In this issue of *Critical Care*, Patschan and colleagues [1] present a study of endothelial progenitor cells (EPCs) in patients with sepsis. The importance of this study is in focusing attention on several frequently ignored aspects of sepsis. Among those are the phenomenon of microvascular dysfunction, which is potentially responsible for profound metabolic perturbations at the tissue level, and the role of endothelial progenitors in repair processes. Other important aspects of the study are the regenerative capacity of mobilized EPCs and the dissociation between the numerical value and clonogenic competence. Attempting to restore the competence to EPCs should be a priority in the future.

Regenerative capacity and the dissociation between the numerical value and clonogenic competence represent the crux of the problem in sepsis. Reactive oxygen species, proinflammatory cytokines and chemokines, adrenergic stimulation, and other factors compromise various aspects of stem cell functions, their mobilization, niche properties, engraftment, and signaling, all of which result in the exhaustion of the EPC pool or incompetence of EPCs or both [4]. In addition, aging is the most common cause of stem cell dysfunction [5]. Therefore, the end result of the numerical and clonogenic dissociation of stem cell response to sepsis, the proverbial *vox clamantis in deserto*, is a complex integral of their quantity and quality. Hence, one of the potential clinical goals could be restoring stem cell competence.

While the fact of sepsis-induced mobilization of EPCs does not seem to cause dispute [6], the definition of EPCs and the significance of their recruitment are contentious subjects. The origins of these cells, their homogeneity, and identification markers are but a few unsettled issues as discussed by the authors, who in the midst of the existing debates have elected rational strategies to assess EPCs numerically and functionally. What I perceive as an even more serious challenge, however, is the fact that, along the path(s) from the quiescence of a niche environment to the re-programming signals in the circulation and target tissues, these cells are continuously changing.
their character and marker make-up. A single measurement provides but a snapshot of rapidly changing events in the context of evolving pathophysiological presentations of sepsis. It is necessary to perform fate tracing of various stem and progenitor cells in experimental animals subjected to a model of sepsis to gain insights into the pathways from niches to tissues, expression of various markers, and potential bifurcations along the path in order to test the validity of such findings in human disease.

I hope that the authors, having demonstrated EPC responses to sepsis, will conduct longitudinal numerical and functional testing of EPCs with the concomitant analysis of clinical presentations and outcomes in a large cohort of patients with sepsis. It is important to examine EPC responses in septic patients of various ages, in males and females, in patients with a preexisting chronic kidney or cardiovascular disease and those without them, and in patients who are immune-competent and those who are not.

**Abbreviation**
EPC, endothelial progenitor cell.

**Competing interests**
The author declares that he has no competing interests.

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