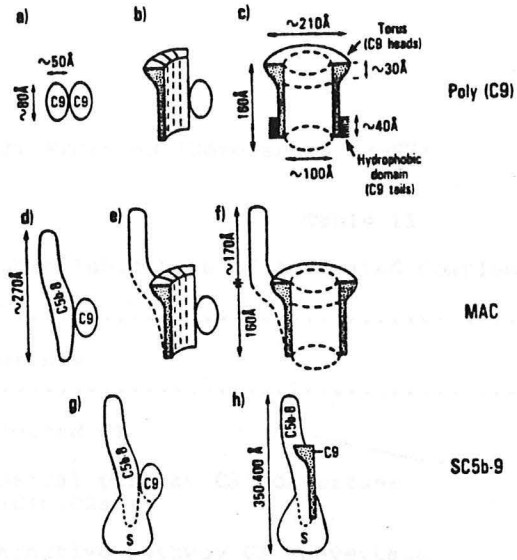
Schematic representation of assembly of the MAC and its control by S-protein. The *asterisks* denote metastable forms of C5b and C5b-7, respectively.

Properties of the proteins of the membrane attack pathway

Protein	M_r	Subunits	M_r Carbohydrate	S-rate	Serum concentration (μg/ml)
C5	191,000	α: 115,000 β: 75,000	5,200	8.7S	70
C5b	180,000	α': 104,000 β: 75,000	3,000	7.5S	—
C6	120,000	Single chain	4,000	6.0S	64
C7	110,000	Single chain	6,000	5.6S	56
C8	151,000	α: 64,000 β: 64,000 γ: 22,000	N.A.[a]	8.0S	55
C9	71,000	Single chain	5,500	4.7S	59
S-protein	83,000	Single chain	N.A.	4.0S	505

[a] N.A.: Information not available.

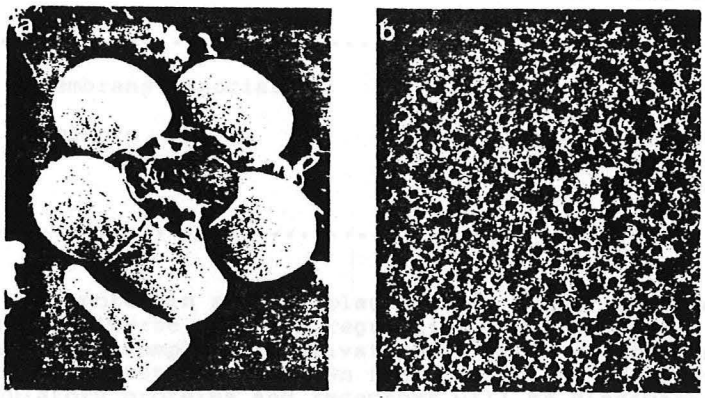
(From reference 48)



Schematic models of poly C9, MAC and SC5b–9. a–c: Hypothetical model for C9 polymerization. Monomeric C9 (a) interacts with another C9 molecule causing restricted unfolding to activated C9 (b) which interacts with further C9 molecules until the tubule is complete (c). d–f: C9 polymerization in the MAC. C5b–8 interacts with the first C9 molecule (d) causing C9 unfolding and activation (e) and tubular C9 polymerization as in a–c. Part of C5b–8 (C6, C7, C8α–γ—see text) becomes integrated into the tubule whereas C5b and C8β form the 170-Å-long attachment. g–h: Lack of C9 polymerization in SC5b–9. Binding of S-protein(s) blocks C9 polymerization either by preventing unfolding of C9 (g) or by interfering with the polymerization of unfolded activated C9 (h).

Figure 15

From Ref #49



Role of complement in removal of target blood cells. **a** Adherence of a human erythrocyte bearing C3 fragment to a complement receptor-bearing mononuclear cell. **b** Holes in an erythrocyte membrane resulting from complement-mediated damage

Figure 16

From ref #71

Regulatory Proteins (References 52-57)

Table 11

Known Inhibitors of Activated Complement Components

Reactants	Inhibitors
Activated C1	C1-INH
Classical pathway C3 convertase (C4b,C2a)	C4b-bp, DAF, CR1
Alternative pathway C3 convertase (C3b,Bb)	H, DAF, CR1
C3b	H, I, CR1
Membrane Attack Complex (C5b-9)	C8-bp
C3a	Carboxypeptidase N
C5a	Carboxypeptidase N C5a Inhibitor
Membrane associated	DAF, CR1, C8-bp
Soluble	C1-INH, C4-bp, H, I Carboxypeptidase N, C5a Inhibitor

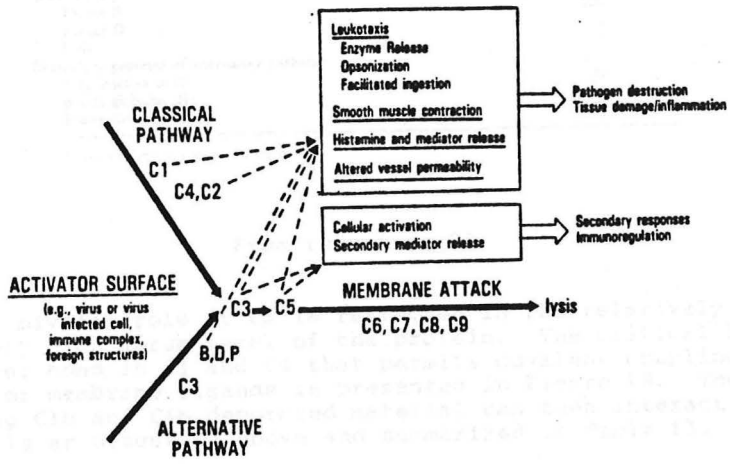
As noted in several places above these regulatory proteins work in diverse roles in regulating fliud phase and membrane associated complement activation. Recent studies and the precedents set by the known factors predict that several more regulatory proteins and receptors will be discovered in the near future. In turn we are likely to discover the causes of disparate clinical syndromes. Deficiencies in these proteins, discussed below, result in or contribute susceptibility to infections, autoimmune diseases, hemolytic anemia (PNH), chronic urticaria,

anaphylaxis, angioedema, and Familial Mediterranean Fever.

Biological Activities of Complement (References 58 - 71)

The principal physiologic activities of complement are well known. Viruses are neutralized by application of a coat of protein consisting of antibody and complement components, by aggregation, by lysis, by inducing an inflammatory reaction, by activating infiltrating cells, by facilitating the binding of effector cells to organisms and infected cells, and by lysing virus infected cells (58). The diversity of the roles of complement is illustrated in the results with different classes of viruses presented below. Similar mechanisms are mobilized to deal with various bacterial organisms with the addition of C3 facilitated immune adherence and phagocytosis. These concepts are illustrated in the next illustrations.

Figure 17



From reference 58

Table 12

Components of the Human Complement System

COMPONENT	SERUM CONCENTRATIONS*
Classical pathway components	
C1q	70
C1r	34
C1s	31
C2	25
C3	1600
C4	600
C5	85
C6	75
C7	55
C8	55
C9	60
Regulatory proteins of classical pathway	
C1 inhibitor	180
C4 binding protein	—
C3b inactivator (I)	34
β-1-H globulin (H)	500
S protein	7300
Alternative pathway components	
Factor B	200
Factor D	1
C3b	0
Regulatory proteins of alternative pathway	
C3b inactivator (I)	34
β-1-H globulin (H)	500
Properdin	25

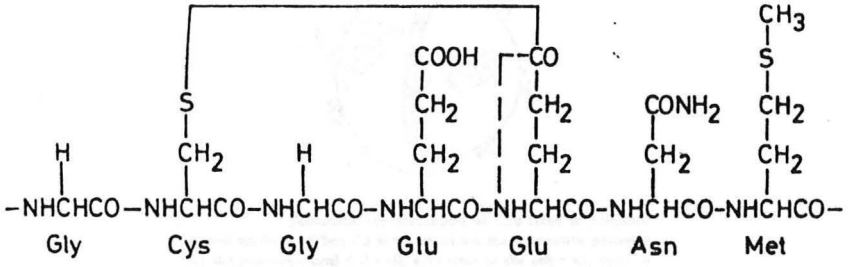
*Concentration is given in μg per ml.

From reference 72

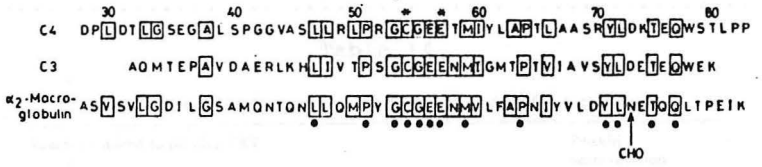
The pivotal role of C3 is reflected in the relatively and absolutely high serum level of the protein. The critical labile thiolester bond in C3 and C4 that permits covalent coupling to soluble or membrane ligands is presented in Figure 18. The resulting C3b and C4b decorated material can then interact with many cells as discussed above and summarized in Table 13.

