Mediators of multiple organ failure

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Abstract. Multiple Organ Failure (MOF) has largely been attributed to bacterial sepsis, though conclusive evidence of an essential role for bacteria and/or their endotoxins is still lacking. On the other hand, MOF and the clinical syndrome of sepsis may be aseptically induced in germ-free animals. This paper reviews the evidence that excessive activation of endogenous humoral mediators and inflammatory cells may cause this highly lethal syndrome.

Key words: Multiple organ failure — ARDS — Sepsis — Complement — Elastase — Neopterin

The adult respiratory distress syndrome (ARDS) with subsequent sequential failure of multiple organ functions (MOF) and the clinical syndrome of sepsis, still carries a mortality of 60%. Since the first authors to describe ARDS noticed that these patients subsequently die of sepsis [1], there is a consensus that bacterial overgrowth is the cause of this highly lethal syndrome. However the evidence for such a causal relationship is poor: (1) MOF also develops in patients with primarily non-bacterial problems such as severe pancreatitis severe trauma before bacterial invasion is obvious, (2) no single study could reliably demonstrate positive blood cultures or elevated levels of circulating endotoxin preceding MOF [2–8], (3) no clinical, biochemical or morphological differences could be found between patients with the “clinical” sepsis syndrome (no bacteremia, no focus) and patients with the “classical” sepsis syndrome (bacteremia, septic focus) [2, 8], (4) the drainage of pus [9], administration of antibiotics or decontamination of the gastro-intestinal tract does not necessarily prevent or suppress MOF [10], (5) a MOF-like syndrome may be induced aseptically in germ-free rats by intraperitoneal inoculation of zymosan [11].

Evidence is slowly gathering that excessively activated endogenous inflammatory compounds and cells may be themselves responsible for structural damage and functional deterioration in remote vital organ systems. In this article a brief and necessarily incomplete summary is given of the — possibly harmful — biological effects of several inflammatory mediators, products and cells, and of the available evidence of their activity in patients with ARDS, and the subsequent syndrome of MOF and “clinical” sepsis.

Inflammation

The sequence of events in inflammation, e.g. after local tissue trauma begins with the local activation of the different cascade systems (complement, coagulation, fibrinolytic and kinin-kallikrein), generating mediators from circulating proteins. Some of these mediators (anaphylatoxins: C3a, C5a) have strong chemotactic effects on circulating inflammatory cells (granulocytes, monocytes), activate these cells to produce proteolytic enzymes and toxic oxygen radicals, and have effects on local mast-cells which release histamine. In the next phase, cellular mediators have an important role. The wound granulocytes and macrophages release systemic signals (e.g. GM-CSF, PGE-2, TNF, IL-1, IL-6) to adapt the organism to the local requirements of the local problem. The wound therefore has been aptly called an endocrine organ [12].

Though inflammation is intended to be a local process, it is obvious that in severely ill patients with signs of generalised “sepsis” a systemic activation or spill-over of inflammatory products and mediators may be expected. From experience, clinicians are well aware of the “risk-factors” for such an event, and the actual incidence of ARDS, MOF and sepsis in some prospective studies of patients at risk was up to 80%. The “abnormal” systemic presence of any inflammatory mediator would then be a Marker of the MOF-syndrome, and the change from normal should correlate with the severity of MOF. However, if these compounds are themselves causing damage to otherwise healthy tissues and their specific functions, their detection in abnormal amounts in the systemic circulation should predict MOF. At present only a very few Predictor studies are available.
Mediators from circulating proteins
In general, mediators derived from circulating proteins are products of a cascade of activation steps that sequentially convert proenzymes to their active counterpart. The endogenous mediator activity is modulated by inhibitors, inactivators, the half-life of the mediator, the responsiveness of the target organ and — in some cases — the cellular destruction of the mediator [13]. In order to cause MOF, these mediators should (1) be found in abnormal concentrations in the blood prior to MOF, with a high specificity and sensitivity (2) induce hemodynamic, biochemical and morphological alterations resembling MOF if administrated experimentally.

