The Role of Complement

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CONTENTS

Introduction

The bactericidal effect of blood has been known for more than 100 years [1, 2]. As early as the late nineteenth century it was demonstrated that serum contains factors that mediate lysis of bacteria and antibody sensitized cells [3]. Complement is an essential system for protection against invading microorganisms like virus and bacteria. Split products of this cascade will enhance phagocytosis, bacterial killing and promote leukocytosis [4, 5]. Lysis of foreign invaders by complement requires components C5b-C9 from the terminal part of the complement cascade. This complex is also called the membrane attack complex [6]. Individuals with different hereditary complement protein defects suffer from recurrent and sometimes life threatening infections [7–9].

Formation of anaphylatoxins may initiate pathophysiological events that lead to the development of adult respiratory distress syndrome (ARDS) or multisystem organ failure (MOF). Trauma and other ethiologies behind circulatory shock are associated with activation of the complement system and with ARDS or MOF development [10–15]. As an end product of complement activation, the terminal C5b-9 complement complex is formed [16]. This complex exists in one form which is found in plasma and in another as a membrane-bound form. The complex which can be found in plasma has no known biological effects while the other form triggers different pathophysiological reactions. It will lead to lysis of erythrocytes and activation of leukocytes and platelets [17–20]. It has for example been demonstrated that the terminal C5b-9 complex may be deposited on erythrocytes and leukocytes in association with activation of the complement cascade [21].

Activators of Complement

Classical Activation

The complement cascade can be activated via the classical pathway or the alternative pathway (Fig. 1).

Bacteria, virus, immune complexes, and heparin-protamine complex are known activators of the classical pathway [22–27]. Polysaccharide components from the cell walls of gram-negative bacteria activate the cascade non-specifically while the lipid A is able to initiate the classical pathway [23]. The Hageman factor and immunoglobulin G and immunoglobulin M are also known to activate the classical pathway of complement [28].

Alternative Activation

Foreign material (zymosan, cobra venom factor, nylon, acrylate, cellophane), gram-negative and

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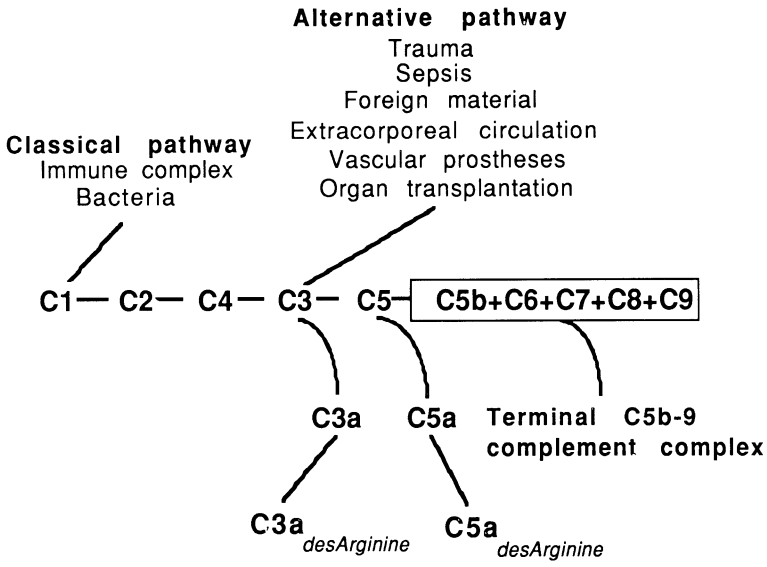

Fig. 1. Simplified scheme of the complement cascade and activation pathways

gram-positive bacteria, and tissue changed by trauma or heat are possible activators of the alternative pathway [29–32]. Activation of complement with the release of anaphylatoxins and terminal C5b-9 complement complexes occur in many categories of patients [33–36]. The most profound degree of activation has, except for patients with septic shock, been observed in association with multiple injuries, acute pancreatitis, and in patients undergoing cardio-pulmonary bypass [37–39].

Biological Effects of Complement Activation

Vascular Effects

When the complement system is activated, polypeptides with inflammatory properties are released (Fig. 1) [40]. The anaphylatoxins (C3a and C5a) increase smooth muscle contraction, and enhance vascular permeability [41, 42]. They also constrict smooth muscles in the bronchial tree and the gastrointestinal tract [43, 44]. Studies indicate that C3a induces tachycardia, impairs cardiac function and induces coronary vasoconstriction [45]. A study by Yancey and coworkers indicate that C5a will induce wheal and flare reactions in humans even in nanogram doses. The study also demonstrates that C5a is a more potent mediator of wheal and flare reactions than histamine and C3a [46]. Human C3a promotes a histamine-mediated contraction of guinea-pig ileal tissue at a concentration of 10^{-9} mol/l. The vascular permeability of human skin vessels is increased at a concentration of 10^{-10} mol/l.

Cellular Effects

C5a is highly chemotactic for neutrophils, causing aggregation. It also stimulates the oxidative metabolism [47]. Once formed in the blood, the C3a and C5a molecules are converted to spasmogenically inactive $C3a_{desArginine}$ and $C5a_{desArginine}$ derivates [48]. The desArginine form of C5a retains part of its ability to induce neutrophil chemotaxis [47, 48]. Human neutrophils bind released C5a with great avidity. The neutrophils internalize receptor-bound C5a. These processes explain why C5a is not found free in plasma until the total neutrophil binding capacity is exceeded [48]. C5a induces secretion of lysosomal enzymes from macrophages and neutrophils and cause non-specific deactivation of granulocytes. C5a may also induce interleukin and prostaglandin production from macrophages [49–52]. Release of C5a will lead to increased expression of the receptors CR1 and CR3 by neutrophils [53, 54].