The specific impact of complement activation is as diverse as the agents that provoke the process. Figure 19 illustrates, while the Pneumococcus activates complement via the alternative pathway, the C3b binding occurs at the cell wall, below the capsule and functionally buried. Antibody to the capsule leads to the deposition of C3b at a functionally useful site. Tables 14-16 demonstrate the varying roles of complement in responses to viruses and virus infected cells.

Figure 18



The postulated thiolester structure of C3 and α_2M. In C4, the sequence is identical except that asparagine is replaced by threonine. The dashed line shows the probable formation of an N-terminal pyrollidone carboxylic acid residue with the breaking of the Glu-Glu peptide bond on denaturation of the native protein.



The amion acid sequences around the postulated thiolester bond in C4, C3 and α_2M. Boxed residues are homologous and spots show identity. Asterisks denote the cysteine and glutamic residues forming the intrachain thiolester bond.

From reference 101

Table 13

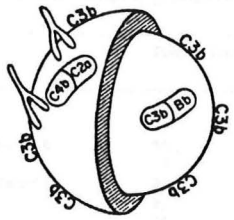
Complement Receptors on Cells

CELL TYPE	COMPLEMENT RECEPTOR*
Neutrophil	C1q, C3b, C3d, C4b, C3a, Ba
Basophil	C3a, C5a
Eosinophil	C3b, C3d, C4b
Macrophage	C3a, C3b, C4b, C5a, Bb
Mast cell	C3a, C5a
Platelets	C3a, C3b
Smooth muscle	C3a, C5a
Lymphocyte	C1q, C3b, C3d, C5b

*Complement receptors identified in vitro on human or animal leukocytes, or both.

From reference 72

Figure 19



Schematic representation of C3b fixed to pneumococcal surfaces. When C3 is activated via the alternative pathway by the pneumococcal cell wall, C3b fixes to the cell wall, deep to the capsule. In contrast, when C3 is activated via the classical pathway by anticapsular antibody, C3b fixes to the capsule.

From reference 63

Table 14

Neutralization of EBV by cross-reacting IgG antibody and purified C components

Reactants added to purified EBV	Percent neutralization
Cross-reacting IgG antibody	−2
Serum containing cross-reacting IgG antibody	85
Purified C1, C4, C2, C3	4
Cross-reacting IgG antibody + purified C1, C4, C2	2
Cross-reacting IgG antibody + purified C1, C4, C2, C3	69

From reference 58

Table 15

Complement requirements for neutralization of polyoma virus

Reagents added to polyoma virus-antibody	Percent neutralization
None	0
Human serum	80
Human C1q	60
Human C1	0
Human C1, C4	0
Human C1, C4, C2	0
Human C1, C4, C2, C3	84

From reference 58

Table 16

Requirements for the alternative complement pathway for the lysis of measles virus infected human cells[a]

Treatment of human serum containing specific antibody	Percent lysis
None	95
Factor B depleted	5
Factor B depleted + purified factor B	95
Factor D depleted	7
Factor D depleted + purified factor D	95
C4 depleted	95
C2 deficient	95

From reference 58

.....

Complement Factor Deficiencies (references 72-98)

As presented below, deficiencies in specific C' factors or regulatory proteins can be compatible with apparent good health, but characteristic syndromes are recognized. Not surprisingly, patients with homozygous C3 deficiency have frequent, severe infections, since this protein is pivotal for classical or alternative pathway activation of most effector systems. Patients with early classical pathway deficiencies may have recurrent infections, but most do not. Patients with MAC defects are unusually prone to Nisserial infections.

Surprisingly, these patients are remarkably prone to illnesses thought to be the result of autoimmune inflammation, particularly SLE. Recent studies indicate that marked reduction in C' as a result of consumption, as in hereditary angioedema, also is a risk factor for autoimmune disease. The specific illnesses acquired appear to be dictated by other factors such as disease associated HLA genes.

This paradox, increased complement mediated disease in early classical pathway complement deficient patients, may be the result of faulty clearance of immune complexes, infection with low virulence organisms that induce immune complexes, or faulty immunoregulation.

While C' deficiencies are rare in the general population, the prevalence of such defects is significant in specific patient groups. Approximately 6% of patients with SLE have genetic C' deficiencies. Some 10% to 25% of adults with sporadic meningococcal disease have a C' deficiency. Patients with late

component deficiencies have a 40% chance of acquiring disseminated N. meningitidis or N. gonorrhoeae infections. Relapses occur 10 times more frequently in these patients and recurrences are seen in 45%.

Clearly physicians must be aware of the association of C' deficiencies with these syndromes.

Table 17

Complement components and deficiency states

Component	Synonym	Activation/ Breakdown Product(s)	Known Deficiency Syndrome
C1q	—	—	yes
C1r	—	—	yes
C1s	C1 esterase	—	yes (with C1r)
C4	β1E	C4a, C4b	yes
C2	—	C2a, C2b	yes
B	C3 Proactivator C3 PA; GBG; Glycine-rich β glycoprotein	Ba, Bb	no
D	C3 proactivator convertase	—	no
P	properdin	—	yes
C3	β1C	C3a, C3b (β1A), C3c, C3d, C3e	yes
C5	β1F	C5a, C5b	yes
C6	—	—	yes
C7	—	—	yes
C8	—	—	yes
C9	—	—	yes
C4 binding protein	C4bp	—	no
Protein S	Fraction V protein	—	no
C1 esterase inhibitor	C1 Inh	—	yes
H	β1H	—	yes
I	C3b Inactivator; KAF	—	yes

From reference 76

Table 18

INCIDENCE OF COMPLEMENT DEFICIENCY IN NORMAL POPULATIONS

source	population	number studied	complement deficiency encountered	nature of deficiency
Hassig *et al.* (1964)	Swiss army recruits	40000	14	largely low C4 + C2 (no genetic data)
Torisu *et al.* (1970)	Japanese mass medical examination	42000	3	C4 low (sera inactivate C4) no genetic data
F. Stratton (personal communication)	Manchester blood transfusion panel	15000	1	C2-deficient (no family data)
Lachmann *et al.* (1978)	Cambridge hospital outpatients	2000	1	C6 + C7 deficient (inherited)
			1	low C1, C4, C2, C1 inhib and C3, hereditary angio-oedema with systemic lupus erythematosus
			2	low C1, C4, C2, C1 inhib I/C + +. Caldwell's syndrome

From reference 73

Table 19

Disease associations in genetic complement deficiency states[1]

Deficiency State	Immunologic Disease			Bacterial Infection				Mycobacterial or Intracellular Bacteria	Viral	Normal	Total # of homozygotes
	Alone	+ Neisserial Infection	+ Other Infection	Neisserial	Streptococcal or *H. influenzae*	GNR[2]	S. aureus				
C1, C2, C4	72 (64)	1 (.9)	21 (19)	3 (2.7)	11 (9.8)	5 (4.5)	3 (2.7)	6 (5.4)	2 (1.8)	18 (16)	112
Properdin	0	0	0	1 (25)	0	0	0	0	0	1 (25)	4
C3, I, H	9 (41)	1 (4.5)	5 (22.7)	5 (22.7)	8 (36.4)	2 (9)	0	0	0	1 (4.5)	22
C5, C6, C7, C8, C9	11 (11)	0	2 (2)	52 (50)	1 (1)	1 (1)	0	3 (2.9)	0	24 (23)	104

[1] Numbers in parenthesis represents % of total number of homozygotes.
[2] GNR—gram negative rods.

From reference 76

Table 20

Comparisons of disease frequencies (%) in propositus (P) and non-propositus (NP) homozygous complement-deficient individuals

		N[1]	Menin-gitis	Bacter-emia	Pneu-monia	SLE[2]	DLE[3]	Vasculitis	Glomerulo-nephritis
C1	P	14	21	7	7	71	14	0	14
	NP	8	13	0	13	25	0	25	25
C4	P	9	0	11	0	78	0	0	11
	NP	4	25	25	0	25	0	0	25
C2	P	56	13	16	16	38	13	7	21
	NP	21	10	0	5	0	5	0	14
C3	P	9	33	22	44	11	0	11	11
	NP	5	20	0	0	20	0	40	40
I	P	5	60	20	40	0	0	0	0
	NP	1	0	0	100	0	0	0	0
P	P	2	50	0	50	0	0	0	0
	NP	2	50	0	0	0	0	0	0
H	P	1	0	0	0	0	0	0	0
	NP	1	0	0	0	0	0	0	0
C5	P	7	71	29	0	14	0	0	14
	NP	6	50	33	0	0	0	0	0
C6	P	24	63	29	8	4	4	0	4
	NP	9	11	0	0	0	0	0	0
C7	P	16	50	19	0	6	0	0	0
	NP	6	17	0	0	0	0	0	0
C8	P	22	50	18	0	9	0	0	5
	NP	9	0	0	0	0	0	0	0
C9	P	5	20	0	0	0	0	0	0
	NP	0	—	—	—	—	—	—	—

[1] number of individuals.
[2] systemic lupus erythematosus.
[3] discoid lupus erythematosus.

