done much to disseminate information and to promote awareness of the disease, but they are neither uniform nor unified.

I would like to use this editorial platform to exhort those with an interest in sarcoidosis who have access to patients with sarcoidosis to generate the momentum necessary to establish an organized method to share data, experiences, and expertise. The need for this can be no more clearly exemplified than by the plight delineated by the current authors.

The ACCESS group and the recently established North American chapter of WASOG are the most readily identifiable groups that could help spearhead the initiative that I would like to propose: to establish a national or international registry and database of sarcoidosis patients and a research consortium. This could serve as a potential resource to all investigators and clinicians, fostering participation in the development or utilization of treatment and research protocols and guidelines. In turn, this would greatly expand the ability to accumulate important information and would allow us to more rapidly develop new protocols and, ultimately, to better serve the unfortunate patient with severe debilitating sarcoidosis who may not have direct access to centers with significant expertise.

The suggestion to establish a registry and research initiative is not novel. But neither has it yet been done for sarcoidosis. We have a specific issue presented by Preston and coworkers: should iNO and epoprostenol be approved for use in patients with sarcoidosis. We have a specific issue presented by Preston and coworkers: should iNO and epoprostenol be approved for use in patients with sarcoidosis? I believe we would all respond that yes.

Will this require a lot of hard work and planning? Without a doubt. But, it is time to move the field forward. In addition to this particular question, many other perplexing issues and problems emanating from this fascinating and challenging disorder could be addressed. Let’s get the ball rolling!

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REFERENCES


Protein C Levels in Severe Sepsis

In this issue of CHEST (see page 915), Yan and colleagues demonstrate that 90% of a population of 70 patients who met the standard clinical criteria for severe sepsis had significantly reduced protein C levels. These investigators examined plasma samples from patients at study entry from a multicenter sepsis trial (the ibuprofen study) and repeated coagulation assays on plasma samples from patients 44 h after study entry. While low baseline levels of
protein C portend an unfavorable outcome, the results at 44 h after study entry were more predictive of fatal outcome (p < 0.05). These results are consistent with a considerable body of literature attesting to the adverse prognostic significance of low protein C levels in patients with severe sepsis.\(^2\) In addition to a rather predictable “dose-response” relationship (lower protein C levels, higher mortality rate), this study and several other recent investigations have documented that the failure of low protein C levels to recover in septic patients is highly correlated with a poor prognosis.\(^4\)

In the current investigation, protein C levels were significantly reduced even in those patients (9 of 10 patients) with normal global measures of coagulation activation, such as prothrombin time, partial thromboplastin time, platelet count, and fibrinogen levels. These results indicate that protein C measurement is a highly sensitive marker of coagulation activation and, more importantly, clinically evident severe sepsis. If these results can be replicated in a larger patient population, these results have important clinical implications for clinical trial design. If the vast majority of patients who meet standard clinical criteria for severe sepsis already have low protein C levels, does this obviate the need for actual measurement of protein C before initiating therapy for protein C deficiency? The answer to this question awaits the final answer from the recently completed phase III clinical trial of activated protein C in severe sepsis.\(^5\)\(^,\)\(^6\)

It is worth reflecting on the recent history of sepsis research and clinical trials designed to improve the outcome of patients with severe sepsis. For the last 25 years, the main focus of research has been directed against elements of the host immune response to systemic infection. Coagulation activation has been relegated to secondary importance in the pathogenesis and treatment of sepsis. The coagulation activation was assumed to be an epiphenomenon of ongoing systemic inflammation. It was incorrectly expected that regulation of the disordered inflammatory response of sepsis would allow for passive correction of the coagulation abnormalities. It now appears the opposite may be more clinically relevant. Control of disordered coagulation is of primary importance, and the interactions of coagulation and inflammation are central to the pathophysiology of septic shock. Resolution of the systemic inflammatory response may follow therapeutic interventions to re-establish homeostasis of the coagulation and fibrinolytic system.\(^6\)

A number of investigators have systematically dissected the intricate interactions between coagulation, inflammation, and the pathogenesis of sepsis. It is now quite clear that, at least in experimental models, repletion of acquired protein C deficiency in sepsis not only corrects the coagulation abnormality but results in a survival benefit.\(^7\)\(^–\)\(^9\) There are tantalizing hints that the same strategy may be true in clinical sepsis as well. Case reports of protein C infusion in patients with meningococccemia have revealed promising results.\(^4\)\(^,\)\(^10\) Results of a large phase III clinical trial in severe sepsis also support the value of activated protein C therapy in the treatment of severe sepsis.\(^5\)