In a recent study incubation of heparinized whole blood and incubation of leukocytes with recombinant human C5a was performed [55]. An incubation time of 30 min was chosen for heparinized whole blood and for the cell suspension. Zymosan was used as a positive control. Whole blood was drawn from six healthy individuals and incubated with recombinant human C5a in different concentrations. Polymorphonuclear leukocytes from six healthy normal donors were isolated using a discontinuous two-step Percoll gradient according to Dwenger et al. [56]. The isolated cells were resuspended to a concentration of 6–8 $\times 10^6$ cells/ml. Different concentrations of recom-

binant C5a were added to whole blood for incubation for 30 min at 37 °C. The release of PMN elastase, interleukin 1β, and interleukin 6 by different concentrations of recombinant C5a showed a dose-dependent formation (Figs. 2–4). A suspension of isolated human neutrophils was incubated with different concentrations of recombinant C5a, and with zymosan. The release of PMN elastase induced by recombinant C5a showed a dose-response relationship (Fig. 5).

Interactions

Activation of the coagulation and the fibrinolytic system, of the kinin-kallikrein system and of the complement system have been proposed as important etiological mechanisms behind development of the adult respiratory distress syndrome and of multisystem organ failure. Activation of one system will influence the other. Important interactions are known among the complement, prostanoid, coagulation, and fibrinolytic systems [57–62]. For example it is known that C3a, C5a, and terminal C5b-9 complement complexes stimulate biosynthesis of different arachidonic products [63–65].

Clinical Relevance of Complement Activation

Trauma and Shock

Hypoperfusion and ischemia induce activation of complement. Ischemic tissue is a source of this activation. Patients with ischemic limbs have been studied [66]. It was then demonstrated that high plasma levels of anaphylatoxins occurred in circulating blood before amputation of the ischemic

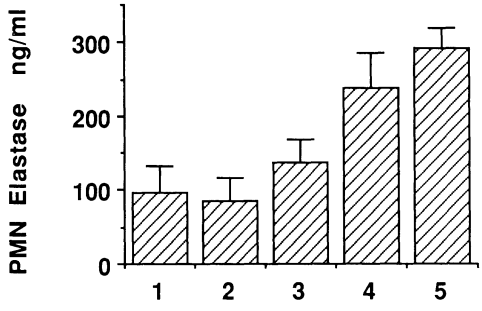

Fig. 2. PMN elastase release after incubation of human heparinized whole blood with 0 ng (*1*), 10 ng (*2*), 100 ng (*3*), and 1000 ng (*4*) of recombinant C5a and with zymosan (*5*) 3.5 mg/ml. Mean ± SEM ($n = 6$)

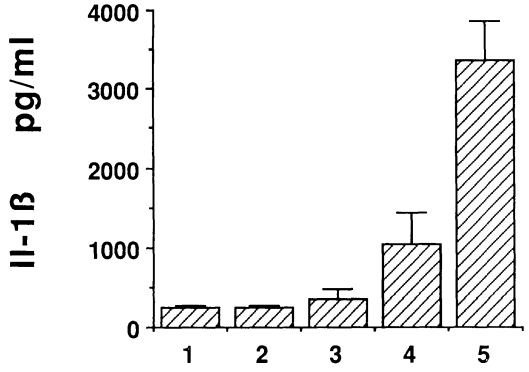

Fig. 3. Interleukin 1β release after incubation of human heparinized whole blood with 0 ng (*1*), 10 ng (*2*), 100 ng (*3*), and 1000 ng (*4*) of recombinant C5a and with zymosan (*5*), 3.5 mg/ml. Mean ± SEM are given

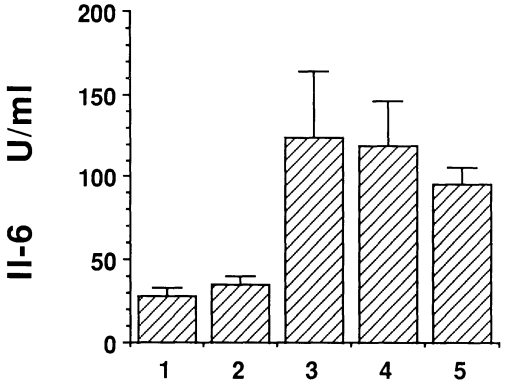

Fig. 4. Interleukin 6 release after incubation of human heparinized whole blood with 0 ng (*1*), 10 ng (*2*), 100 ng (*3*), and 1000 ng (*4*) of recombinant C5a and with zymosan (*5*) 3.5 mg/ml. Mean ± SEM are given

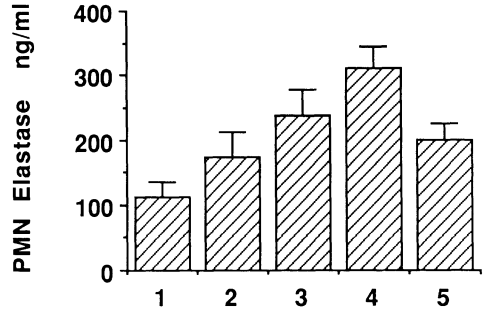

Fig. 5. PMN elastase release after incubation of a human neutrophil suspension with 0 ng (*1*), 10 ng (*2*), 100 ng (*3*), and 1000 ng (*4*) of recombinant C5a and with zymosan (*5*) 3.5 mg/ml. Mean ± SEM are given ($n = 6$)

limb. The plasma levels of the anaphylatoxins returned to the normal range within 1 week after resection of ischemic tissue. Numerous studies also indicate that trauma activates the complement cascade.

