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Multiple organ failure – the discrepancy between our scientific knowledge and understanding and the management of our patients

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Abstract The excitement of molecular biology and of genetic knowledge and their possibilities must be balanced against our limitations in using this information for the care of our patients. There is a great discrepancy between what we know and what we can do. There are many reasons for this. A major one is that science must simplify/reduce the variables in experimentation and then generalize in terms of a specific factor or effect, whereas patients are complex with variables that we do not yet understand completely. This powerful science is now teaching us about the genetic diversity in both susceptibility and outcome of disease, and the diversity in life experiences and anti-

gen exposures. Clinicians have tried to lump together and treat in a similar way many diverse human diseases. This has not worked well. Pancreatitis and perforated diverticulitis both produce inflammation and sepsis, but they are different processes and may both lead to multiple organ failure. This lumping together has contributed to the failure of so-called magic bullets. There are new contributors to organ damage. Gender, lifestyle and prior disease differences also complicate the care of patients. Despite this, we are slowly and gradually improving the care of our surgical patients by careful pre-, intra- and postoperative support and better, simpler and safer operations.

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Introduction

There is a tremendous difference between what we know in science and what we can do for our patients. The extraordinary explosion of knowledge about inflammation, mediators and critically ill patients has greatly increased our knowledge of these processes. Therapy has improved, but at a slower and more gradual pace, primarily by better monitoring and support of organ function.

A classic example of this phenomenon is demonstrated by the presentation of the 1999 Nobel Prize in Physiology and Medicine to Robert Furchgott, Louis Ignarro and Ferid Murad [1]. These scientists demonstrated that vascular endothelial cells form nitric oxide (NO) through nitric oxide synthase (NOS), which in turn stimulates cyclic guanosine monophosphate (cGMP) synthesis in the underlying vascular smooth muscle causing relaxation or vasodilatation. This exciting contribution opened up the

entire world of NO and its many biologic functions. It is an important mechanism whose activities are still being mapped out. This led to the study of excess vasodilatation in septic shock, which was thought to be due to the overproduction of NO. Many animal and clinical studies suggested that this phenomenon was occurring. It was then proposed that a NOS inhibitor would help prevent this problem of excess vasodilatation and decreased blood flow in septic shock [2,3]. Many trials and experiments of NOS inhibitors were performed in animals and patients. However, in a recent issue of *Critical Care Medicine*, Grover et al. [4] reported that the randomized, double-blind clinical trial of an NOS inhibitor was discontinued due to increased mortality and adverse outcomes in patients who received the drug. There is now a moratorium against the clinical use of such agents until more is learned about them. Here, then, is an example of a Nobel Prize being awarded for the study of endothelial

cell-produced NO on the one hand, and the concept of excess vasodilatation in septic shock, the hypothesis that this was due to NO and a clinical trial blocking NO that increased mortality on the other. Some would say that a specific NOS, such as inducible NOS, would have more promise.

Bloom [5] made a comparison of the last millennium from St. Thomas Aquinas to Newton and his *Principia*. “St. Thomas Aquinas’ view was that knowledge is of two types – that which man could know and that which was ‘higher than man’s knowledge’ and not to be sought through reason.” Newton’s *Principia*, on the other hand, stated “that our universe and all within it are indeed knowable.” I add to this that all things may be knowable, but perhaps not doable.

The tremendous amount of information generated by molecular biology – the techniques of DNA identification; the human genome project; mediators; signal transduction; the immune system; the response to injury; organ, cell, endothelium and membrane function – all stretch the imagination. There have been improvements in the way we care for patients, but they have been modest and slow and have not been easy to document. It has not been possible to apply most of the information of molecular biology to patient care. I believe that there are three major reasons for this discrepancy. You may have others.

