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Sequential Metabolic Changes following Induction of Systemic Inflammatory Response in Patients with Severe Sepsis or Major Blunt Trauma

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Abstract. We have recently completed studies in critically ill patients with severe sepsis or major trauma that investigated sequential changes in the metabolic response following admission to the intensive care unit. Protein, water, and energy metabolism were measured using in vivo neutron activation analysis, tracer dilution, dual-energy x-ray absorptiometry, and indirect calorimetry. Over the 3-week study period both groups of patients lost 13% of their total body protein. The severe sepsis patients retained twice the volume of fluid of those with major trauma, and the return to normal hydration in the sepsis group was correspondingly prolonged, especially for those in the elderly age group. In both groups of patients resting energy expenditure increased progressively over the first week to around 40% above normal and was still elevated 3 weeks from onset of illness. A twofold increase in total energy expenditure occurred in both groups of patients between the first and second weeks of critical care admission. The prolonged hypermetabolism throughout the study period was not reflected in the concentrations of circulating proinflammatory cytokines, which fell rapidly over the first week. The pattern of changes seen in plasma proinflammatory and antiinflammatory cytokine concentrations is similar for sepsis and trauma. The remarkably similar metabolic sequelae seen in critically ill patients following the onset of severe sepsis or major trauma may constitute a universal response to the induction of the systemic inflammatory response syndrome.

Cuthbertson showed more than 50 years ago that the injured patient early after trauma demonstrates a characteristic response in which hypermetabolism occurs, protein and fat are consumed, and body water and salt are conserved [1]. These metabolic alterations are characteristic also of the patient with severe infection. Indeed, patients surviving resuscitation after major trauma remain at risk of progressive organ failure and death due to what appears to be an uncontrolled inflammatory process. This systemic inflammatory response manifests as if the patient is infected. A septic cause, however, is usually not identifiable. The term systemic inflammatory response syndrome (SIRS) was proposed by the expert consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine [2] to describe this generalized inflammatory process. Many investigators have speculated that a final common pathway may apply to all catabolic states. It is not known if the systemic response to infection and that induced by a noninfectious insult results in similar metabolic responses. We have recently carried out studies that quantify, in the context of modern trauma and surgical care, the sequential changes in the metabolic response occurring in severely septic surgical patients and critically injured patients after blunt trauma.

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Sequential Changes in Body Composition following Severe Sepsis or Major Trauma

Longitudinal studies of the changes in body composition that occur in critically ill patients with major trauma or severe sepsis have recently been conducted in our department. These studies were approved by the North Health Ethics Committees, and written informed consent was obtained from each patient or, usually, the patient's next of kin. Of the 23 patients recruited into the study with generalized peritonitis secondary to perforation of an abdominal viscus, 12 completed the protocol. All underwent urgent surgery and were then treated in our critical care unit (median time in critical care 13 days). Clinical details are given in Table 1. The results of this study have recently been published [3]. Of the 12 patients, 2 died (on postoperative days 24 and 28) but the other 10 survived and left hospital in a median time of 29.5 days. The median time from enrollment to the first body composition scan was 2 days (range 1–4 days). Of 65 patients admitted to our intensive care unit (ICU) with major trauma and recruited into the study, 21 completed the protocol. Of these 21 patients, 18 sustained a major blunt head injury; the other 3 patients suffered blunt abdominal trauma. Their median stay in critical care was 9 days (Table 1). The median time from enrollment to the first body composition scan was 3 days (range 0–5 days). Of the 21 patients, 7 developed septic complications while in critical care.

The patients underwent body composition measurements as soon as they were hemodynamically stable (day 0) and again 5, 10, and 21 days later. Major trauma patients were also measured on day 15. The measurements included total body protein (TBP) by in vivo neutron activation analysis, total body water (TBW), and extracellular water (ECW) by tritium and bromide dilution, respectively, total body fat by dual-energy x-ray absorptiometry (DEXA), and total body potassium by whole-body counting. Details of the methodology have been reported elsewhere [3, 4].

Table 1. Demographic and clinical data of 12 patients with serious sepsis and 21 patients with critical injury.

Parameter	Trauma	Sepsis
Male/female	18/3	6/6
Age (years)	21 (16–70)	67 (25–76)
ISS	34 (16–59)	
APACHE II		21.5 (12–34)
Days on ventilator	6 (0–24)	9 (2–24)
ICU stay (days)	9 (2–26)	13 (3–29)
Hospital stay (days)	35 (12–78)	29.5 (12–120)

Results are medians (range).

ISS: injury severity score; APACHE II: Acute Physiology and Chronic Health Evaluation score; ICU: intensive care unit.

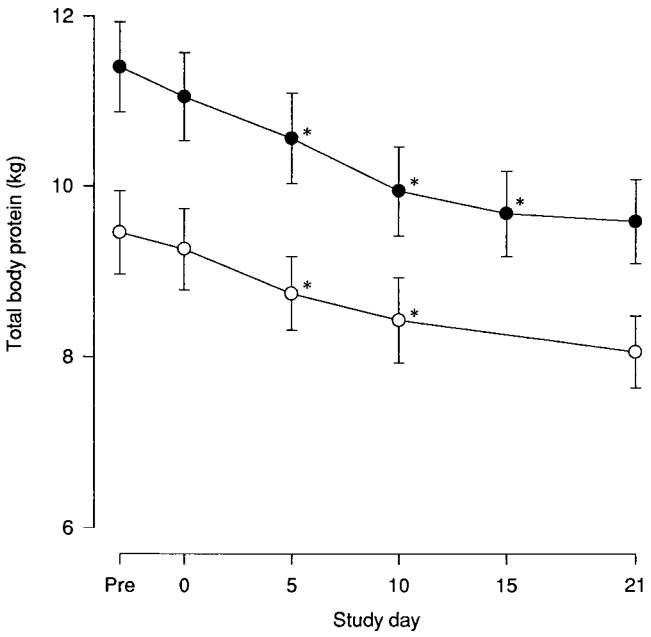

Fig. 1. Total body protein in 12 patients with severe sepsis (open circles) and 21 patients with major trauma (closed circles) measured over a 21-day period after onset of illness with estimated preillness values (mean ± SEM). *Significant ($p < 0.05$) change from the preceding measurement.

Protein Metabolism

Figure 1 shows the sequential changes in total body protein over a 21-day period following onset of illness with estimated preillness values. In both groups losses were greatest during the first 10 days, amounting to approximately 0.9% and 1.0% of TBP per day during sepsis and trauma, respectively. Total protein lost over the study period averaged 1.21 ± 0.13 (SEM) kg in the sepsis patients ($p < 0.0001$) and 1.47 ± 0.20 kg in the trauma patients ($p < 0.0001$): 13% of day 0 TBP in each of the groups. During the first 10 days of the study in the sepsis patients and during the first 5 days in the trauma patients, approximately 70% of the total protein lost came from skeletal muscle. After these intervals more of the protein lost was derived from the nonmuscle tissues.