Even elective surgery leads to consumption of C3 [67, 68]. Kapur and coworkers showed a positive correlation between the severity of injury or the extent of the surgical procedure and the degree of complement activation. They also showed that the C3 concentrations returned to the normal range in uncomplicated cases. However, these levels remained low in patients with septic complications. There are, however, very few studies indicating that anaphylatoxins or terminal C5b-9 complement complexes are released in association with elective surgery or trauma not involving the thoracic cavity. Fosse and coworkers have shown that patients with multiple injuries and thoracic involvement already have elevated concentrations of terminal C5b-9 complement complexes and C3d levels on hospital arrival [69, 70]. Activation of complement has also been demonstrated in elective vascular surgery [71]. It seems, however, that the aortic clamping procedure is the etiology behind complement activation in this situation. Tissue hypoperfusion leading to hypoxic cell injury may be the primary activating factor. Heideman and coworkers have shown that injured and hypoperfused tissue initiates the complement cascade [72]. Hansson and coworkers have in recent studies shown that intermediate filaments from injured cells bind to IgG when the interior of the cells comes in contact with the plasma proteins. The IgG binding to the cytoskeletal intermediate filaments then activates the complement cascade which leads to the release of C3a and C5a [73]. This process has been shown to be Ca^{2+}, Mg^{2+} and C1q-dependent, indicating that it is acting via the classical pathway.

Septic Shock

The primary role of complement is to protect against infection. Patients with hereditary complement protein defects suffer from repeated and sometimes life-threatening infections. The effects on the complement cascade of sepsis and septic shock are discussed by Bengtsson et al., pp 447–458.

Vascular Surgery

Different studies indicate that complement is activated and that anaphylatoxins are released during aortic reconstructive surgery. This has been studied in both elective and acute operations for aortic aneurysms [71]. CH_{50} activity will decrease during the operation. Complement proteins (C3, C4, and C5) in plasma will decrease during the clamping period. In addition, during the clamping period it has been demonstrated that high levels of anaphylatoxins are formed. There is a positive correlation between clamping time and the formation of anaphylatoxins. The highest C3a and C5a concentrations have been determined in patients undergoing operation for acute aneurysms. It has also been demonstrated that patients developing ARDS or MOF after aortic surgery have higher plasma C3a and C5a compared to patients with uneventful postoperative courses. Elevated C3a and C5a concentration has been observed as early as 1 day after the operation. This will occur before other clinical variables can distinguish patients who will develop MOF from those who will not.

Extracorporeal Circulation

Different forms of extracorporeal circulation lead to activation of the complement system. High concentrations of anaphylatoxins and terminal C5b-9 complement complexes have been determined in association with cardiopulmonary bypass, hemodialysis, liver and limb perfusion due to malignancy, and autotransfusion of homologous blood [74–79]. Complement activation with release of anaphylatoxins has been discussed as being one etiology behind the postperfusion syndrome, not seldom seen in association with the cardiopulmonary bypass procedure. This syndrome is characterized by intravascular hemolysis, leukopenia, and coagulopathy. It has been demonstrated that the probability of postoperative complications can be predicted by determination of the degree of complement activation. High C3a concentrations 3 h after the operation were paralleled by a high risk of cardiac, pulmonary, and renal dysfunction postoperatively [80, 81]. These authors were also able to correlate the cardiopulmonary bypass time with anaphylatoxin release and with postoperative cardiac dysfunction.

Liver perfusion with cytostatic-containing perfusate for cancer therapy is a kind of treatment introduced 30 years ago. It has been shown to induce regression of liver metastases from colorectal cancer [82, 83]. Procedures for isolation and hyperthermic perfusion of the liver have been developed [84, 85]. The perfusate is circulated by an extracor-

poreal procedure. It is known that extracorporeal circulation during coronary bypass surgery and during hemodialysis will activate the complement cascade. Recent studies have demonstrated that anaphylatoxins (C3a and C5a) as well as terminal C5b-9 complement complexes are released in association with liver and limb perfusion with hyperthermic and cytostatic-containing perfusates [86, 87].

Twelve patients with nonresectable secondary liver cancer were studied. Liver perfusion with hyperthermic and cytostatic-containing perfusate was performed. Cisplatin and melphalan were used as cytostatic agents. The perfusion was continued for 60 min after administration of melphalan. Cisplatin was added to the perfusate as a bolus injection 40 min after perfusion with melphalan. Arterial blood samples for terminal C5b-9 complement complexes were drawn before perfusion and after anesthesia was instituted, 1 min before start of perfusion, 1, 2, and 3 h after start of perfusion, and 24 h after start of the operation. Concentrations of terminal C5b-9 complement complexes in the perfusate were determined 1 h after the start of the perfusion procedure. The plasma concentrations of terminal C5b-9 complement complexes were increased 1, 2, and 3 h after the start of perfusion in both patients undergoing liver as well as limb perfusion compared to the levels found preoperatively and 1 min prior to the start of perfusion ($p < 0.05$). Patients undergoing liver perfusion had significantly higher terminal C5b-9 complement complex levels compared to those undergoing limb perfusion 60, 120, and 180 min after start of perfusion ($p < 0.05$). Twenty-four hours later the levels were within the normal in both groups. The concentrations of terminal C5b-9 complement complex in the perfusate were increased compared to the levels simultaneously found in systemic blood ($p < 0.001$). The concentrations of terminal C5b-9 complement complex in the perfusate did not significantly differ between perfusate from liver or limb perfusion.

