turnover occurs even in the normal pancreas, although the source of the new beta cells remains controversial. This persistent turnover suggests that, in principle, it should be possible to develop strategies for reconstituting the beta cell population in diabetics. Attempts to devise techniques for promoting endogenous regenerative processes by using combinations of growth factors, drugs, and gene therapy have failed thus far, but this remains a potentially viable approach. A number of different cell types are candidates for use in stem cell replacement strategies, including iPS cells, ES cells, hepatic progenitor cells, pancreatic ductal progenitor cells, and MSCs. Successful therapy will depend on the development of a source of cells that can be amplified to produce large numbers of progeny with the ability to synthesize, store, and release insulin when it is required, primarily in response to changes in the ambient level of glucose. The proliferative capacity of the replacement cells must be tightly regulated to avoid excessive expansion of beta cell numbers and the consequent development of hyperinsulinemia/hypoglycemia; moreover, the cells must withstand immune rejection. Although it has been reported that ES and iPS cells can be differentiated into cells that produce insulin, these cells have a low content of insulin and a high rate of apoptosis and generally lack the capacity to normalize blood glucose levels in diabetic animals. Thus, ES and iPS cells have not yet been useful for the large-scale production of differentiated islet cells. During embryogenesis, the pancreas, liver, and gastrointestinal tract are all derived from the anterior endoderm, and transdifferentiation of pancreas to liver and vice versa has been observed in a number of pathologic conditions. There is also substantial evidence that multipotential stem cells reside within gastric glands and intestinal crypts. These observations suggest that hepatic, pancreatic, and/or gastrointestinal precursor cells may be reasonable candidates for cell-based therapy for diabetes, although it is unclear whether insulin-producing cells derived from pancreatic stem cells or liver progenitors can be expanded in vitro to clinically useful numbers. MSCs and neural stem cells both reportedly have the capacity to generate insulin-producing cells, but there is no convincing evidence that either cell type will be clinically useful. Clinical trials of MSCs, USCs, HSCs, and ASCs in both type 1 and type 2 diabetes are ongoing.

Nervous System Substantial progress has been made in the development of methodologies for generating neural cells from different stem cell populations. Human ES or iPS cells can be induced to generate cells with the properties of neural stem cells, and these cells in turn give rise to neurons, oligodendroglia, and astrocytes. Reasonably large numbers of these cells can be transplanted into the rodent brain with formation of appropriate cell types and no tumor formation. Multipotent stem cells present in the adult brain also can be easily amplified in number and used to generate all the major neural cell types, but the need for invasive procedures to obtain autologous cells is a major limitation. Fetal neural stem cells derived from miscarriages or abortions are an alternative but raise ethical concerns. Nevertheless, clinical trials of fetal neural stem cells have commenced in amyotrophic lateral sclerosis (ALS), stroke, and several other disorders. Transdifferentiation of MSCs and ASCs into neural stem cells, and vice versa, has been reported by numerous investigators, and clinical trials of such cells have begun for a number of neurologic diseases. Clinical trials of a conditionally immortalized human cell line and of USCs in stroke are also in progress. Because of the incapacitating nature of neural disorders and the limited endogenous repair capacity of the nervous system, clinical trials of stem cells in neurologic disorders have been particularly numerous, including trials in spinal cord injury, multiple sclerosis, epilepsy, Alzheimer's disease, ALS, acute and chronic stroke, numerous genetic disorders, traumatic brain injury, Parkinson's disease, and others. In diseases such as ALS, possible benefits are more likely to be due to indirect trophic effects than to neuron replacement. In Parkinson's disease, the major motor features of the disorder result from the loss of a single cell population: dopaminergic neurons within the substantia nigra; this circumstance suggests that cell replacement should be relatively straightforward. However, two clinical trials of fetal nigral transplantation failed to meet their primary endpoint and were complicated by the development of dyskinesia. Transplantation of stem cell–derived dopamine-producing cells offers a number of potential advantages over the fetal transplants, including the ability of stem cells to migrate and disperse within tissue, the potential for engineering regulatable release of dopamine, and the ability to engineer cells to produce factors that will enhance cell survival. Nevertheless, the experience with fetal transplants points out the difficulties that may be encountered.

At least some of the neurologic dysfunction after spinal cord injury reflects demyelination, and both ES cells and MSCs can facilitate remyelination after experimental spinal cord injury (SCI). Clinical trials of MSCs in this disorder have commenced in a number of countries, and SCI was the first disorder targeted for the clinical use of ES cells. However, the ES cell trial in SCI was terminated early for nonmedical reasons. At present, no population of transplanted stem cells has been shown to have the capacity to generate neurons that extend axons over long distances to form synaptic connections (as would be necessary for replacement of upper motor neurons in ALS, stroke, or other disorders). For many injuries, including SCI, the balance between scar formation and tissue repair/regeneration may prove to be an important consideration. For example, it may ultimately prove necessary to limit scar formation so that axons can reestablish connections.

Liver Liver transplantation is currently the only successful treatment for end-stage liver diseases, but the shortage of liver grafts limits its application. Clinical trials of hepatocyte transplantation demonstrate its potential as a substitute for organ transplantation, but this approach is limited by the paucity of available cells. Potential sources of stem cells for regenerative strategies include endogenous liver stem cells (such as oval cells), ES cells, MSCs, and USCs. Although a series of studies in humans as well as animals suggested that transplanted MSCs and HSCs can generate hepatocytes, fusion of the transplanted cells with endogenous liver cells, giving the erroneous appearance of new hepatocytes, appears to be the underlying event in most circumstances. The available evidence suggests that transplanted HSCs and MSCs can generate hepatocyte-like cells in the liver only at a very low frequency, but there are beneficial consequences presumably related to indirect paracrine effects. ES cells can be differentiated into hepatocytes and transplanted in animal models of liver failure without the formation of teratomas. Clinical trials are in progress in cirrhosis with numerous cell types, including MSCs, USCs, HSCs, and ASCs.

Other Organ Systems and the Future The use of stem cells in regenerative strategies has been studied for many other organ systems and cell types, including skin, eye, cartilage, bone, kidney, lung, endometrium, vascular endothelium, smooth muscle, and striated muscle, and clinical trials in these and other organs are ongoing. In fact, the potential for stem cell regeneration of damaged organs and tissues is virtually limitless. However, numerous obstacles must be overcome before stem cell therapies can become a widespread clinical reality. Only HSCs have been adequately characterized by surface markers so that they can be unambiguously identified, a prerequisite for reliable clinical applications. The pathways for differentiating stem cells into specific cellular phenotypes are largely unknown, and the ability to control the migration of transplanted cells or predict the response of the cells to the environment of diseased organs is presently limited. Some strategies may employ the coadministration of scaffolding, artificial extracellular matrix, and/or growth factors to orchestrate differentiation of stem cells and their organization into appropriate constituents of the organ. There is currently no way to image stem cells in vivo after transplantation into humans, and it will be necessary to develop techniques to do so. Fortunately, stem cells can be engineered before transplantation to contain a contrast agent that may make their in vivo imaging feasible. The potential for tumor formation and the problems associated with immune rejection are impediments, and it will also be necessary to develop techniques for ensuring vascularization of regenerated tissues. There already are many strategies for supporting cell replacement, including coadministration of vasoactive endothelial growth factor to foster vascularization of the transplant. Some strategies also include the genetic engineering of stem cells with an inducible suicide gene so that the cells can be easily eradicated in