J. Donald Smiley

Medical Grand Rounds
Parkland Memorial Hospital November 1, 1973

ROLE OF COMPLEMENT IN HUMAN DISEASES

Inflammation which accompanies disease processes results from the interaction of several complex systems of defense, selected by nature to sound the alarm, mobilize the army of cellular defenders and ultimately to destroy or expel the noxious stimulus. These systems include bradykinin release, clotting and fibrinolysis, the immune response and activation of the complement pathways (Ref. 1). Each system has one or more points of interrelationship with the others, often sharing common activators, such as Hageman factor or inhibitors such as C1 inhibitor (Ref. 2).

Defects, imbalances, hyper- or hypofunction among these interacting systems of serum proteins in themselves can produce or augment disease entities. Those diseases involving the complement system have drawn a flurry of medical attention during the last three years, and include pathology in almost every organ. These developments are outlined in the order to be discussed below:

I. Biologic functions of the classical and alternate complement pathways.

II. Genetic defects of complement components or their serum inactivators.

III. Hypocomplementemic glomerulonephritis and partial lipodystrophy.

IV. Diseases in which defective chemotaxis of polymorphonuclear leukocytes may be related to the complement system.

V. Diseases in which impaired opsonization of bacteria and other antigens by polymorphonuclear leukocytes is produced by alternate complement pathway abnormalities.

VI. Role of the complement system in the accelerated hemolysis of erythrocytes in paroxysmal nocturnal hemoglobinuria and related disorders.

VII. Participation of complement in inflammatory skin diseases (bullous pemphigoid, dermatitis herpetiformis, herpes gestationis and systemic lupus erythematosus).

VIII. Interaction of the complement system with the kinin, clotting and fibrinolytic systems in shock and diffuse intravascular coagulation.

IX. Measurement of complement components as diagnostic tools in the rheumatic diseases.

I. BIOLOGIC FUNCTIONS OF THE CLASSICAL AND ALTERNATE COMPLEMENT PATHWAYS

Figure 1.

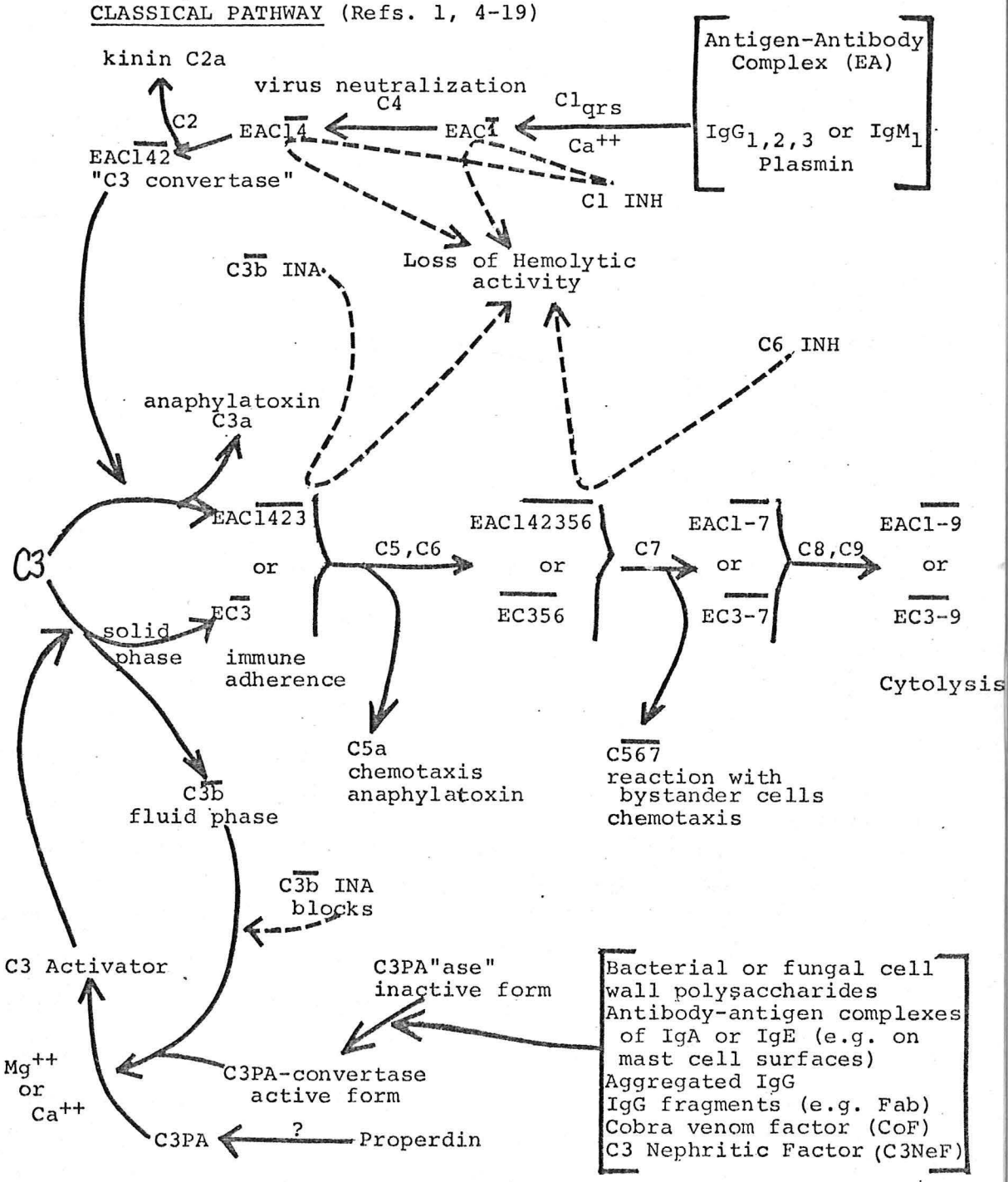


Table I. Physiocochemical Characteristics of Proteins of the Complement System (From Ruddy, et al, Ref. 1 and Lachmann, Ref. 3)

Name	Molecular Weight (Daltons)	Electro-phoretic mobility	Approximate Serum Conc. µg/ml	Major Fragments
Classic Components:				
Cl_q	400,000	γ2	190	
Cl_r	168,000	β	---	
Cl_s	79,000	α2	120	
C4	240,000	β1	430	C4a,C4b
C2	117,000	β2	30	C2a,C2b
C3	185,000	β1	1,300	C3a,C3b
C5	185,000	β1	75	C5a,C5b
C6	125,000	β2	60	
C7	---	β2	<1	
C8	150,000	γ1	<1	
C9	79,000	α	<1	
Alternate pathway factors:				
Properdin	223,000	γ2	20	
C3PA	105,000	β2	225	a-fragment b-fragment
C3PA convertase	40,000	α	<1	
Control proteins:				
$C\overline{1}INH$	90,000	α2	180	
$C\overline{3b}INA$	100,000	β2	25	
$C\overline{6}INA$	---	β1	--	
Anaphylatoxin INA	310,000	α	--	