Different techniques for reinfusion of wound drainage blood have been developed during the last decades. Reinfusion of erythrocyte concentrates and of whole blood have been used. Several studies have, however, demonstrated changes in the transfused blood. Transmission of different types of infections and immunological reactions from homologous blood transfusions have led to development of different techniques for autologous transfusions [88, 89]. Whole blood and erythrocyte concentrate have been used for reinfusion of wound drainage blood [90, 91]. During the last 20 years, autologous transfusions have been tried in different types of acute and elective surgery [92, 93]. The coagulation and the fibrinolytic systems as well as the complement system will be activated during this procedure. Other investigators have demonstrated that complications like hemolysis and air embolization and formation of microaggregates may occur during reinfusion of wound drainage blood [94, 95]. There are different commercially available techniques for reinfusion of erythrocyte concentrates [96, 97]. The goal is to recover shed blood and mix the blood with an anticoagulant and then remove unwanted tissue. The red cells are concentrated and the erythrocytes are washed. This means that the major part of the plasma is removed. This technique has a smaller effect on cascade systems than methods with reinfusion of whole blood. It has been demonstrated that there is less activation of the coagulation and the fibrinolytic systems from reinfusion of erythrocyte concentrate than from whole blood. In addition, our own studies indicate that a smaller amount of complement split products is infused when the shed blood has been washed and centrifugated.

We have recently evaluated the formation of complement-derived anaphylatoxins (C3a and C5a) and terminal C5b-9 complement complexes by reinfusion of wound drainage blood. Eighteen patients undergoing hip or knee arthroplasty were studied. Blood samples from the patients were drawn prior to transfusion of autologous blood, 15 min after start of retransfusion and 15 min after completed retransfusion. Samples were also taken from the infusion bag and distal to the microporous filter just prior to the infusion. A drainage suction equipment allowing reinfusion of aspirated wound blood was used (Solcotrans, Solco Basle Ltd., UK). No significant changes in plasma C3a, C5a, and terminal C5b-9 complement complexes could be observed during reinfusion of the wound drainage blood. In wound drainage blood, the concentrations of C3a, C5a, and terminal C5b-9 complement complexes were markedly increased compared to levels found in venous blood.

Thirteen patients undergoing hip arthroplasty or Harrington rod procedure were studied in regard to activation of complement during retransfusion of autologous erythrocyte concentrate. The patients received erythrocytes from an autotransfusion system. The erythrocytes were concentrated by centrifugation and washed with saline. There were no significant differences regarding the complement variables (C3a, C5a, and terminal C5b-9

complement complexes) found in circulating blood after retransfusion compared to the concentrations found just before start of retransfusion. However, the C3a levels were slightly increased in the solution of transfused washed cells. The levels of C5a and terminal C5b-9 complement complexes were not higher in the transfused suspension of erythrocytes.

In a recent study by Sieunarine et al. the release of PMN elastase in association with the use of a cell saver system was evaluated [88]. Sixteen patients undergoing aortic or orthopedic surgery were studied. They were given blood transfusions by an intraoperative cell saver system. Blood samples were drawn from the patients (arterial blood) and from the collected blood before and after washing. Elevated concentrations were found in the collected blood before washing. After washing, the PMN elastase levels were normalized. This study indicates that the process of collecting wound blood leads to degranulation and/or destruction of leukocytes. However, the washing procedure was effective in removing the enzymes.

Studies demonstrating patients developing organ dysfunction in association with blood transfusions have been published [89, 90]. Ketai et al. demonstrated development of ARDS or MOF after large transfusion of bank blood [89]. However, severe complications after retransfusion of homologous blood have also been published. Bull et al. described in a recent publication development of adult respiratory distress syndrome following administration of washed autologous red cells [90]. It is important to keep in mind that the reason why the patients receive blood transfusions may itself be an important factor behind activation of complement and leukocytes and the development of ARDS or MOF.

Preeclampsia/HELLP

Recent studies indicate that complement activation and the release of anaphylatoxins (C3a and C5a) and terminal C5b-9 complement complex occur in pregnancy complications such as preeclampsia and the syndrome of hemolysis, elevated liver enzymes and low platelet count (HELLP syndrome) [93–95].

Fourteen consecutive pregnant women with severe preeclampsia were studied. All were normotensive before and through their first 24 weeks of pregnancy. Their previous medical histories were normal. The criteria for severe preeclampsia were blood pressure >160/110 mmHg and proteinuria >0.3 g/l or blood pressure >140/90 mmHg and proteinuria >5.0 g/l in a 24-h urine sample. Fourteen consecutive normal pregnant women were studied as controls. Plasma samples were collected in association with delivery and 1 and 7 days afterwards. None of the women had any signs of infection at the time of plasma sampling. The preeclamptic women had higher blood pressure at delivery than the women with uncomplicated pregnancies. All preeclamptic women had proteinuria exceeding 0.3 g/l. The hemoglobin levels and the platelet counts were lower in the preeclamptic women than in the normal pregnant women. The plasma levels of C5a were increased at delivery and 1 and 7 days after delivery in preeclamptic women as compared to the uncomplicated pregnancies. Plasma levels of C5a were more elevated in the preeclamptic patients at the time of delivery as compared with the levels in the same group 7 days postpartum. Terminal C5b-9 complement complex levels in plasma were elevated in patients with preeclampsia compared to normals at delivery and 1 day after delivery. The terminal C5b-9 complement complexes in the preeclamptic patients were elevated at delivery compared to 1 day and 7 days after delivery in the same group.

Microvascular injury can be seen in different organs, e.g., lungs, liver, and kidneys in women with preeclampsia/HELLP. One possible explanation of the microvascular injury may be complement activation with release of anaphylatoxins and the stimulation of neutrophils and macrophages with the release of biologically active inflammatory mediators. The most important of these mediators are the cytokines, lysosomal enzymes, free oxygen radicals, and prostaglandins.