Water Metabolism

Figure 2 shows the changes in TBW that occurred over the 21-day study period with estimated preillness values. Once hemodynamic stability had been reached (day 0), TBW began to return toward normal. In the trauma group, despite the mean value of TBW returning to the pretrauma level by day 21, relative overhydration of the fat-free mass (FFM) was still present (TBW/FFM = 0.74 ± 0.01, which should be compared with normal values of 0.71 and 0.73 for men and women, respectively [5]). At day 21 in the sepsis group this overhydration was more marked (0.77 ± 0.01) despite having lost an average of 10.8 ± 1.4 liters of water. These changes during and after resuscitation can be largely accounted for by changes in ECW, as shown in Figure 2, where the excess over normal levels of ECW are shown [6]. Figure 3 shows that in elderly patients with sepsis (age > 60 years) the period of ECW expansion is more prolonged than in their younger counterparts, and there is no appreciable mobilization of excess ECW for at least 10 days [6].

Cell Composition

Significant losses of total body potassium and intracellular water are observed following severe sepsis [3] and major trauma [4]. In contrast, the intracellular potassium concentration remains relatively constant, albeit at a lower than normal level.

Energy Metabolism during Severe Sepsis and Major Trauma

Figure 4 shows daily measurements of resting energy expenditure (REE) by indirect calorimetry, expressed as a ratio to the predicted REE (REE/REEp), commencing 2 to 3 days after onset of illness and continuing for 10 days with further measurements 11 days later [7]. It can be seen that the REE/REEp ratio increased over the first 4 to 5 days, peaking around days 9 to 12. The ratio peaked at 1.37 ± 0.06 during sepsis and 1.60 ± 0.13 during trauma ($p = 0.11$). Significant hypermetabolism was still observed at days 23 to 24. The difference in the behavior of REE/REEp with time over days 3 to 12 for the two groups was not statistically significant (ANOVA, $p = 0.07$ for the group × time interaction).

Energy intake in the trauma patients, who were fed enterally, was higher during the second 5-day period of the 10-day study period (1473 ± 115 vs. 1974 ± 107 kcal/day; $p = 0.002$). Energy intake in the sepsis patients, who received early intravenous nutrition, not was statistically different between the first and second 5-day study periods (1853 ± 175 vs. 2041 ± 190 kcal/day; $p = 0.27$). Total energy expenditure (TEE) was calculated over 5-day study periods as the difference between energy intake and the changes in the body energy stores of protein, fat, and carbohydrate [8]. The TEE/REE ratio over the second 5-day study period was significantly higher than that over the first 5-day study period in the sepsis patients but not the trauma patients (1.66 ± 0.18 vs. 0.98 ± 0.20, $p = 0.042$, in sepsis patients; 1.79 ± 0.21 vs. 1.08 ± 0.21, $p = 0.089$, in trauma patients). All the sepsis patients were ventilated over the first 5-day period, whereas in the trauma group two patients were off ventilation prior to this period and three came off ventilation during it.

Changes in the components of energy expenditure between the first and second 5-day periods are examined in Table 2, where the results are indexed to the hydration-corrected fat-free mass (FFMc) to reduce the influence of changing body size over the 10-day study period. When expressed in this way it can be seen

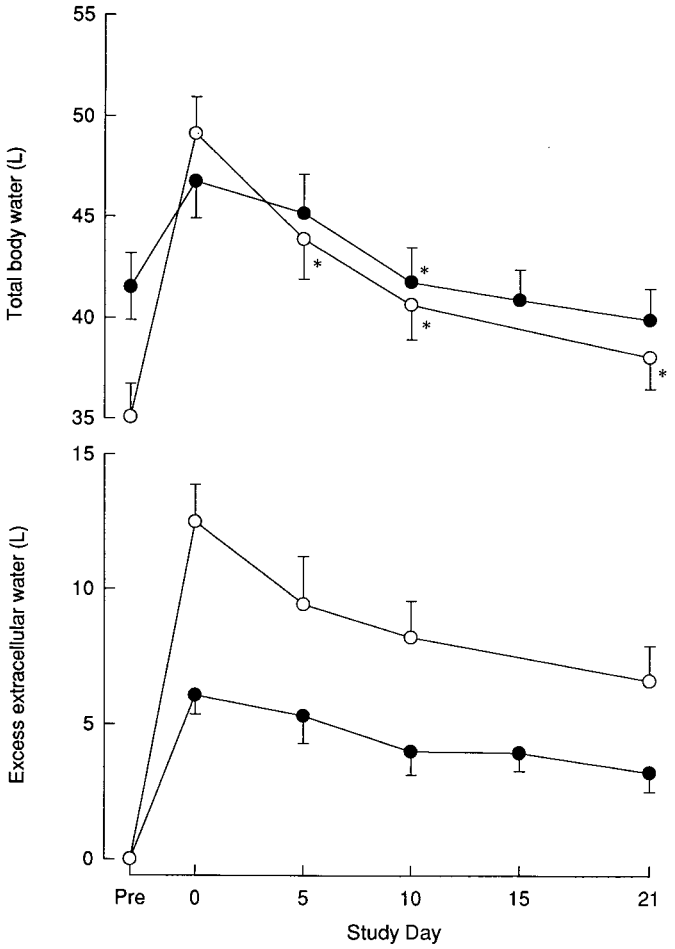

Fig. 2. Total body water **(top)** and excess extracellular water **(bottom)** in 12 patients with severe sepsis (open circles) and 21 patients with major trauma (closed circles) measured over a 21-day period after onset of illness with estimated preillness values (mean ± SEM). *Significant ($p < 0.05$) change from the preceding measurement.

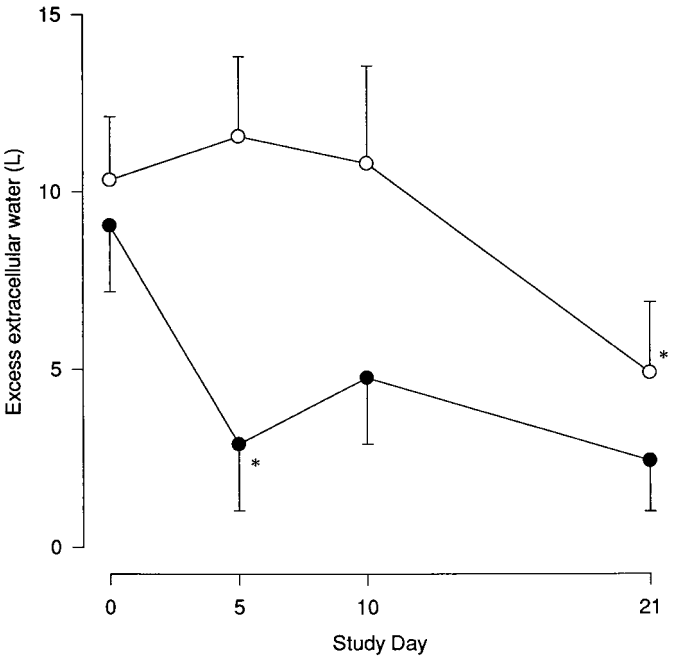

Fig. 3. Excess extracellular water in eight elderly (open circles) and six young patients (closed circles) with severe sepsis measured over a 21-day period after onset of sepsis (mean ± SEM). *Significant ($p < 0.05$) change from the preceding measurement.