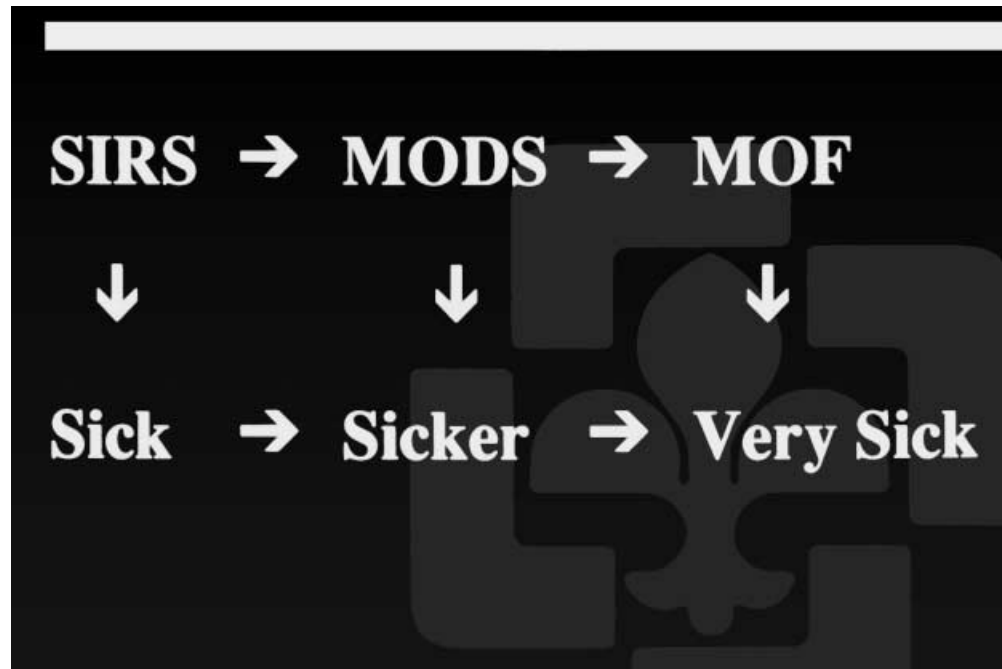
1. There are differences between individuals (diversity) which may not be measurable and which are not taken into consideration in therapy and clinical trials. We do not look, act or respond alike. Our genetic differences dictate how we will respond to injury, an operation, infection or stress. Genetic studies are now beginning to describe these extensive genomic differences. Sir William Osler once said, “As no two faces, so no two cases are alike in all respects, and unfortunately it is not only the disease itself which is so varied but the subjects themselves have peculiarities which modify its action” [6].
2. Our experiences in life are all different – our exposure to antigens, prior illness and injury; our immune history; and our group experiences. We are not genetically pure animals living in the same cage for our lifetimes before an insult occurs. There is also much evidence for these powerful and complex acquired differences and exposures.
3. We have tried to lump together and treat human abnormalities according to symptoms and signs rather than to the basic causes of their diseases – we have tried to treat inflammation, sepsis, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS) rather than what caused them; perforated diverticulitis is not acute pancreatitis and neither are ventilator-associated pneumonia and appendicitis.

All of these differences and factors complicate our scientific understanding and make developing appropriate therapy for patients based on molecular biology more complex. The wonders of science are revealing the complexities of human disease. The picture is becoming clearer – genetic polymorphisms, antigen exposure, etc. [7]. Patient care is improving, but slowly. This should not be discouraging, but we must try harder.

Multiple organ failure

Next, a word about MOF, its meaning and its relationship to these complexities. In 1975, I wrote an editorial entitled “Multiple, Progressive or Sequential Systems Failure: A Syndrome of the 1970s” [8]. In it, I described three examples of patients that I observed who developed multiple organ problems. One patient had acute hemorrhagic pancreatitis. Another had a colon resection and developed an anastomotic leak leading to peritonitis. A third was a patient of mine in whom I had performed a double valve replacement (aortic and mitral valves); the patient had an extremely low cardiac output for the next 6 weeks or so and died. I reviewed the clinical course of these patients and then the autopsy findings. In one patient, for example, the autopsy indicated bronchopneumonia, necrotizing bacterial arteritis, hyaline membranes in the lung, healed and acute renal infarcts and acute tubular necrosis in the kidneys, hemorrhagic foci in the gut, pseudomembranous enterocolitis in the colon, and massive acute central lobular necrosis of the liver. Thus, in this patient there was pathologic evidence of severe multiple organ dysfunction and/or failure. This led to the development of the concept of MOF. During a sabbatical in Munich, Germany, I worked with Dr Eugen Faist. Together we reviewed the experience at the Klinikum Grosshadern, Ludwigs Maximilians Universität of the problem of MOF after injury. This was reported by Faist at a meeting of the American Association for the Surgery of Trauma in Colorado Springs, USA [9]. In 433 consecutive patients with multiple injuries, 50 patients had single organ failure (SOF) and 34 had MOF. Mortality for MOF patients was 56%. There were 78 deaths overall (18%). Faist described two patterns: a rapid single-phase pattern of development of MOF due to trauma and shock; and a delayed second-phase MOF due to trauma, shock and then sepsis. The temporal sequence of events of organ failure was the lung first, then the clotting system, the kidney and the liver, with sepsis ultimately being the cause of death in a number of patients. Definitions of failure of each organ system were also given. For example, cardiovascular failure was defined as the presence of one or more of the following: (a) a heart rate of <54/min; (b) mean arterial pressure of <49 mmHg; (c) occurrence of ventricular tachycardia and/or ventricular fibrillation; (d) pH<7.24 with a PaCO₂ of <49 mmHg.

Fig. 1 SIRS progresses to MOF and then to death



Respiratory failure was described as one or more of the following: (a) a respiratory rate of <5 or >49 /min; (b) $\text{PaCO}_2 > 50$ mmHg; (c) $\text{A}_a\text{PO}_2 > 350$ mmHg, $\text{FiO}_2 > 0.40$, positive end-expiratory pressure (PEEP) > 5 ; (d) dependence on a ventilator on the fourth day of organ system failure. In the same way, failure of all organs and systems – the kidney, liver, gastrointestinal tract, nervous system, etc. – were defined. These figures were also updated and reported by Faist et al. [10] in the German literature.