Liver Transplantation

Liver transplantation is associated with perioperative complications like hypotension and acute cardiac insufficiency [96, 97]. During orthotopic liver transplantation significant hemodynamic changes occurs in about 30% of transplanted patients immediately following reperfusion of the grafted liver [98]. The etiology behind these complications are not fully understood. It is, however, known that hypoperfusion and tissue injury lead to activation of the complement cascade.

Eleven patients with end stage liver disease undergoing orthotopic liver transplantation were included in the study. Transplantation was performed because of end stage liver disease with a

standard technique without the use of veno-venous bypass. The complement variables C3a, C5a, and terminal C5b-9 complement complex were determined before start of the operative procedure, 1 min before start of anhepatic phase, 1 min before reperfusion of the grafted liver and 2, 15, and 60 min after reperfusion of the grafted liver and 24 h postoperatively. There were no significant alterations in the C3a levels before start of reperfusion of the grafted liver. The plasma concentrations of C3a increased during reperfusion of the grafted liver. The plasma C3a concentrations were higher 15 and 60 min after the start of reperfusion than the previous concentrations. The plasma concentrations of terminal C5b-9 complement complex increased during the reperfusion period. The concentrations 1 h after start of reperfusion were higher than the previous concentrations.

Orthotopic liver transplantation leads to activation of the complement cascade. This is evidenced by the formation of anaphylatoxins and terminal C5b-9 complement complexes after reperfusion of the grafted liver.

Possible etiologies for activation of the complement cascade during the liver transplantation procedure are immunological incompatibility between the grafted liver and the host, hypoxically injured cells of the grafted liver, hypoperfusion during the operation, and the trauma itself.

Ways to Modulate Complement Activation

There are no known specific inactivators or inhibitors of the complement cascade or of split products of the cascade used in clinical practice. The most important therapeutic intervention is to remove the source of complement activation. Resection of nonviable tissue, adequate treatment of infections with antibiotics, and surgical drainage of abscesses lead to decreased levels of circulating anaphylatoxins and terminal C5b-9 complement complexes [98, 99]. The effects on the complement system by corticosteroids and specific anti-C5a antibodies are discussed in Bengtsson et al., pp 447–458.

The anesthetic technique may influence the activation of the complement cascade. Preoperative epidural blockade in association with aortic surgery will lead to a less pronounced increase of plasma C3a and C5a. Improved peripheral circulation beyond vascular clamping due to efficient dilation of collaterals by the blocking of sympathetic nerve activity may be one explanation why the amount of hypoperfused ischemic tissue and thereby the degree of complement activation during surgery is less pronounced with general anesthesia combined with an epidural block than with general anesthesia alone. Another explanation may be influence of the local anesthetic on the complement cascade.

Conclusions

Complement is activated and biologically active anaphylatoxins and terminal C5b-9 complement complexes are released in several groups of critically ill patients.

Complement activation plays an important role in the development of ARDS and MOF. The results are based on plasma analysis which is due to the existence of more and more specific complement assays for human plasma. Activation of leukocytes with the release of inflammatory mediators is also of importance for development of ARDS and MOF in critically ill patients. These complications occur, however, also in neutropenic patients. In addition to the effects on leukocytes, the anaphylatoxins have direct vascular effects that influence edema formation in areas remote from the initial injury.

There are different possibilities to minimize the negative effects of complement activation. It is of the highest importance to optimize tissue perfusion in critically ill patients. The maintenance of adequate peripheral circulation with acceptable tissue oxygenation is important for avoiding extensive formation of anaphylatoxins and terminal C5b-9 complement complexes. Devitalized tissue must be removed as early as possible, and abscesses must be drained promptly. The use of epidural blockade in addition to general anesthesia during surgery will also diminish anaphylatoxin formation.

References

1. Nutall G (1888) Experimente über die bakterienfeindlichen Einflüsse des thierischen Körpers. Z Hyg Infektionskr 4:353
2. Buchner H (1889) Ueber die nähere Natur der bakterientödtenden Substanz in Blutserum. Centralbl Bakteriol Parasitenkd 6:561–565
3. Bordet J (1895) Les leucocytes et les propriétés du sérum chez les vaccines. Ann Inst Pasteur 9:504–506
4. Ross SC, Rosenthal PJ, Berberich HM, Densen P (1987) Killing of *Neisseria meningitidis* by human neutrophils: implications for normal and com-