From the available data on the different cascade systems in (predicting) MOF, only the complement system has been well-studied (for non-complement mediators, see [6, 13–15]). The complement system is activated by antigen-antibody complexes, endotoxin, enzymes released from PMNs and macrophages, plasmin, platelet products, products of virus-infected cells and by exposed collagen. The biologically active substances are C3a and C5a and the cytolytic terminal complement complex C5-C9. C3a and C5a have strong chemotactic properties, activate PMNs, release enzymes from PMNs, and release histamine from mast cells. In this respect C5a is 100 times more potent than histamine and 1000 times more than C3a [16]. C5a also increases capillary permeability in collaboration with PGF2α [17], and induces IL-1 and TNF production.

Experimental infusion of autologous zymosan-activated plasma in rabbits has been shown to induce tachypnoea, leucopenia, granulocyte aggregation and sequestration in the lung, liver, kidney and heart [18] resembling the early morphological changes in ARDS and MOF [19]. These alterations, however, are not severe and are largely reversible. Only with an additional stimulus such as hypoxia, could severe MOF-like morphological changes be induced in the experiment [18]. On the other hand, in complement depleted or complement deficient experimental animals, the pulmonary response to inflammatory stimuli is significantly diminished [20, 21]. Low plasma-levels of the complement compounds C3 and C4 have been found in MOF-patients [14, 22] indicating complement activation, but possibly also decreased synthesis. Elevated plasma-levels of C3a have been found prior to the development of ARDS by several authors [23–25]. C5a assessed with radio-immuno assay could not be correlated or was not predictive of MOF in several studies [14, 23–25], while C5a-like activity assessed by aggregometry was predictive [26, 27]. In most studies however, elevated levels of the anaphylatoxins could only be found at an early stage of disease. Also C5a has a short half-life as it is rapidly internalised by PMNs. Possibly the most suitable compound for assessment in the complement cascade is the stable split-product of C3, C3d [14, 27], which also was predictive of MOF [14].

Inflammatory cells and their products
PMNs
Though ARDS has been described in neutropenic patients, the direct and indirect involvement of PMNs in ARDS and MOF has by now clearly been established [18, 19, 28–30]. Studying the numbers and functions of circulating PMNs in MOF however, may not be relevant [31], since biologically active PMNs aggregate and stick to endothelial cells, and peripheral blood PMNs may not be representative of the activated population. Also the peripheral white-cell count only reflects the balance between bone marrow synthesis and de-margination of PMNs, and margination and breakdown of PMNs. Most information about PMN-dynamics would be obtained by PMN-turnover, but we have no method to assess this rate of turnover.

At the site of inflammation, PMNs release numerous active substances, such as proteolytic enzymes (elastase, collagenase, cathepsin G) and toxic oxygen-radicals, vasoactive substances (PAF-acether, leukotrienes, PGE2) and wound-hormones (MAF, GM-CSF). Actually it might be more appropriate to measure these substances as an index of PMN activity. Presently, the measurement of most of these substances (leukotrienes, eicosanoids, PAF, MAF, GM-CSF, oxygen radicals and lipid-peroxidation products) in clinical patients is either impossible, impractical (LTB4 only in bile, PAF by bio-assay) or has barely been done. Increasing data are available on elastase, products of the cyclo-oxygenase pathway and free radicals.

Elastase. Elastase is a serine-protease that is capable of degrading elastin, collagen III and IV, proteoglycans, fibronectin, clotting factors and fibrinolytic factors, complement factors C3 and C5, immunoglobulins, protease-inhibitors and transport proteins such as ferritin. Elastase is essential for PMN-mediated endothelial injury [32, 33]. The fact that 60% of plasma-proteins are protease-inhibitors illustrates that the body needs a thorough protection against proteinases.