Following this presentation, many joined in the battle. Beale and Bihari [11] stated that “the search for a unifying mechanism and, hence, perhaps an effective therapy for MOF has been intense.” I reviewed our experience with MOF at St. Louis University in almost 6000 patients who underwent cardiac operations over several years [12]. MOF occurred in 128 patients (2.1%), primarily after emergency operations and in high-risk patients. However, 78% of these MOF patients died. Mortality in all patients was 4.7%. Thus, most were elective cardiac surgical procedures and the risk was low.

A new proposal

Recently, a new proposal was developed by a consensus conference of physicians, intensivists and surgeons [13]. They defined the concept of SIRS and MODS.

SIRS is defined as the response to a variety of severe clinical insults with two or more of the following conditions: a temperature >38 or $<36^\circ\text{C}$; a heart rate >90 beats/min; a respiratory rate of >20 breaths/min; or a

$\text{PaCO}_2 < 32$ torr (<4.3 kPa) or a white blood count of $>12,000$ or <4000 cells/ mm^3 , or $>10\%$ immature or band forms.

MODS was described simply as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention. Since that time, many have continued to use SIRS and MODS as a concept [14,15]; however, this has been criticized by many [16], including myself. I stated then that “our ingenuity in developing terminology exceeds our abilities to take care of these patients” [17]. For example, Jones and Lowes [18] found that SIRS is not a very good predictor of bacteremia, the positive predictive value being only 7%.

SIRS, MODS and MOF are constructs or concepts. They are not diseases or even syndromes. They cannot be treated other than to support organ function. MOF is the final common pathway to death in the modern organ-supporting intensive care unit (ICU). Blakiston’s Gould Medical Dictionary (3rd edition) defines a syndrome as a group of symptoms and signs which, when considered together, characterize a disease or lesion [19]. Thus, none of these concepts are diseases and, therefore, are not treatable as such.

In a recent article, I described the concept (shown in Figure 1) that SIRS to MODS to MOF is simply going from sick to sicker to very sick [20]. Some have focused on SIRS indicating an inflammatory process. As Goris et al. [21] demonstrated that inflammation alone, as produced by Zymosan in the peritoneal cavity of animals, can lead to MOF. Nor is inflammation a disease. It is a complex biologic process of host defense and repair of injury.

Many years ago, John Hunter stated that, “Inflammation in itself is not to be considered as a disease – and in disease, where it can alter the disease mode of action, it likewise leads to a cure; but where it cannot accomplish that salutary purpose, it does mischief” [22].

The failure of magic bullets

The scientific advances of molecular biology developed a number of substances and approaches that, in terms of animal experimentation, suggested possible help for patients. These were called “magic bullets” after the concept developed by Ehrlich and Morgenroth [23] at the turn of the twentieth century. There are a number of so-called magic bullets that have failed to improve overall mortality (Table 1). For details and references to these trials and reviews of them, I refer the reader to papers by Opal [24], Eidelman and Sprung [25], the late Roger Bone [26], and Zeni et al. [27]. I have also reviewed the reasons why I think many of these trials have failed [28].

There have been more recent clinical trials using what some thought might be magic bullets and these have also failed. One such trial used Diaspirin cross-linked Hgb, which was found to increase mortality [29]. Trials were halted. N-acetylcysteine, an antioxidant, was found to be of no help in patients and actually may be harmful despite early encouraging results in adult respiratory distress syndrome (ARDS) [30]. The use of Leptin to control obesity has not been impressive in clinical trials [31] and the NOS inhibitor 546C88 increased mortality [4]. Ibuprofen did not decrease shock, ARDS or mortality in

Table 1 Failed magic bullets. *MAB* monoclonal antibodies; *TNF* tumor necrosis factor; *IL* interleukin; *PAF* platelet-activating factor; *IgM* immunoglobulin M; *LPS* lipopolysaccharide; *IgG* immunoglobulin G; *IVIG*, intravenous immune globulin; *SOD* superoxide dismutase.

Methyl prednisolone for septic shock
E-5 MAb to endotoxin
Human MAb, HA-1A to endotoxin
MAB to hTNF α
Dimeric receptors
rhIL-1ra antagonist
PAF receptor antagonist
IgM antibodies
Bradykinin antagonists
Prostaglandin antagonists
Taurolidine
T88-antienterobacterial MAB
IVIG – core LPS hyperimmune globulin
CB0006 murine anti-TNF MAB
Bay X 1351 murine anti-TNF MAB
sTNFr-Fc fusion protein
TNFr55-IgG-TNF-55 receptor fusion protein
MAK 195F-anti-TNF MAB
CDP571-humanized anti-TNF MAB
SOD

septic patients [32]. Antithrombin III treatment in severely injured patients did not attenuate the inflammatory response or improve outcome [33]. Another study of a platelet-activating factor (PAF) receptor (BB-882) antagonist in septic patients also offered no advantages [34].