From reference 76

Table 21

Comparison of the frequency of *Neisseria sp.*, *S. pneumoniae* and *H. influenzae* infection and age at first infection in complement deficiency states

Deficiency	C1, C4, C2	C3, I, H	P	C5-9	Total
No. of homozygotes	112	22	4	104	242
Neisseria sp.					
No. of patients (%)	3 (3)	5 (23)	1 (25)	52 (50)	61 (25)
Median age at 1st episode (yrs)	21	11	15	17	17
S. pneumoniae					
No. of patients	12 (11)	8 (36)	0	1 (1)	21 (9)
Median age at 1st episode (yrs)	4	2	—	49	2.5
H. influenzae					
No. of patients	3 (3)	2 (9)	0	0	5 (2)
Median age at 1st episode (yrs)	6.5	18.5	—	—	6.5

From reference 76

Table 22

Clinical Manifestations of Hereditary Deficiencies of the Complement System

COMPLEMENT COMPONENT DEFICIENCY	CLINICAL MANIFESTATION
C1q	SLE, infections, glomerulonephritis, normal*
C1r	SLE, infections, renal failure, normal
C1s	SLE, normal
C4	SLE, glomerulonephritis, Schönlein-Henoch purpura, normal
C2	SLE, DLE, glomerulonephritis, vasculitis, dermatomyositis, common variable immunodeficiency, Hodgkin's disease, inflammatory blood disease, atrophoderma, cold urticaria, infections, normal
C3	Infections, SLE
C5	*Neisseria* infections, SLE, normal
C6	*Neisseria* infections, SLE, normal
C7	*Neisseria* infections, SLE, ankylosing spondylitis, Raynaud's disease, normal
C8	*Neisseria* infections, SLE, normal
C9	Normal
Properdin	*Neisseria* infections
Regulatory Proteins	
C1inh	Hereditary angioedema, SLE, DLE
C3bina	Infections, aquagenic urticaria
Carboxypeptidase	Angioedema

*normal = a person with no clinical manifestations of a disease

From reference 72

Table 23

REPORTED CASES OF COMPLEMENT DEFICIENCIES AND ASSOCIATED DISEASES

Component	Number with homozygous deficiency	Associated diseases	
		IC disease	Infections
Classical pathway:			
C1q	15	14	Many pyogenic
C1r or C1s	8	6	
C4	16	14	
C2*	66	38	
C1 inhibitor	>500	2%	
C3 and alternative pathway:			
C3	11	8	10 pyogenic (+*Neisseria*)
B/D	..	..	..
Properdin	3†	..	2 (+3 died of fulminant infections); *Neisseria*
C3b inact (I)	5	1	4 pyogenic
βIH (H)	2‡	1 (HUS)	
Membrane attached complex:			
C5	12	1	9 *Neisseria*
C6	17	2	10
C7	14	1	6
C8	14	2	8
C9	Many	..§	

From reference 91

Table 24

Immunoregulatory diseases in HAE

Patient No.	Phenotype	Autoimmune disease	Relevant HLA type	Serology	Race	Sex	Autoimmune disease age onset (yr)
6	I	SLE	DR2,DR3	Pos ANA, extractable nuclear antibodies, SS-B	W	F	29
7	I	Drug-induced lupus	DR4	Pos ANA, syphilis screen	W	F	62
8	I	Thyroiditis	DR3	(1:6400) Antithyroid microsomal antibodies	W	F	31
9	I	Thyroiditis	—	(1:6400) Antithyroid microsomal antibodies	B	F	43
10	I	Primary Sjögren's syndrome	B8 DR3,DR4	Neg	W	F	67
11	I	Secondary Sjögren's syndrome, rheumatoid arthritis	DR2,DR4	Rheumatoid factor, 1600 IU	W	F	19
12	I	Secondary Sjögren's syndrome	DR4	—	W	F	51
13	I	Sicca syndrome	B8 DR2,DR3	Neg	W	M	25
14	I	Juvenile rheumatoid arthritis, IgA deficiency	—	—	W	M	22
15	II	Incipient pernicious anemia	DR2	Antiparietal cell antibodies	W	F	37
16	I	Ulcerative colitis	—	—	W	M	36
17	I	Crohn's disease	— (DR4)	—	W	M	23
18	II	Crohn's disease	— (DR4)	—	W	M	32
10	I	Partial lipodystrophy	—	Normal C3	W	M	—
20	II	Raynaud's disease	—	—	W	F	36
21	I	Raynaud's disease	—	—	W	F	51
22	I	Alopecia universalis	—	—	W	M	5

— = No information; pos = positive; neg = negative; W = white; B = black.

From reference 85

Table 25

Hereditary Angioedema

Clinicopathologic features of patients with renal involvement

	Patient No.				
	1	2	3	4	5
Sex	F	F	F	M	F
HAE phenotype	I	I	I	I	I
At renal biopsy					
Age (yr)	18	47	44	32	10
Duration HAE symptoms (yr)	17	37	40	22	0
Creatinine (mg/dl)	0.8	1.3	1.2	1.2	0.9
Clearance (ml/min)	103	76	70	95	116
Proteinuria (gm/day)	0.2	2.6	0	0.2	10.9
Urinalysis					
Hemoglobin	3+	2+	2+	0	Trace
RBC	10	5 to 10	5 to 10	0 to 3	3 to 6
Cellular casts	RBC/WBC	RBC/WBC	RBC/WBC	RBC/WBC	Not known*
Biopsy					
Date	11/77	2/79	3/79	3/81	5/76
Class	MPGN	MES	MES	MES	MPGN
Follow-up:					
Date	10/82	7/83	6/79	6/83	2/84
Duration (months)	72	53	3	26	93
Creatinine (mg/dl)	1.1	1.0	1.1	1.5	†
Sediment					
Protein	1+	0	0	Trace	*
Hemoglobin	1+	Trace	1+	0	
RBC	5 to 10	5 to 10	1 to 5	0	
Casts	Hyaline, granular	Hyaline, granular	Hyaline	Hyaline, granular	
Significant lab results					
HLA/DR phenotype	DR6	DR3,DR4	Not known	DR6	B8,DR3,DR6
Immune complexes	Pos	Pos	Neg	Pos	Pos
ANA	Neg	Neg‡	Neg	Neg	Neg

Pos = positive; Neg = negative.
*Performed at St. Louis Children's Hospital of Washington University.
†Patient on hemodialysis.
‡Titers range from negative to 1:40 with negative anti-DNA, SS-A and SS-B, and extractable nuclear antigen antibodies.

From reference 85

Table 26

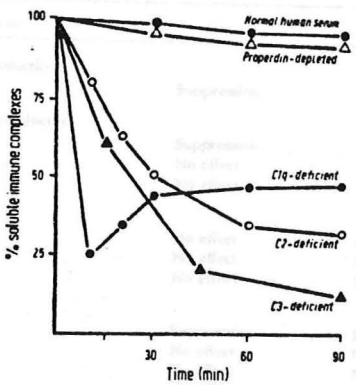
HLA type in patients with HAE HLA/DR–associated immunoregulatory diseases

HLA-associated disease	Patient's relevant HLA
Apresoline-induced SLE	HLA-DR4
Idiopathic SLE	HLA-DR2, DR3
Thyroiditis	HLA-B8, DR3
Primary Sjögren's syndrome	HLA-DR3, DR4
Secondary Sjögren's syndrome, rheumatoid arthritis	HLA-DR4
Secondary Sjögren's syndrome	HLA-DR4
Sicca syndrome*	HLA-DR2, DR3
Pernicious anemia, incipient	HLA-DR2

All eight patients with HAE who developed an autoimmune disease with a known HLA/DR association developed the disease associated with their HLA/DR haplotype ($p = 0.014$). One additional patient has sicca symptoms and chronic conjunctivitis but normal rose bengal and slit lamp examinations, normal Schirmer's test, and no objective findings of xerostomia except for an abnormal parotid scan. Her DR phenotype included DR3.
*Sicca symptoms: keratoconjunctivitis, positive Schirmer's and parotid scan, nondiagnostic minor salivary gland biopsy specimen.