Experimental administration of elastase results in elevated pulmonary vascular resistance, decreased cardiac output, pulmonary leucostasis, DIC, and increased venous admixture of oxygen [34]. Elastase can be monitored in clinical patients as the complex with its inhibitor α1-antiprotease by an ELISA-method, and more recently by a rapid IMAC-test [35]. All studies available have shown a positive relation between elastase and severity of ARDS, sepsis or MOF in several conditions such as major trauma, burns and peritonitis [6, 8, 14, 35–41]. A few studies found elastase to predict MOF [14, 35, 36]. One study could demonstrate that the rise in EVLW in trauma patients occurred subsequent to a prior rise in elastase and C3a [41].

The present evidence suggests an important role for elastase as a marker of PMN-activity, and possibly as a predictor of ARDS and MOF, though specific plasma levels have yet to be set for this predictive value.

Cyclooxygenase pathway products. Whenever cell-membranes are damaged, the arachidonic acid cascade is activated. Especially activated PMNs, but also macrophages, platelets and endothelial cells may produce large amounts of the most potent vasodilator prostacyclin and vasoconstrictor thromboxane. The action of prostacyclin and thromboxane is primarily expressed in the local environ-
ment. Their half-lives are short, while a systemic spillover is completely cleared from the blood during the first passage through the pulmonary capillaries. The early pulmonary hypertension in ARDS and sepsis is due to the action of thromboxane and abolished by cyclo-oxygenase inhibitors. Cyclo-oxygenase inhibitors are however, unable to block the sequence of events leading to full-blown ARDS and MOF. Also in ARDS, the pulmonary clearance of prostacyclin is incomplete, leading to systemic vasodilation, possibly contributing to the hyperdynamic circulation and supply-dependent oxygen consumption in these patients.

Though several clinical studies have shown elevated plasma-levels of these compounds in ARDS and MOF, the available data are conflicting and the alterations found are not predictive (for review see [42]). Experimental administration of these compounds induces only part of the (circulatory) alterations seen in ARDS and MOF.

Presently the prostaglandins of the E series have been studied in ARDS and sepsis because of their immunomodulatory and anti-inflammatory capacities. PGE₁ is also a pulmonary vasodilator. Administration of PGE₁ in the animal experiment could not prevent ARDS [43], and administration to patients with ARDS has not improved survival [44]. PGE₂ – a product of PMNs, macrophages and various pulmonary cells, and also released whenever increased cell-membrane arachidonic acid release occurs – down-regulates the aspecific immune system by stimulating the suppressor cell line and suppressing T-cell proliferation. PGE₂ depresses PMN function, is anti-inflammatory on macrophages, turns down TNF and IL-1 production. PGE₂ thus may initiate the events leading to immunodepression.

In vitro, adding PGE₂ strongly increases vascular permeability induced by C5a and PMNs [17]. Hitherto, no studies are available on the effects of experimental administration of PGE₂ in relation to MOF. In clinical patients, elevated PGE₂ levels correlated with sepsis [45].

Free radicals. Free radicals are unstable atoms, with an unpaired electron in their outer electron-ring. Free radicals of oxygen are formed by activated phagocytes (oxidative burst), by most cells upon reoxyegenation after hypoxia through activation of xanthine-oxidase, and as a by-product of activation of the arachidonic acid cascade. Free radicals induce the process of lipid-peroxidation (e.g. leading to cell-membrane damage with deleterious influx of calcium into the cell), to inactivation of enzymes (e.g. of α₁-antiprotease leading to uncontrolled activity of free elastase) and of detoxifying agents, e.g. glutathion (for review see [46]). Through all these effects, free radicals are potent inflammatory agents. Experimental administration of (agents inducing) free radicals closely mimicks ARDS [47] and MOF [48].

Human PMNs have been demonstrated to produce much higher concentrations of free radicals in response to inflammatory stimuli than bovine, ovine or porcine PMN [49], possibly explaining why the human race is so sensitive to inflammatory stimuli.