Why have there been failures of so many potential magic bullets? Many reasons have been proposed by a number of authors [24,25,26,27,28]. The three major reasons that I described earlier for the discrepancy between science and patient care also apply here. In addition, specific problems affect trials of “magic bullets”, including:

1. The causality of disease: many different complex diseases are being lumped together and treated with one of these magic bullets. SIRS has been used as the entry criteria in some studies. It is no wonder that they have failed to improve 28-day mortality, which is the usual endpoint for success. I do not believe that there is a single treatment or agent which will help all or many different complex disease processes in patients.
2. Redundancy and overlap of mediators: there is considerable overlap of the activities of cytokines and other mediators.
3. There is no single factor that acts as the lethal activator.
4. The timing of treatment is extremely important. In experimental studies in animals, pretreatment before the insult will help. Obviously, this cannot be performed for injured, sick or septic patients.
5. There is the problem of modulation of an essential biologic function – inflammation. Can we control inflammation without doing harm to the host? That is a real question that has not been resolved.
6. Is there immune deficiency or immune excess? Perhaps both occur. T-cell immune deficiency occurs after injury, whereas immune excess of the non-specific immune system such as neutrophil activation may be harmful. Thus, both may be at work. How do we sort out which is most important and which should be treated or blocked?

Another example is the treatment of patients with sepsis syndrome with a soluble TNF receptor (sTNFr) [35]. This was a phase II controlled trial of a novel P75 soluble receptor fusion (fused with IgFc fragment) protein. At higher doses there was increased mortality, and in lower doses there was no difference from the controls.

Some have proposed that physiologic improvement in a critically ill patient should be used as an endpoint for a clinical trial rather than 28-day mortality. The problem with this is, what if there is some physiologic improvement such as ventilation function but the patient dies anyway. What difference does it make? Goldfarb [36] described investigations into the polydeterminate nature of sepsis. He stated that, “A fundamental concept of modern pharmacology is: for each pathologic condition (disease) a single pharmaceutical can be found to correct

or reverse that state.” I believe that there is no magic bullet for sepsis because it is not a disease. It is a complex of many factors. Some of the consensus conference participants were unable to define exactly what sepsis is. Is it infection? Is it inflammation? What is it?

I believe we must go back to the suggestions of Stehbens [37,38]. He stated that, “Treatment of a disease, when based on symptoms or clinical manifestations is at best palliative and nonspecific.” All of us use or give therapy based on symptoms or clinical manifestations. When we get a cold or the flu, we may take aspirin or a non-steroidal anti-inflammatory agent. This is for palliation, to help us feel better, but it will not alter the basic disease process. Only specific treatment of a disease will improve the mortality and alter the disease process. How do you treat an injury severity score (ISS) of 26, an Apache III score of 30, SIRS, MOF, the sepsis syndrome, or a consensus conference definition of a human state. It is impossible to treat such abnormalities. Fortunately, some of the gurus of critical care agree that it is time for a reevaluation of these definitions [39].

Solbach et al. [40] wrote that “lymphocytes play the music, but the macrophages call the tune.” They stated that, “Dealing with a single cytokine on an isolated population of cells (or an organism) may be a gross oversimplification of events *in vivo*.” I believe that they have hit the nail on the head.

I have now reviewed the third reason for the discrepancy between excellent science and patient care. I will now go back to reasons 1 and 2. First, the differences between individuals.

Variations in patients

These variations include:

1. Genetic differences in cytokine response to sepsis, including DNA polymorphism of tumor necrosis factor (TNF), interleukin (IL) -1 and IL-1ra. Some seem to protect, while others are associated with a poor prognosis. Some of these have been described by Zehnbauser et al. [41]. An IL-1ra polymorphism may increase susceptibility to sepsis [42]. There is the possibility of another IL-1 predisposition to sepsis that may also vary in populations in the UK from those in Australia [43]. A TNF2 allele is strongly associated with death from septic shock [44] and another TNFb gene is associated with sepsis in trauma patients [45].
2. There are differences in preoperative, pre-illness immunity and prior immune history. An example of this was described by Bennett-Guererro et al. [46], who measured the endotoxin core antibody Endocab. A low preoperative level of Endocab in patients undergoing cardiac operations predicted an adverse outcome, whereas high levels suggesting previous expo-

sure to either gram-negative bacteria or endotoxin predicted an improved outcome. This finding has been confirmed by Hamilton-Davies et al. [47].

