Editorials

An Exemplary Performance

ELSEWHERE IN THIS ISSUE there appears a report of a critical appraisal of what its proponents have termed "clinical ecology." The Scientific Board of the California Medical Association created a distinguished task force to do this appraisal. This was done in response to repeated requests from some clinical ecologists who wished to have the California Medical Association consider the evidence justifying their diagnostic and treatment methods.

It is not the purpose of this editorial to comment on clinical ecology, those who engage in its practice or the findings of the task force. Rather the purpose is to call attention to the process the task force used to examine this sensitive subject, and how by this means it developed the conclusions and recommendations. The report was approved by the full Scientific Board as it was submitted, and subsequently endorsed by the governing Council of the California Medical Association.

This critical appraisal is published here in the hope that the method and the process it describes may somehow serve as a generic model for others who may need to do critical appraisals of the scientific validity of what physicians (and sometimes other "health care providers") may on occasion advocate. Dr Wiederholt and the other members of the task force are to be complimented for the scientific criteria they used and for the thoroughness with which they studied all the evidence made available to them on this subject. They are to be commended for an exemplary performance.

MSMW

Treatment of Bacteremia

DRS JACOBSON AND YOUNG in this issue of the journal have reviewed "new developments in the treatment of Gram-negative bacteremia," which is, indeed, "one of the major current in-hospital infectious problems." Gram-negative bacteremia requires prompt therapy both to eliminate bacteremia and to reverse the metabolic alterations which may proceed to cause septic shock and death even when the microbes in the blood have been controlled by antibiotics. I am pleased to be asked to comment on this important problem.

The authors acknowledge that while "many signs and symptoms of nosocomial Gram-negative bacteremia are similar to those seen in Gram-positive bacteremia and fungemia," they state that it is "best to view [Gram-negative bacteremia] as a distinct clinical entity." Unfortunately, there is nothing distinctive about the syndrome of septicemia produced by Gram-negative bacteria when compared with episodes produced by Gram-positive bacteria or fungi (especially yeasts): both can also produce the syndrome of septicemia and shock. The clinical manifestations of septicemia are well described, and the authors do state that the clinical features of Gram-negative and Gram-positive infections are "similar." In my opinion, the crucial clinical point is to recognize who may have sepsis; one worries later about the specific causative microbe. Initiation of broad empiric therapy is the key to having any chance of success with a septicemic patient.

While most patients with sepsis present with fever, some may present in more subtle and confusing ways. As pointed out, from 15% to 20% of bacteremic patients are either afebrile or *hypo*thermic. Hypothermia, therefore, should promptly trigger an evaluation and therapy for presumed sepsis. In an afebrile patient, confusion, tachypnea, unexplained hypotension and a variety of dermal manifestations (from frank *ecthyma gangrenosum* or purpura to a few petechiae) may be the only symptoms or signs of septicemia. Not commonly appreciated is the fact that the increased capillary leakage during bacteremia, caused by endothelial cell damage, can result in pronounced edema formation; thus, a patient with progressive edema of indeterminant cause should also be evaluated and treated for the possibility of occult septicemia.[1]

The therapeutic approach is well outlined by the authors. The first priority is "to maintain adequate tissue perfusion with volume replacement" while, of course, quickly but thoroughly evaluating the patient, seeking the primary septic focus, culturing blood and other body fomites and then initiating broad, empiric antibiotic therapy. The type of volume replacement to be used is a matter of controversy not addressed by the authors. Isotonic crystalloid solutions may be used initially and certainly will transiently increase plasma volume and cardiac output. There is a growing consensus, however, that colloid-containing solutions are best for volume replacement in severely septic patients. Colloid solutions seem to be more effective than crystalloids in expanding plasma volume, and there is no evidence that they are harmful.[2] Studies need to be done to define more precisely the situations in which and patient groups in whom colloid solutions do a better job than crystalloid solutions, especially since colloid solutions are more expensive.

The use of corticosteroids is well discussed by the authors, but they fall short of a formal recommendation. My own feelings on the matter have recently been published.[3] To summarize, there are overwhelming animal data showing that early, very high doses (at least 30 mg per kg of body weight of methylprednisolone sodium succinate [MPSS]) administered over a few hours prevent shock either from an infusion of purified endotoxin or of live whole Gram-negative organisms. Clinical studies are available, and are well reviewed by Jacobson and Young, showing that survival in humans is prolonged and that mortality is probably reduced by high-dose corticosteroid administration. Thus, I recommend that following recognition and evaluation of the septic-appearing patient, volume replacement and antibiotic therapy should, of course, be promptly instituted. *Adequate* replacement of volume alone will hemodynamically stabilize most patients: adequacy of volume replacement can be difficult to assess, and the use of invasive hemodynamic monitoring may be required. Patients who remain unstable—that is, severely orthostatic or with frank hypotension, confusion or tachypnea,