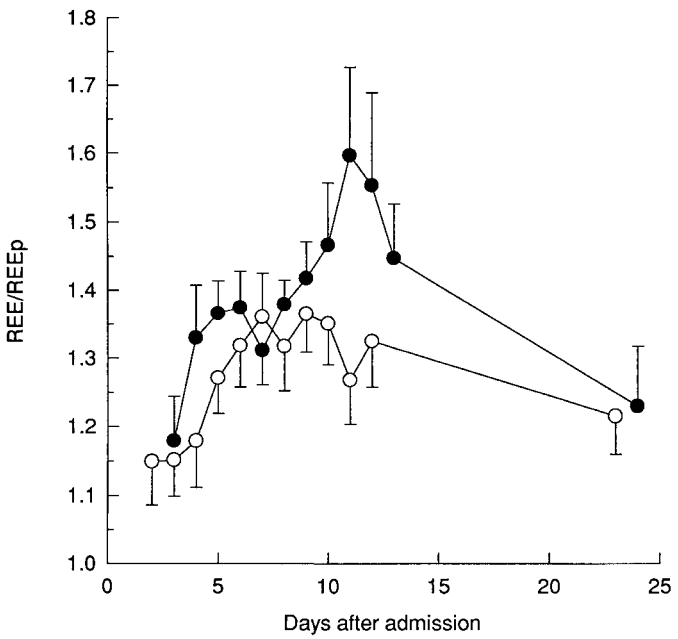

Fig. 4. Changes in the ratio of measured resting energy expenditure to predicted energy expenditure (REE/REEp) for 12 patients with serious sepsis (open circles) and 12 patients with major trauma (closed circles) plotted from 2 to 3 days after admission to hospital through days 12 to 13, with subsequent measurements 11 days later.

that a statistically significant twofold increase in TEE occurred in both groups of patients. REE/FFMc also increased significantly in both groups, and the greater variability in the activity energy expenditure (AEE = TEE − REE) measurement means that significance was borderline for the trauma patients. All three components of energy expenditure had similar values for the sepsis and trauma groups.

Cytokine Responses following Severe Sepsis and Major Trauma

Figure 5 shows the changes in concentrations of circulating tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), IL-8, and IL-10 in patients with peritonitis over the 12 days immediately following the onset of their illness. Not shown are levels of IL-1β which was not detected in all patients (detection limit 0.3 pg/ml). When detectable, IL-1β concentrations fell rapidly over the first 24 hours. TNFα, IL-6, IL-8, and IL-10 all showed similar patterns of change, with the initially high concentrations falling rapidly over the first 24 to 48 hours and then declining more slowly up to 12 days. Shown in Figure 6 are the concentrations of the cytokine antagonists IL-1 receptor antagonist (IL-1ra) and soluble 75-kilodalton (kDa) TNF receptor (sTNF-RII) in these patients. IL-1ra concentrations decreased rapidly over the first 48 hours

Table 2. Energy balance indexed to hydration-corrected fat-free mass measured over days 0–5 and 5–10 in 12 patients with sepsis and 12 patients with trauma.

	Sepsis			Trauma		
Measurement	Days 0–5	Days 5–10	p^*	Days 0–5	Days 5–10	p^*
EI/FFMc	39 ± 4	47 ± 6	0.14	28 ± 2	41 ± 3	0.0007
EB/FFMc	0 ± 8	−28 ± 9	0.044	−15 ± 8	−43 ± 9	0.093
TEE/FFMc	38 ± 7	75 ± 11	0.017	43 ± 8	84 ± 9	0.026
REE/FFMc	39 ± 2	44 ± 2	0.033	40 ± 1	47 ± 2	0.0010
AEE/FFMc	−1 ± 7	31 ± 10	0.024	3 ± 8	37 ± 9	0.055

Values are means ± SEM in kcal/kg/day.

EI: energy intake; FFMc: hydration-corrected fat-free mass; EB: energy balance; TEE: total energy expenditure; REE: resting energy expenditure measured by indirect calorimetry; AEE: activity energy expenditure.

*Two-tailed paired *t*-test.

followed by a more gradual decline. sTNF-RII concentrations remained elevated up to 12 days with an initial drop at 8 hours but with the 96-hour concentration exceeding the initial level. All these cytokines were measured using sandwich enzyme-linked immunosorbent assay (ELISA) immunoassays (Quantikine; R&D Systems, Abingdon, UK) [3]. Other studies examining circulating cytokine responses in a sequential manner in groups of patients with secondary intraabdominal sepsis have found patterns of change in TNFα and IL-6 broadly similar to those observed in the present study [10–18]. Others have shown differences in responses of TNFα and IL-6 between survivors and nonsurvivors and demonstrated significant associations with Acute Physiologic and Chronic Health Evaluation (APACHE) II scores [10–14, 16, 18]. In other studies of sepsis, high levels of IL-10, sTNF-RII, and IL-1ra have been observed, with levels of sTNF-RII and IL-1ra being orders of magnitude higher than the corresponding concentrations of TNFα and IL-1, respectively [19–24].