A major problem in determining the involvement of free radicals in patients prone to ARDS and MOF is the difficulty of demonstrating their presence or effects in vivo, as free radicals have an extremely short half-life and are rapidly inactivated by ubiquitous free-radical scavengers. One way to circumvent this problem, is to measure stable end-products of lipid-peroxidation, such as malondialdehyde (MDA). MDA is elevated in plasma after cardiac-pulmonary bypass [50], and in pulmonary tissue of trauma-patients dying of ARDS and sepsis [51]. The MDA-method, however, is subject to criticism, and more studies are urgently needed utilising newer methods such as lipofuscin and hydroxy-nonenal.

Macrophages

Macrophages are present in most tissues such as the brain (glia-cells), the lung (alveolar macrophages), the kidney (mesangial cells, the peritoneum, the spleen. The hepatic Kupffer cells comprise 70% of the total population of fixed tissue macrophages. Circulating monocytes are attracted to the site of inflammation, and differentiate locally to macrophages. Macrophages are activated directly by C5a, and by a score of signals from PMNs such as GM-CSF, low molecular MSF and PMN -IL1 like activity (for review see [52]).

Macrophages that have been treated with activated complement or interferon are referred to as "inflammato-
ry" or "elicited" macrophages, as these stimuli are insufficient to completely activate them. Treatment with more potent stimuli such as LPS stimulates macrophages fully, and these are referred to as "activated" macrophages [52]. Apparently it takes several days after triggering to develop the full inflammatory reaction of macrophages.

Upon stimulation, macrophages may release some 53 different classes of secretory products [53], of whom some are pro-inflammatory (proteolytic enzymes, oxygen radicals, IL-1, TNF), others anti-inflammatory (PGE₂), immunosuppressive (IL-2) or pro-coagulatory. Again, most of these mediators are difficult to monitor clinically. One solution may be to measure neopterin, a stable end-product of macrophage activity.

Interleukin-1. IL-1 (endogenous pyrogen) induces fever and hypermetabolism, stimulates fibroblasts and endothelial cells to produce GM-CSF and PGE₂, enhances PGE₂ synthesis in the hypothalamus, increases skeletal muscle proteolysis, has a priming effect on macrophages, is important for maintaining the gut-mucosal barrier and turns on the liver synthesis of acute phase proteins (for review see [53, 54]).

Experimental administration in rabbits results in hypotension, decreased peripheral resistance, increased heart rate and cardiac output, leukopenia and thrombocytopenia [55]. IL-1 thus possesses the ability to induce hemodynamic and hematologic changes typical of sepsis and to duplicate a series of events in MOF, but at present no easy "in-vivo" assay is available.

Tumor necrosis factor. TNF (cachectin) induces fever, hyperglycemia and hyperkalemia, increases PMN-aggregation, phagocytosis, adherence to endothelial cells and oxygen radical formation, blocks the proliferation of endothelial cells and enhances the killing of endothelial
cells by PMN, decreases the synthesis of key-enzymes, induces IL-1 production. TNF-activity is suppressed by PGE₂ (for review see [53, 56]). Experimental administration of TNF results in fever, diarrhea, tachypnea, hypotension, metabolic acidosis, elevated lactate levels, lethargy, ARDS-like changes in the lung, hemorrhagic necrosis of the kidneys and adrenals, and finally death [56–58]. These alterations closely resemble the effects of endotoxin in administration in man [59].

At present, only a limited number of studies are available on TNF in relation to sepsis and MOF [7, 60]. TNF plasma levels correlated well with lactate levels, severity of illness and mortality [7, 60]. No correlations were found with positive blood cultures [61], endotoxin-levels [7], nor with subsequent ARDS, shock or mortality [61].