3. There are male/female gender differences in both animals and patients as described by Chaudry et al. [48] and others.
4. The age of the patient makes a big difference.
5. Prior illness, such as chronic obstructive pulmonary disease (COPD), coronary artery disease, etc., make a difference.
6. Lifestyle, obesity, poor nutrition, lack of exercise, etc. are all factors!

There are other variations in patients, including cytokine pleiotropy and redundancy, as described by Sánchez-Cuenca et al. [49]. Examples of this are that the blocking of TNF- does not alter other products [50], the polymorphisms of interferon- microsattelites [51], discordant TNF- super family gene expression [52], IL-1 receptor antagonist polymorphism [42], leukocyte receptors for TNF differences [53], different polymorphic heat shock proteins (HSPs) and variations [54], and variations in different populations, such as the difference in UK and Australian population responses to various substances [43].

Complexities in human biology

Aasen et al. [55] studied the immunologic and inflammatory consequences of surgical trauma and found extensive immunologic and inflammatory responses taking place in the closed surgical wound that would not be recognized in blood samples. Other complexities include pleiotropy and redundancy in cytokines, genetic variations in the response to lipopolysaccharide (LPS) [56], polymorphic HSPs, and differential receptor subtypes as cited above. Also present are discordant super family gene expression, a gene promoter polymorphism and receptor antagonist polymorphism and, of course, cytokine microsattelites [57]. An example was described by Sh et al. [7]. The association of TNF microsattelites with outcome in sepsis indicated that TNF⁻⁶ and TNF⁻¹ levels increase in septic patients; however, TNF⁻¹⁰ increased in non-survivors [44, 45].

There is a tremendous disparity between scientific knowledge about endotoxin and the clinical usefulness of that knowledge. There is nothing at the present time that seems clinically useful about the knowledge on endotoxin. We know that it is present in the walls of gram-negative organisms. We know that it does all sorts of bad things when it is injected into animals and people, but we still have no information about what it does in various sick patients and what we might do about it. New developments may help [58].

O'Reilly et al. [59] reported on endotoxin sepsis and the primrose path. They reviewed how the use of endo-

toxin models has failed to identify a clinically useful therapeutic agent for the treatment of sepsis. Archibald Philip Primrose was the Fifth Earl of Roseberg. He promoted the concept that the aristocracy and monarchy are no longer necessary. This was labeled the “primrose path, a tempting but hazardous course.” Endotoxin models of sepsis may be the primrose path of research.

New and confusing concepts of organ damage

There are a number of new and confusing concepts relating to organ damage that have been heretofore unknown. One of these is that arteriosclerosis may be the result of infection, a possibility suggested by the finding of organisms in arteriosclerotic plaques. Hatch [60] reported finding the organism *Chlamydia pneumoniae* in 70% of arteriosclerotic plaques. Herpes simplex virus (HSV) has been implicated, as has cytomegalovirus (CMV) [61,62]. Others have suggested that *Helicobacter pylori* may be involved [63]. Dental infection and remote infection elsewhere in the extremities have been implicated in rapid occlusion of coronary arteries [64]. Are these the causes or are they associations that are not totally worked out? The circumstantial evidence is very interesting. There are also tremendous genetic differences in disease susceptibility and these are now being studied vigorously.

Gender gap

Chaudry et al. [48] found in animals with trauma that infection was more prevalent in males and that this was related to testosterone. They performed a number of studies supporting this relationship [65]. The male swagger and ornamentation in animals suggests a decreased humoral immune response as the basis for this [66]. Eachempati et al. [67], however, described increased mortality from sepsis in female patients, as did Crabtree et al. [68]. However, Offner et al. [69] found increased infections in males after trauma. In autoimmune diseases, estrogen and prolactin seem to be the problem [70]. In comparison with males, multiple sclerosis occurs two times more commonly in females, rheumatoid arthritis occurs three times more frequently, and lupus erythematosus occurs nine times more often. What is the answer to this gender gap? It seems that if you are injured, you are better off being female; however, if you develop an infection, then you are better off being male. What should you do if you are injured and develop an infection?

Another new and confusing concept of organ damage is recent evidence that the mesenteric lymph of animals in shock is toxic and, when it returns to the central circulation, it activates neutrophils which produce cell dam-

age [71]. In a clinical study, thoracic lymph was diverted and sampled in patients with MOF and no toxicity was found [72]. Others found that mesenteric lymph is a problem and this must be explored further in order to ascertain what its consequences are in man [73,74]. In experimental animals, there seems little doubt about this phenomenon [75].

Postimplantation inflammation has been described by Zimmer et al. [76]. The implantation of a device in a patient produces an inflammatory reaction that can be quite severe. There is also a question as to whether we should replace rather than block various mediators. For example, increasing the level of protein C could be helpful.

There is a question as to whether transgenic knockout animals, which provide fascinating information, will explain the redundancies, the overlap, and the interactions between cytokines and various other mediators. They may not be able to indicate the problems of cell-cell interaction such as the interactions between neutrophils and platelets [77].