II. GENETIC DEFECTS OF COMPLEMENT COMPONENTS OR THEIR SERUM INACTIVATORS (Ref. 38, 39, 40)

Table II

Missing Component	Associated Clinical Features	(References)
Cl_q	Lymphopenic agammaglobulinemia, severe repeated infections	(41,42)
Cl_r	Systemic lupus erythematosus, repeated infections	(43)
C2	Systemic lupus erythematosus	(44,45,46)
C3	Repeated infections	(47,48)
C5	Defective chemotaxis, gram negative bacterial infections	(49)
C6	No persistent disease, no abnormality of hemostasis	(50,51)
$C\bar{1}INH$	Hereditary angioneurotic edema	(52,53,54,55)
C3bINA	Repeated infections, low C3 and non-γ Coombs positive anemia	(56)
C3 Activator present	Partial lipodystrophy, repeated infections, (? missing inhibitor)	(57)

III. HYPOCOMPLEMENTEMIC GLOMERULONEPHRITIS AND PARTIAL LIPODYSTROPHY

When renal biopsy specimens are stained for complement (C3) and IgG in patients with membranoproliferative glomerulonephritis without other associated systemic illness, between 10 and 25% show C3 but no IgG (Refs. 58, 59). Children and occasional adults with these findings often have persistently low C3 in their serum (Ref. 60) and possess a factor (Ref. 61) C3 nephritic factor (C3NeF) capable of degrading the C3 in normal serum. A fragment of C3 (C3d) is also consistently present in the serum of patients with this form of nephritis (Ref. 62) and reflects the continued active destruction of C3 *in vivo*. In addition to this accelerated destruction, the body synthesis of C3 is also decreased (Ref. 63) causing the serum level to fall even further.

When kidney biopsies from patients with this form of nephritis are stained with the Jones methenamine silver method, a lobular proliferative glomerulonephritis is noted with some type of non-silver staining material separating the glomerular basement membrane into two portions giving a pattern described as a "tram track" appearance (Ref. 58). More selective fluorescent antibody staining of the renal glomeruli from patients with hypocomplementemic membranoproliferative glomerulonephritis have shown C3PA and properdin (Ref. 64), in addition to C3 to be present.

In order for C3NeF to activate C3, it must interact with C3PA (Ref. 65). It has been suggested that this occurs in the kidney glomerulus allowing $C\overline{3b}$ to attach to the capillary walls leading to glomerular damage (Ref. 66). The requirement of $C\overline{3b}$ for C3NeF action reinforces the role of the alternate pathway (Refs. 67, 68, 69) in hypocomplementemic glomerulonephritis. Nephrectomy does not eliminate C3NeF from the blood or restore C3 to normal, suggesting extrarenal C3NeF formation. However, both spontaneous and steroid-induced disappearance of C3NeF have been observed (Ref. 58).

Other forms of glomerulonephritis have been found to have C3NeF with selective depletion of the alternate and late complement pathway components. These include acute post streptococcal glomerulonephritis (Refs. 69, 70, 71) and an unusual hereditary nephropathy (Ref. 72).

Paradoxically, in one study of 21 adults with glomerulonephritis in whom elevations above 2 standard deviations of the mean C'H50 (total hemolytic complement) were found, a significantly shortened life expectancy ($p = <0.01$) was present (Ref. 73) causing some doubt about the potential harm to the kidneys induced by C3 depletion.

Table III. COMPLEMENT PROFILE IN PARTIAL LIPODYSTROPHY (Refs. 77, 78)
(% normal human ref. serum)

Patient	Symptoms	Cl_q,C4, C6,C7	C3	C3PA	C3d	C3NeF	$C\overline{3b}$INA
1	Recurrent URI's	all normal	11	nl	+	+	ND
2	Behavior prob.	all normal	13	nl	+	+	ND
3	Behavior prob.	all normal	28	nl	+	+	ND
4	Edema, HBP	all normal	28	85	+	+	+
5	Edema, HBP	all normal	20	65	+	+	+
6	Proteinuria,HBP	normal (C6,C7,ND)	25	100	+	+	+
Normal range			68-126	65-115	0	0	+

ed cells of patients 4, 5 and 6 were non-γ Coomb's (C3) positive, patients 1, 2 and 3 were not tested.

PATIENT WITH PARTIAL LIPODYSTROPHY, SYSTEMIC LUPUS ERYTHEMATOSUS AND HYPOCOMPLEMENTEMIC NEPHRITIS.

[redacted]). This 34 year-old [redacted] female was admitted for evaluation of a syndrome consisting of liver disease, diabetes, arthritis, pleurisy and pericarditis. At age 4 or 5 she had developed partial lipodystrophy with loss of fat from the subcutaneous tissues of the upper half of the body except for mammary tissues. Laboratory findings included occasionally positive antinuclear antibody, 4+ positive RA latex fixation test and persistently low C3 in the range of 20 to 30 mg% (normal 90-170 mg%). She had a long history of multiple infections throughout childhood including draining lymphadenitis, meningococcal meningitis 1956, pneumonia 1963, urinary tract infections 1966 and 1968 and recurrent polyserositis since 1959. In the [redacted] Arthritis Clinic in the past, she has shown moderate improvement when treated with prednisone 15-30 mg/day, but always failed to raise the serum C3 level. A renal biopsy in 1967 showed "mesangial glomerulitis".

Physical findings in [redacted] 1973 showed prominent upper body lipodystrophy, a pericardial friction rub, liver enlargement, and patches of monilia on the buccal mucosa. Clinical evaluation of renal function showed normal BUN, creatinine and creatinine clearance. Blood sugars ranged from 300 to 400 mg%. C3 = 38 mg%, C'H50 = 45 Units (nl. range = 60-110), SGOT = 98 (nl. = 40), alkaline phosphatase = 27.

The patient's mother who is clinically asymptomatic has a C3 level of 58 mg%. Bacterial opsonization by normal polymorphonuclear leukocytes was markedly impaired in pt.and mother's sera; both were capable of causing conversion of C3 to C3b when mixed with normal serum compatible with the presence of C3NeF.

COMMENT Low C3 and the presence of C3NeF have been observed in relatives of patients with lipodystrophy who do not have clinically evident disease, including another mother-daughter combination currently being followed by Dr. Norma Battles at [redacted] in [redacted]. The variable presence of partial lipodystrophy, of mesangioproliferative glomerulonephritis, and in the case of our patient, [redacted]., of associated SLE suggests a genetic factor which provides susceptibility coupled with exogenous factors (? chronic viral infections) which lead to the diseases observed in some patients and not in others.

The delayed onset of the lipodystrophy at age 4, for example in [redacted], or older in other observed patients and the long duration of partial lipodystrophy in some patients 15 to 20 years prior to the onset of rapidly progressive glomerulonephritis would be consistent with this impression (Refs.74-78).

Dr. Havel and his coworkers (Ref. 75) have observed insulin-resistant hyperglycemia, blunted responses in serum levels of free fatty acids after norepinephrine infusions, and decreased release of insulin following carbohydrate challenge in patients with partial lipodystrophy, not unlike that which might be observed in patients subjected to pheochromocytoma.

IV. DISEASES IN WHICH DEFECTIVE CHEMOTAXIS MAY BE RELATED TO THE COMPLEMENT SYSTEM.

Chemotaxis, the chemical attraction of polymorphonuclear leukocytes to the local site of an inflammatory stimulus may be achieved by at least five serum factors as well as closely related polypeptides derived from bacteria such as *E. coli*. All of these factors are restricted to their local function by a high concentration in the serum of a potent chemotactic factor inactivator (Ref. 79).