**Neopterin.** Though in itself inactive, neopterin (a pteridine related to dopamine) [62] may offer a practical way of monitoring macrophage activity in patients with or at risk of ARDS, sepsis and MOF. γ-Interferon and LPS cause the release from macrophages of neopterin in a dose dependent way [63]. Plasma-neopterin levels in endotoxemia correlated well with the clinical signs of sepsis but not with the plasma level of endotoxin [64]. In clinical studies, plasma-levels of neopterin correlated well with the severity of ARDS, MOF and sepsis and could accurately predict non-survivors several days before the event [8, 65, 66].

**Mast cells**

Mast cells are present in virtually every tissue. Their perivascular location permits exposure to circulating factors as well as rapid release of mediators into the circulation. The mast cell mediator content of human skin alone exceeds that needed to cause cardiac arrest and proteolysis by 2000-fold [13]. The content of heparin in these cells is estimated to be 100-fold greater than that needed to cause full anticoagulation [13]. PAF from mast cells may activate platelets. Despite their ubiquitous presence and strong inflammatory properties, presently no method is available to monitor the activity of mast cells in ARDS and MOF.

**Summary and conclusion**

Summarizing the inflammatory capacities of the three types of inflammatory cells — PMNs, macrophages and mast cells — each type seems able to induce a lethal whole body reaction. This whole body inflammation has hitherto largely escaped our attention, as in clinical studies inappropriate methods have been used such as counting peripheral leukocytes, and as monitoring key-enzymes, key-cells (activated PMNs, macrophages and mast cells) hitherto was impossible. Presently a new set of methods is available, allowing a closer look at this whole body inflammation, such as elastase (monitoring PMN activity), neopterin (monitoring macrophage activity) and hopefully clinically practicable methods to monitor cytokines as well as endotoxin-levels. Only after such comprehensive studies have been performed, might it be concluded that — as in the experimental animal — sepsis and MOF may not necessarily be caused by bacteria or their endotoxins, but by an untoward autodestructive and self-sustaining activation of our own inflammatory cells.