plement-deficient individuals. J Infect Dis 155: 1266–1275
5. Ghebrehiwet B, Müller-Eberhard HJ (1979) C3e: an acidic fragment of human C3 with leukocytosis inducing activity. J Immunol 123:616–621
6. Mayer MM (1973) The complement system. Sci Am 229:54–66
7. Densen P, Weiler JM, Griffiss JM, Hoffmann LG (1987) Familial properdin deficiency and fatal meningococcemia. N Engl J Med 316:922–926
8. Molad Y, Zimran A, Sidi Y, Pinkhas J (1990) Posttraumatic meningococcemia in a patient with deficiency of the C7 complement component. Isr J Med Sci 26:90–92
9. Alper CA, Rosen FG (1984) Inherited deficiencies of complement proteins in man. Springer Semin Immunopathol 7:251–261
10. Lachmann PJ (1988) Complement and disease. Recenti Prog Med 79:293–299
11. Dalmasso AP (1986) Complement in the pathophysiology and diagnosis of human disease. CRC Crit Rev Clin Lab Sci 24:123–183
12. McPhaden AR, Whaley K (1985) The complement system in sepsis and trauma. Br Med Bull 41: 281–286
13. Sundsmo JS (1982) The leukocyte complement system. Fed Proc 41:3094–3098
14. Byrne K, Carey PD, Sugerman HJ (1987) Adult respiratory distress syndrome. Acute Care 13: 206–234
15. Schlag G, Redl H (1982) New aspects of shock lung. Anasth Intensivther Notfallmed 17:86–91
16. Müller-Eberhard H (1986) The membrane attack complex of complement. Annu Rev Immunol 4:503–528
17. Hänsch GM, Seitz M, Betz M (1987) Effects of late acting complement components C5b-9 on human monocytes: release of prostanoids, oxygen radicals and a factor which induced cell proliferation. Int Arch Allergy Appl Immunol 82:317–320
18. Betz M, Seitz M, Hänsch GM (1987) Thromboxane B2 synthesis in human platelets induced by the late complement components C5b-9. Int Arch Allergy Appl Immunol 82:313–316
19. Hänsch GM, Seitz M, Martinotti G, Betz M, Rauterberg EW, Gemsa D (1984) Macrophages release arachidonic acid, prostaglandin E2, and thromboxane in response to late complement components. J Immunol 133:2145–2150
20. Hamilton KK, Hattori R, Esmon CT, Sims PJ (1990) Complement proteins C5b-9 induce vesiculation of the endothelial plasma membrane and expose catalytic surface for assembly of the prothrombinase enzyme complex. J Biol Chem 265:3809–3814
21. Salama A, Hugo F, Heinrich D, Höge R, Müller R, Kiefel V, Müller-Eckhardt C, Bhakdi S (1988) Deposition of terminal C5b-9 complement complexes on erythrocytes and leukocytes during cardiopulmonary bypass. N Engl J Med 318:408–414
22. Colomb MG, Arlaud GJ, Villiers CL (1984) Structure and activation of C1: current concepts. Complement 1:69–80
23. Cooper NR, Morrison DC (1978) Binding and activation of the first component of human complement by the lipid A region of lipopolysaccharides. J Immunol 120:1862–1868
24. Porter RR, Reid KBM (1979) Activation of the complement system by antibody-antigen complexes: the classical pathway. Adv Protein Chem 33:1–64
25. Tenner AJ, Ziccardi RJ, Cooper NR (1984) Antibody-independent C1 activation by *E. coli*. J Immunol 133:886–891
26. Ziccardi RJ (1984) The role of immune complexes in the activation of the first component of human complement. J Immunol 132:283–288
27. Shastri KA, Phillips MJ, Raza S, Logue GL, Rustagi PK (1988) Effect of RBCs on the activation of human complement by heparin-protamine complexes. Blood 71:36–40
28. Ghebrihiwet B, Silverberg M, Kaplan AP (1981) Activation of the classical pathway of complement by Hageman factor fragment. J Exp Med 153:665–676
29. Pangburn MK (1983) Activation of complement via the alternative pathway. Fed Proc 42:139–143
30. Gelfand JA, Donelan M, Burke JF (1983) Preferential activation and depletion of the alternative complement pathway by burn injury. Ann Surg 198:58–62
31. Joiner KA (1986) Role of complement in infectious disease. In: Ross GD (ed) Immunobiology of the complement system. Academic, New York, pp 183–195
32. Pangburn MK, Schreiber RD, Müller-Eberhard HJ (1983) C3b deposition during activation of the alternative complement pathway and the effect of deposition on the activating surface. J Immunol 131: 1930–1935
33. Morrison DC, Kline LF (1977) Activation of the classical and properdin pathways of complement by bacterial lipopolysaccharides (LPS). J Immunol 118:362–368
34. Langlois PF, Gawryl MS (1988) Detection of the terminal complement complex in patient plasma following acute myocardial infarction. Artherosclerosis 70:95–105
35. Langlois PF, Sharon GE, Gawryl MS (1989) Plasma concentrations of complement-activation complexes correlated with disease activity in patients diagnosed with isolated central nervous system vasculitis. J Allergy Clin Immunol 83:11–16
36. Haeger M, Bengtsson A, Karlsson K, Heideman M (1989) Complement activation and anaphylatoxin (C3a and C5a) formation in preeclampsia and by amniotic fluid. Obstet Gynecol 73:551–556
37. Kapp A, Meske-Brand S, Maly FE, Müller W (1984) Komplementaktivierung bei Patienten mit chronischer Polyarthritis gemessen anhand des Komplement Bruckstückes C3a im Plasma. Z Rheumatol 43:103–105