Two of the most potent of these factors, $C\overline{567}$ and C5a are derived from C5. When this component of the complement system is genetically absent chemotaxis is severely impaired and severe gram negative infections result (Ref. 49). Similarly, patients with hypocomplementemic nephritis may show a severe chemotactic defect (Ref. 80).

TABLE IV. FACTORS CHEMOTACTIC FOR NEUTROPHILES

Source	Mol. Wt. Daltons	References
Complement - related		
$C\overline{567}$	17,000	(81)
C5a	10,000	(82, 83)
C3a	6,800	(84)
Hageman Factor-related		
from prekallikrein	unknown	(85)
from plasminogen proactivator	unknown	(86)
Soluble bacterial factors	~2,000	(87)
Lysosomal factors in polys	unknown	(87)
Products of collagen hydrolysis	unknown	(87)

V. DISEASE RELATED TO IMPAIRED OPSONIZATION OF BACTERIA AND OTHER ANTIGENS BY NEUTROPHILES DUE TO ALTERNATE PATHWAY ABNORMALITIES

Some of the most dangerous microorganisms for man such as *Pneumococci* (Refs. 88, 89, 90) and *Pseudomonas* (Refs. 91, 92) are not killed by whole serum even when high titers of specific antibody are present, but require the participation of neutrophiles for bactericidal effect. The chemical signals for opsonization of bacteria have been termed "opsonins" and are, unlike antibody, destroyed by heating serum to 56°C for 30 minutes (Ref. 93). Recent work has shown the most important opsonins to be by-products of the alternate complement pathway (Ref. 94, 95). Patients with inherited defects of the early complement components of the classical pathway have approximately 60% of normal bacterial opsonization (Ref. 38) because cell wall components of most bacteria and fungi can activate the alternate pathway and allow bacterial phagocytosis even in agammaglobulinemic serum (Ref. 96). About 15% of new-born infants have such low levels of the alternate pathway (properdin) components that their serum does not provide adequate bacterial opsonization and they are at increased risk for serious infections (Refs. 97, 98). Other diseases such as SLE with acquired complement depletion also show low serum opsonic capacity (Ref. 99).

The immunologic "short circuits" provided by bacterial activation of the complement pathways in the complete absence of specific antibody represent a first line of defense which ordinarily limits bacterial multiplication by facilitation of phagocytosis (Ref. 100). Staphylococcal protein A does this by forming a non-immunologic complex with IgG which depletes the classical pathway beginning with C1 (Ref. 101).

Some rheumatoid factors (anti-IgG) including those which are formed in SBE in man compete for the complement ($C1q$) binding site on the heavy chain portion of IgG (Refs. 102, 103) and may severely impair opsonization of *Streptococcus viridans* providing an additional explanation for bacterial survival on valvular surfaces in patients with very high specific antibody titers. This adverse effect on neutrophile opsonization may extend to other diseases in which rheumatoid factors are found.

Meningococci require specific antibody and the participation of the classical pathway (Ref. 104), while *Pneumococci* are just as readily phagocytosed and killed in C4-deficient serum as normal serum indicating an absolute requirement for alternate complement pathway activation (Ref. 90).

Gram negative bacterial endotoxin (lipopolysaccharide) is actually detoxified by interaction with complement components beginning with alternate pathway activation, yet another example of a protective function for this system (Refs. 105, 106, 107).

VI. ROLE OF THE COMPLEMENT SYSTEM IN HEMATOLOGIC DISORDERS

Autoimmune hemolytic anemia, cold agglutinin disease and paroxysmal nocturnal hemoglobinuria (PNH)

The normal adult synthesizes about 80 mg of C3 per hour. This increases only slightly with autoimmune hemolytic anemia of the cold agglutinin type or in that induced by α-methyldopa ingestion. However, it approximately doubles in patients with active hemolysis related to PNH (Ref. 108).

Usually, hemolysis of human red cells requires a permanent fixation of specific antibody to the erythrocyte surface. The transient attachment of IgM-cold agglutinin allows a conversion of C3 to $\overline{C3b}$, some of which adhers to the adjacent red cell membrane, but often fails to activate later components and produce direct lysis. Phagocytosis and intracellular destruction of erythrocytes may follow this event, however (Ref. 109), but the surface bound $\overline{C3b}$ is usually rapidly converted to an inactive product by $\overline{C3b}$INA (Ref. 110). Only when extreme cold stress leads to accelerated $\overline{C3b}$ attachment does intravascular hemolysis occur.

The difference in susceptibility to intravascular hemolysis noted with normal red cells when compared to erythrocytes from patients with PNH can be explained by 1) an increased number of $\overline{C3b}$ binding sites on the PNH cell surface and 2) a much greater susceptibility to complement lysis of the erythrocyte membrane in this disorder (Refs. 111, 112).

This lysis of PNH erythrocytes has now been shown to occur via the alternate complement pathway, and it can be greatly enhanced by slight increases in the serum magnesium concentration (Ref. 113). The latter finding is the basis for a more sensitive test for PNH cells in which 0.6 mEq/liter of $MgCl_2$ is added to the Ham test (acidified serum) producing a selective hemolysis of the abnormal red cells.

Mechanism for the increased susceptibility to infections in patients with sickle-cell disease

Any form of intravascular red cell destruction which releases erythrocyte stroma may activate the alternate complement pathway (Ref. 114).

The earlier observations of a significant increase in life-threatening infections such as pneumococcal meningitis (Ref. 115) or salmonella osteomyelitis in patients with sickle-cell disease are now believed related to an acquired defect in the level of properdin pathway constituents (Ref. 116) which are required for adequate opsonization of these bacteria. *In vitro* studies of bacterial opsonization in the presence of sera from patients with sickle-cell disease have shown a marked decrease in phagocytosis when relatively low levels of specific antibody are present (Ref. 117).

VII. PARTICIPATION OF COMPLEMENT IN INFLAMMATORY SKIN DISEASES

TABLE V

Skin Disease (No. of patients)	Immunofluorescent Staining: Site of Deposit	Ig	Complement Components	Reference
Herpes gestationis (1)	B.M.	None	C3,C5 properdin	(119)
Dermatitis herpetiformis (19)	B.M.	IgA	C3	(120)
Bullous pemphigoid (6)	B.M.	IgG	Cl_q, C3,C3PA properdin	(119)
Systemic lupus erythematosus (25)	B.M.	IgG IgM	Cl_q, C3,C4,C5 C3PA-12% properdin-20%	(119)
Pemphigus vulgaris	epidermal cement substance	IgG	C3, C4	(121)

B.M. = basement membrane of involved skin.

It is believed that some mechanism of activation of only the alternate pathway of complement activation is present in Herpes gestationis (no known association to virus infection), a rare vesicular skin eruption appearing spontaneously in one out of 11,000 pregnancies, usually during the last trimester or post-partum and worse with each subsequent pregnancy. The condition is not usually fatal, and recedes without leaving permanent scarring. It may last many months. No effective treatment is known.

