Immigration denied

Pasko Rakic

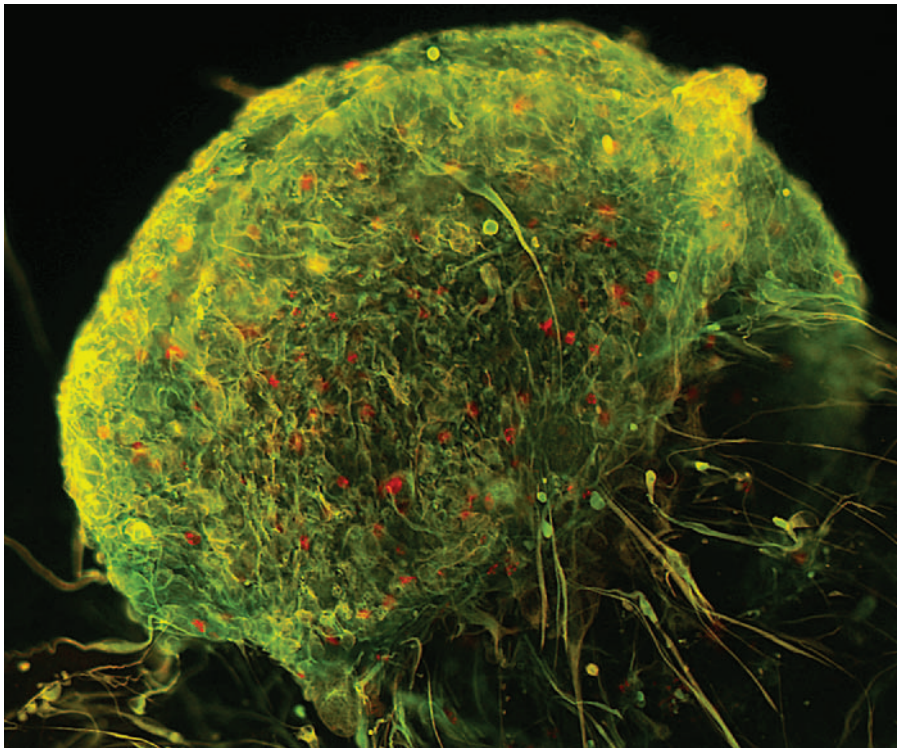
The adult human brain cannot replace lost neurons. This might be because it is reluctant to accept newcomers into an already established neural network, rather than because potential progenitors are absent.

Neural stem cells are a focus of strong interest because of the possibility that they could be used to replace neurons that have been damaged or lost — perhaps as a result of injury such as trauma or stroke, or through neurodegenerative disorders such as Parkinson's disease. These stem cells can give rise to neurons and their supporting cells, glia, and it is hoped that something akin to neural stem cells in the adult human brain could be stimulated to generate replacement neurons.

Non-mammalian vertebrates, such as the salamander, can regenerate large portions of their brain and spinal cord, but humans have evidently lost this capacity during evolution. Therefore, most research on neural stem cells is carried out on mammals such as rodents, which are genetically closer to humans. However, although mammalian genomes may be similar, this similarity masks vast species differences in the way the brain is organized and in its capacity for regeneration and susceptibility to environmental insults. The failure of brain repair in clinical trials based on the promising results seen after the use of similar procedures in rodents is sobering testimony to the importance of such species-specific distinctions.

Human neural stem cells behave differently from their rodent equivalents in culture[1], but the direct study of human brain tissue by Sanai *et al.*[2], described on page 740 of this issue, shows additional significant and clinically relevant species-specific differences. The authors' investigations on a large number of postmortem and biopsy samples reveal two basic findings. First, neural stem cells that can potentially give rise to neurons, as well as to two types of glial cell (astrocytes and oligodendrocytes), are situated in a region of the forebrain known as the subventricular zone. Second, a pathway known as the rostral migratory stream — which in adult rodents contains neurons that migrate from the subventricular zone to the brain region concerned with sensing smell — is absent in humans.