**References**

1. Ashbaugh DG, Petty TL (1972) Sepsis complicating the acute respiratory distress syndrome. Surg Gyneco Obstet 135:865–869
2. Goris RJA, te Boekhorst TPA, Nuytinck JKS, Gembirene JSF (1985) Multiple organ failure. Generalised autodestructive inflammation? Arch Surg 120:1109–1115
3. Mc Ardle CS, MacDonald JAE, Ledingham IMA (1975) A three year retrospective analysis of septic shock in a general hospital. Scott Med J 20:79–84
4. Border JR, Bone LB, Steinberg SM, et al. (1990) Metabolic response to trauma and sepsis. In: Border JR et al. (eds) Blunt multiple trauma. Dekker, New York, pp 191–258
5. van Deventer SJH, Buller HR, ten Cate JW, Sturk A, Pauw W (1988) Endotoxaemia: an early predictor of septicaemia in febrile patients. Lancet 1:605–608
6. Schoeffel U, Lenz T, Rutf G, Mittmayer Ch, Lausen M (1987) “Sepsis parameters” in patients with lethal burn. In: Paubert-Braquet M (ed) Lipid mediators in the immunology of shock. Plenum Publishing, New York
7. Damas P, Gijzen PH, Lopez M, Gathy R, Vrindts Y, Reuter A, Demonty J, Lammy M, Franchimont P (1988) Cachectin (TNFα) serum levels in human during septic shock (Abstr). First Int Congress on immune consequences of trauma, shock and sepsis. Munich
8. Nast-Kolb D, Waydhas Ch, Jochem M, duswald KF, Schweißer L (1989) Organversagens beim Polytarma – Wertigkeit der Infektiologie (Abstr) Anaesthesist 38:340
9. Norton LW (1985) Does drainage of intraabdominal pus reverse multiple organ failure? Am J Surg 149:347–350
10. Goris RJA, van Bebber ITP (in press) Selective decontamination of the gastrointestinal tract does not prevent Multiple Organ Failure. An experimental study. Arch Surg
11. Goris RJA, Boekholtz WKF, van Bebber ITP, Nuytinck JKS, Schillings PHM (1986) Multiple organ failure and sepsis without bacteria. An experimental model. Arch Surg 121:897–901
12. Wilmore DW (1986) The wound as an organ. In: Little RA, Frayn KN (eds) The scientific basis for the care of the critically ill patient. Manchester University Press
13. Yurt RW (1986) Noncomplement mediators. In: Davis JM, Shires GT (eds) Advances in host defense mechanisms, vol 6. Raven Press, New York
14. Nuytinck JKS, Goris RJA, Redl H, Schlag G, van Munster PJJ (1986) Posttraumatic complications and inflammatory mediators. Arch Surg 121:886–890
15. Aasen A (1985) The proenzyme functional inhibition index. A new parameter for evaluation of the severely injured and septic patient. Acta Chir Scand [Suppl] 522:37–233
16. Jose PJ, Forrest MJ, Williams TJ (1981) Human CSa des Arg increases vascular permeability. J Immunol 127:2376–2380
17. Wedmore CV, Williams TJ (1981) Control of vascular permeability by polymorphonuclear leucocytes in inflammation. Nature 282:66–80
18. Nuytinck JKS, Goris RJA, Weerts IGE (1986) Acute generalised microvascular injury by activated complement and hypoxia: the basis of ARDS and MOF? Br J Exp Pathol 67:537–548
19. Nuytinck JKS, Offermans XJ, Kubat K, Goris RJA (1988) Whole body inflammation in trauma patients. An autopsy study. Arch Surg 123:1519–1524
20. Dehling DJ, Steinberg SM, Wismar BL, Lowery BD, Carey LC, Cloutier CT (1987) Complement depletion in an porcine model of septic acute respiratory distress. J Trauma 27:615–625
21. Olson LM, Moss GS, Baukus O, Das Gupta T (1985) The role of C5 in septic lung injury. Ann Surg 85:771–776
22. Heideman M, Saravis C, Clowes GHA (1982) Effect of non-viable tissue and abscesses on complement depletion and the development of bacteremia. J Trauma 22:527–532
23. Solomkin JS, Cotta LA, Satoh PS, Hurst JM, Nelson RD (1985) Complement activation and clearance in acute illness and injury: evidence for C5a as a cell-directed mediator of ARDS in man. Surgery 97:668–678
24. Slotman GJ, Burchard KW, Yelling SA, Williams JJ (1986) Prostaglandin and complement interaction in clinical acute respiratory failure. Arch Surg 121:271–274