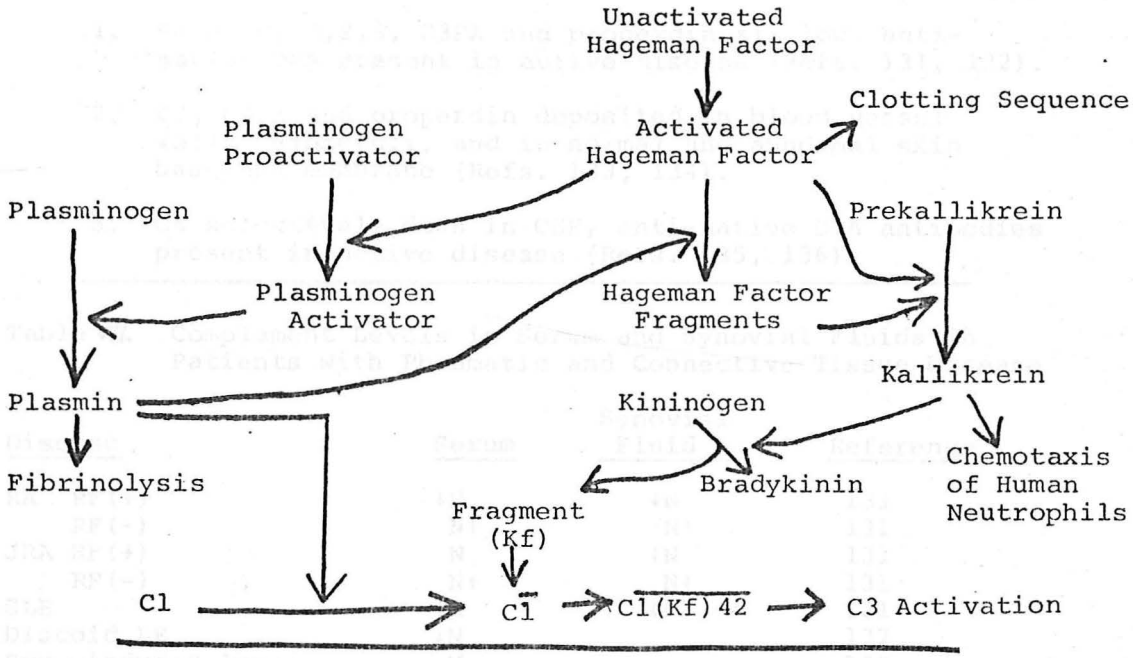
In dermatitis herpetiformis, there are deposits of IgA in the basement membrane of the skin and activation of the alternate complement pathway is characteristic. It is a benign, but troublesome disorder. The high association of a gluten-related sprue with this disorder strongly suggests some immunological reaction involving gluten allergy in these patients.

Bullous pemphigoid is a relatively benign condition in which crops of superficial bullae filled with serosanguinious fluid appear. The latter contain C3 activator as well as components of the classical complement pathway (Ref. 118). This data, together with that obtained by fluorescent antibody staining presented in Table V above suggest that both pathways are being activated, probably by anti-basement membrane antibody of IgG type.

Pemphigus vulgaris is a serious disorder characterized by deposits of IgG around the epidermal cells in the region of the intracellular cement substance. This is associated with activation of the classical complement pathway.

VIII. INTERACTION OF THE COMPLEMENT SYSTEMS WITH THE KININ, CLOTTING AND FIBRINOLYTIC SYSTEMS IN SHOCK AND IN DIFFUSE INTRAVASCULAR COAGULATION

Fig. 2.



The initiating event in the generation of bradykinin in human plasma (Fig. 2) is the activation of Hageman factor by a variety of biologic materials (Ref. 1). Activated Hageman factor not only initiates the clotting sequence but also interacts with plasminogen proactivator, to initiate fibrinolysis via the conversion of plasminogen to plasmin (Ref. 2). Plasmin in turn digests active Hageman factor to form the Hageman-factor fragments which can activate prekallikrein to kallikrein. This diverts the reaction sequence from coagulation to kinin release (Ref. 2).

Activation of Hageman factor initiates coagulation by converting plasma thromboplastin antecedent to its active form, and can directly activate prekallikrein to kallikrein at a limited rate in the fluid phase. Plasmin is a protease which can split fibrin and fibrinogen, cleave C3 to produce C3a, activate C1 to an active $\overline{C1}$ and split Hageman factor. Kallikrein splits an α-globulin, kininogen to form bradykinin, and is also a chemotactic factor for neutrophils independent of the complement pathways.

This interplay of systems provides a reserve of overlapping functions which often protect the individual with isolated genetic defect in one protein component.

The technical details of these interactions are given in Refs. 122-130.

IX. COMPLEMENT COMPONENTS AS DIAGNOSTIC TOOLS IN RHEUMATIC DISEASES

Table VI. Complement and Antibodies to Native DNA in Systemic Lupus Erythematosus

1. Serum C1,4,2,3, C3PA and properdin all low, anti-native DNA present in active disease (Refs. 131, 132).
2. C3, C3PA and properdin deposited in blood vessel walls, glomeruli, and in normal and abnormal skin basement membrane (Refs. 133, 134).
3. C4 selectively down in CSF, anti-native DNA antibodies present in active disease (Refs. 135, 136).

Table VII. Complement Levels in Serum and Synovial Fluids in Patients with Rheumatic and Connective Tissue Disease

Disease	Serum	Synovial Fluid	Reference
RA RF(+)	↓N	↓N	131
RF(-)	N↑	N↑	131
JRA RF(+)	N	↓N	131
RF(-)	N↑	N↑	131
SLE	↓N	↓N	131
Discoid LE	↓N		137
Drug-induced lupus	N		137
Osteoarthritis	N		138
Rheumatic fever	N↑		139
Gout	N↑	↓N↑	137, 140
Pseudogout		↓N↑	140
Reiter's syndrome	N↑	↑	137, 140, 141
Scleroderma	↓N		137, 142, 143
Dermatomyositis	N↑		142, 144
Sjögren's syndrome	↓N		137, 145
Lupoid hepatitis	↓N		137, 146
Polyarteritis	N↑		137, 142
Acute polyarthritis	N↑	N↑	137, 140
Acute bacterial arthritis		↓N↑	140
Psoriatic arthritis		N	140
Ankylosing spondylitis		↑	147
Cryoglobulinemic purpura	↓		
Serum sickness	↓N		
Hepatitis (Au +) with arthritis	↓N		148

N = normal

REFERENCES

GENERAL

1. Ruddy, S., I. Gigli, and K.F. Austen, The complement system in man (four parts), *N. Eng. J. Med.* 287:489, 545, 592, 642 (1972).

2. Schreiber, A.D., A.P. Kaplan and K.F. Austen, Inhibition by C1INH of Hageman factor fragment activation of coagulation fibrinolysis and kinin generation, *J. Clin. Invest.* 52:1402 (1973).

3. Lachmann, P.J. and P. Nicol, Reaction mechanism of the alternate pathway of complement fixation, *Lancet* i:465 (1973).

BIOLOGIC FUNCTIONS OF THE CLASSIC AND ALTERNATE COMPLEMENT PATHWAYS

4. Vroon, D.H., D.R. Schultz and R.M. Zarco, The separation of nine components and two inactivators of components of complement in human serum, *Immunochemistry* 7:43 (1970).

5. Linscott, W.D. and W.E. Levinson, Complement components required for virus neutralization by early immunoglobulin antibody, *Proc. Natl. Acad. Sci (U.S.)* 64:520 (1969).

6. Oroszlan, S. and R.V. Gilden, Immune virolysis: Effect of antibody and complement on C-type RNA virus, *Science* 168: 1478 (1970).

7. Lerner, R.A., M.B.A. Oldstone and N.R. Cooper, Cell cycle-dependent immune lysis of Moloney virus-transformed lymphocytes: Presence of viral antigen, accessibility to antibody, and complement activation, *Proc. Natl. Acad. Sci. (U.S.)* 68:2584 (1971).