In studies of patients with major trauma [Injury Severity Score (ISS) $\geq$ 16], as has been found with sepsis, IL-1β is difficult to detect in the circulation [25–30]. In contrast to severe sepsis, measurements of circulating TNFα concentrations in patients with major injury have generally shown no significant elevation above normal values even where such patients developed acute respiratory distress syndrome (ARDS) [25–29, 31–37]. However, Svodoba et al. [25] have shown that dramatic increases in plasma TNFα concentrations can occur following development of multiple organ failure (MOF), and they were associated with 100% mortality. Because the half-life of TNF is only 5 to 20 minutes it remains possible that TNF was cleared or degraded before the earliest samples were obtained in these studies. A recent report has shown high levels of TNF in nearly all major trauma patients studied when sampling was achieved within 4 hours of injury [38]. Persistently elevated serum TNF levels have been seen for 5 days following major head injury [39], with elevations similar to those seen with sepsis. Plasma IL-6, on the other hand, generally shows a pattern of response similar to that seen in sepsis patients, with an early peak and persistent elevation for many days [9, 25–27, 31, 33–35, 40–46]. Serum IL-6 concentrations measured in trauma patients who developed multiple organ dysfunction [9] are compared in Figure 5 with our results in patients with severe sepsis. Others have shown that systemic IL-6 concentrations tend to be lower in trauma patients than those with septic shock [31]. IL-6 concentrations have been shown to be higher in severely injured patients than those with mild or moderate injury [33, 40, 46] and increase following development of ARDS [26] or MOF [25]. Extreme elevations have been observed in association with infectious complications [44]. Elevated levels of plasma IL-8 are seen in the posttrauma patient [26, 27, 33, 38, 41, 43, 47], with peak levels associated with the degree of injury [33] and evidence of higher concentrations developing in patients with ARDS [26, 27] or MOF [41, 47]. Limited data are available on the plasma levels of the antiinflammatory cytokines IL-4 and IL-10 following major trauma. Peak IL-4 levels were found to be related to severity of injury [48]. IL-10 was markedly elevated in trauma patients who went on to develop multiple organ dysfunction (Fig. 5) [9]. Circulating IL-1ra and sTNF-R have been measured in patients with major trauma. IL-1ra levels measured within 4 hours of injury (ISS $>$ 16) were not as high as those seen with peritonitis but were significantly higher than those in patients with less severe injury [30]. Concentrations averaging 30 ng/ml were reported by Seekamp et al. [9] in major trauma patients (ISS $\geq$ 20) 24 hours after injury who later developed multiple organ dysfunction (Fig. 6). IL-1ra levels measured early after injury showed a peak (approximately 60 ng/ml) 4 to 6 hours after injury, following which the concentrations fell more rapidly in survivors than nonsurvivors [29]. As observed in sepsis patients, serum levels of sTNF-R55 and R75 were elevated above normal in major trauma patients within 1 hour of injury, and high levels persisted for at least 14 days [9, 29, 30, 32, 41, 49], although these levels were lower than those seen with severe sepsis (Fig. 6).

Sequential Changes in Plasma Proteins and Insulin-like Growth Factor-1 (IGF-1) in Severe Sepsis and Major Trauma

Acute-phase Plasma Proteins

Figure 7 shows that C-reactive protein (CRP) on day 0 (normally present only at low levels) was markedly elevated during both sepsis and trauma; and by day 21 it had returned to almost normal levels. A similar but less marked response is seen for α_1-antitrypsin. Correction for the dilution effect of an expanded ECW exaggerated the changes in CRP and placed all α_1-antitrypsin results above the normal range [50].

Constitutive Plasma Proteins

The sequential changes in plasma transferrin and prealbumin are shown in Figure 8 for the sepsis and trauma groups. Transferrin and prealbumin concentrations were below the normal range

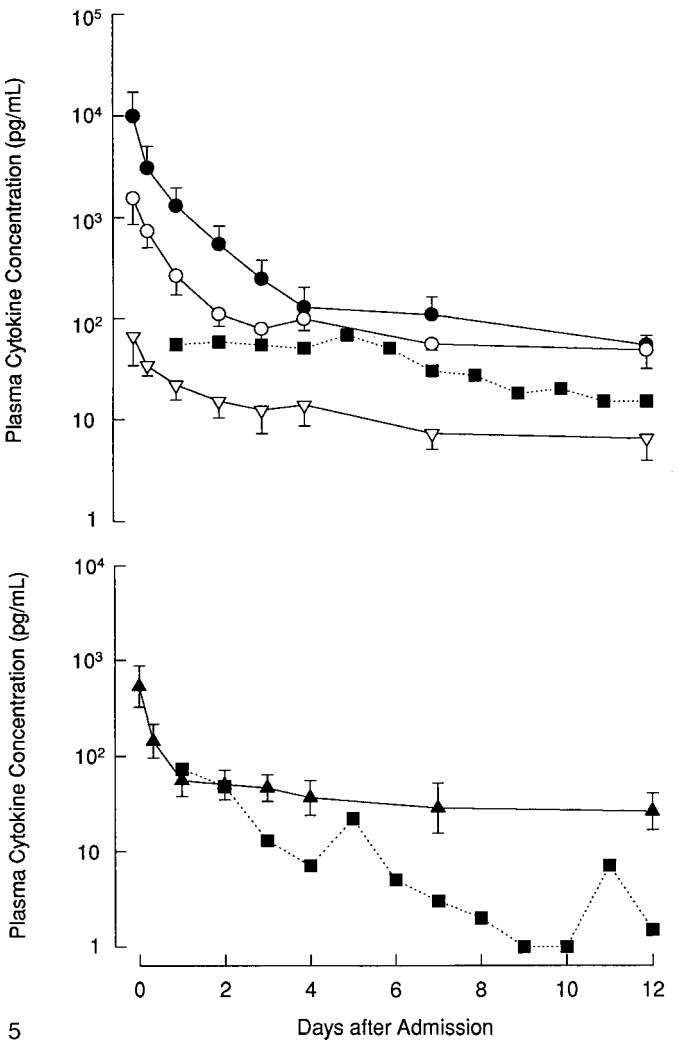

Fig. 5. Top: Plasma concentrations of interleukin-6 (IL-6) (closed circles) and IL-8 (open circles) in nine patients with peritonitis and tumor necrosis factor-α (TNFα) (triangles) in five patients with peritonitis measured during a 12-day period after onset of sepsis (geometric mean ± SEM), with comparative data for IL-6 in eight patients with major trauma who developed multiple organ dysfunction (squares). **Bottom:** Plasma concentrations of IL-10 (triangles) in nine patients with peritonitis measured during a 12-day period after onset of sepsis (geometric mean ± SEM) with comparative data in eight patients with major trauma who developed multiple organ dysfunction (squares). (The comparative data for both panels in this figure were rescaled from Seekamp et al. [9].)

Fig. 6. Plasma concentrations of soluble 75-kDa TNF receptor (sTNF-RII) (closed circles) and IL-1 receptor antagonist (IL-1ra) (open circles) in nine patients with peritonitis, measured during a 12-day period after onset of sepsis (geometric mean ± SEM), with comparative data in eight patients with major trauma who developed multiple organ dysfunction (closed squares, open squares, respectively). (Comparative data were rescaled from Seekamp et al. [9].)

when first measured on day 0. Concentrations then rose at rates consistent with their known turnover rates, with prealbumin returning to within the normal range between days 5 and 10 and transferrin somewhere after day 10 or 15. When corrected for ECW expansion, prealbumin did not fall outside the normal range, but the changes in the concentrations remained statistically significant.

IGF-1

Figure 8 also shows the sequential changes in plasma insulin-like growth factor-1 (IGF-1) for the two groups of patients. Subnormal concentrations are present on day 0, and significant increases were observed by day 10. When corrected for ECW expansion the mean concentrations were still below the normal range on days 0 and 5, and the increase by day 10 remained statistically significant.

Discussion

Our studies of total body protein changes in critically ill patients following major traumatic injury or severe sepsis show the striking similarity in response in these two groups of patients over the 21 days of study. In both groups 13% of body protein stores was lost over this period, despite state-of-the-art intensive care including modern nutritional therapy. Such erosion of the functional and structural components of the body undoubtedly contributes to prolonging convalescence and the rapidity with which these patients can be weaned from ventilatory support, discharged from hospital, and resume normal activities. The time required for restoration of this protein loss to preillness levels is not known, but it is likely to be many months [51].