38. Roxvall L, Bengtsson A, Heideman M (1989) Anaphylatoxin generation in acute pancreatitis. J Surg Res 47:138–143
39. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW (1981) Complement activation during cardiopulmonary bypass. Evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med 304:497–503
40. Hugli TE (1979) Complement anaphylatoxins as plasma mediators, spasmogens and chemotaxins. In: Bing DH (ed) The chemistry and physiology of human plasma proteins. Pergamon, New York, pp 255–280
41. Grant JA, Dupree E, Goldman AS, Schultz DR, Jackson AL (1975) Complement-mediated release of histamine from human leukocytes. J Immunol 114:1101–1106
42. Hugli TE, Marceau F (1985) Effects of the C5a anaphylatoxin and its relationship to cyclo-oxygenase metabolites in rabbit vascular strips. Br J Pharmacol 84:725–733
43. Stimler NP, Brocklehurst WE, Bloor CM, Hugli TE (1981) Anaphylatoxin-mediated contraction of guinea pig lung strips: a non-histamine tissue responses. J Immunol 126:2258–2261
44. Hugli TE, Marceau F, Lundberg C (1987) Effect of complement fragments on pulmonary and vascular smooth muscle. Am Rev Respir Dis 135:S9–S13
45. Hachfeld del Balzo U, Levi R, Polley MJ (1985) Cardiac dysfunction caused by purified human C3a anaphylatoxin. Proc Natl Acad Sci USA 82:886–890
46. Yancey KB, Hammer CH, Harvath L, Renfer L, Frank MM, Lawley TJ (1985) Studies of human C5a as a mediator of inflammation in normal human skin. J Clin Invest 75:486–495
47. Webster RO, Hong SR, Johnston Jr RB, Henson PM (1980) Biological effects of the human complement fragments C5a and $C5a_{desArg}$ on neutrophil function. Immunopharmacology 2:201–219
48. Hugli TE (1984) Structure and function of the anaphylatoxins. Springer Semin Immunopathol 7: 193–219
49. Goldstein IM, Brai M, Osler AG, Weissmann G (1973) Lysosomal enzyme release from human leukocytes: mediation by the alternate pathway of complement activation. J Immunol 111:33–37
50. Goodman MG, Chenoweth DE, Weigle WO (1982) Induction of interleukin 1 secretion and enhancement of humoral immunity by binding of human C5a to macrophage surface C5a receptors. J Exp Med 1156:912–917
51. Scholz W, McClurg MR, Cardenas GJ, Smith M, Noonan DJ, Hugli TE, Morgan EL (1990) C5a-mediated release of interleukin 6 by human monocytes. Clin Immun Immunopathol 57:297–307
52. Henson PM, Larsen GL, Webster RO, Mitchell BC, Goins AJ, Henson J (1982) Pulmonary microvascular alterations and injury induced by complement fragments: synergistic effect of complement activation, neutrophil sequestration, and prostaglandins. Ann NY Acad Sci USA 384:287–300
53. Fearon DT, Collins LA (1983) Increased expression of C3b receptors on polymorphonuclear leukocytes induced by chemotactic factors and by purification procedures. J Immunol 130:370–375
54. Lee J, Hakim RM, Fearon DT (1984) Increased expression of the C3b receptor and complement activation during hemodialysis. Clin Exp Immunol 56:205–214
55. Haeger M, Unander M, Norder-Hansson B, Tylman M, Bengtsson A (1992) Complement, neutrophil and macrophage activation in women with severe preclampsia and HELLP syndrome. Obstet Gynecol (in press)
56. Dwenger A, Schweitzer G, Regel G (1986) Bronchoalveolar lavage fluid and plasma proteins, chemiluminescence response and protein contents of polymorphonuclear leukocytes from blood and lavage fluid in traumatized patients. J Clin Chem Clin Biochem 24:73–88
57. Habal FM, Movat HZ, Burrows CE (1974) Isolation of two functionally different kininogens from human plasma separation from proteinase inhibitors and interaction with plasma kallikrein. Biochem Pharmacol 23:2291–2303
58. Kaplan AP (1978) Initiation of the intrinsic pathways of man: the role of surfaces, Hageman factor, prekallikrein, high-molecular-weight kininogen, and factor XI. Prog Hemost Thromb 4:127–175
59. Sundsmo JS, Fair DS (1983) Relationship among the complement, kinin, coagulation and fibrinolytic systems. Springer Semin Immunopathol 6:231–258
60. Slotman GJ, Burchard KW, Williams JJ, D'Arezzo A, Yellin SA (1986) Interaction of prostaglandins, activated complement, and granulocytes in clinical sepsis and hypotension. Surgery 99:744–751
61. Kongsgaard UE, Smith-Erichsen N, Geiran O, Björkskau L (1989) Different activation patterns in the plasma kallikrein-kinin and complement systems during coronary bypass surgery. Acta Anesthesiol Scand 33:343–347
62. Pottemeyer E, Vassar MJ, Holcroft JW (1986) Coagulation, inflammation and response to injury. Crit Care Clin 2:683–702
63. Dahlén S-E, Björk J, Hedqvist P, Arfors KE, Hammarström S, Lindgren JA, Samuelsson B (1981) Leukotrienes promote plasma leakage and leukocyte adhesion in postcapillary venules. In vivo effects with relevance to the acute inflammatory response. Proc Natl Acad Sci USA 78:3887–3891
64. Björk J, Hedqvist P, Arfors KE (1982) Increase in vascular permeability induced by leukotriene B4 and the role of polymorphonuclear leukocytes. Inflammation 6:189–200
65. Fantone JC, Ward PA (1982) Role of oxygen-derived free radicals and metabolites in leukocyte-dependent inflammatory reactions. Am J Pathol 107:397–418
66. Bengtsson A, Holmberg P, Heideman M (1987) The