In adult mammals, including humans, the subventricular zone (more commonly known as the subependymal zone[3–5]) contains cells that have the characteristics of glial cells and that can generate neuronal cells in culture[6–8]. Sanai *et al.*[2] show that in adult humans these 'glial progenitor cells' form a prominent layer, or ribbon, that is restricted to a specific region in the brain that lines the lateral cerebral ventricle (Fig. 1). This region is also present in non-human primates, but it is thinner and less well delineated than in humans[4,9–11]. Based on the knowledge that about 0.7% of cells in the human subventricular zone contain a specific nuclear protein, Ki-67, that is associated with DNA synthesis and hence cell division, Sanai and colleagues[2] infer that these cells can proliferate. However, the number of cells that are actually dividing is probably smaller than this, as Ki-67 can also be present in dying cells[12,13]. Importantly, although the cells that were positive for Ki-67 also contained marker molecules for astrocytes, they did not contain markers for immature neurons. This observation is similar to that seen with subependymal cells in other parts of the adult mammalian brain, such as the spinal cord or brain stem, which also do not generate neurons *in vivo*. However, if these cells are cultured or are transplanted to acceptable cellular environments such as the hippocampus, they can show some neuronal features[14].



N. SANAI *ET AL.*

Figure 1 **Proliferative potential. Astrocytes that can behave as neural stem cells are present in the walls of the lateral ventricle in the adult human brain. This culture containing proliferating astrocytes labelled with glia fibrillary acidic protein (GFAP; green) and the cell division marker Ki-67 (red) was derived from cells taken from a patient during the removal of part of the walls of the lateral ventricle[2].**

Sanai and colleagues' second key finding[2] is the absence in humans of the rostral migratory stream, which in mammals with a highly developed sense of smell supplies neurons to the olfactory bulb. It seems that these migratory neuronal precursors are present in humans during infancy but disappear during childhood[5]. This is not unexpected, considering the dramatic loss of olfactory receptor genes in the relatively small human olfactory bulb[15] and the substantial reduction in the size of the rostral migratory stream in non-human primates[16]. However, it highlights the danger of extrapolating results from rodents to humans. Sanai and colleagues' findings therefore add to the evidence that, with the exception of a specific cell type in the hippocampus[17], the human brain shows no sign of spontaneous neuronal turnover[11,18].

Back to the potential glial progenitors, then — what might be their function, given that they do not give rise to neurons? Apart

from serving as a major source for the turnover of astrocytes and oligodendrocytes, which occurs normally in the adult primate brain, they also provide a reservoir for a certain type of astrocyte that migrates to sites of traumatic, infectious or degenerative brain damage. In addition, their uncontrolled proliferation is considered to be a main cause of certain types of invasive glial brain tumour. However, it is instructive that these dormant glial progenitors never generate malignant tumours of any neuronal cell type. This indicates that there are probably formidable suppressors that block the production of neuronal cells in the adult human brain[11].

The main lesson from this comprehensive study is that the lack of neuronal turnover and/or replacement of injured neurons in the adult human brain is not due to the absence of potential neural stem cells. Rather, it is more likely to be due to a remarkable resistance to accept such cells into a mature neuronal network. The systematic decrease in the extent of adult neurogenesis during vertebrate evolution, culminating in primates, may be the result of an adaptation to keep neuronal populations with their accumulated experience for an entire lifespan[11]. Although the therapeutic transplantation of new neurons to regions of the human brain that are responsible for more advanced brain functions may be counterproductive, their transplantation to other regions, such as the sensory or motor systems of the brain, could have enormous clinical significance. So the identification of the cellular and molecular mechanisms that prevent adult neural stem cells from becoming integrated into functional neuronal networks would be a major achievement. Without this, the stimulation of dormant neural stem cells, and even their survival, may not be sufficient to accomplish brain repair. ■

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Palaeoclimate

Low-down on a rhythmic high

Katharina Billups

Changes in the amount of solar energy reaching Earth account for certain climate cycles at high and low latitudes. Surprisingly, the effects of a high-latitude cycle evidently reached into the tropics.