During the resuscitation phase of their illnesses both groups of patients retained fluid within the extracellular space, which was dissipated slowly so that at 21 days these patients were still overhydrated. The severe sepsis patients retained twice the volume of fluid as those with major trauma, and the return to normal hydration in the sepsis group was correspondingly prolonged, especially in the elderly. Evidence from rodent models of peritonitis suggests that much of the retained fluid can be found in the abdominal cavity, which may add to the prolonged bowel dysfunction often observed in such critically ill patients [52].

Our results for REE show a progressive increase over the first week following the onset of severe sepsis or major trauma to a maximum around 40% more than normal. This is clear illustration of the effect of nutritional support (diet-induced thermogenesis) but also partly due to the developing flow phase of the classically

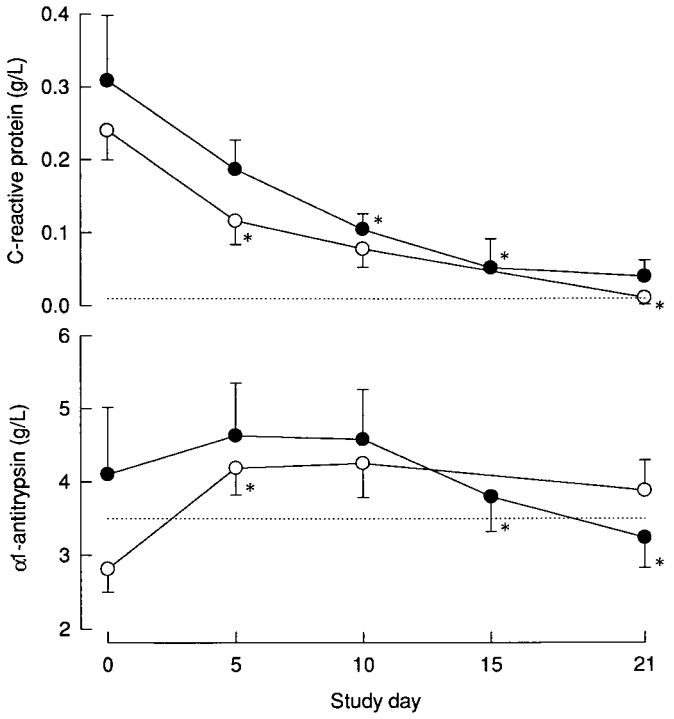

Fig. 7. Plasma concentrations of C-reactive protein **(top)** and α_1-antitrypsin **(bottom)** in 14 patients with severe sepsis (open circles) and 10 patients with major trauma (closed circles), measured over a 21-day period after onset of illness. Dotted line represents the upper limit of the normal range. *Significant ($p < 0.05$) change from the preceding measurement.

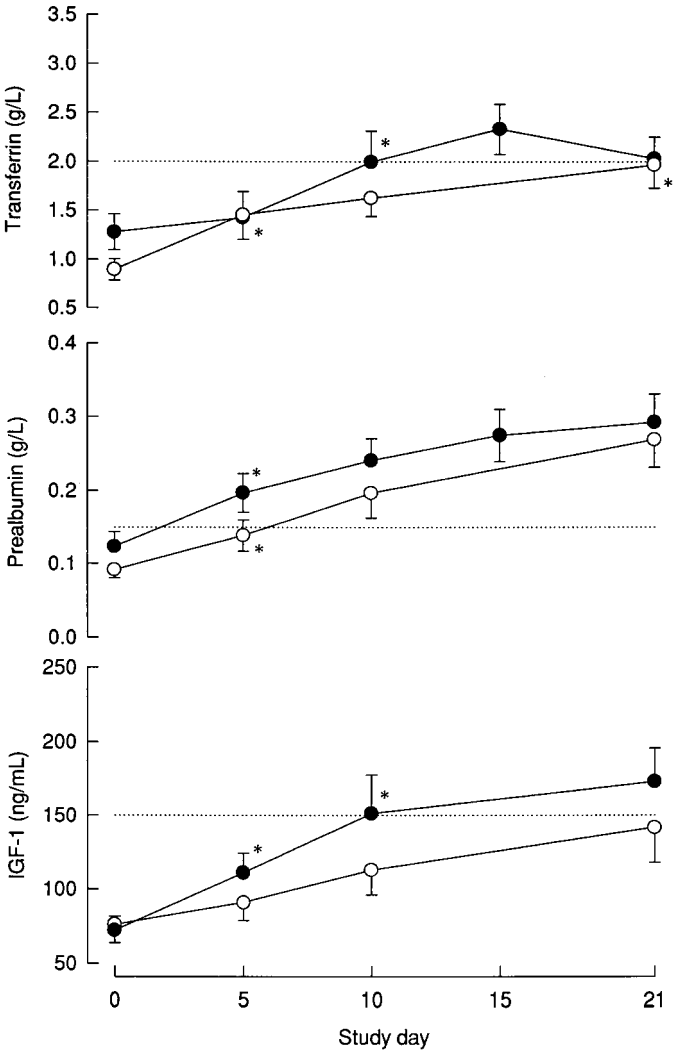

Fig. 8. Plasma concentrations of transferrin **(top)**, prealbumin **(middle)**, and insulin-like growth factor-1 (IGF-1; **bottom**) in 14 patients with severe sepsis (open circles) and 10 patients with major trauma (closed circles), measured over a 21-day period after onset of illness. Dotted line represents the lower limit of the normal range. *Significant ($p < 0.05$) change from the preceding measurement.

described metabolic response to sepsis and trauma. The REE was still higher than normal (approximately 20%) when measured 3 weeks after onset of illness. For the first week, when the patients were in the ICU mainly on ventilatory support, the TEE was close to the REE; but during the second week after admission to hospital the TEE was 70% to 80% higher than the REE. This relative increase in TEE was particularly apparent in the trauma patients whose activity component, secondary to cerebral irritation, was more marked.

The prolonged hypermetabolism observed in our septic patients was not reflected in the behavior of proinflammatory cytokines measured in the circulation, which were elevated early and then returned toward normal within a week or so. The evidence from the literature suggests that during major trauma a similar pattern ensues albeit at generally reduced overall concentrations. In both groups of patients similar responses are seen for the natural cytokine antagonists. Thus it may appear that the cytokine concentrations in the plasma are dissociated from the changes in energy metabolism and body composition, which persist much longer. Some have suggested this could in part be explained by the compartmentalization and sustained high concentrations (even following surgery and drainage [53]) of cytokines within the abdominal cavity [54]. More recently, as the result of animal studies in which total abdominal vagotomy has been performed, it was suggested that cytokines compartmentalized within the abdominal cavity may communicate with the brain via the vagus nerves [55], accounting for continuing catabolism as the result of a neuroendocrine response.