Polymerase chain reaction (PCR) will contribute greatly to our understanding of human disease [78]. PCR detects microbial DNA in blood and is much more sensitive than blood cultures. A consensus PCR will provide information about shared conserved genetic sequences. There is also representational difference analysis (RDA) and pathogen detection chips. DNA microarray techniques and gene expression immune cells will provide similar responses. It is possible, in the future, that everyone with sepsis or SIRS may be found to have an infection of some sort, a virus which cannot be cultured, bacteria which cannot be cultured, or some other microbial factor [79,80,81].

Other new concepts of organ damage include superantigen-mediated lethal shock [82]. The bacteria *H. pylori* produces gastric ulcer and duodenal ulcer disease, and perhaps gastric cancer. Does *H. pylori* modulate the response to injury and is it a nosocomial infection [83,84]?

It is known that neutrophils in the inflammatory response are both a culprit and a solution with delayed apoptosis, cytotoxicity, activation of neutrophils, and the production and release of elastase and superoxide anions, which damage cells [87,88]. The effect of granulocyte colony-stimulating factor (G-CSF) is important. For example, the use of neupogen, a G-CSF compound, is encouraging [89], whereas Root [90] reported that rG-CSF (filgrastin) did not alter morbidity or mortality in the treatment of pneumonia, sepsis and septic shock [89]. There is considerable information about these factors, but what to do about them is far from being established. These are presently imponderables.

The timing of treatments is critical. For example, Knox et al. [91] found that recombinant human growth hormone (rHGH) can be helpful in burns when given at an appropriate time; however, in other studies, it was found to increase mortality. The relationships of infec-

tion and cancer are becoming increasingly apparent. Hepatitis B, *H. pylori*, the Lyme disease spirochete and other organisms are associated with increased incidence of certain malignancies. Patients with short-bowel syndrome have benefited from rHGH [92], as have patients with burns [93]. A multicenter phase III trial in Europe administered rHGH to patients after operations, trauma or with ARDS and after 5 days of intensive care. The company allegedly called off the trial because of a two-fold increase in mortality in the treated group. This has not been reported yet (D. Wilmore, pers. comm.).

There are other differences that must be considered. For example, the neutrophil response to trauma depends on the bacterial species. In addition, septic serum signaling is diverse and complex [94]. Genes are expressed in the serum of septic patients which were not previously associated with sepsis or known to have any relationship with sepsis. Other differences include: AB T-cell receptor diversity differences in species sensitivity of hormones; variability in the G-CSF response; and LPS stress variability in various species.

An additional problem is that of autoimmunity, which may be related to molecular mimicry. Albert et al. [95] recently described the relationship that may pertain. For example, if the host acquires an infection with an agent that has an antigen similar to host antigens, tolerance to the autoantigens may break down. The pathogen response then cross-reacts to cause tissue damage and an autoimmune response.

Are we improving patient care and, if so, how?

Prevention of MOF is the goal. We know that we cannot treat specifically but can only support MOF, MODS and SIRS; therefore, we must prevent them by means of better patient care.

Are we improving patient care, are we winning the battle [96,97], and is MOF disappearing? In Levine et al. [98] we reviewed this recently, raising the question: MOF – is it disappearing? Our answer to this question was no: MOF is not disappearing and, as we help more severely injured and sick patients to survive, MOF may actually increase and the mortality will remain high. I will now review the evidence for this.

Zimmerman et al. [99] compared the risks and outcomes for patients with organ system failure from 1982 to 1990. They found that “The incidence and overall outcome of organ system failure have not changed significantly over the past eight years. There has been significant improvement in survival of patients with persistent severe organ system failure.” Thus, this report confirms again (1) that better intensive care is helping, and (2) my insistence that the secret to MOF is prevention.

Regel et al. [101] reported on the results of patients with multiple trauma (3406 patients) treated between

1972 and 1991 at a German level one trauma center. They found increased head and thoracic injuries in the second decade. In the second decade, there was a decrease in renal failure and ARDS, but an increase in MOF from 15.4 to 28.2%. Lethal MOF increased from 13.8 to 18.6%; however, overall mortality decreased from 37 to 22%. Regel et al. believed that more severely injured patients stayed alive longer to develop MOF and then die.

Christou et al. [101] reported on the delayed hypersensitivity response and host resistance in surgical patients, and on the results of surgical care over a 20-year period. They found that overall surgical mortality decreased from 11.4% in the 1970s to 10.2% in the 1980s and to 2.4% in the 1990s. They believe that this was due to improved pre-, post- and intra-operative care. However, there was no decrease in surgical ICU deaths. The ICU remains a problem. O’Keefe et al. [102] reported 10-year trends in costs, resource utilization and survival in an established trauma center. They found no change in mean age or ISS over the 10-year period. Crude mortality did not change. It stayed at 8%. Length of stay decreased from 9.5 to 6.8 days, while costs increased by 16.7%. Adjusting for ISS and accidental injury score, the mortality decreased by 3%/year in patients with an ISS >16.