Protein C may be uniquely positioned to serve as an essential regulator of the microcirculation in health and disease. Protein C undergoes extensive posttranslational modification, including vitamin K-dependent \(\gamma\) carboxylation of glutamic acid residues, hydroxylation of aspartic acid, intramolecular cleavage with a single disulfide bridge, and four N-linked glycosylation sites.\(^2\)\(^,\)\(^11\) All of these modifications are essential for activity but are insufficient to generate a functional serine protease that inhibits factors Va and VIIIa.

Protein C is a zymogen (proenzyme) that necessitates activation by excision of 12 amino acids off the amino terminus of the heavy chain of protein C. This vital activation process is mediated by thrombin itself in association with an endothelial surface protein known as thrombomodulin. Thrombomodulin is concentrated only on capillary endothelial surfaces.\(^12\) Thus, activated protein C exists precisely in the optimal location within the microcirculation that limits procoagulant activity.\(^13\)

Regrettably, tumor necrosis factor inhibits the expression of thrombomodulin, thereby limiting protein C activation during systemic inflammatory states.\(^14\) Tumor necrosis factor also reduces endothelial protein C receptor on endothelial surfaces, further limiting protein C activation. In this manner, pro-inflammatory cytokines may contribute to microvascular thrombosis, thrombin-mediated endothelial cell, platelet and neutrophil activation, and multiorgan dysfunction.\(^15\)\(^–\)\(^17\)

In addition to its anticoagulant properties, activated protein C is distinguished from other antithrombotics by its profibrinolytic activity (inhibition of plasminogen activated inhibitor-1 and reduced activity of thrombin activatable fibrinolysis inhibitor)\(^18\) and significant anti-inflammatory activity (attenuation of leukocyte gene expression)\(^19\) and reduction of neutrophil-endothelial cell interactions.\(^20\) The clinical relevance of the latter two activities to improved outcome in sepsis is unclear at present but a focus of considerable basic research currently.

The results of Yan and colleagues add further evidence in support of the therapeutic rationale for protein C supplementation in severe human sepsis. Activated protein C may be the preferred method of replenishment of protein C levels in patients with...
severe sepsis. Results of the current phase III trial of activated protein C and subsequent clinical studies with this recombinant human protein should clarify the ultimate role of the protein C pathway in septic shock.

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REFERENCES

4 Fisher CJ, Yan SP. Protein C levels as a prognostic indicator of outcome in sepsis and related diseases. Crit Care Med 2000; 28:S49–S56
9 Esmon CT. Introduction: are natural anticoagulants candidates for modulating the inflammatory response to endotoxin? Blood 2000; 95:1113–1116

Monitoring Tissue Oxygenation

The Quest Continues

In 1997, I wrote an editorial for CHEST regarding the search for a method to monitor the adequacy of tissue oxygenation that could be used by clinicians to guide the treatment of physiologically unstable patients. At that time, I likened this to the quest for the Holy Grail. Here it is 4 years later and, like the search for the grail, the goal appears to remain tantalizingly out of reach. While elusiveness is a wonderfully romantic part of the fascination with a quest, it is disappointing that more progress has not been made. The article by Marik in this issue of CHEST (see page 923) provides additional evidence that monitoring changes in luminal PCO₂, reflecting the interstitial hydrogen ion concentration, signals a change in overall homeostasis that correlates with a bad outcome. This additional proof of principal is welcomed, but begs the question of whether this variable can be put to use in a clinically useful and reliable manner.

Over the years, many indexes have been suggested as ways of monitoring tissue oxygenation. Most of these, such as venous PO₂, lactate, and O₂ consumption–O₂ delivery relationships have fallen by the way either because they could not stand up to rigorous clinical appraisal or because they were successfully challenged by newer theoretical understandings of the microcirculation and tissue metabolism. Some techniques, such as direct magnetic resonance or near infrared spectroscopic measurements of tissue metabolic state, would probably be quite useful, but have not yet been developed to the point of clinical applicability.

In 1964, Bergofsky showed that hollow organs such as the bladder could be used as an in vitro tonometer to approximate tissue gas tensions. 2 Fidldian-Green et al 3 in the early 1980s used this approach to measure interstitial PCO₂ in the gut and offered this measurement as an index of tissue