Our results confirm that there is a reprioritization of hepatic protein synthesis during critical illness [56] that is obligatory and independent of changes in total body protein. Concentrations of IGF-1 and the constitutive plasma proteins decreased, and the acute-phase proteins rose early in the course of illness. After a few days, as the acute phase reaction subsided, levels of IGF-1 and the constitutive proteins returned to the normal range. These obligatory changes in hepatic protein levels occurred in the face of continuing massive proteolysis and high energy expenditure. There were no correlations between the changes in TBP and those of IGF-1 or any of the constitutive plasma proteins. Our study confirms that measurements of IGF-1 or constitutive plasma proteins have no value in demonstrating changes in total body protein early in the course of critical illness.

The similarity in the metabolic responses to sepsis and trauma that is evident from this work indicates a common pattern com-

patible with an underlying process that may best be described as the SIRS. Other work we have carried out in patients with severe sepsis categorized as urosepsis, pneumonia, or meningococcal meningitis [57] and in patients with severe pancreatitis [58] likewise show metabolic responses indistinguishable from those described in the current work. We were not able to detect differences in the metabolic responses between our patients with major trauma who developed septic complications and those who did not. However, we have shown elsewhere in this symposium that the wound healing response is particularly impaired when the clinical course of trauma patients is complicated by sepsis [59]. Recent conceptual developments have differentiated between the proinflammatory SIRS and the compensatory antiinflammatory response syndrome (CARS), distinguishing also an intermediate, mixed inflammatory response syndrome (MARS) [60, 61]. The precipitous falls in proinflammatory mediators observed in critically ill patients with major trauma or serious sepsis together with continued and prolonged supranormal levels of antiinflammatory mediators support the hypothesis of a two-sided response that at any point during progression of the illness may be dominated by SIRS or CARS. Here may lie the way ahead for antiinflammatory therapies of the future [62]. The rapid induction of SIRS after a major insult almost certainly requires preemptive anticytokine or other antagonist interventions to modulate this response significantly. On the other hand, the presence of a predominantly CARS state may require immunostimulant or antiantagonist therapies to achieve useful benefits [63]. A single "magic bullet" is unlikely to prove useful for the spectrum of responses that accompany critical illness [64].

Résumé

Nous avons récemment examiné les dossiers des patients atteints de sepsis ou de traumatisme sévères pour déterminer les changements séquentiels dans la réponse métabolique après admission en soins intensifs. On a mesuré le métabolisme en protéines, en eau, et en énergie par une analyse d'activation de neutrons in vivo, la dilution de traceurs, l'absorptimétrie des rayons-X en énergie double et la calorimétrie indirecte. Pendant les trois semaines de l'investigation, les deux groupes de patients ont perdu 13% des protéines du corps entier. Les patients en sepsis sévère ont retenu deux fois plus de volume de fluides par rapport à ceux ayant eu un traumatisme majeur et la réhydration des patients septiques était plus difficile à obtenir, surtout pour le groupe de patients plus âgés. Dans les deux groupes, la dépense d'énergie au repos a augmenté progressivement pendant la première semaine (40% au-dessus des valeurs normales) et était toujours élevée à trois semaines du début de la maladie. On a noté une augmentation de 200% en dépenses énergétiques dans les deux groupes de patients entre la première et la seconde semaine d'admission en soins intensifs. Pendant tout l'étude, l'hypermétabolisme prolongé n'a pas influencé les concentrations en cytokines pro-inflammatoires circulants dont la concentration a diminué rapidement pendant la première semaine. Les modifications observées dans les concentrations de cytokines pro- et anti-inflammatoires plasmatiques étaient similaires pour le sepsis et le trauma. Les conséquences métaboliques observées après l'agression que constituent un sepsis sévère ou un traumatisme majeur pourraient constituer une réponse universelle à l'induction de la réponse inflammatoire systémique (SIRS).

Resumen

Hemos culminado una serie de estudios en pacientes en estado crítico por sepsis severa o por trauma mayor, orientados a investigar los cambios secuenciales que suceden en la respuesta metabólica luego de su ingreso a la unidad de cuidado intensivo. Se hicieron mediciones del metabolismo energético, de proteina y de agua mediante análisis in vivo de activación de neutrones, dilución de trazadores, absorciometría energética dual de rayos X y calorimetría indirecta. Los dos grupos de pacientes exhibieron una pérdida del 13% de la proteína corporal total en el curso de las tres semanas del estudio. Los pacientes con sepsis severa retuvieron el doble de líquido que los pacientes con trauma mayor y el retorno a un estado de deshidratación normal que consecuentemente más prolongado en el grupo séptico, especialmente en los pacientes de edad avanzada. En ambos grupos, el séptico y el de trauma mayor, el gasto energético en reposo apareció incrementado hasta alrededor de 40% sobre lo normal en el curso de la primera semana y se mantuvo todavía elevado a las tres semanas del comienzo de la enfermedad. En los dos grupos se observó un incremento del doble en el gasto energético en reposo entre la primera y la segunda semana de la admisión a la unidad de cuidado intensivo. El prolongado hipermetabolismo registrado a lo largo del periodo de estudio no se reflejó en los niveles séricos de citocinas proinflamatorias, los cuales descendieron en forma rápida en el curso de la primera semana. El patrón de cambios observados en los niveles de citocinas proinflamatorias y antiinflamatorias apareció similar en la sepsis y en el trauma. Las notoriamente similares secuelas metabólicas presentes en los pacientes en estado crítico por sepsis severa o por trauma mayor, pueden constituir una respuesta universal a la inducción de la respuesta inflamatoria sistémica (SIRS).

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References

1. Cuthbertson, D.P.: The physiology of convalescence after injury. Br. Med. Bull. *3*:96, 1945
2. Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit. Care Med. *20*:864, 1992
3. Plank, L.D., Connolly, A.B., and Hill, G.L.: Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis. Ann. Surg. *228*:146, 1998
4. Monk, D.N., Plank, L.D., Franch-Arcas, G., Finn, P.J., Streat, S.J., and Hill, G.L.: Sequential changes in the metabolic response in critically injured patients during the first 25 days after blunt trauma. Ann. Surg. *223*:395, 1996
5. Beddoe, A.H., Streat, S.J., and Hill, G.L.: Hydration of fat free body in protein depleted patients. Am. J. Physiol. *249*:E227, 1985
6. Cheng, A.T.H., Plank, L.D., and Hill, G.L.: Prolonged overexpansion