From reference 85

Figure 20

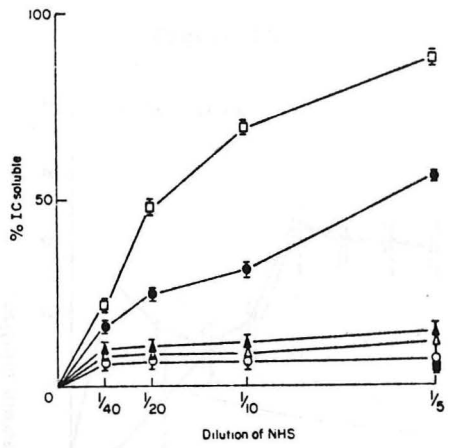


Immune precipitation in complement-deficient and complement-depleted serum samples.

Immune precipitation is blocked in normal and properdin-depleted serum. Slow aggregation takes place in C2-deficient and C3-deficient serum, going to completion in the absence of C3, whereas some complexes remain soluble in the C2-deficient serum. The fast initial precipitation in C1q-deficient serum is identical to the control precipitation done in the absence of any complement function. However, it is followed by partial solubilisation of the precipitate

From reference 91

Figure 21



Dose-response curves for the inhibition of immune precipitation by normal serum (□——□) and reaction mixtures containing C3, B, P and D̄ (○——○), C3, B, P, D̄ and H (△——△), C3, B, P, D̄ and I (▲——▲) and C3, B, P, D̄, H and I (●——●). The concentration of the alternative pathway components were adjusted so that they were the same as those which were present in the serum dilutions. A 1:5 dilution of serum contained 300 μg C3, 50 μg B, 6 μg P, 50 μg H and 10 μg I. D̄ was added to the highest concentration at 100 u ml. Each point represents the mean (± s.e.) of three determinations.

From reference 90

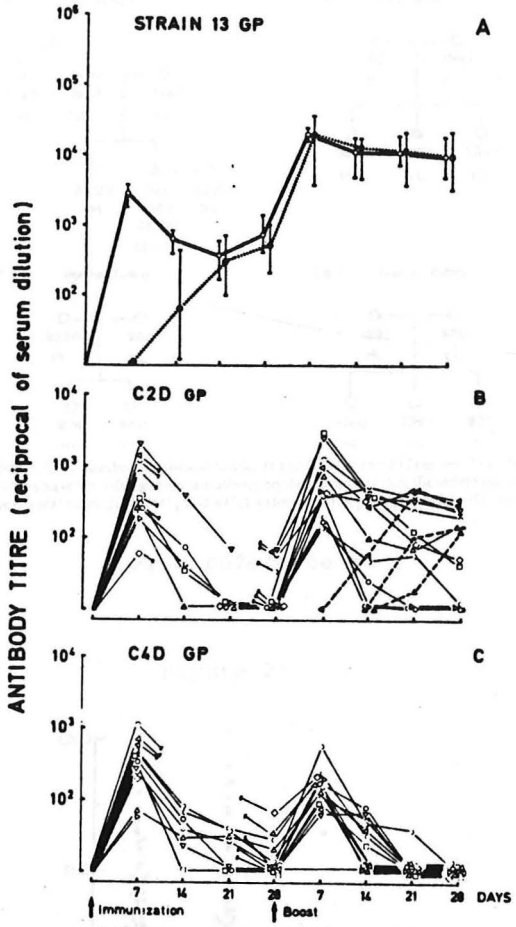
Table 27

Summary of immunoregulatory effects

Immune response	C3a	C5a
Specific antibody production		
SRBC	Suppression	Enhancement
Polyclonal antibody production		
Fc fragment	Suppression	Enhancement
PWM	No effect	No effect
LPS	No effect	No effect
B cell proliferation		
Fc fragment	No effect	No effect
LPS	No effect	No effect
PWM	No effect	No effect
T cell proliferation		
Tetanus toxoid	Suppression	Enhancement
Concanavalin A	No effect	No effect
PHA	No effect	No effect
PWM	No effect	No effect
Mixed lymphocyte reaction	No effect	Enhancement
T cell-mediated cytotoxicity	Suppression	Enhancement
Natural killer cell activity	No effect	No effect

From reference 67

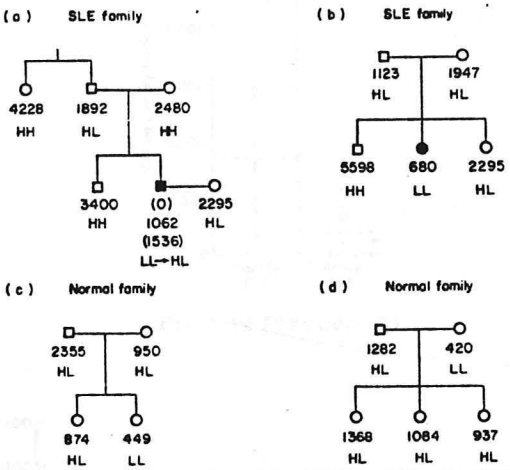
Figure 22



Antibody responses of strain 13 GP (*A*, n = 6), C2D-GP (*B*, n = 11), and C4D-GP (*C*, n = 12). Phage was injected at a dose of 1×10^9 PFU/kg body weight at days 0 and 28 as indicated by arrows. Antibody titers, expressed as reciprocal of that serum dilution that gives 50% neutralization in the neutralization assay, were determined at weekly intervals. For normal animals, median and range are given; for complement-deficient GP each animal is represented by a single symbol. For each serum sample, total phage-specific antibodies and phage-specific IgG antibodies were determined. Total antibody titers are given by open symbols and solid line; IgG titers are given by closed symbols and broken line (only detectable IgG titers are figured); note the log scale. In some complement-deficient GP, antibody determinations in primary phase were done only on days 7 and 28 in order to take care of the animals, inasmuch as the course of antibody titer was evident. This is indicated by an interrupted solid line (— —).

From reference 79

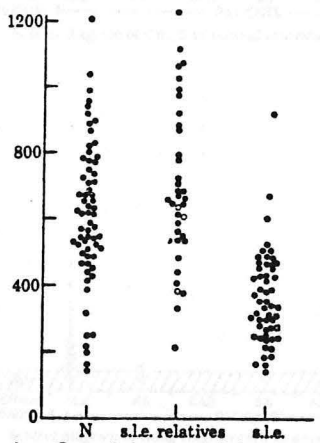
Figure 23



Family studies of CR1 numbers in normal (c and d) and SLE (a and b) families. The phenotypes shown below the CR1 numbers have been designated tentatively on the possibility that the inflections in the cumulative frequency curve for normal individuals (18% and 64%) distinguish the phenotypes LL, HL and HH (Wilson *et al.*, 1982).

From reference 81

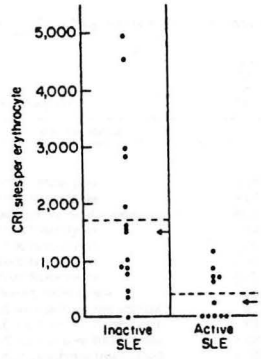
Figure 24



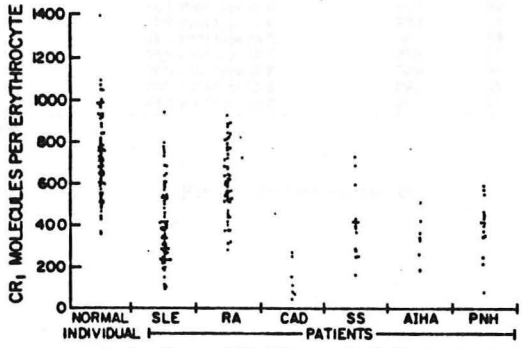
Erythrocyte CR1 numbers. Open circle, spouse of s.l.e. patient; open square, C2 deficient; partly shaded square, C2 heterozygote. From Walport *et al.* (1984).

From reference 73

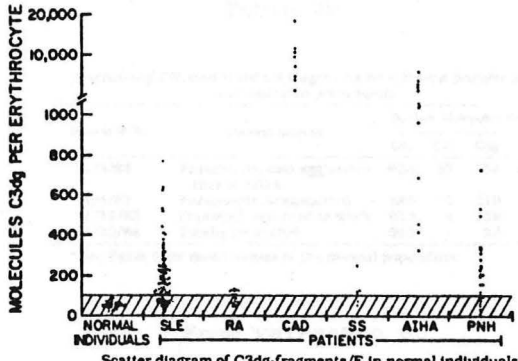
Figure 25



From reference 81



Scatter diagram of CR_1/E in normal individuals and patient groups.