25. Heideman M, Hugi T (1984) Anaphylatoxin generation in multiple system organ failure. J Trauma 24:1038–1043
26. Hammerschmidt DE, Weaver LJ, Hudson LD, Craddock PR, Jacob HS (1980) Association of complement activation and elevated plasma-C5a with ARDS. Lancet 1:947–949
27. Duchateau J, Haas M, Schreyen H, Radoux L, Sprangers H, Noel X, Braun M, Lamy M (1984) Complement activation in patients at risk of developing ARDS. Am Rev Respir Dis 100:1058–1064
28. Schlag G, Redl H (1983) Posttraumatic ultrastructural changes and the role of granulocytes in the lungs, liver and skeletal muscle. Intensive Care Med 9:148
29. Heftin AC, Brigham KL (1979) Granulocyte depletion prevents increased lung vascular permeability after endotoxemia in sheep (abstr). Clin Res 27:399A
30. Flick MR, Perel A, Staub NC (1981) Leukocytes are required for increased lung microvascular permeability after microembolisation in sheep. Circ Res 48:344–351
31. Russell Martin R (1987) In host defense, leukocytes that are counted may not count. J Lab Clin Med 109:378–379
32. Smedley LA, Tonnesen RA, Sandhaus RA, Haslett C, Guthrie LA, Johnston RB, Henson PM, Worthen GS (1986) Neutrophil-mediated injury to endothelial cells. J Clin Invest 77:1233–1243
33. Henson PM, Johnston RB (1987) Tissue injury in inflammation. J Clin Invest 79:669–674
34. Stokke T, Burchardi H, Hensel I, Kostering H, Kathner T, Rahlf G, Redi H, Pacher R, Woloszczuk W: Acute pulmonary failure-comparison of neutrophils from a variety of species when stimulated by opsonized zymosan and P-Met-Leu-Ph. J Comp Pathol 96:189–196
35. Lang H, Jochum M, Redl H, Fritz H (1988) Validity of elastase as an indicator of pathobiochemical alterations of neutrophils in septic patients (1987) In: Pfleiderer W (ed) Biochemical and clinical aspects of pteridines, vol 5. de Gruyter, New York
36. Redi H, Pacher R, Woloszczuk W: Acute pulmonary failure-comparison of neopterin and granulocyte elastase in septic and non-septic patients (1987) In: Pfleiderer W (ed) Biochemical and clinical aspects of pteridines, vol 5. W. de Gruyter, New York
37. Dusswald KH, Jochum M, Schram W, Fritz H (1985) Released granulocyte elastase: an indicator of pathobiochemical alterations of neutrophils from a variety of species when stimulated by opsonized zymosan and P-Met-Leu-Ph. J Comp Pathol 96:189–196
38. Dittmer H, Jochum M, Fritz H (1986) Freisetzung von granulozytärer Elastase und Plasmaproteinveränderungen nach traumatisch-bakterieller Lungenschaden nach schwerem Trauma. Langenbecks Arch Chir [Suppl] 217–222
39. Redi H, Pacher R, Woloszczuk W: Acute pulmonary failure-comparison of neopterin and granulocyte elastase in septic and non-septic patients (1987) In: Pfleiderer W (ed) Biochemical and clinical aspects of pteridines, vol 5. de Gruyter, New York
40. Beutler B, Cerami A (1986) Cachectin and tumor necrosis factor as two sides of the same biological coin. Nature 320:584–588
41. Tracey KJ, Beutler B, Lowry SF, Merryweather J, Wolpe S, Millsark IW, Haviiri J, Fahey T, Zentella A, Albert JD, Shires GT, Cerami A (1986) Shock and tissue injury induced by recombinant human cachectin. Science 246:446–45
42. Gaskill HV (1986) Continuous infusion of TNF: mechanisms of toxicity in the rat. J Surg Res 44:664–671
43. Miche HR, Spriggs DR, Manogue KR, Sherman ML, Revhaug A, D'wyer ST, Arthur K, Dinarello CA, Cerami A, Wolff SM, Kufe DW, Wilmore DW (1988) Tumor necrosis factor and endotoxin induce similar metabolic responses in human beings. Surgery 104:280–286
44. Girardin E, Grau GE, Dayer JM, Roux-Lombard P, the J5-study group, Lambert PH (1988) TNF and interleukin-1 in the serum of children with severe infections purpura. N Engl J Med 319:397–400