8. Wallis, C. and J.L. Melnick, Herpesvirus neutralization: The role of complement, *J. Immunol.* 107:1235 (1971).

9. Yonemasu, K., R.M. Stroud, W. Niedermeier and W.T. Butler, Chemical studies on Cl_q: A modulator of immunoglobulin biology, *Biochem. and Biophy. Res. Commun.* 43:1388 (1971).

10. Yonemasu, K. and R.M. Stroud, Cl_q: Rapid purification method for preparation of monospecific antisera and for biochemical studies, *J. Immunol.* 106:304 (1971).

11. Bing, D.H., Purification of the first component of human complement by affinity chromatography on human γ-globulin linked to sepharose, *J. Immunol.* 107:1243 (1971)..

12. DeBracco, M.M.E. and R.M. Stroud, Cl_r, subunit of the first complement component: Purification, properties, and assay based on its linking role, *J. Clin. Invest.* 50:838 (1971).

13. Bach, S., S. Ruddy, J.A. MacLaren and K.F. Austen, Electrophoretic polymorphism of the fourth component of human complement (C4) in paired maternal and foetal plasmas, *Immunol.* 21:869 (1971).

14. Tedesco, F. and P.J. Lachmann, The quantitation of C6 in rabbit and human sera, *Clin. exp. Immunol.* 9:359 (1971).

15. Pensky, J. and H.G. Schwick, Human serum inhibitors of C'1 esterase: Identity with α2-neuraminoglycoprotein, *Science* 163:698 (1969).

16. Gigli, I., S. Ruddy and K.F. Austen, The stoichiometric measurement of the serum inhibitor of the first component of complement by the inhibition of immune hemolysis, *J. Immunol.* 100:1154 (1968).

17. Ruddy, S. and K.F. Austen, C3 inactivator of man. I. Hemolytic measurement by the inactivation of cell-bound C3. *J. Immunol.* 102:533 (1969).

18. Ruddy, S. and K.F. Austen, C3 inactivator of man. II. Fragments produced by $C3_b$ inactivator cleavage of cell-bound or fluid phase $C3_b$, *J. Immunol.* 107:742 (1971).

19. Tamura, N. and R.A. Nelson, Jr., Three naturally occurring inhibitors of complement in guinea pig and rabbit serum, *J. Immunol.* 99:582 (1967).

20. Pillemer, L., L. Blum and I.H. Lepow, The properdin system and immunity: I. Demonstration and isolation of a new serum protein, properdin and its role in immune phenomena, *Science* 120:279 (1954).

21. Naff, G.B., Properdin - its biologic importance, *N. Engl. J. Med.* 287:716 (1972).

22. Goodkofsky, I. and I.H. Lepow, Functional relationship of Factor B in the properdin system to C3 proactivator in human serum, *J. Immunol.* 107:1200 (1971).

23. Nicol, P.A.E. and P.J. Lachmann, The alternate pathway of complement activation. The role of C3 and its inactivator (KAF), *Immunol.* 24:259 (1973).

24. May, J.E. and M.M. Frank, A new complement-mediated cytolytic mechanism - the C1-bypass activation pathway, *Proc. Natl. Acad. Sci. (U.S.)* 70:649 (1973).

25. Ishizaka, T., C.M. Sian and K. Ishizaka, Complement fixation by aggregated IgE through alternate pathway, *J. Immunol.* 108:848 (1972).

26. Day, N.K., H. Geiger, R. McLean, J. Resnick, A. Michael and R.A. Good, The association of respiratory infection, recurrent hematuria, and focal glomerulonephritis with activation of the complement system in the cold (by an IgA cryoglobulin), *J. Clin. Invest.* 52:1698 (1973).

27. Götze, O. and H.J. Müller-Eberhard, The C3-activator system: an alternate pathway of complement activation, *J. Exp. Med.* 134:90s (1971).

28. Spitzer, R.E., A.E. Stitzel, V.L. Pauling, N.C. Davis, and C.D. West, The antigenic and molecular alterations of C3 in the fluid phase during an immune reaction in normal human serum, *J. Exp. Med.* 134:656 (1971).

29. Müller-Eberhard, H.J. and O. Götze, C3 proactivator convertase and its mode of action, *J. Exptl. Med.* 135:1003, (1972).

30. Alper, C.A., T. Boenisch, and L. Watson, Genetic polymorphism in human glycine-rich beta-glycoprotein (C3PA), *J. Exptl. Med.* 135:68 (1972).

31. Brade, V., C.T. Cook, H.S. Shin and M.M. Mayer, Studies on the properdin system: Isolation of a heat-labile factor from guinea pig serum related to a human glycine-rich beta-glycoprotein (GBG or Factor B) (C3PA), *J. Immunol.* 109: 1174 (1972).

32. Eden, A., G.W. Miller and V. Nussenzweig, Human lymphocytes bear membrane receptors for C3b and C3d, *J. Clin. Invest.* 52:Dec. (1973).

33. Shevach, E.M. R. Herberman, M.M. Frank and I. Green, Receptors for complement and immunoglobulin on human leukemic cells and human lymphoblastoid cell lines, *J. Clin. Invest.* 51:1933 (1972).

34. Miller, G.W., P.H. Saluk and V. Nussenzweig, Complement-dependent release of immune complexes from the lymphocyte membrane, *J. Exptl. Med.* 138:495 (1973).

35. Hunsicker, L.G., S. Ruddy and K.F. Austen, Alternate complement pathway: Factors involved in cobra venom factor (CoVF) activation of the third component of complement (C3), *J. Immunol.* 110:128 (1973).

36. Cooper, N.R., Formation and function of a complex of the C3-proactivator with a protein from cobra venom, *J. Exptl. Med.* 137:451 (1973).

37. Alper, C.A., I. Goodkofsky and I.H. Lepow, The relationship of glycine-rich β-glycoprotein to Factor B in the properdin system and to the cobra factor-binding protein of human serum, *J. Exptl. Med.* 137:424 (1973).

GENETIC DEFICIENCIES OF COMPLEMENT COMPONENTS OR THEIR SERUM INACTIVATORS

38. Lachmann, P.J., Genetic deficiencies of the complement system, *In* Ontogeny of Acquired Immunity, A Ciba Foundation Symposium, Elsevier-Excerpta Medica - North Holland, Assoc. Scientific Publishers, Amsterdam, 1972, p. 193.

39. Colten, H.R., Ontogeny of the human complement system: *In vitro* biosynthesis of individual complement components by fetal tissues, *J. Clin. Invest.* 51:725 (1972).

40 Kohler, P.F., Maturation of the human complement system I. Onset time and sites of fetal Cl_q, C4, C3 and C5 synthesis, *J. Clin. Invest.* 52:671 (1973).

41. Gewurz, H., R.J. Pickering and R.A. Good, Complement and complement component activities in diseases associated with repeated infections and malignancy, *Int. Arch. Allergy* 33:368 (1968).

42. Stroud, R.M., K. Nagaki, R.J. Pickering, H. Gewurz, R.A. Good and M.D. Cooper, Sub-units of the first complement component in immunologic deficiency syndromes: independence of Cls and Cl_q, *Clin. exp. Immunol.* 7:133 (1970).