During the 1920s, Milutin Milankovitch, a Serbian mathematician, calculated the effects of alterations in Earth's motion around the Sun on the amount of solar energy reaching different latitudes[1]. Since then, some of the long-period, cyclic changes seen in archives of past environmental conditions on Earth have been explained by these changes in insolation. For example, a 41,000-year cycle in a climate record is commonly ascribed to changes in the planet's tilt, which affects insolation at high latitudes, and a 19,000–23,000-year cycle is ascribed to changes in the planet's wobble, which dominates insolation at low and middle latitudes[2,3].

Eighty years after Milankovitch's innovative work, Liu and Herbert (page 720 of this issue[4]) have unearthed surprising evidence that the views based on his conclusions are incomplete. The authors provide a record of low-latitude sea surface temperature (SST) that is in phase with the 41,000-year rhythm reminiscent of high-latitude insolation. Although their record represents only the past 1.8 million years, a small portion of Earth's history, their findings force us to think further about a climate system that we already knew to be complex.

How does the geological record document past climate change? Perhaps the most ubiquitous recorders of past climate change are the fossil shells of foraminifera, calcareous marine organisms. To a large degree, the oxygen-isotope ratio of the calcium carbonate shell of foraminifera reflects the oxygen-isotope ratio in sea water, which in turn is a function of the hydrologic cycle and thus the amount of fresh water stored as ice at the poles. Because ice-sheet growth and decay are affected by cycles in insolation, the $H_2{}^{18}O/H_2{}^{16}O$ ratio of sea water varies at the same frequency as does the $^{18}O/^{16}O$ ratio of the carbonate shells of the foraminifera in the world ocean. Over time, foraminifers accumulating on the bottom of the ocean build an archive of information about glacial to interglacial climate change.

These types of record provide the backbone of palaeoclimate studies. For example, over the past 5 million years perhaps the most profound change in Earth's climate history was the onset of glaciation in the Northern Hemisphere, recorded by the increase in foraminiferal $^{18}O/^{16}O$ ratios between 3 million and 2 million years ago (Fig. 1). However, the isotopic composition of sea water, and hence global ice extent, is not the only variable determining foraminiferal $^{18}O/^{16}O$ ratios; water temperature affects the preference of one isotope over the other incorporated in calcium carbonate during

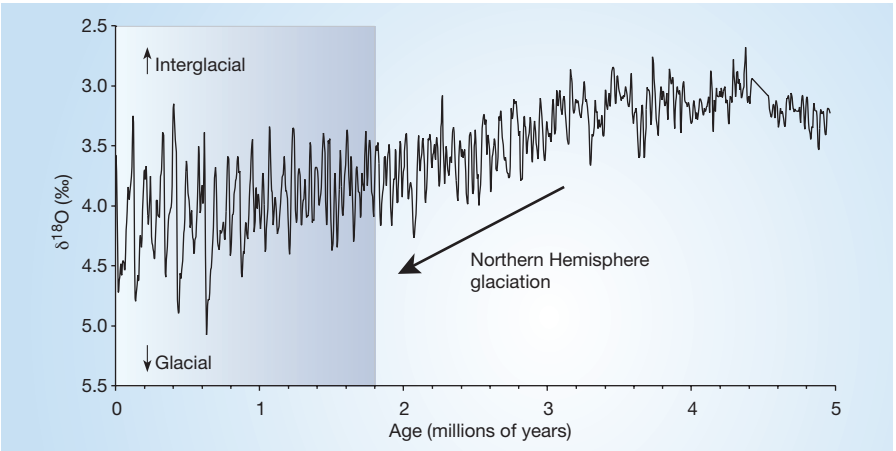

Figure 1 **Global climate change from 5 million years ago to the present. This record is inferred from the foraminiferal oxygen-isotope archive from the eastern equatorial Pacific[12], with $^{18}O/^{16}O$ ratios plotted as a per mil deviation from a standard — $\delta^{18}O$ (‰). Over this time there has been a general trend towards cooler climate; at the moment, we are in a peak warm interval within the overall cooling trend. The increase in foraminiferal $\delta^{18}O$ values between 3 million and 2 million years ago signifies the (poorly understood) growth of ice sheets in the Northern Hemisphere. Liu and Herbert[4] have constructed a separate record for the eastern equatorial Pacific from 1.8 million years ago (shaded), and provide evidence that cyclic processes operating at high latitudes produce a surface-ocean response at low latitudes.**