Scatter diagram of C3dg-fragments/E in normal individuals and the same patient groups listed in Figure 2. Because E bore little, if any, C3c antigen, the amount of bound C3g antigen detected with ^{125}I-monoclonal anti-C3g represented the amount of fixed C3dg per E. E from normal individuals carried <100 C3dg/E (shaded area), with a mean of 50 ± 23 C3dg/E.

Figure 26

From ref. #83

Table 28

Analysis of CR_1 and fixed C3 fragments on E from patients with AIHA and PNH

		Surface Molecules Per E			
		CR_1	C3c	C3d	C3g
Mean Value for Normal Subjects		707	21	52	48
	disease status				
AIHA Patients					
BH	active hemolysis	328	75	6145	5691
DA 11/14/83	active hemolysis	413	96	4112	3357
1/25/84	post-splenectomy; remission	894	38	645	324
MC	active hemolysis	182	n.d.[a]	487	413
EB	active hemolysis	278	8	964	572
LW 2/16/84	active hemolysis	591	50	1780	260
2/20/84	active hemolysis	417	105	2318	1187
2/27/84	reduced hemolysis	416	111	1232	171
JA 1/3/85	SLE and active hemolysis	51	n.d.	2488	510
1/10/85	SLE and active hemolysis	64	n.d.	2440	599
1/31/85	SLE and active hemolysis	122	n.d.	1859	974
3/14/85	SLE, hemolysis improving	175	n.d.	1136	423
PNH Patients					
MK	23% PNH type II E	273	20	303	91
DL	36% PNH type II E	401	35	207	160
BS	98% PNH type II E	70	5	718	104
FK	20% PNH type III E	407	56	371	358
FZ	28% PNH type III E	150	26	281	154
MB	35% PNH type III E	283	9	145	49
AV	39% PNH type III E	287	45	614	566
SM	55% PNH type III E	265	21	231	201
FY	56% PNH type III E	325	81	478	404
KG	90% PNH type III E	621	29	107	56
FN	95% PNH type III E	651	18	102	113

[a] n.d. = Not done.

From reference 83

Table 29

Analysis of CR_1 and fixed C3 fragments on E from a patient with mycoplasma pneumonia

Patient W.R.	Disease Activity	Surface Molecules Per E[a]			
		CR_1	C3c	C3g	C3d
11/3/83	Pneumonia; cold agglutinin titer of 1024	634	82	254	312
11/4/83	Pneumonia, hospitalized	585	90	310	357
11/29/83	Improved, returned to work	653	4	139	192
4/30/84	Totally recovered	982	1	23	72

[a] See Table II for mean values of the normal population.

From reference 83

Table 30

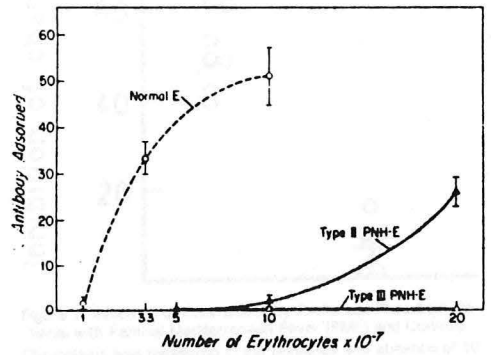
Complement Profile in Angioedema

	C1inh FUNCTION	C1inh LEVEL	C_4	C1
Classical HAE	↓	↓	↓ or nl	nl
Variant HAE	↓	nl	↓ or nl	nl
Acquired deficiency of C1inh	↓	↓	↓	↓
Idiopathic angioedema	nl	nl	nl	nl

nl = normal

From reference 72

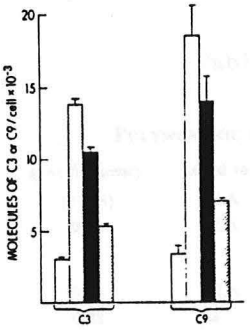
Figure 27



Capacity of intact normal E and PNH-E to adsorb neutralizing anti-DAF-IgG. After interaction with the dose of E indicated, the nonbound anti-DAF-IgG was quantitated by its capacity to neutralize 2 units of functional DAF activity; 100% of IgG added neutralized 95% of the DAF activity. Type II PNH-E were from patient K; type III PNH-E were from patient L.

From reference 92

Figure 28



Comparison of the binding of C3 and C9 to normal (□), PNH II (▨), PNH III (■), and AET-treated (⊡) erythrocytes after classical pathway activation of whole serum complement. The values depicted by the bars represent the mean±1 SD, $n = 3$.

From reference 93

Figure 29

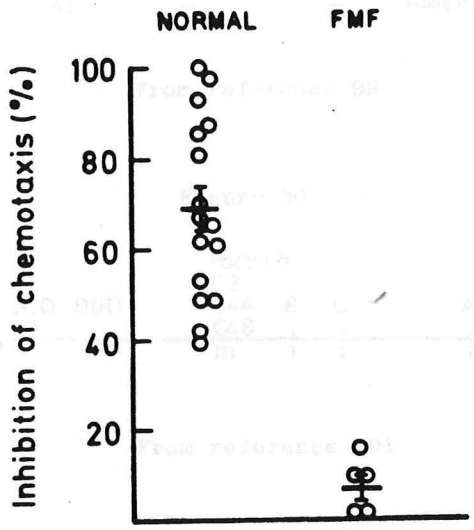


Figure 1. Inhibition of Chemotaxis by Peritoneal Fluid from Patients with Familial Mediterranean Fever (FMF) and Controls.

Chemotaxis was measured in the presence and absence of 10 per cent (vol/vol) of the fluid to be studied, with 1 per cent zymosan-activated serum as a chemoattractant. In the absence of fluid, random migration was 44.1±2.6 μm and chemotaxis 46.5±2.8 μm for controls; random migration was 35.1±3.8 μm and chemotaxis 53.3±6.0 μm for patients.

Each data point represents the mean of replicate determinations of chemotactic activity in each sample — i.e., 28 experiments with 16 specimens from controls, and 12 experiments with 5 specimens from patients. The bars indicate the means ±1 S.E. for each group.

From reference 97

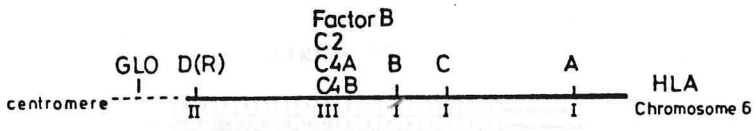
Table 31

POLYMORPHIC COMPLEMENT COMPONENTS

component	gene frequency	linked to	chromosome	reference
C4	(2 loci)	HLA	6	O'Neill *et al.* (1978)
C2	0.05	HLA	6	Hobart & Lachmann (1976) Alper *et al.* (1976) Meo *et al.* (1976)
Factor B	0.28	HLA	6	Allen (1974)
C3	0.22	Le	19	
C8 α-γ β	0.4	PGM1	1	Mevag *et al.* (1984) Alper *et al.* (1983)
C6	0.33	C7	?	Hobart *et al.* (1975)
C7	0.01	C6	?	Hobart *et al.* (1978)
C5	0.05 (Mel)	—	—	Hobart *et al.* (1981)
Factor D	0.05 (Neg)	—	—	Hobart & Lachmann (1976)
C4-binding protein	0.02	—	—	Rodrigues de Cordoba *et al.* (1983)
CR1	0.1	—	—	Wong *et al.* (1983)

From reference 99

Figure 30



From reference 101

Table 32

Effect of amino group modification of E_a on the uptake of C4A and C4B onto EAC1 cells[a]

C4 Isotype	C4 Deposited on Normal Cells (ng)	C4 Deposited on Ethylacetimidate-Treated Cells	Ratio of Deposition Ethylacetimidate: Normal
C4A (Ve)	202 (± 4)	100 (± 9)	0.50
C4B (Be)	609 (± 101)	666 (± 44)	1.09

[a] Values are mean ± SD of triplicate measurements. The number of cell per assay was 1.6×10^7.