Thus, to answer the question – is MOF disappearing? –, in the last decade the incidence varied from 2 to 25%, depending on the clinical setting, with a mortality rate of 40–80%. Regel et al. [100] found that the mortality from trauma decreased, but the mortality from MOF increased. Christou et al. [101] found that overall surgical mortality decreased, but ICU mortality did not change. I found that, in cardiac surgery, the overall incidence of MOF was unchanged, but more re-operations were performed recently where the incidence of MOF was higher.

O’Keefe and Maier [103] concluded that there are documented improvements in the treatment of septic shock, trauma, ARDS, and that these are “due to overall and cumulative improvements in care in the ICU rather than to any isolated specific intervention.” They predicted, “as survival rates improve, the ability to test specific interventions and document relevant improvements will become more difficult.”

The promissory note in scientific research

I have described the results of wonderful studies of science and injury and how some investigators concluded, by predicting usefulness in patient care, beyond what their studies allow [104]. This phenomenon continues and is unfortunate. Extending the results beyond what the study actually shows is a form of “hype”. For example, an author may state that these biologic effects suggest a promising candidate for the treatment of sepsis in

humans from a study based on 30 rats. Recent examples of this include a paper by Forceville et al. [105], from Paris, where it was stated, "In severely ill ICU patients with SIRS, we observed an early 40% decrease in plasma selenium." They then went on to state "... this could explain the threefold increase in morbidity and mortality rates in these patients ..." This is ridiculous of course. Wong [106] stated that, "In molecular terms, MODS may occur when endothelial cells undergo disparate patterns of gene expression either simultaneously or consecutively." That does not help me understand MODS.

In 1960, I sat at a dinner of the American Heart Association with the great pioneer Wilhelm Kolff. Kolff was the developer of the artificial kidney, an immense contribution from a man who dedicated his life to this concept and the science behind it. At this dinner, Kolff talked about how science and technology would advance. He stated that, "Advances in science and technology will easily be able to develop a satisfactory long-term implantable artificial heart." He said that it would be just like going to the moon, a simple scientific problem. I asked him whether he thought there would be any biologic problems. He said no, those were surmountable. It is now the year 2000, 40 years later, and there is still no satisfactory, long-term implantable artificial heart, nor is one on the immediate horizon.

Have there been any clinical advances in the care of patients in the past 20 years?

There have been a number of advances, but they are difficult to document on a patient-by-patient basis. They can only be documented by the types of experience that were cited earlier in the section entitled "Are we improving patient care and, if so, how?: "Is multiple organ failure disappearing?" Are we winning the battle? One such advance is better resuscitation and initial care. There certainly have been improvements in monitoring. Early definitive operations for fracture immobilization allow patients to move about and decreases the need for ventilatory support and the development of ARDS [107]. Better circulatory, pulmonary and gut support are provided by various agents, ventilator strategies and enteral and immune nutritional support [96,97]. Immune-enhancing diets seem to make a difference [108]. Hemodiafiltration has been helpful in certain circumstances [109,110]. In addition, immunomodulation has made a contribution. Some of the new therapeutic agents, such as glucan, ketoconazole, and antithrombin III, remain controversial, depending on how they are used.

Other advances include some approximation of microcirculatory blood flow by measuring intercellular pH in the stomach [111], by minimal surgical procedures, the widespread use of epidural block and other adjuncts. There remains the contrast between molecular biology

and minimal surgery and the disparity between them [112]. Minimal surgery has certainly contributed to better patient care. There are other procedures on the horizon such as the measurement of hemodynamic patterns during high-risk elective operations, as performed by Shoemaker et al. [113]. They found that lethal circulatory dysfunction may occur during the operation. During an operation, non-survivors were found to have a decreasing cardiac index and stroke index and stroke work, a decrease in oxygen delivery, and a decrease in oxygen consumption [114]. Identifying these factors during surgery may allow immediate corrective measures. We found, for example, that using oxygen consumption and delivery as endpoints for resuscitation in critically ill patients is not particularly helpful. Oxygen parameters are more useful as predictors of outcome than as endpoints for resuscitation [115]. We have known for many years that surgical and injured patients must increase oxygen transport, cardiac index and oxygen consumption to survive.

Integrative (non-linear) biology and chaos theory

Goodwin [116] stated that, "The great gift of chaos theory to the practice of medicine has been the simple but profound negative statement: 'Traditional science cannot predict complex systems'." People (patients) are such complex systems.

Another reason for the discrepancy between our science and patient care is that much of science today is based on traditional concepts. The "milieu interieur" of Bernard [117] is important, as is the contribution to homeostasis by Cannon [118]. Now there is a new science of non-linear integration, which, according to Schultz [119], may be another emerging scientific revolution. He stated that, "Molecular biology provides parts of a puzzle which are dynamic or plastic. Putting them together is the problem." It is our job to put them together by learning the rules of association or integration. Schultz described non-linearity as "the shape of the 'whole' cannot be predicted by knowing only the shapes of the separated parts."