of extracellular water in elderly patients with sepsis. Arch. Surg. *133*:745, 1998
7. Uehara, M., Plank, L.D., and Hill, G.L.: Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. Crit. Care Med. *27*:1295, 1999
8. Franch-Arcas, G., Plank, L.D., Monk, D.N., Gupta, R., Maher, K., Gillanders, L., and Hill, G.L.: A new method for the estimation of the components of energy expenditure in patients with major trauma. Am. J. Physiol. *267*:E1002, 1994
9. Seekamp, A., Jochum, M., Ziegler, M., van Griensven, M., Martin, M., and Regel, G.: Cytokines and adhesion molecules in elective and accidental trauma-related ischemia/reperfusion. J. Trauma *44*:874, 1998
10. Patel, R.T., Deen, K.I., Youngs, D., Warwick, J., and Keighley, M.R.B.: Interleukin 6 is a prognostic indicator of outcome in severe intra-abdominal sepsis. Br. J. Surg. *81*:1306, 1994
11. Riché, F., Panis, Y., Laisné, M., Briard, C., Cholley, B., Bernard-Penaru, O., Graulet, A., Guéris, J., and Valleur, P.: High tumor necrosis factor serum level is associated with increased survival in patients with abdominal septic shock: a prospective study in 59 patients. Surgery *120*:801, 1996
12. Hamilton, G., Hofbauer, S., and Hamilton, B.: Endotoxin, TNF-alpha, interleukin-6 and parameters of the cellular immune system in patients with intraabdominal sepsis. Scand. J. Infect. Dis. *24*:361, 1992
13. Függer, R., Zadrobilek, E., Götzinger, P., Klimann, S., Rogy, M., Winkler, S., Andel, H., Mittelböck, M., Roth, E., Schulz, F., and Fritsch, A.: Perioperative TNFα and IL-6 concentrations correlate with septic state, organ function, and APACHE II scores in intra-abdominal infection. Eur. J. Surg. *159*:525, 1993
14. Holzheimer, R.G., Schein, M., and Wittmann, D.H.: Inflammatory response in peritoneal exudate and plasma of patients undergoing planned relaparotomy for severe secondary peritonitis. Arch. Surg. *130*:1314, 1995
15. Hammond, J.M.J., and Potgeiter, P.D.: The influence of surgery on cytokines in patients with intra-abdominal sepsis. Anaesth. Intensive Care. *24*:430, 1996
16. Tang, J., Kuo, C., Yen, T., Yen, T., Kuo, H., Chan, K., Yien, H., and Lee, T.: Perioperative plasma concentrations of tumor necrosis factor-α and interleukin-6 in infected patients. Crit. Care Med. *24*:423, 1996
17. Sautner, T., Götzinger, P., Redl-Wenzl, E., Dittrich, K., Felfernig, M., Sporn, P., Roth, E., and Függer, R.: Does reoperation for abdominal sepsis enhance the inflammatory host response? Arch. Surg. *132*:250, 1997
18. Wakefield, C.H., Barclay, G.R., Fearon, K.C.H., Goldie, A.S., Ross, J.A., Grant, I.S., Ramsay, G., Howie, J.C., and Scottish Sepsis Intervention Group: Proinflammatory mediator activity, endogenous antagonists and the systemic inflammatory response in intra-abdominal sepsis. Br. J. Surg. *85*:818, 1998
19. Marchant, A., Devière, J., Byl, B., De Groote, D., Vincent, J., and Goldman, M.: Interleukin-10 production during septicaemia. Lancet *343*:707, 1994
20. Gómez-Jiménez, J., Martin, M.C., Sauri, R., Segur, R.M., Esteban, F., Ruiz, J.C., Nuvials, X., Bóveda, J.L., Peracaula, R., and Salgado, A.: Interleukin-10 and the monocyte/macrophage-induced inflammatory response in septic shock. J. Infect. Dis. *171*:472, 1995
21. Van der Poll, T., Malefyt, R., Coyle, S.M., and Lowry, S.F.: Antiinflammatory cytokine responses during clinical sepsis and experimental endotoxemia: sequential measurements of plasma soluble interleukin (IL)-1 receptor type II, IL-10, and IL-13. J. Infect. Dis. *175*:118, 1997
22. Goldie, A.S., Fearon, K.C.H., Ross, J.A., Barclay, R., Jackson, R.E., Grant, S., Ramsay, G., Blyth, A.S., and Howie, J.C.: Natural cytokine antagonists and endogenous antiendotoxin core antibodies in sepsis syndrome. J.A.M.A. *274*:172, 1995
23. Froon, A.H.M., Bemelmans, M.H.A., Greve, J.W., van der Linden, C.J., and Buurman, W.A.: Increased plasma concentrations of soluble tumor necrosis factor receptors in sepsis syndrome: correlation with plasma creatinine values. Crit. Care. Med. *22*:803, 1994
24. Ertel, W., Scholl, F.A., Gallati, H., Bonaccio, M., Schildberg, F., and Trentz, O.: Increased release of soluble tumor necrosis factor receptors into blood during clinical sepsis. Arch. Surg. *129*:1330, 1994
25. Svoboda, P., Kantorova, I., and Ochmann, J.: Dynamics of interleukin 1, 2, and 6 and tumor necrosis factor alpha in multiple trauma patients. J. Trauma *36*:336, 1994
26. Meade, P., Shoemaker, W.C., Donnelly, T.J., Abraham, E., Jagels, M.A., Cryer, H.G., Hugli, T.E., Bishop, M.H., and Wo, C.C.J.: Temporal patterns of haemodynamics, oxygen transport, cytokine activity, and complement activity in the development of adult respiratory distress syndrome after severe injury. J. Trauma *36*:651, 1994
27. Donnelly, T.J., Meade, P., Jagels, M., Cryer, H.G., Law, M.M., Hugli, T.E., Shoemaker, W.C., and Abraham, E.: Cytokine, complement, and endotoxin profiles associated with the development of the adult respiratory distress syndrome after severe injury. Crit. Care Med. *22*: 768, 1994
28. Suter, P.M., Suter, S., Girardin, E., Roux-Lombard, P., Grau, G.E., and Dayer, J.M.: High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon, and elastase, in patients with adult respiratory distress syndrome after trauma, shock, or sepsis. Am. Rev. Respir. Dis. *145*:1016, 1992
29. Cinat, M., Waxman, K., Vaziri, N.D., Daughters, K., Yousefi, S., Scannell, G., and Tominaga, G.T.: Soluble cytokine receptors and receptor antagonists are sequentially released after trauma. J. Trauma *39*:112, 1995
30. Ertel, W., Keel, M., Bonaccio, M., Steckholzer, U., Gallanti, H., Kenney, J.S., and Trentz, O.: Release of anti-inflammatory mediators after mechanical trauma correlates with severity of injury and clinical outcome. J. Trauma *39*:879, 1995
31. Martin, C., Boisson, C., Haccoun, M., Thomachot, L., and Mege, J-L.: Patterns of cytokine evolution (tumor necrosis factor-α and interleukin-6) after septic shock, hemorrhagic shock, and severe trauma. Crit. Care Med. *25*:1813, 1997
32. Tan, L.R., Waxman, K., Scannell, G., Ioli, G., and Granger, G.A.: Trauma causes early release of soluble receptors for tumor necrosis factor. J. Trauma *34*:634, 1993
33. Hoch, R.C., Rodriguez, R., Manning, T., Bishop, M., Mead, P., Shoemaker, W.C., and Abraham, E.: Effects of accidental trauma on cytokine and endotoxin production. Crit. Care Med. *21*:839, 1993
34. Foëx, B.A., Lamb, W.R., Roberts, T.E., Brear, S.G., Mccartney, I., Hammer, M., and Brenchley, P.E.C.: Early cytokine response to multiple injury. Injury *24*:373, 1993
35. Moore, F.A., Moore, E.E., Poggetti, R., McAnena, O.J., Peterson, V.M., Abernathy, C.M., and Parsons, P.E.: Gut bacterial translocation via the portal vein: a clinical persepctive with major torso trauma. J. Trauma *31*:629, 1991
36. Rabinovici, R., John, R., Esser, K.M., Vernick, J., and Feuerstein, G.: Serum tumor necrosis factor-alpha profile in trauma patients. J. Trauma *35*:698, 1993
37. Pullicino, E.A., Carli, F., Poole, S., Rafferty, B., Malik, S.T., and Elia, M.: The relationship between the circulating concentrations of interleukin 6 (IL-6), tumor necrosis factor (TNF) and the acute phase response to elective surgery and accidental injury. Lymphokine Res. *9*:231, 1990
38. Ferguson, K.L., Taheri, P., Rodriguez, J., Tonapi, V., Cardellio, A., and Dechert, R.: Tumor necrosis factor activity increases in the early response to trauma. Acad. Emerg. Med. *4*:1035, 1997
39. Goodman, J.C., Robertson, C.S., Grossman, R.G., and Narayan, R.K.: Elevation of tumor necrosis factor in head injury. J. Neuroimmunol. *30*:213, 1990
40. McClain, G., Cohen, D., Phillips, R., Ott, L., and Young, B.: Increased plasma and ventricular fluid interleukin-6 levels in patients with head injury. J. Lab. Clin. Med. *118*:225, 1991
41. Law, M.M., Cryer, H.G., and Abraham, E.: Elevated levels of soluble ICAM-1 correlate with the development of multiple organ failure in severely injured trauma patients. J. Trauma *37*:100, 1994
42. Kowal-Vern, A., Sharp-Pucci, M.M., Walenga, J.M., Dries, D.J., and Gamelli, R.L.: Trauma and thermal injury: comparison of hemostatic and cytokine changes in the acute phase of injury. J. Trauma *44*:325, 1998
43. Ott, L., McClain, C.J., Gillespie, M., and Young, B.: Cytokines and metabolic dysfunction after severe head injury. J. Neurotrauma *11*: 447, 1994
44. Ertel, W., Faist, E., Nestle, C., Hueltner, L., Storck, M., and Schildberg, F.W.: Kinetics of interleukin-2 and interleukin-6 synthesis following major mechanical trauma. J. Surg. Res. *48*:622, 1990
45. Kossmann, T., Hans, V.H., Imhof, H.G., Stocker, R., Grob, P., Trentz,