43. Day, N.K., H. Geiger, R. Stroud, M. deBracco, B. Mancado, D. Windhorst and R.A. Good, Cl_r deficiency: An inborn error associated with cutaneous and renal disease, *J. Clin. Invest.* 51:1102 (1972).

44. Klemperer, M.R., Hereditary deficiency of the second component of complement in man: An immunological study, *J. Immunol.* 102:168 (1969).

45. Agnello, V., M.M.E. deBracco and H.G. Kunkel, Hereditary C2 deficiency with some manifestations of systemic lupus erythematosus, *J. Immunol.* 108:837 (1972).

46. Day, N.K., H. Geiger, R. McLean, A. Michael and R.A. Good, C2 deficiency. Development of lupus erythematosus, *J. Clin. Invest.* 52:1601 (1973).

47. Alper, C.A., R.P. Propp, M.R. Klemperer and F.S. Rosen, Inherited deficiency of the third component of human complement (C'3), *J. Clin. Invest.* 48:553 (1969).

48. Alper, C.A., Colten, H.R., F.S. Rosen, A.R. Rabson, G.M. Macnab and J.S.S. Gear, Homozygous deficiency of C3 in a patient with repeated infections, *Lancet* ii:1179 (1972).

49. Miller, M.E. and U.R. Nilsson, A familial deficiency of the phagocytosis-enhancing activity of serum related to a dysfunction of the fifth component of complement (C5), *New Engl. J. Med.* 282:354 (1970).

50. Leddy, J.P., M.M. Frank, T. Gaither, J. Baum and M.R. Klemperer, Hereditary deficiency of the sixth component of complement (C6) in man. I. Immunochemical, biologic and family studies, *J. Clin. Invest.* 53:Feb (1974).

51. Heusinkveld, R.S., J.P. Leddy, M.R. Klemperer and R.T. Breckenridge, Hereditary deficiency of the sixth component of complement (C6) in man. II. Studies of hemostasis, *J. Clin. Invest.* 53:Feb. (1974).

52. Rosen, F.S. and K.F. Austen, The "neurotic edema" (hereditary angioedema), *New Engl. J. Med.* 280:1356 (1969).

53. Dennehy, J.J., Hereditary angioneurotic edema. Report of a large kindred with defect in C'1 esterase inhibitor and review of the literature, *Ann. Int. Med.* 73:55 (1970).

54. Johnson, A.M., C.A. Alper and F.S. Rosen, C1 inhibitor: Evidence for decreased hepatic synthesis in hereditary angioneurotic edema, *Science* 173:553 (1971).

55. Sheffer, A.L., K.F. Austen and F.S. Rosen, Tranexamic acid therapy in hereditary angioneurotic edema, *New Engl. J. Med.* 287:452 (1972).

56. Abramson, N., C.A. Alper, P.J. Lachmann, F.S. Rosen and J.H. Jandl, Deficiency of C3 inactivator in man, *J. Immunol.* 107:19 (1971).

57. Alper, C.A., K.J. Bloch and F.S. Rosen, Increased susceptibility to infection in a patient with type II essential hypercatabolism of C3, *New Engl. J. Med.* 288:601 (1973).

HYPOCOMPLEMENTEMIC GLOMERULONEPHRITIS AND PARTIAL LIPODYSTROPHY

58. West, C.D., Serum complement and chronic glomerulonephritis, *Hosp. Pract.* 5:75 (1970).

59. Verroust, P.J., C.B. Wilson, N.R. Cooper, T.S. Edgington and F.J. Dixon, Glomerular complement components in human glomerulonephritis, *J. Clin. Invest.* 53:Jan. (1974).

60. Gotoff, S.P., F.X. Fellers, G.F. Vawter, C.A. Janeway and F.S. Rosen, The β_{1c}-globulin in childhood nephrotic syndrome: Laboratory diagnosis of progressive glomerulonephritis, *New Engl. J. Med.* 273:524 (1965).

61. Pickering, R.J., H. Gewurz, and R.A. Good, Complement inactivation by serum from patients with acute and hypocomplementemic chronic glomerulonephritis, *J. Lab. Clin. Med.* 72:298 (1968).

62. West, C.D., S. Winter, J. Forristal, J.M. McConville and N.C. Davis, Evidence for *in vivo* breakdown of β_{1c}-globulin in hypocomplementemic glomerulonephritis, *J. Clin. Invest.* 46:539 (1967).

63. Alper, C.A., A.S. Levin and F.S. Rosen, β_{1C}-globulin: Metabolism in glomerulonephritis, *Science* 153:180 (1966).

64. McLean, R.H. and A.F. Michael, Properdin and C3 proactivator: Alternate pathway components in human glomerulonephritis, *J. Clin. Invest.* 52:631 (1973).

65. Ruley, E.J., J. Forristal, N.C. Davis, C. Andres and C.D. West, Hypocomplementemia of membranoproliferative nephritis. Dependence of the nephritic factor reaction on properdin Factor B (C3PA), *J. Clin. Invest.* 52:896 (1973).

66. Editorial, Hypocomplementaemic Nephritis, *Lancet* ii:368 (1972).

67. Williams, D.G., J.A. Charlesworth, P.J. Lachmann and D.J. Peters, Role of C3b in the breakdown of C3 in hypocomplementemic mesangiocapillary glomerulonephritis, *Lancet* i:447 (1973).

68. Peters, D.K., A. Martin, A. Weinstein, J.S. Cameron, T.M. Barratt, C.S. Ogg and P.J. Lachmann, Complement studies in membranoproliferative glomerulonephritis, *Clin. exp. Immunol.* 11:311 (1972).

69. Gewurz, H., R.J. Pickering, S.E. Mergenhagen and R.A. Good, The complement profile in acute glomerulonephritis, systemic lupus erythematosus and hypocomplementemic chronic glomerulonephritis, *Int. Arch. Allergy* 34:556 (1968).

70. Williams, D.G., O. Kourilsky, L. Morel-Maroger and D.K. Peters, C3 breakdown in serum from patients with acute post-streptococcal nephritis, *Lancet* ii:360 (1972).

71. Gewurz, H., R.J. Pickering, G. Naff, R. Snyderman, S.E. Mergenhagen and R.A. Good, Decreased properdin activity in acute glomerulonephritis, *Int. Arch. Allergy* 36:592 (1969).

72. Teisberg, P., K.A. Grottum, E. Myhre and A. Flatmark, In-vivo activation of complement in hereditary nephropathy, *Lancet* ii:356 (1973).

73. Gabriel, R.; A.A. Glynn and A.M. Joekes, Raised complement in nephritis: Prognostic significance, *Lancet* ii:55 (1972).

PARTIAL LIPODYSTROPHY

74. Senior, B. and S.S. Gellis, The syndromes of total lipodystrophy and of partial lipodystrophy, *Ped.* 26:593 (1964).

75. Piscatelli, R.L., W.V.R. Vieweg and R.J. Havel, Partial lipodystrophy. Metabolic studies in three patients, *Ann. Int. Med.* 73:963 (1970).

76. Williams, D.G., J.W. Scopes and D.K. Peters, Hypocomplementaemic membranoproliferative glomerulonephritis and nephrotic syndrome associated with partial lipodystrophy of the face and trunk, *Proc. Roy. Soc. Med.* 65:591 (1972).

