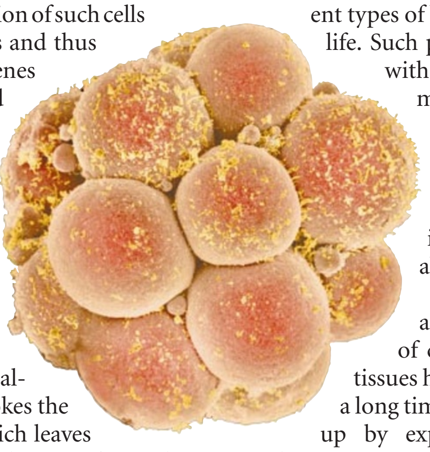
A cellular cornucopia

Stem cells generate new possibilities for research and therapy.

Margaret Buckingham

Cells with the capacity to re-make parts of the body, or a whole organism, have always excited the imagination. The magic of the process by which a single fertilized egg develops into an embryo, leading to the birth of a new individual, can now be unmasked at the molecular level. The actions of signalling molecules gradually restrict a cell's possibilities, modifying the repertoire of genetic information that it expresses. The universal nature of this selective strategy, with similar molecules acting at different sites within the same embryo in species as different as insects and humans, has been one of the revelations of modern developmental biology.

A major technological breakthrough was the isolation of early embryonic cells that can be replicated *in vitro* while retaining their capacity to contribute to all tissue types. This phenomenon of totipotency opened the way to genetic manipulation of such cells to create mouse mutants and thus test the function of genes during development and in the adult.



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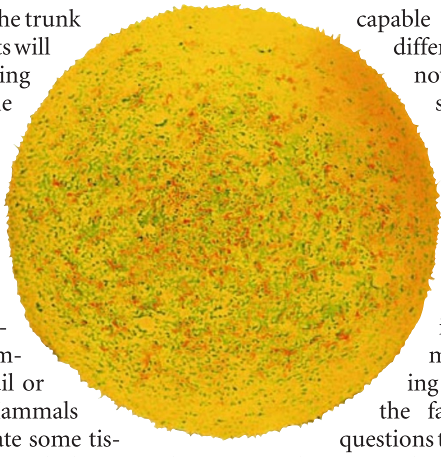
Such totipotent cells, together with multipotent cells that can renew themselves and contribute to some, but not all, cell types, were called stem cells long before they had become an experimentalist's tool. Their name evokes the stem of a plant from which leaves and flowers bud. It is also the root of a word that remains after all suffixes or prefixes have been removed. It is here that the linguistic comparison becomes interesting. The stem, from the Latin for a thread, grows up from the root to generate all the other parts of the plant. In German, *Stammzellen* has similar connotations to the English stem cells, but in French, *les cellules souches* implies something slightly different. The *souche* of a tree is what is left when the tree is cut down — the roots and base of the trunk from which new shoots will grow, eventually leading to new trees. Hence the French word incorporates the idea of regeneration as well as of birth.



Adult animals, even adult vertebrates, can undergo a degree of regeneration. A lizard, for example, can regrow its tail or even an entire limb. Mammals can partially regenerate some tissues, such as liver or muscle, but not others, such as heart. Bone marrow is an adult tissue where replicating precursor cells are present, leading to the repeated generation of different types of blood cell throughout life. Such plasticity is associated with a susceptibility to malignancy, not seen in tissues such as the heart, where the lock that prevents cells re-entering the cycle is virtually unbreakable.

The existence of adult stem cells capable of contributing to many tissues had been suspected for a long time, but was not backed up by experimental evidence; even the regenerative lizard's tail probably depends on the reversion of differentiated cells. Cells are not totally inflexible in the fate that they adopt — a classic experiment in frogs showed that the nucleus of an adult cell introduced into an embryonic cell can contribute to embryo development. The recent production of Dolly the sheep was a further demonstration that it is possible to clone an individual by using the genetic information from one of its cells to make a 'genocopy'; although, despite all the media hype associated with this phantasm of immortality, a genocopy is not necessarily a phenocopy.

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In the case of Dolly, it is not exactly clear what the adult cell was. In the past two years, however, thanks to the availability of appropriate molecular markers, it has now been demonstrated that many adult tissues do contain stem cells. This was first shown in bone marrow, which contains cells capable of colonizing many different tissue types. It is now possible to separate such cells, which have unlimited proliferative capacity and are multipotent, from many different adult tissues. The embryonic origin of these cells and why they remain blind to the instructions that normally restrict cell fate during development are among the fascinating fundamental questions to be answered.

The potential applications of stem cells for the repopulation of damaged tissue is of major biomedical interest. The use of human embryonic stem cells raises ethical issues as well as practical problems, not the least of which is controlling the behaviour of an embryonic cell in an adult environment. For adult stem cells, the issue is why they do not play a bigger role in regeneration normally and how to manipulate them so that they can. At the dawn of the new century, we have found the elusive stem cell. Now we have to master its magic so that new tissue can indeed stem from it, as new shoots grow from the *souche* of the tree. ■

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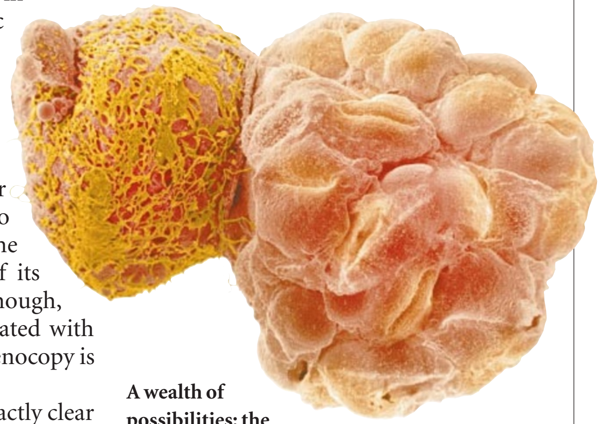

A wealth of possibilities: the cells in young embryos can differentiate into a multitude of different tissues.