transplantation. For small animal experiments, grafts typically involve ~10^6 cells, and this number of SKP cells can be produced in ~30 days from the initial cell isolation from skin. Furthermore, once a culture is established, it will double every 2–3 days, suggesting that enough cells could be produced for grafting procedures on humans.

This work also makes us think about the nature of stem cells and how they might be fitted into the conceptual framework of developmental biology. The generally promiscuous behaviour of transplanted stem cells has led to a revival of the idea that they are 'embryonic reserve cells': pluripotent cells that are left over from the embryo and that will grow to form anything, given the right opportunity[15]. Although it is always very difficult to prove the absence of some rare hypothetical entity, this idea has not in the past been sustained either in the context of regeneration or of cancer, both once ascribed to growth from embryonic reserve cells but both now understood to originate from normal cells. In this context, it is relevant to consider the possible significance of nestin as a general stem cell marker. Nestin is a neurofilament-like intermediate filament protein that was originally discovered because of its association with neural stem cells[16,17]. It is indeed expressed by some other stem cells, for example by pluripotent cells from the pancreas[18]. However, it is not exclusively associated with stem cells because it is also normally expressed in muscle[19,20], and it is not clear that the 'stem-ness' of stem cells is attributable to nestin itself.

Figure 1 shows a conventional diagram of the subdivision of regions that occurs in a vertebrate embryo, to which is added the identities of some of the types of stem cell that have been described in recent years. It is clear from analyses of cell surface markers and other properties that these various stem cells are not all the same. The surprise is that, on transplantation, they seem to be able to generate more cell types than would be expected given their position in the developmental hierarchy. However, it should be remembered that the transplantation results are often looking at a very small number of cells, and cases in which major organ replacement has occurred involve long growth periods, under selection, starting from a small number of graft cells[21]. Grafting might be directly into the target tissue or might be intravenous but, in either case, individual graft cells will end up surrounded by host cells. Embryologists have always known that isolated cells are more labile than cells surrounded by others of their own kind, so it is perhaps not so surprising that grafted stem cells should often populate unexpected tissues. This behaviour is not incompatible with the idea that the stem cells *in vivo* retain the developmental commitment of the embryonic rudiment that gave rise to them. We might in fact be able to learn more about stem cells by studying embryonic rudiments, because these are often homogeneous whereas the stem cells are always a small minority of the total cells in a mature tissue.

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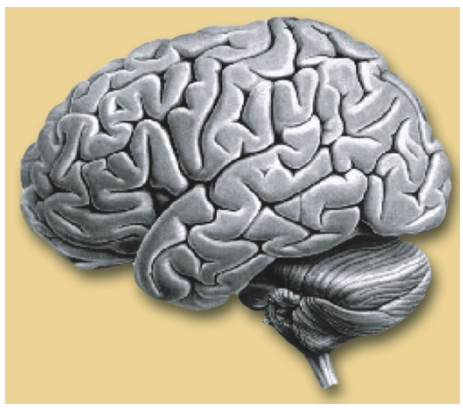
Brain dead (or alive)

Huntington's disease (HD) is one of a family of neurodegenerative diseases that are associated with the accumulation of aggregates of a mutant form of a protein bearing glutamine repeats, in this case the Huntingtin protein (Htt). It is still a matter of debate whether these aggregates are a cause or a consequence of neural loss. Another issue is whether neurodegeneration is caused by the function of mutant Htt or by loss of function of wild-type Htt—as there is evidence in favour of each hypothesis—or indeed by a combination of both.

Elena Catteneo and her collaborators have recently reported in *Science* **293,** 493–497 (2001) that wild-type Htt enhances the survival of striatal neurons—those that degenerate in HD—by driving the expression of the brain-derived neurotrophic factor (BDNF) by neighbouring cortical neurons in the brain. This function is lost in neurons expressing mutant Htt. Furthermore, they found reduced levels of BDNF in aging model animals expressing mutant Htt—which show a selective loss of striatal neurons—compared with mice expressing wild-type Htt.

These new findings pave the way for therapeutic treatments for HD involving BDNF. However, it remains to be established how Htt regulates BDNF transcription and how the expression of mutant Htt leads to reduced BDNF levels. Interestingly, Htt aggregates have been reported to sequester CREB, a transcription factor that positively regulates BDNF expression (*Nature Med.* **7,** 528–530; 2001), which provides a possible explanation. Taken together with the fact that wild-type Htt has been reported to



protect neurons by interfering with the activation of caspases, an enzyme required for apoptotic cell death (*J. Biol. Chem.* **276,** 14545–14548; 2001), whereas aggregates of mutant Htt might contribute to the activation of caspases (Neuron **3,** 623–633; 1999), these data indicate that neurodegeneration is probably due to both a loss of the beneficial effects of Htt and the destructive effects of mutant Htt.

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