77. Peters, D.K., D.G. Williams, J.A. Charlesworth, J.M. Boulton-Jones, J.G.P. Sissons, D.J. Evans, O. Kourilsky and L. Morel-Maroger, Mesangiocapillary nephritis, partial lipodystrophy and hypocomplementemia, *Lancet* ii:535 (1973).

78. Thompson, R.A. and R.H.R. White, Partial lipodystrophy and hypocomplementemic nephritis, *Lancet* ii:679 (1973).

DEFECTIVE CHEMOTAXIS RELATED TO THE COMPLEMENT SYSTEM

79. Berenberg, J.L. and P.A. Ward, Chemotactic factor inactivator in normal human serum, *J. Clin. Invest.* 52:1200 (1973).

80. Gewurz, H., A.R. Page, R.J. Pickering and R.A. Good, Complement activity and inflammatory neutrophil exudation in man, *Int. Arch Allergy* 32:64 (1967).

81. Clark, R.A., M.M. Frank and H.R. Kimball, Generation of chemotactic factors in guinea pig serum via activation of the classical and alternate complement pathways, *Clin. Immunol. & Immunopath.* 1:414 (1973).

82. Snyderman, R., J.K. Phillips and S.E. Mergenhagen, Biological activity of complement *in vivo*. Role of C5 in the accumulation of polymorphonuclear leukocytes in inflammatory exudates, *J. Exp. Med.* 134:1131 (1971).

83. Horwitz, D.A. and M.A. Garrett, Use of leukocyte chemotaxis *in vitro* to assay mediators generated by immune reactions. I. Quantitation of mononuclear and polymorphonuclear leukocyte chemotaxis with polycarbonate (Nuclepore) filters, *J. Immunol.* 106:649 (1971).

84. Bokisch, V.A., H.J. Müller-Eberhard and C.G. Cochrane, Isolation of a fragment (C3a) of the third component of human complement containing anaphylatoxin and chemotactic activity and description of anaphylatoxin inactivator in human serum, *J. Exptl. Med.* 129:1109 (1969).

85. Weiss, A.S., J.I. Gallin and A.P. Kaplan, Fletcher factor deficiency: Abnormalities of coagulation fibrinolysis, chemotactic activity, and kinin generation attributable to absence of prekallikrein, *J. Clin. Invest.* 53: Feb. (1974).

86. Kaplan, A.P., E.J. Goetzl and K.F. Austen, The fibrinolytic pathway of human plasma. II. Activation of plasminogen proactivator, *J. Clin. Invest.* 52:2591 (1973).

87. Ward, P.A., Neutrophil chemotactic factors and related clinical disorders, *Arth Rheum.* 13:181 (1970).

IMPAIRED BACTERIAL OPSONIZATION DUE TO ABNORMALITIES OF THE ALTERNATE COMPLEMENT PATHWAY.

88. Smith, M.R. and W.B. Wood, Jr., Heat labile opsonins to pneumococcus. I. Participation of complement, *J. Exptl. Med.* 130:1209 (1969).

89. Shin, H.S., M.R. Smith and W.B. Wood, Jr., Heat labile opsonins to pneumococcus II. Involvement of C3 and C5, *J. Exptl. Med.* 130:1229 (1969).

90. Winkelstein, J.A., H.S. Shin and W.B. Wood, Jr., Heat labile opsonins to pneumococcus. III. Participation of immunoglobulin and of the alternate pathway of C3 activation, *J. Immunol.* 103:1681 (1972).

91. Young, L.S. and D. Armstrong, Human Immunity to *Pseudomonas aeruginosa.* I. *In vitro* interaction of bacteria, polymorphonuclear leukocytes and serum factors, *J. Infect. Dis.* 126:257 (1972).

92. Young, L.S., Human immunity to *Pseudomonas aeruginosa.* II. Relationship between heat-stable opsonins and type-specific lipopolysaccharides, *J. Infect. Dis.* 126:277 (1972).

93. Rosen, F.S., The complement system and increased susceptibility to infection, *Seminars in Hematol.* 8:221 (1971).

94. Jasin, H.E., Human heat labile opsonins: Evidence for their mediation via the alternate pathway of complement activation, *J. Immunol.* 109:26 (1972).

95. Alper, C.A., N. Abramson, R.B. Johnston, Jr., J.H. Jandl and F.S. Rosen, Studies *in vivo* and *in vitro* on an abnormality of the metabolism of C3 in a patient with increased susceptibility to infection, *J. Clin. Invest.* 49:1975 (1970).

96. Williams, R.C., Jr. and P.G. Quie, Opsonic activity of agammaglobulinemic human sera, *J. Immunol.* 106:51 (1971).

97. Stossel, T.P., C.A. Alper and F.S. Rosen, Opsonic activity in the newborn: Role of properdin, *Pediatrics* 50:173 (1973).

98. Forman, M.L. and E.R. Stiehm, Impaired opsonic activity but normal phagocytosis in low-birth-weight infants. *New Eng. J. Med.* 277:926 (1969).

99. Jasin, H.E., J.H. Orozco and M. Ziff, Serum heat labile opsonins in systemic lupus erythematosus, *J. Clin. Invest.* 53:Feb (1974).

100. Kronvall, G. and R.C. Williams, Jr., Immunologic "short circuits", *Ann. Int. Med.* 70:1043 (1969).

101. Kronwall, G. and H. Gewurz, Activation and inhibition of IgG-mediated complement fixation by staphylococcal protein A., *Clin. Exptl. Med.* 7:211 (1970).

102. Messner, R.P., T. Laxdal, P.G. Quie and R.C. Williams, Serum opsonin, bacteria and polymorphonuclear leukocyte interactions in subacute bacterial endocarditis. Anti-γ-globulin factors and their interaction with specific opsonins, *J. Clin. Invest.* 47:1109 (1968).

103. Quie, P.G., R.P. Messner and R.C. Williams, Phagocytosis in subacute bacterial endocarditis. Localization of the primary opsonic site to Fc fragment, *J. Exp. Med.* 128: 553 (1968).

104. Roberts, R.B., The relationship between group A and group C meningococcal polysaccharides and serum opsonins in man, *J. Exp. Med.* 131:499 (1970).

105. Johnson, K.J. and P.A. Ward. The requirement for serum complement in the detoxification of bacterial endotoxin, *J. Immunol.* 108:611 (1972).

106. Gewurz, H., H.S. Shin and S.E. Mergenhagen, Interactions of the complement system with endotoxic lipopolysaccharide: Consumption of each of the six terminal complement components, *J. Exptl. Med.* 128:1049 (1968).

107. Björnson, A.B. and J.W. Alexander, Alterations in serum opsonins in patients with severe thermal injury, *J. Lab. Clin. Med.* (in press) (1973).

ROLE OF COMPLEMENT IN HEMATOLOGIC DISORDERS

108. Petz, L.D., D.J. Fink, E.A. Letsky, H.H. Fudenberg and H. Müller-Eberhard, *In vivo* metabolism of complement. I. Metabolism of the third component (C'3) in acquired hemolytic anemia, *J. Clin. Invest.* 47:2469 (1968).

109. May, J.E., I. Green and M.M. Frank, The alternate complement pathway in cell damage: Antibody-mediated cytolysis of erythrocytes and nucleated cells, *J. Immunol.* 109:595 (1972).

110. Logue, G.L., W.L. Rosse and J.P. Gockerman, Measurement of the third component of complement bound to red blood cells in patients with the cold agglutinin syndrome, *J. Clin. Invest.* 52:493 (1973).