ischaemic leg as a source of complement activation. Br J Surg 74:697–700
67. Kapur MM, Jain P, Gidh M (1988) Estimation of serum complement and its role in management of trauma. World J Surg 12:211–216
68. Pacher R, Redl H, Frass M, Petzl DH, Schuster E, Woloszczuk W (1989) Relationship between neopterin and granulocyte elastase plasma levels and the severity of multiple organ failure. Crit Care Med 17:221–226
69. Fosse E, Mollnes TE, Ingvaldsen B (1987) Complement activation during major operations with or without cardiopulmonary bypass. J Thorac Cardiovasc Surg 93:860–866
70. Fosse E, Mollnes TE, Ingvaldsen B (1987) Complement activation during major operations with or without cardiopulmonary bypass. J Thorac Cardiovasc Surg 93:860–866
71. Bengtsson A, Heideman M (1986) Altered anaphylatoxin activity during induced hypoperfusion in acute and elective abdominal aortic surgery. J Trauma 26:631–636
72. Heideman M (1979) Complement activation in vitro induced by endotoxin and injured tissue. J Surg Res 26:670–675
73. Hansson GK, Lagerstedt E, Bengtsson A, Heideman M (1987) IgG binding to cytoskeletal intermediate filaments activates the complement cascade. Exp Cell Res 70:338–350
74. Cavarocchi NC, Pluth JR, Schaff HV, Orszulak TA, Homburger HA, Solis E, Kaye MP, Clancy MS, Kolff J, Deeb GM (1986) Complement activation during cardiopulmonary bypass. Comparison of bubble and membrane oxygenators. J Thorac Cardiovasc Surg 91:252–258
75. Lee J, Hakim RM, Fearon DT (1984) Increased expression of the C3b receptor and complement activation during hemodialysis. Clin Exp Immunol 56:205–214
76. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW (1981) Complement activation during cardiopulmonary bypass. Evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med 304:497–503
77. Herzlinger GA, Bing DH, Stein R, Cumming RD (1981) Quantitative measurement of C3 activation at polymer surfaces. Blood 57:764–770
78. Westaby S, Dawson P, Turner MW, Pridie RB (1985) Angiography and complement activation. Evidence for generation of C3a anaphylatoxin by intravascular contrast agents. Cardiovasc Res 19:85–88
79. Bengtsson A, Milocco I, Heideman M, Berggren H (1989) Altered concentrations of terminal complement complexes, anaphylatoxins and leukotrienes in the coronary sinus during cardiopulmonary bypass. J Cardiothorac Anesthesiol 3:305–310
80. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD (1983) Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 86:845–857
81. Kirklin JK, Chenoweth DE, Naftel DC, Blackstone EH, Kirklin JW, Bitran DD, Curd JG, Reves JG, Samuelson PN (1986) Effects of protamine administration after cardiopulmonary bypass on complement, blood elements, and the hemodynamic state. Ann Thorac Surg 41:193–199
82. Ausman RK, Aust JB (1959) Isolated perfusion of the liver with HN_2. Proceedings of the Forum Sessions 45th Clinical Congress of the American College of Surgeons, Atlantic City, New Jersey
83. Aigner K, Walther H, Tonn J, Wenzl A, Hechtel R, Merker G, Schwemmle K (1983) First experimental and clinical results of isolated liver perfusion with cytotoxins in metastases from colorectal primary. In: Schwemmle K, Aigner K (eds) Vascular perfusion in cancer therapy. Springer, Berlin Heidelberg New York, pp 99–102 (Recent results in cancer research, vol 86)
84. Quebbeman EJ, Skibba JL, Petroff RJ (1984) A technique for isolated hyperthermic liver perfusion. J Surg Oncol 27:141–145
85. Aigner KR, Walther H, Tonn JC, Link KH, Schock P, Schwemmle K (1984) Die isolierte Leberperfusion bei fortgeschrittenen Metastasen kolorektaler Karzinome. Onkologie 1:13–21
86. Bengtsson A, Arnestad J-P, Bengtson J-P, Henriksson BÅ, Stenqvist O, Naredi P, Hafström LO (1991) Formation of anaphylatoxins and terminal complement complexes by perfusion of limbs with malignant melanoma. Reg Cancer Treat 3:308–311
87. Arnestad J-P, Bengtsson A, Bengtson J-P, Henriksson BÅ, Stenqvist O, Naredi P, Hafström LO (1992) Isolated hyperthermic liver perfusion with cytostatic-containing perfusate activates the complement cascade. Br J Surg 79:948–951
88. Sieunarine K, Langton S, Lawrence-Brown MMD, Goodman MA, Prendergast FJ, Hellings M (1990) Elastase levels in salvaged blood and the effect of cell washing. Aust N Z J Surg 60:613–616
89. Ketai LH, Grum CM (1986) C3a and adult respiratory distress syndrome after massive transfusion. Crit Care Med 14:1001–1003
90. Bull MH, Bull BS, Van Arsdell GS, Smith LL (1988) Clinical implication of procoagulant and leukoattractant formation during intraoperative blood salvage. Arch Surg 123:1073–1078
91. Keeling MM, Gray LA Jr, Bring MA, Hillerich VK, Bland KI (1983) Intraoperative autotransfusion. Experience in consecutive 725 cases. Ann Surg 197:536–540
92. Hallowell P, Bland JHL, Buckley MJ (1972) Transfusion of fresh autologous blood in open-heart surgery. J Thorac Cardiovasc Surg 64:941–945
93. Tedesco F, Radillo O, Candussi G, Nazzaro A, Mollnes TE, Pecorari D (1990) Immunohistochemical detection of terminal complement complex and S protein in normal and pre-eclamptic placentae. Clin Exp Immunol 80:236–240
94. Haeger M, Bengtsson A, Karlsson K, Heideman M (1989) Complement activation and anaphylatoxin

(C3a and C5a) formation in preeclampsia and by amniotic fluid. Obstet Gynecol 73:551–556
95. Haeger M, Unander M, Bengtsson A (1990) Enhanced anaphylatoxin and terminal C5b-9 complement complex formation in patients with the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol 76:698–702
96. Carmichael FJ, Lindop MJ, Farman JV (1985) Anesthesia for hepatic transplantation: cardiovascular and metabolic alterations and their management. Anesth Analg 64:108–116
97. Aggerwal S, Kang Y, Freeman JA, Fortunato FL, Pinsky MR (1987) Postreperfusion syndrome: cardiovascular collapse following hepatic reperfusion during liver transplantation. Transplant Proc 19: 54–55
98. Bengtsson A, Holmberg P, Heideman M (1983) The ischemic limb as a source of complement activation. Br J Surg 74:697–700
99. Heideman M, Hugli TE (1984) Anaphylatoxin generation in multisystem organ failure. J Trauma 24:1038–1043