O., and Morganti-Kossmann, C.: Intrathecal and serum interleukin-6 and the acute-phase response in patients with severe traumatic brain injuries. Shock *4*:311, 1995
46. Giannoudis, P.V., Smith, M.R., Evans, R.T., Bellamy, M.C., and Guillou, P.: Serum CRP and IL-6 levels after trauma: not predictive of septic complications in 31 patients. Acta Orthop. Scand. *69*:184, 1998
47. Botha, A.J., Moore, F.A., Moore, E.E., Peterson, V.M., Silliman, C.C., and Goode, A.W.: Sequential systemic platelet-activating factor and interleukin 8 primes neutrophils in patients with trauma at risk of multiple organ failure. Br. J. Surg. *83*:1407, 1996
48. DiPiro, J.T., Howdieshell, T.R., Goddard, J.K., Callaway, D.B., Hamilton, R.G., and Mansberger, A.R., Jr.: Association of interleukin-4 plasma levels with traumatic injury and clinical course. Arch. Surg. *130*:1159, 1995
49. Houdijk, A.P.J., Rijnsburger, E.R., Jansen, J., Wesdorp, R.I.C., Weiss, J.K., McCamish, M.A., Teerlink, T., Meuwissen, S.G.M., Haarman, H.J.T.M., Thijs, L.G., and Leeuwen, P.A.M.: Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet *352*:772, 1998
50. Clark, M.A., Hentzen, B.T.H., Plank, L.D., and Hill, G.L.: Sequential changes in insulin-like growth factor-1, plasma proteins, and total body protein in severe sepsis and multiple injury. J. Parenter. Enteral Nutr. *20*:363, 1996
51. Christie, P.M., and Hill, G.L.: Return to normal body composition after ileoanal J-pouch anastomosis for ulcerative colitis. Dis. Colon Rectum *33*:584, 1990
52. Wilmore, D.W.: Does loss of body protein determine outcome in patients who are critically ill? Ann. Surg. *228*:143, 1998
53. Billing, A., Winter, H., Steines, W., Jochum, M., and Schildberg, F.W.: The surgeon's impact on the abdominal compartment in abdominal sepsis. Br. J. Surg. *85*:853, 1998
54. Schein, M., Wittmann, D.H., Holzheimer, R., and Condon, R.E.: Hypothesis: compartmentalization of cytokines in intraabdominal infection. Surgery *119*:694, 1996
55. Watkins, L.R., Goehler, L.E., Relton, J.K., Tartaglia, N., Silbert, L., Martin, D., and Maier, S.F.: Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune-brain communication. Neurosci. Lett. *183*:27, 1995
56. Sganga, G., Siegel, J.H., Brown, G., Coleman, B., Wiles, C.E., Belzberg, H., Wedel, S., and Placko, R.: Reprioritization of hepatic plasma protein release in trauma and sepsis. Arch. Surg. *120*:187, 1985
57. Clark, M.A., Plank, L.D., Connolly, A.B., Streat, S.J., Hill, A.A., Gupta, R., Monk, D.N., Shenkin, A., and Hill, G.L.: Effect of a chimeric antibody to tumor necrosis factor-α on cytokine and physiologic responses in patients with severe sepsis: a randomized, clinical trial. Crit. Care Med. *26*:1650, 1998
58. Hill, G.L.: Disorders of Nutrition and Metabolism in Clinical Surgery: Understanding and Management, Edinburgh, Churchill Livingstone, 1992, pp. 264–265
59. Clark, M.A., Plank, L.D., and Hill, G.L.: Wound healing associated with severe surgical illness. World J. Surg. *24*:648, 2000
60. Bone, R.C.: Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Ann. Intern. Med. *125*:680, 1996
61. Bone, R.C.: Sir Isaac Newton, sepsis, SIRS, and CARS. Crit. Care Med. *24*:1125, 1996
62. Bone, R.C.: Why sepsis trials fail. J.A.M.A. *276*:565, 1996
63. Davies, M.G., and Hagen, P-O.: Systemic inflammatory response syndrome. Br. J. Surg. *84*:920, 1997
64. Baue, A.E.: Multiple organ failure, multiple organ dysfunction syndrome, and systemic inflammatory response syndrome: why no magic bullets? Arch. Surg. *132*:703, 1997