111. Jenkins, D.E., Jr., R.C. Hartmann and A.L. Kerns, Serum-red cell interactions at low ionic strength: Erythrocyte complement coating and hemolysis of paroxysmal nocturnal hemoglobinuria cells, *J. Clin. Invest.* 46:753 (1967).

112. Rosse, W.L., G.L. Logue, J. Adams and J.H. Crookston, Mechanisms of immune lysis of the red cells in hereditary erythroblastic multinuclearity with a positive acidified-serum test (HEMPAS) and paroxysmal nocturnal hemoglobinuria (PNH), *J. Clin. Invest.* 53:Jan (1974).

113. May, J.E., W. Rosse and M.M. Frank, Paroxysmal nocturnal hemoglobinuria. Alternate-complement-pathway-mediated lysis induced by magnesium, *New Eng. J. Med.* 289:705 (1973).

114. Poskitt, T.R., H.P. Fortwengler, Jr. and B.J. Lunskis, Activation of the alternate complement pathway by autologous red cell stroma, *J. Exp. Med.* 138:715 (1973).

115. Winkelstein, J.A. and R.H. Drachman, Deficiency of pneumococcal serum opsonizing activity in sickle-cell disease, *New Eng. J. Med.* 279:459 (1968).

116. Johnston, R.B., S.L. Newman and A.G. Struth, An abnormality of the alternate pathway of complement activation in sickle-cell disease, *New Eng. J. Med.* 288:804 (1973).

117. Rosen, Fred S., Sickle-cell disease and the properdin system, *New Engl. J. Med.* 288:845 (1973). (Editorial).

PARTICIPATION OF COMPLEMENT IN INFLAMMATORY SKIN DISEASES.

118. Jordon, R.E., N.K. Day, W.M. Sams, Jr. and R.A. Good, The complement system in bullous pemphigoid I. Complement and component levels in sera and blister fluids, *J. Clin. Invest.* 52:1207 (1973).

119. Provost, T.T.and T.B. Tomasi, Jr., Evidence for complement activation via the alternate pathway in skin diseases. I. Herpes gestationis, systemic lupus erythematosus and bullous pemphigoid, *J. Clin. Invest.* 52:1779 (1973).

120. Seah, P.P., L. Fry, M.R. Mazaheri, J.F. Mowbray, A.V. Hoffbrand and E.J. Holborow, Alternate-pathway complement fixation by IgA in the skin in dermatitis herpetiformis, *Lancet* ii:175 (1973).

121. Beutner, E.H. and W.F. Leva, Autoantibodies in pemphigus vulgaris, *JAMA*, 192:682 (1965).

INTERACTION OF THE COMPLEMENT SYSTEMS WITH THE KININ, CLOTTING AND FIBRINOLYTIC SYSTEMS.

122. Cochrane, C.G., K.D. Wuepper, B.S. Aiken, S.D. Revak and H.L. Spiegelberg, The interaction of Hageman Factor and immune complexes, *J. Clin. Invest.* 51:2736 (1972).

123. Harpel, P.C., $C\bar{1}$ inactivator inhibition by plasmin, *J. Clin. Invest.* 49:568 (1970).

124. Kaplan, A.P., A.B. Kay and K.F. Austen, A prealbumin activator of prekallikrein. III. Appearance of chemotactic activity for human neutrophils by the conversion of human prekallikrein to kallikrein, *J. Exp. Med.* 135:81 (1972).

125. Ward, P.C. and R.C. Talamo, Deficiency of the chemotactic factor inactivator in human sera with α_1-antitrypsin deficiency, *J. Clin. Invest.* 52:516 (1973).

126. McCabe, W.R., Serum complement levels in bacteremia due to gram-negative organisms, *New Eng. J. Med.* 288:21 (1973).

127. Kane, M.A., J.E. May and M.M. Frank, Interactions of the classical and alternate complement pathway with endotoxin lipopolysaccharide. Effect on platelets and blood coagulation, *J. Clin. Invest.* 52:370 (1973).

128. Polak, L. and J.L. Turk, Suppression of the haemorrhagic component of the Schwartzmann reaction by anti-complement serum, *Nature* 223:738 (1969).

129. May, J.E. and M.M. Frank, Complement-mediated tissue damage: Contribution of the classical and alternate complement pathways in the Forssman reaction, *J. Immunol.* 108:1517 (1972).

130. Spear, G.S. and I. Kihara, Complement and heterophile shock, *Johns Hopkins Med. J.* 126:210 (1970).

COMPLEMENT COMPONENTS AS DIAGNOSTIC TOOLS IN THE RHEUMATIC DISEASES

131. Schur, P.H. and K.F. Austen, Complement in the rheumatic diseases, *Bull. Rheum. Dis.* 22:666 (1972).

132. Ginsberg, B. and H. Keiser, A millipore filter assay for antibodies to native DNA in sera of patients with systemic lupus erythematosus, *Arth. Rheum.* 16:199 (1973).

133. Landry, M. and W.M. Sams, Jr., Systemic lupus erythematosus. Studies of the antibodies bound to skin, *J. Clin. Invest.* 52:1871 (1973).

134. Gilliam, J., Personal communication.

135. Petz, L.D., G.C. Sharp, N.R. Cooper and H. Holman, Serum and cerebral spinal fluid complement and serum autoantibodies in systemic lupus erythematosus, *Medicine* 50:259 (1971).

136. Harbeck, R.J., DNA antibodies and DNA: Anti-DNA complexes in cerebrospinal fluid (CSF) of patients with SLE, *Arth. Rheum.* 16:552 (1973).

137. Townes, A.S., Complement levels in disease, *Johns Hopkins Med. J.* 120:337 (1967).

138. Ruddy, S., M.C. Button, P.H. Schur and K.F. Austen, Complement components in synovial fluid: Activation and fixation in seropositive rheumatoid arthritis, *Ann.N.Y.Acad. Sci.* 168:16 (1969).

139. Fischel, E.E., R.H. Pauli and J. Tesk, Serological studies in rheumatic fever. II. Serum complement in the rheumatic state, *J. Clin. Invest.* 28:1172 (1949).

140. Townes, A.S. and J.M. Sowa, Complement in synovial fluid. *Johns Hopkins Med. J.* 127:23 (1970).

141. Pekin, T.J., Jr., T.I. Molinen and N.J. Zvaifler, Unusual synovial fluid findings in Reiter's syndrome, *Ann. Int. Med.* 66:677 (1967).

142. Williams, R.C., Jr. and D.H. Law, IV, Serum complement in connective tissue disorders, *J. Lab. and Clin. Med.* 52: 273 (1958).

143. Schur, P.H. and G.P. Rodnan, Unpublished observations.

144. Wedgwood, R.J.P. and C.A. Janeway, Serum complement in children with "collagen diseases," *Ped.* 11:569 (1953).

145. Talal, N., E. Zisman and P.H. Schur,Renal tubular acidosis, glomerulonephritis and immunologic factors in Sjögren's syndrome, *Arth. Rheum.* 11:774 (1968).

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

147. Calabro, J.J., R.M. Katz and B.A. Maltz, Ankylosing spondylitis, *J. Ped.* 75:912 (1969).

148. Alpert, E., K.J. Isselbacher and P.H. Schur, Pathogenesis of arthritis associated with viral hepatitis, *New Eng. J. Med.* 285:185 (1971).