From reference 106

Table 33

Comparison of the uptake of C4A and C4B onto various C1-bearing cells

Expt.	C1-Bearing Cell[a]	Sensitizing Antibody	C4 Isotype[b]	C4 Deposited (ng)	C4B:C4A Deposition Ratio
1[c]	E_H	Human anti-A	C4A (Bu)	58 ± 12	2.2
			C4B (Ca)	125 ± 6	
	U937	Rabbit IgG anti-β_2-microglobulin	C4A (Bu)	64 ± 5	2.0
			C4B (Ca)	131 ± 13	
	K562	Human IgM anti-I	C4A (Bu)	168 ± 19	1.5
			C4B (Ca)	245 ± 9	
	E_s	Rabbit IgM anti-Forssman	C4A (Bu)	125 ± 4	4.8
			C4B (Ca)	603 ± 16	
2[d]	E_H	Human anti-A	C4A (Ve)	323	1.7
			C4B (Be)	552	
	E_H	Human IgM anti-I	C4A (Ve)	275	2.4
			C4B (Ca)	654	
	E_H (group O)	Human IgG anti-P	C4A (Ve)	20	1.5
			C4B (Ca)	29	
	U937	Rabbit IgG anti-β_2-microglobulin	C4A (Ve)	990	1.6
			C4B (Be)	1548	
	K562	Human IgM anti-I	C4A (Ve)	805	1.8
			C4B (Be)	1463	
	E_s	Rabbit IgM anti-Forssman	C4A (Ve)	623	4.7
			C4B (Be)	2940	
	E_s	Rabbit IgG anti-E_s	C4A (Ve)	1544	4.9
			C4B (Ca)	7513	

[a] For E_H and E_s, the number of cells per assay was 1.6×10^7. For U937 and K562 cells, the number per assay was 3.4×10^6.

[b] The C4 phenotypes of the donors were as follows. Bu: A3,3.2 BQ0,Q0; Ve: A3,3 BQ0,Q0; Ca: AQ0,Q0 B1,1; Be: AQ0,Q0 B1,1.

[c] The values reported in experiment 1 represent the means and standard deviations of triplicate measurements done by using the oil phase separation technique (see *Materials and Methods*).

[d] The values reported in experiment 2 were obtained from cells bearing ^{125}I-C4 of each isotype before the preparation of membranes for SDS-PAGE analysis (see *Materials and Methods*). For E_H and E_s, the number of cells per assay was 2.5×10^8. For U937 and K562 cells, the number per assay was 1.0×10^7.

From reference 106

Figure 31

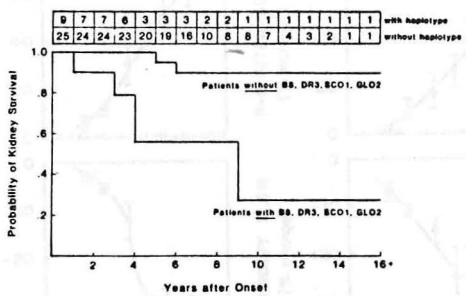


Figure 2. Life-Table Analysis of Kidney Survival (Serum Creatinine ≤2.0 mg per deciliter [177 μmol per liter] without Dialysis or Transplantation) in Patients with Membranoproliferative Glomerulonephritis.

Nine patients had the extended haplotype B8,DR3,SC01,GLO2, and 25 patients did not.

From reference 107

Table 34

Biological and Physicochemical Characterization of Anaphylatoxins

Approximate order	C3a ED_{50}	C5a ED_{50}
(1) Smooth muscle contraction GP Ileum	$6\text{-}9 \times 10^{-9}$ M	$4\text{-}6 \times 10^{-10}$ M
(2) Vascular Permeability in human skin	$10^{-10}\text{-}10^{-12}$ moles	$10^{-13}\text{-}10^{-14}$ moles
(3) Mast cell, histamine release rat mast cells	$10^{-15}\text{-}10^{-6}$ M	yes, not quantitated
(4) Induce PMN migration: Human Neutrophils	Inactive	$1\text{-}3 \times 10^{-9}$ M
	Physico-chemical characteristics	
Molecular weight	9000	11000
Amino acid residue	77	74
Carbohydrate	—	+
Ip	9.4-9.6	8.4-8.6
Alpha-helix	40-45%	40%
Heat stability	> 90 C	> 90 C
Acid stability (rm temp/1 hour)	pH 0-13	pH 0-13

From reference 140

Figure 32

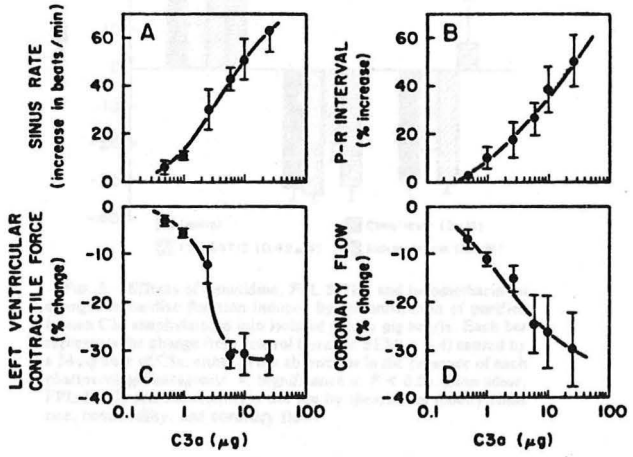


FIG. 1. Dose–response relationships for the effects of purified human C3a anaphylatoxin on sinus rate (*A*), atrioventricular conduction time (i.e., P–R interval) (*B*), left ventricular contractile force (*C*), and coronary flow rate (*D*) in isolated guinea pig hearts. Each point (mean, 4–6 hearts; ±SEM) represents the maximum change from control occurring within 4 min of the administration of each C3a dose. Control values (mean ± SEM) were as follows: sinus rate, 219 ± 5 beats/min; P–R interval, 65 ± 2 msec; contraction, 6.4 ± 0.3 g; coronary flow, 4.5 ± 0.2 ml/min (n = 30).

From reference 118

Table 34

Relative cardiac effects of C3a and C3a des-Arg

	C3a	C3a des-Arg
Sinus rate	+25 ± 3	+7 ± 5
P–R interval	+18.0 ± 5.1	+1.0 ± 1.0
Contractility	−24.1 ± 3.6	−3.1 ± 1.1
Coronary flow	−19.2 ± 4.3	−4.7 ± 1.0

Numbers indicate mean percentage changes in atrioventricular conduction time, left ventricular contractility, and coronary flow, or changes in beats/min for sinus rate (±SEM; $n = 4$), in isolated guinea pig hearts, after administration of a 6-μg dose of C3a or C3a des-Arg. C3a was incubated for 30 min at 37°C (pH 7.6) with carboxypeptidase B or saline, respectively. Each change caused by C3a was significantly different ($P < 0.03$) from the corresponding C3a des-Arg value.

From reference 118

Figure 35

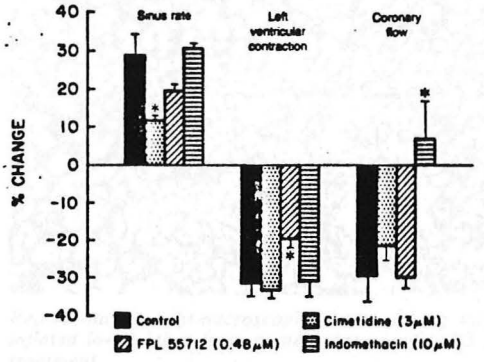
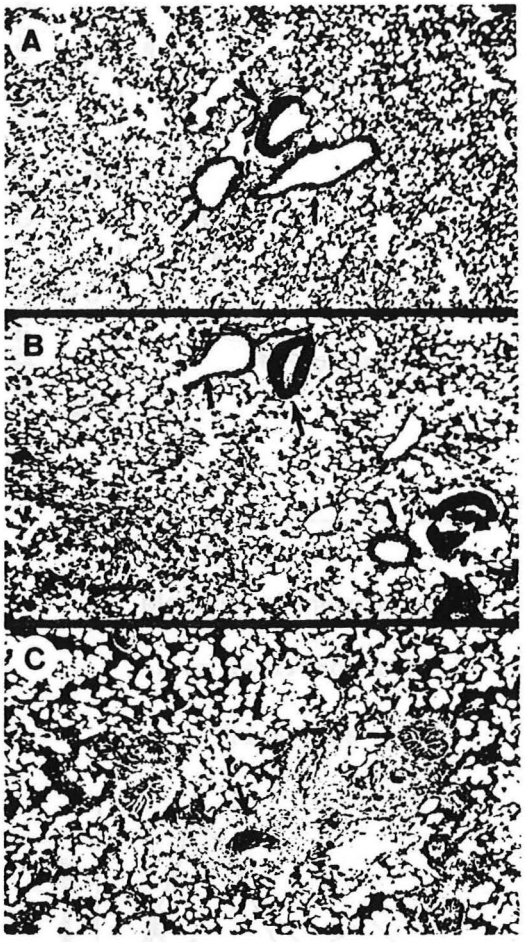


FIG. 5. Effects of cimetidine, FPL 55712, and indomethacin on changes in cardiac function induced by administration of purified human C3a anaphylatoxin into isolated guinea pig hearts. Each bar represents the change from control (mean ± SEM; $n = 4$) caused by a 24-μg dose of C3a, either in the absence or in the presence of each pharmacologic antagonist. *, Significance at $P < 0.05$. Cimetidine, FPL 55712, and indomethacin did not by themselves modify sinus rate, contractility, and coronary flow.

