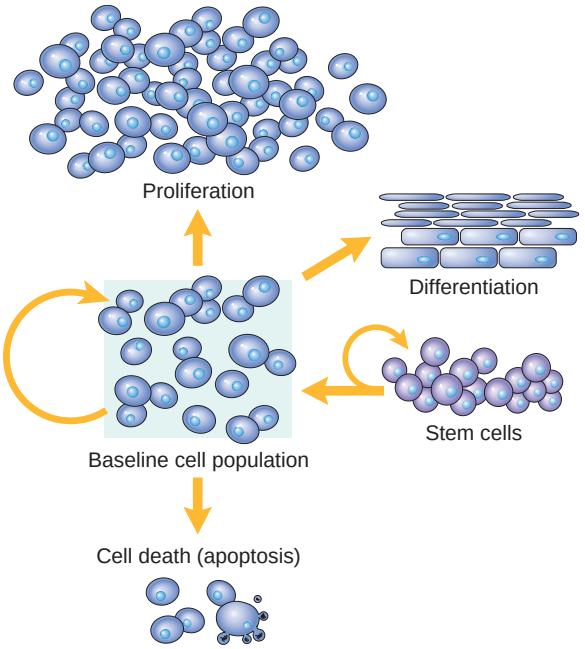

Figure 1-19 Mechanisms regulating cell populations. Cell numbers can be altered by increased or decreased rates of stem cell input, cell death due to apoptosis, or changes in the rates of proliferation or differentiation. (Modified from McCarthy NJ, et al: Apoptosis in the development of the immune system: growth factors, clonal selection and bcl-2. Cancer Metastasis Rev 11:157, 1992.)

Although there is a tendency in the scientific literature to partition stem cells into several different subsets, fundamentally there are only two varieties:

- *Embryonic stem cells (ES cells)* are the most undifferentiated. They are present in the inner cell mass of the blastocyst, have virtually limitless cell renewal capacity, and can give rise to every cell in the body; they are thus said to be *totipotent* (Fig. 1-20). While ES cells can be maintained for extended periods without differentiating, they can be induced under appropriate culture conditions to form specialized cells of all three germ cell layers, including neurons, cardiac muscle, liver cells, and pancreatic islet cells.
- *Tissue stem cells* (also called *adult stem cells*) are found in intimate association with the differentiated cells of a given tissue. They are normally protected within specialized tissue microenvironments called *stem cell niches*. Such niches have been demonstrated in many organs—including the brain, where neural stem cells inhabit the subventricular zone and dentate gyrus. Skin stem cells are found in the bulge region of the hair follicle, and in the cornea they are found at the limbus. Soluble factors and other cells within the niches keep the stem cells quiescent until there is a need for expansion and differentiation of the precursor pool (Fig. 1-21). Adult stem cells have a limited repertoire of differentiated cells that they can generate. Thus, although adult stem cells can maintain tissues with high (e.g., skin, and gastrointestinal tract) or low (e.g., heart and brain) cell turnover, the adult stem cells in any given tissue can usually only produce cells that are normal constituents of that tissue.

The most extensively studied of the tissue stem cells are the hematopoietic stem cells that continuously replenish all the cellular elements of the blood as they are consumed. Hematopoietic stem cells may be isolated directly from bone marrow, as well as from the peripheral blood after administration of certain colony stimulating factors (CSF) that induce their release from bone marrow niches. Although rare, hematopoietic stem cells can be purified to virtual homogeneity based on cell surface markers and ability to give rise to blood cell of lineages. Clinically, these stem cells can be used to repopulate marrows depleted

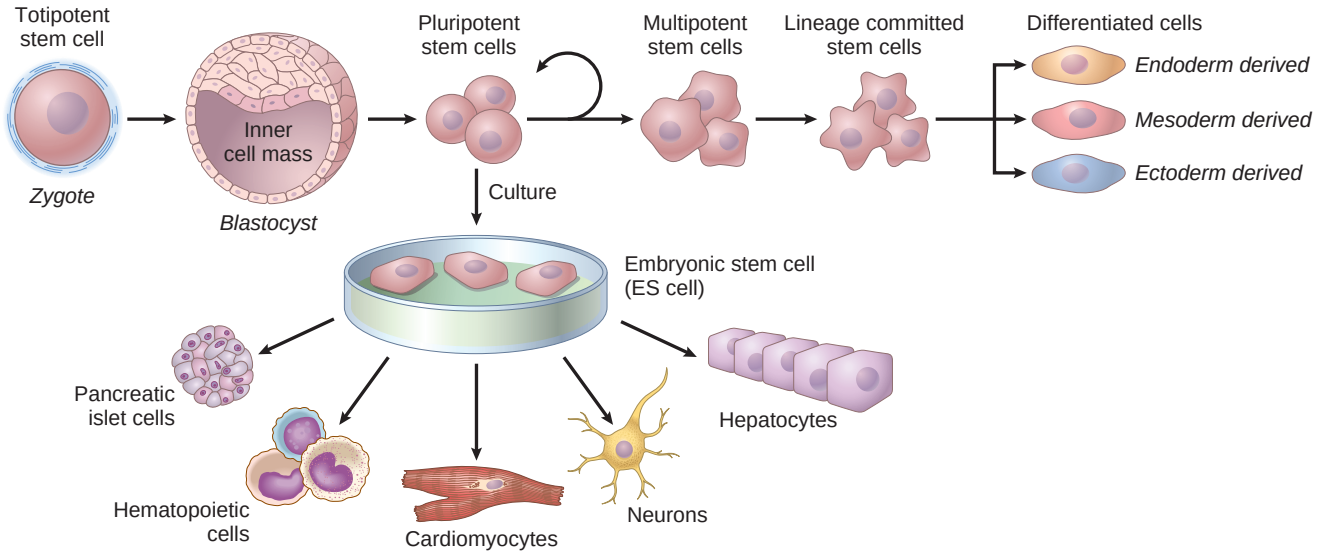

Figure 1-20 Embryonal stem cells. The zygote, formed by the union of sperm and egg, divides to form blastocysts, and the inner cell mass of the blastocyst generates the embryo. The pluripotent cells of the inner cell mass, known as embryonic stem (ES) cells, can be induced to differentiate into cells of multiple lineages. In the embryo, pluripotent stem cells can asymmetrically divide to yield a residual stable pool of ES cells in addition to generating populations that have progressively more restricted developmental capacity, eventually generating stem cells that are committed to just specific lineages. ES cells can be cultured in vitro and be induced to give rise to cells of all three lineages.