



Preface



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Guest Editor

The relationship between systemic illness and neurobehavioral changes is both undisputed and poorly understood. Who has not experienced the somnolence, anorexia, fatigue, and social withdrawal that accompany fever and infection? Yet this “malaise” or “sickness behavior,” which is linked to the action of proinflammatory cytokines in the brain [1], is just one component in a sophisticated set of responses triggered in the central nervous system by systemic disease. The breadth and complexity of these responses is beginning to unravel thanks to a growing body of experimental and clinical research, and traditional paradigms of the central nervous system as a “privileged” organ have undergone extensive reevaluation [2]. New data reveal that the brain and extracerebral organs talk to each other in a bidirectional fashion, not only through afferent and efferent neural arcs but by way of physiologic, metabolic, immunologic, and endocrine signaling mechanisms [3–5]. The articles appearing in this issue of *Critical Care Clinics* suggest that the ICU is a unique arena to elucidate this cross-talk, to test hypotheses as to its mechanisms, and to develop strategies for modulating it to therapeutic ends.

Although critical care medicine is fundamentally concerned with the diagnosis and support of failing organ systems, the characterization of acute neurologic failure in the ICU presents unique challenges. Cerebral function is not amenable to meaningful description with any simple quantitative variable or test, such as cardiac output, $\text{PaO}_2/\text{FIO}_2$, serum lactate, or creatinine clearance. The anatomically localizing inferences obtained through detailed neurologic examination are frequently not helpful in the ICU because of

sedation and because the preponderance of neurologic alterations in the ICU involve widely distributed cerebral functions rather than focal lesions. Terms commonly used to depict altered consciousness (stupor, obtundation, lethargy, altered mental status, or impaired sensorium) lack construct validity and reliability. Standardized neurobehavioral assessment tools, such as the Glasgow Coma Scale [6], the Full Outline of UnResponsiveness [7], or the Confusion Assessment Method for the Intensive Care Unit [8], have validity, reliability, and prognostic value; however, they lack any specificity with respect to etiology or underlying diagnosis. Similarly, clinical assessment of peripheral nerve or muscle function in the ICU depends heavily on patient cooperation, which may be confounded by sedation, neuromuscular blockade, and coexisting brain dysfunction [9].

To overcome these limitations, research on the mechanisms of neurologic dysfunction in the ICU has been heavily reliant on biochemical, pathologic, electrophysiologic, and neuroimaging data [10]. Yet as these efforts yield important new insight, their practical significance remains elusive: there are no established, specific treatments or preventive regimens for any of the conditions described in this volume—a painful realization when one considers the burden of neurologic disease in the ICU. Indeed, epidemiologic accounts suggest that patients who have critical illness are faced with overwhelming odds of developing a neurologic syndrome, such as coma, delirium, or critical illness neuromuscular dysfunction [10,11], and that they incur substantial risk for developing long-term neurocognitive and neuromuscular impairment [12]. Our ability to offer these patients therapeutic relief, or to mitigate the extent of neurologic injury, depends critically on how well we understand the underlying mechanisms; such is the overriding theme of this issue.

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