Buchman stated that "if nested, nonlinear models are better representatives of human physiology, than Cannon's collection of negative feedback servomechanisms, then therapy should be redirected toward transitions to a basal range – not therapeutically manipulating things such as cytokines or nitric oxide" [120]. Focusing on the phases of inflammation (pro-anti, etc.) would be Cannon's approach. Blocking one mediator may change not only the effects of that mediator, but may also disturb other mediators and the entire system.

Sir Karl Popper, in his Medawar Lecture in 1986 to the Royal Society in London, stated that "biology cannot be reduced to physics because biochemistry cannot be

reduced to chemistry. Reductionism is not possible in biologic systems. An organism cannot be reduced to a series of systems” [121]. As physicians, we were taught that stability is healthy. Now we are learning that regularity and stability are more characteristic of the beginning of disease. For example, injection of endotoxin into normal human volunteers increased cardiac regularity [122]. Godin and Buchman stated that “a nonlinear system is one whose behavior is not a simple sum or multiples of the inputs to the system. Chaos is irregular behavior of some deterministic, nonlinear systems” [123]. They proposed a theory of uncoupling of biologic oscillators to progress from SIRS to MODS. Biologic systems are always coupling and uncoupling (multiple stable states). Disease is a failure to recouple. Thus, the physiologic states described by Siegel et al. [124] may be a better way to describe and treat human problems. In the meantime, we have much to learn about how non-linear integrative biology will help us to solve clinical problems.

Conclusion

The discrepancy between what we are learning in molecular biology and what we can do for our patients is great. The science is exciting, very worthwhile, and should be encouraged. Eventually it will make contributions to health and patient care. In the meantime, we must focus on better and safer operations, better treatment of injury, and clinical research to improve care and decrease morbidity and mortality.

We must avoid exaggerating the results and significance of animal research because it may not apply to man. All of us remember exciting experiments in the laboratory that have never helped patients.

Our research may eliminate the need for an operation. Professor Edward D. Churchill [125] at Harvard and the Massachusetts General Hospital in Boston once stated that, “Surgery began with trauma and congenital anomalies and therein shall it end.” Even congenital anomalies may be prevented or treated in utero. Angioplasty with stents may eventually take the place of coronary bypass grafting. Many years ago, antibiotics eliminated the need for mastoidectomies, but otolaryngologists went on to other things.

We must be cautious about so-called “magic bullets” and remember the differences in individuals, both in terms of genetics and in life experiences. We must treat disease, not concepts of inflammation or of being sick. We must be careful about “academically-correct biology,” as described by Vogel [126]: “(1) It seeks molecular explanations; (2) It views scientific progress as incremental accretion of detail; (3) The immediate goal is human therapy; (4) Its operation is unabashedly entrepreneurial.”

Latour [127] stated that, “Science does not enter a chaotic society to put order into it anymore but to add new, uncertain ingredients – to the collective process.”

Claude Lenfant [128], Director of the National Heart, Lung and Blood Institute of the National Institutes of Health (NHL&B), stated that, “The real challenge of the new millennium may indeed be to strike an appropriate balance between the pursuit of exciting new knowledge and the full application of strategies that are already known to be extremely effective but considerably underused.”

Finally, I have paraphrased a section of the Old Testament, Ecclesiastes 3:1 [129]:

There is a time for everything and a season for every activity under heaven.

“A time to be born and a time to die,
A time to plant and a time to pluck up,
A time to weep and a time to laugh,
A time to mourn and a time to dance,
A time of war and a time of peace,”

A time to give cytokines and a time to block cytokines,
A time to supplement and a time to modulate,

And a long time to figure out the time for any of these.

Then, if successful, the Lord will invite you to Stockholm

and there will be a time for honor.

Addendum

On 1 and 2 March 2000, the Fifth World Congress on Trauma, Shock, Inflammation and Sepsis took place at the Klinikum Grosshadern, the Ludwig Maximilians Universität, Munich, hosted by Professor Eugen Faist and Professor Wilhelm Schildberg. Thousands attended from more than 60 countries all over the world. I suggest to you that a major theme of this congress, although not stated, was the theme of this presentation – the discrepancy between understanding and management. At this meeting, basic scientists presented the results of their exciting research into molecular biology on the leading edge of scientific knowledge. Clinical investigators presented their equally exciting findings about sick, injured and septic patients. Some of the experiences presented will help us to take better care of our patients. All of these studies are very worthwhile; however, there is a widening gap between our knowledge of human biology, our understanding of it, and our ability to help patients. Why is this?¹

¹ An address at an honorary degree presentation to Dr. Baue by Ludwig Maximilians Universität, Munich, Germany, 28 February 2000.

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