45. De Groote MA, Martin MA, Densen P, Pfeifer MA, Wenzel RP (1989) Plasma Tumor Necrosis Factor levels in patients with presumed sepsis. JAMA 262:249–251
46. Huber Ch, Troppmaier J, Rokos H, Curtius H-Ch (1987) Neopterin in acute multi-organ failure (Abstr) First Int Congress on the immune system organ failure. J Trauma 27:837–848
47. Brigham KL (1986) Role of free radicals in lung injury. Chest 89:529–863
48. Del Maestro RF, Bjork J, Arfors KE (1981) Increase in microvascular permeability induced by enzymatically generated free radicals. In: Novelli GP (ed) Oxygen free radicals in shock. Karger, Basel
49. Young S, Beswick P (1986) A comparative study of the oxidative reactions of neutrophils from a variety of species when stimulated by opsonized zymosan and P-Met-Leu-Ph. J Comp Pathol 96:189–196
50. Westaby S, Fleming J, Royston D (1986) Acute lung injury during cardiopulmonary bypass, the role of neutrophil sequestration and lipid peroxidation. Trans Am Soc Artif Intern Organs 31:604–609
51. Nerlich ML, Seidel J, Regel G, Nerlich AG, Sturm JA (1986) Klinische experimentelle Untersuchungen zum oxidativen Membrandosen nach schwerem Trauma. Langenbecks Arch Chir [Suppl] 217–222
52. West MA (1987) Macrophage effector function in sepsis. Arch Surg 122:242–247
53. Nathan CF (1987) Secretory products of macrophages. J Clin Invest 79:319–326
54. Dinarello CA (1984) Interleukin-1. Rev Infect Dis 6:51–95
55. Okusawa S, Gelfland JA, Ikejima T, Connolly RJ, Dinarello CA (1988) Interleukin 1 induces a shock-like state in rabbits. J Clin Invest 81:1162–1172
56. Beutler B, Cerami A (1986) Cachectin and tumor necrosis factor as two sides of the same biological coin. Nature 320:584–588
57. Tracey KJ, Beutler B, Lowry SF, Merryweather J, Wolpe S, Millsark IW, Haviiri J, Fahey T, Zentella A, Albert JD, Shires GT, Cerami A (1986) Shock and tissue injury induced by recombinant human cachectin. Science 246:446–45
58. Gaskill HV (1986) Continuous infusion of TNF: mechanisms of toxicity in the rat. J Surg Res 44:664–671
59. Miche HR, Spriggs DR, Manogue KR, Sherman ML, Revhaug A, D'wyer ST, Arthur K, Dinarello CA, Cerami A, Wolff SM, Kufe DW, Wilmore DW (1988) Tumor necrosis factor and endotoxin induce similar metabolic responses in human beings. Surgery 104:280–286
60. Girardin E, Grau GE, Dayer JM, Roux-Lombard P, the J5-study group, Lambert PH (1988) TNF and interleukin-1 in the serum of children with severe infections purpura. N Engl J Med 319:397–400
61. De Groote MA, Martin MA, Densen P, Pfeifer MA, Wenzel RP (1989) Plasma Tumor Necrosis Factor levels in patients with presumed sepsis. JAMA 262:249–251
62. Huber Ch, Troppmaier J, Rokos H, Curtius H-Ch (1987) Neopterin in acute multi-organ failure (Abstr) First Int Congress on the immune system organ failure. J Trauma 27:837–848
63. Redi H, Strohmaier W, Pacher R, Woloszczuk W, Inthorn D, Troppmaier J (1988) Possible use of the monococyte/macrophage activation marker neopterin for the clinical monitoring of sepsis related multi-organ failure (Abstr) First Int Congress on the immune consequences of trauma, shock and sepsis, Munich
64. Aasen AO (1988) Role of endotoxin and proteases in MOF (Abstr) Second Vienna Shock Forum
65. Strohmaier W, Redi H, Schlag G, Inthorn D (1987) D-erythro-1:6-10
66. Nightingale P (1988) Prostaglandins in shock. Intensive Care News 97:668–678
67. Modig J, Samuelsson T, Sandin R (1987) Volume substitution and treatment with prostaglandin E1 in a porcine model of endotoxemia-induced pulmonary and cardiovascular failure. Acta Chir Scand 153:165–170
68. Holcroft JW, Vassar MJ, Weber CJ (1986) Prostaglandin E1 and survival in patients with the ARDS. Ann Surg 203:371–378
69. Faust E, Mews A, Baker CC, Strasser Th, Allan SS, Rieber P, Heberer G (1987) Prostaglandin E2-dependent suppression of in-

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