From reference 118

Figure 36

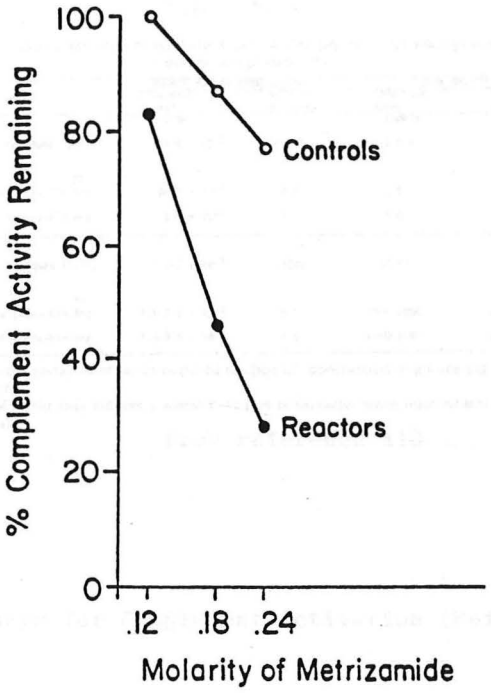


Representative light-microscopic views of lung thin sections of inflated lower lobes from guinea pigs sacrificed 5 minutes after treatment

The guinea pigs were infused via the carotid artery with (A) 40 mg of SCPN inhibitor, (B) cobra venom factor (CVF) alone, or (C) both SCPN inhibitor and CVF. Inflation fixation was performed with buffered formalin at 25 cm H_2O pressure for all sections. The alveolar wall thickness, alveolar space size, bronchiole (↟) and arteriole (↟) wall thickness in lungs of inhibitor-treated animals (Panel A) is indistinguishable from that observed in lung of untreated animals. The lungs of CVF-treated animals (Panel B) gave evidence of some irregularity in the alveolar matrix but otherwise appear unaffected. The tissue section in Panel C appears markedly abnormal with alveolar matrix, bronchioles and arterioles grossly distorted (H and E×60).

From reference 127

Figure 37



From reference 128

Figure 38

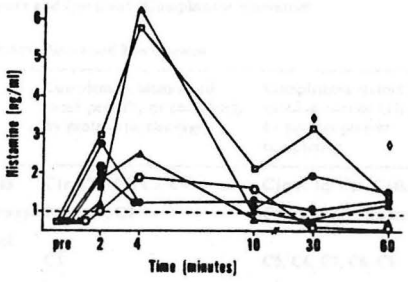


FIG. 1. Plasma histamine levels following infusion of RCM. Of 43 patients studied, 10 patients had elevated plasma histamine levels after RCM infusion. F. C., △. E. W., ○●◇◆▲●○□■. An additional 18 patients had elevated preinfusion histamine levels, and 15 patients had no detectable levels before or after RCM infusions.

From reference 131

Table 35

Inflammatory activities of synthetic C3a and C4a peptides and analogs compared to the natural anaphylatoxins

	Smooth muscle contraction[a]		Skin wheal[b]	
	Effective doses[a] (molar)	Relative activity	Effective doses (nmol)	Relative activity
Native human C3a residues (1-77)	$6-9 \times 10^{-9}$	(100)	0.1-0.2	(100)
70 77 Ala-Ser-His-Leu-Gly-Leu-Ala-Arg	$9-12 \times 10^{-7}$	0.7	5-6	3
Ala-Ala-Ala-Leu-Gly-Leu-Ala-Arg	$5-7 \times 10^{-7}$	1.3	5-6	3
Native human C4a residues (1-77)	$1-2 \times 10^{-7}$	(100)	10-20	(100)
70 77 Lys-Gly-Gln-Ala-Gly-Leu-Gln-Arg	$1.0-1.5 \times 10^{-3}$	0.1	2500-5000	0.3-0.6
Ala-Ala-Ala-Ala-Gly-Leu-Gln-Arg	$1.0-1.5 \times 10^{-4}$	1.0	2500-5000	0.3-0.6

[a]Minimum concentration of factor required to elicit full contraction of guinea-pig ileal strip in a 1.5 ml bath.

[b]Quantity of factor that induces a wheal 8-11 mm in diameter when injected intradermally in guinea-pig skin.

From reference 110

Modern Assays for Complement Activation (References 136-146)

Table 36

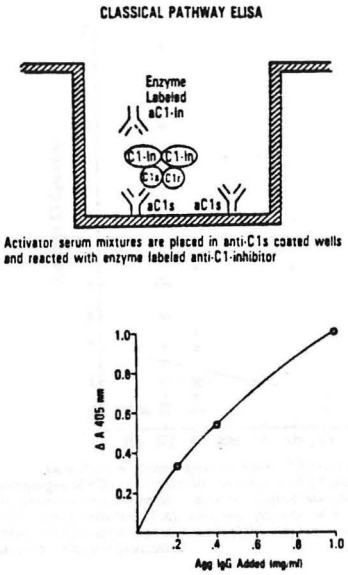
Methods to Detect and Quantitate Complement Activation

Complement Activation Mechanisms

	Complement factors activated partially or completely by proteolytic cleavage	Complement factors activated in part or completely by protein-protein complexing	Complement factors normally not requiring activation
Classical Pathway	C1r, C1s, C2, C3, C4	C1q (C1q, C1s, C1s), C2, C4	C1q
Alternative Pathway	Factor B, C3	Factor B, C3, properdin	Factor D
Membrane Attack Mechanism	C5	C5, C6, C7, C8, C9	C6, C7, C8, C9
Control factors	None	None	Factor H, Factor I, C4b binding protein, Carboxypeptidase N

From reference 136

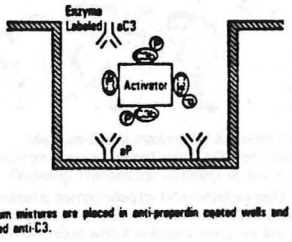
Figure 39



From reference 136

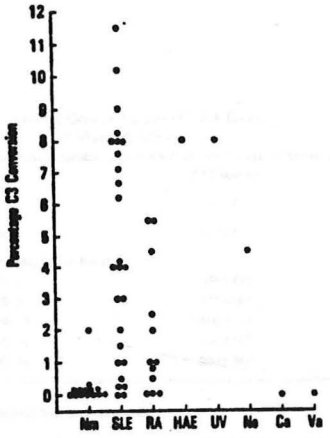
Figure 40

Alternative Pathway ELISA



From reference 136

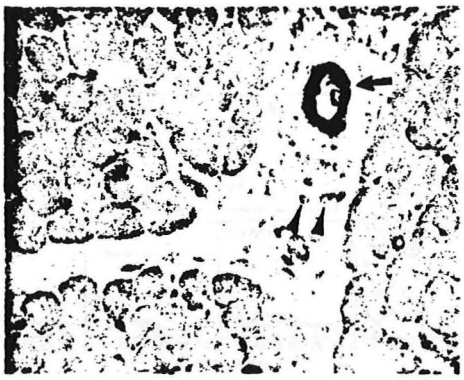
Figure 41



Detection of neoantigen by MoAb 130 in patients' plasma. The percentages of C3 conversion in the plasma of 14 normal individuals (*Nm*), 26 patients with systemic lupus erythematosus (*SLE*), 12 patients with rheumatoid arthritis (*RA*), and one patient each with hereditary angioedema (*HAE*), urticarial vasculitis (*UV*), nephritis (*Ne*), cancer (*Ca*), and vasculitis (*Va*) are presented.

From reference 143

Figure 42



Medium-Sized Perimysial Arteriole (Arrow) in a Biopsy Specimen from a Patient with Childhood Dermatomyositis, Showing Transmural Staining of the Vessel Wall.

This vessel is surrounded by inflammatory cells (arrowheads) that did not react with antibody to the membrane attack complex. Vessels that did react with the attack complex are seen in the endomysium at the left.

From reference 146

Table 37

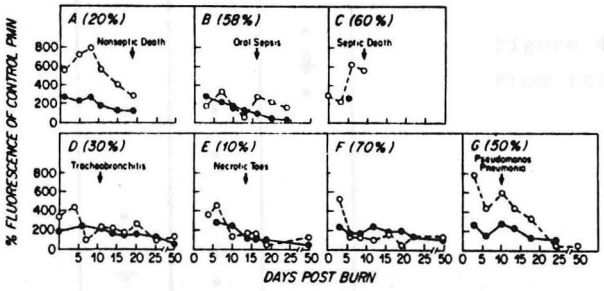
Plasma Concentration of C3A DesArg after Thermal Injury.