especially with a falling partial oxygen pressure or pH, decreasing urine output or early signs of a coagulopathy—should rapidly receive a 30 mg per kg infusion of MPSS (over 10 to 20 minutes) followed by a constant MPSS infusion of 5 mg per kg per hour for eight to ten hours. The constant infusion should be discontinued when the patient becomes well stabilized. Even if shock develops or persists, the MPSS infusion should probably not be continued beyond the initial eight- to ten-hour period. The incidence of secondary suprainfections increases the longer high doses of a glucocorticoid are administered. The constant MPSS infusion method is preferred over intermittent "bolus-type" infusions based on well-done studies on animals by Hinshaw's group in Oklahoma City[4,5]; for whatever reason, constant infusion of MPSS produces significantly better results both in dogs and baboons than do intermittent boluses.

An infusion of antiendotoxin antiserum will also help patients survive Gram-negative bacteremia. Endotoxinlike moieties also exist in the cell walls of Gram-positive bacteria (the peptidoglycan-teichoic acid complex) and in yeast (zymosan-like substances), and those substances trigger the same series of metabolic events under proper circumstances as does endotoxin from the cell wall of Gram-negative bacteria. Thus, though not yet studied, antisera could theoretically be developed and would probably prove to be useful in patients with Gram-positive bacteremia or fungemia. As Jacobson and Young point out, the commercial development of human monoclonal antiendotoxin antibodies is under way and "may become an important part of the therapy undertaken for Gram-negative bacteremia in the near future." I agree! Studies are needed assessing whether antiserum therapy will obviate the need for steroids or whether steroid therapy in any way impairs the effect of antiendotoxin antibody administration.

The authors review the massive activation of the endorphin system in sepsis and the rationale, therefore, for the use of naloxone to counter endorphin-induced hypotension. While the rationale for the use of naloxone is clear, the true clinical effectiveness of the agent is not! As stated by the authors, no evidence exists that prolongation of survival in primates or humans is achievable by the use of naloxone. My own feeling is that volume, antibiotics and, in appropriate subgroups of patients with severe sepsis, glucocorticoids are the mainstays of treatment of bacteremia. Naloxone may help stabilize some patients who continue in shock, requiring increasing doses of vasoactive and cardioactive pharmacologic agents. Occasionally such a patient can be weaned off high doses of dopamine through the use of constant infusions of high doses of naloxone, as outlined by Jacobson and Young.

Finally, and more philosophically, I believe we need to better define subgroups of patients that should *not* be aggressively treated for septicemia. Patients critically ill with rapidly or ultimately fatal diseases who are highly likely to have bacteremia as an expected complication not only do not do well even with aggressive therapy but experience prolonged, uncomfortable and expensive treatment in our intensive care units before death inevitably supervenes. Intensive care unit support *can* extend life in such patients, as shown clearly by Sprung and co-workers[6]; long-term survival, however, is usually not improved. It is useful to remember that untreated sepsis, though unpleasant to observe, is probably a comfortable terminal event because of massive endorphin release. Understanding the role of endogenous endorphin release in severe sepsis explains why "pneumonia is the old man's friend." I would suggest that sepsis also befriends the incurably ill.

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'Society Must Decide'

AN ARTICLE BY RALPH CRAWSHAW appearing elsewhere in this issue introduces two new concepts into the difficult problem of deciding on health service priorities relative to all other social, economic and political priorities when there are not enough resources to do everything for everyone. The first is a concept of biovalues which Crawshaw separates from the concept of bioethics. Biovalues are the values a community or society places on health and life as measured in dedicated social resources such as tax dollars. Bioethics, in this context at least, pertains to what is good and bad health care practice and to moral obligations and duties of physicians, families and others toward patients, rather than to how society allocates its resources.

A second concept is the process through which biovalues were developed in the Oregon Health Decisions project that is described in this article. What appears to be a new concept is the development of what was found to be a workable community-based method of addressing such questions as, how can the present implicit rationing of health care be made explicit and part of recognized and agreed upon societal values? A process to do this is described, and the final resolutions developed by the project (and included in a published report of the project "Society Must Decide") dealt with topics such as (1) autonomy and dignity, (2) prevention of disease, (3) access and justice, (4) cost control and (5) allocation for fairness. And, perhaps most important, the project has apparently resulted in some specific actions being taken by the state, concerned citizens and members of the medical profession itself.

And why might the Oregon Health Decisions project be of wider interest? It appears to link the allocation of health care resources to health care needs as these are perceived by community leaders who become knowledgeable about both. Then, through "town hall" discussions, they determine and agree upon community values and from these recommend allocation of societal resources for health care. (The process is called "biovaluation" in this article.) If such a process can be made