In this issue of *The Journal,* an intriguing article by Zanjani et al. (1) describes the conduciveness of the in utero and subsequent adult environment of sheep for sustenance of early human hematopoietic stem cells with self-renewal capacity. The authors have demonstrated that isolated $CD45^+$ human cells from the marrows of adult sheep, previously injected in utero with human fetal liver cells, can be transferred and have the capacity to engraft the hematopoietic system of secondary sheep recipients. This is a noteworthy extension of previous studies (2, 3), but how does this information complement our present understanding of human stem cells and what limitations are inherent in this model?

We know very little about human long-term marrow repopulating cells, yet their characterization and isolation is of paramount importance for understanding progression and eventual correction of blood disorders. In vitro assays are available for human myeloid progenitor cells (including multipotential as well as more lineage-restricted granulocyte and/or macrophage, erythroid, and megakaryocyte progenitors) and for relatively less mature myeloid cells such as "stem" (S) cells, high proliferative capacity colony-forming cells (HPP-CFC), and long-term culture-initiating cells (LTC-IC), however, it is not obvious that these assays detect long-term human marrow repopulating cells (4). The present paper (1) offers the probability that one can now study long-term human marrow repopulating cells.

In murine models, transplanted murine stem cells can repopulate the hematopoietic system long-term and save the animal from chemotherapy- or radiation-induced death. Functional activity such as this has not been assessed for human cells in the sheep, and some creative maneuvers will have to be used to test for some functional capacity of these cells. Maintenance in sheep of an antigenic profile of early cells (3) is not necessarily proof that the quality of these cells remains intact. How realistic it will be to use this model as a quantitative assay system remains to be determined. Engraftment of human cells is still low in the marrow of the primary sheep ($3.3\pm0.32\%$), and with pooled cells from the primary sheep, only two of six secondary sheep supported the continued growth of human cells. This may be a result of the low numbers of human cells available for transplantation. Efforts to enhance this engraftment, perhaps through the use of human cytokines, could potentially enhance the possibility of using this model as quantitative assay. A limitation, however, will still be the number of recipient sheep available and the cost of their maintenance. It may be possible to complement information from this large animal model with that from mice with severe combined immunodeficiency (SCID) (5). Use of SCID mice might allow for more extensive and quantitative studies than that of sheep, but whether the SCID mice are allowing maintenance or expansion of long-term marrow human repopulating cells still needs to be determined.

A number of areas could benefit from the use of models for human long-term human marrow repopulating cells. The first is the competitive repopulating nature of such cells from different tissue sources and developmental states. For example, would cord blood stem cells have a competitive advantage in vivo over bone marrow and how would fetal liver and cells in adult blood that have been mobilized by chemotherapy and/or growth factors compete in this context? A second area is ex vivo expansion of stem/progenitor cells. Whether the earliest stem cells are being maintained or expanded ex vivo remains to be determined but this is of crucial importance to our use of these cells. A third area is characterization and isolation of the earliest human stem cells. Using combinations of cell surface antigenic determinants one could better evaluate the phenotypic expression of long-term human marrow repopulating cells. A fourth area involves use of gene therapy to correct genetic and other disorders. Transduction procedures have proved efficient for stable integration of genes into early human cells as recognized by in vitro analysis (6). However, transduction efficiency as assessed by in vivo analysis has been relatively disappointing, a problem that may involve inability to transduce efficiently the earliest stem cells. A model for long-term human marrow repopulating cells could evaluate this possibility.

The capacity of early human stem cells to take up residence in sheep marrow (1) along with mouse models that allow growth of human cells, and improved modifications of these in vivo systems, should allow us to evaluate better and thus enhance our understanding of the earliest phases of human blood cell development.

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