	C3A DESARG ng/ml*
Controls	100±5
Patients (days after burn)	
0–5	305±42†
6–8	546±69†
9–13	490±72†
14–19	409±54†
20–50	260±36†

*Mean ±SEM.
†P<0.005 for the difference from the control value.

From reference 144

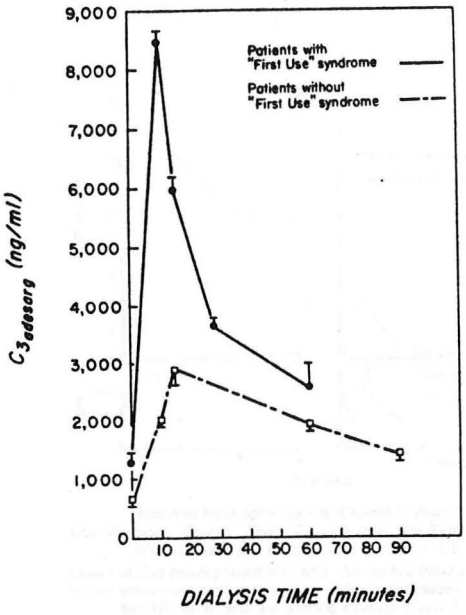
Figure 44



Time Course of Neutrophil (PMN) Expression of CR1 (Open Circles) and CR3 (Closed Circles) in Individual Patients with Burns, as Measured by Indirect Immunofluorescence.

Results are expressed as percentages of fluorescence obtained with neutrophils from normal subjects. Percentages in parentheses refer to the total body-surface area burned.

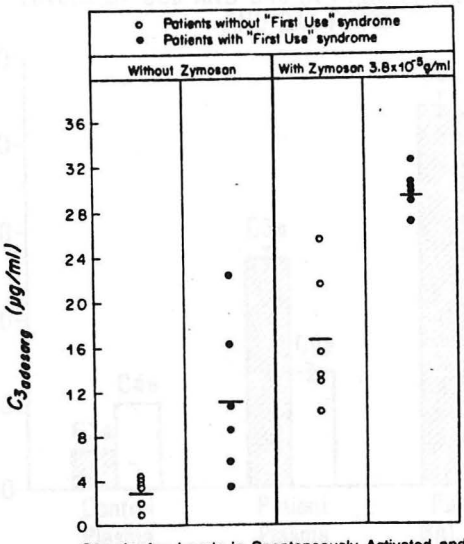
From reference 144



Complement Activation during Hemodialysis with New Cuprophane-Membrane Dialyzers in Patients with and without the First-Use Syndrome.

Each data point is the mean ±S.E.M. for all patients in that group.

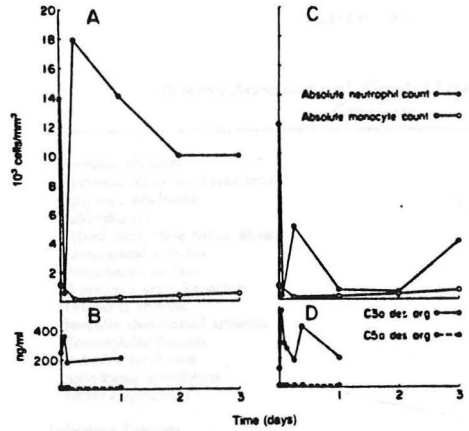
Figure 45
From ref. 134



C3a desArg Levels in Spontaneously Activated and Zymosan-Activated Plasma from Patients with and without the First-Use Syndrome during Hemodialysis.

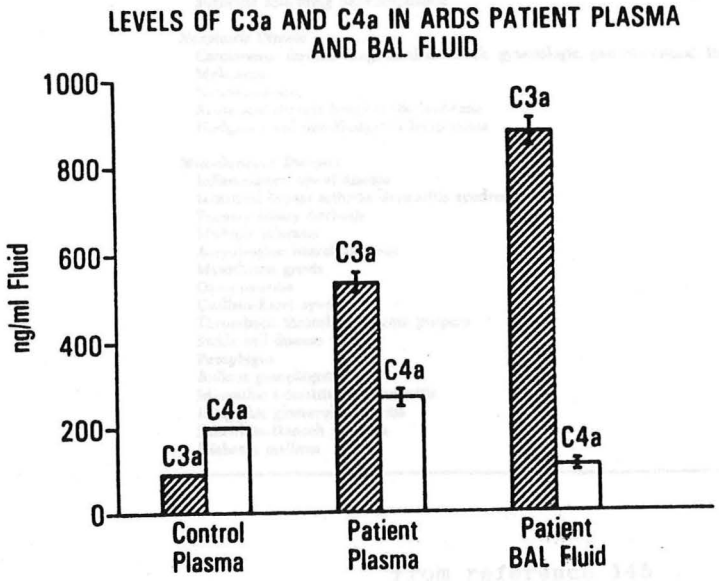
The bar indicates the mean value for the group. Note that there is no overlap between C3a desArg levels in zymosan-activated plasma.

Figure 46
From ref. 134



Absolute Neutrophil Counts (Closed Circles) and Absolute Monocyte Counts (Open Circles) after the First Infusion (Panel A) and the Second Infusion (Panel C).
Levels of C3a desArg (solid line) and C5a desArg (dashed line) in serum are shown as determined by radioimmunoassay after the first (Panel B) and the second infusion (Panel D).

Figure 47
From ref 141



Preliminary data obtained for anaphylatoxin levels in plasma and BAL fluid taken from a patient with adult respiratory distress syndrome (ARDS)
The patient developed ARDS following bone marrow transplantation

Figure 48
From ref. 127

Table 48

Diseases Associated with Elevated Levels of Circulating Immune Complexes

Rheumatic Diseases
- Systemic lupus erythematosus
- Sjögren's syndrome
- Scleroderma
- Mixed connective tissue disease
- Rheumatoid arthritis
- Polyarteritis nodosa
- Wegener's granulomatosis
- Temporal arteritis
- Juvenile rheumatoid arthritis
- Eosinophilic fasciitis
- Behçet's syndrome
- Ankylosing spondylitis
- Reiter's syndrome

Infectious Diseases
- Bacterial endocarditis
- Meningococcemia
- Gonococcemia
- Leprosy
- Syphilis
- Streptococcal infections
- Salmonellosis
- Infected ventriculoatrial shunts
- Dengue
- Viral hepatitis
- Infectious mononucleosis
- Cytomegalovirus
- Subacute sclerosing panencephalitis

Neoplastic Disease
- Carcinomas, (breast, lung, head and neck, gynecologic, gastrointestinal, kidney)
- Melanoma
- Neuroblastoma
- Acute and chronic lymphocytic leukemia
- Hodgkin's and non-Hodgkin's lymphomas

Miscellaneous Diseases
- Inflammatory bowel disease
- Intestinal bypass arthritis dermatitis syndrome
- Primary biliary cirrhosis
- Multiple sclerosis
- Amyotrophic lateral sclerosis
- Myasthenia gravis
- Optic neuritis
- Guillain-Barré syndrome
- Thrombotic thrombocytopenic purpura
- Sickle cell disease
- Pemphigus
- Bullous pemphigoid
- Idiopathic interstitial pneumonitis
- Idiopathic glomerulonephritis
- Schönlein-Henoch purpura
- Diabetes mellitus

From reference 145

Pharmacologic Modulation of Complement Activation and Actions (References 147-152)

While pharmacologic strategies to manage the complement system are primitive for most situations, the knowledge gained to date is encouraging. The use of gene activating drugs (eg danazol), of effective premedication for radiocontrast reactions, of specific factor replacement (C1-INH), colchicine for FMF, and other approaches indicate that many avenues are opening for the future. The complexity of the complement system dictates care when the intricately interacting components are modified in hopes of clinical benefit.

Summary and Speculation

The data reviewed at these rounds indicate that major strides have been made toward understanding the role of complement in human health and disease. New laboratory methods for assessing classical pathway activation, alternative pathway activation, membrane attack complex assembly, anaphylatoxin generation, and complement receptors on cell surfaces have rendered the conventional C3, C4, and total hemolytic complement values archaic for most uses.

Our new knowledge and powerful new assessment methods open the door for more rational and effective investigation, diagnosis, and monitoring of a wide range of diseases (at a minimum the diseases associated with immune complexes - Table 38). Hopefully these rounds will have made the transition to the future easier.

Until recently the human complement system was obscure and relatively inaccessible to the clinician. Neither is true any longer. We are rapidly reducing our ignorance while beginning to effectively monitor and control the complement system.

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