supramolecular approach, functionalized organic molecules (here, benzene-1,3,5-tricarboxylic acid) bind to molecular inorganic species to form the three-dimensional network. The carboxylate groups lead to the formation of dimeric building units that condense to form a neutral three-dimensional system with channels 10 Å in diameter, occupied by loosely bound water molecules.

One of the main reasons that the aluminosilicate zeolites have been so widely exploited for commercial applications is that their structures tend to be stable, even in the absence of pore-filling molecules such as solvent molecules and organic cations. Their porosity can thus be used in applications such as catalysis and separations. Furthermore, their cavities often facilitate high mobility of simple cations, such as alkali metal ions, leading to their use for ion-exchange processes. Other classes of open-framework materials often collapse in the absence of pore-filling species and rarely exhibit high ionic mobility. In these respects the ASU and HKUST materials distinguish themselves. When HKUST-1 is heated to ~100°C, loss of water from the cavities leads to a material that is stable to ~250°C, with a large surface area and an accessible porosity of ~40%. Moreover, the channels can be lined with functional groups by replacing the water ligands with pyridine. In the ASU materials, the organic cations filling the cavities can be exchanged readily for simple metallic cations such as sodium and additional water. The adsorption properties of the resulting compounds, if they remain stable after the solvent is removed, may be extremely interesting. Furthermore, the ASU frameworks are semiconducting, in contrast to the insulating aluminosilicate zeolites, offering the possibility of interesting electronic applications.

Both of these studies significantly increase the possibilities for obtaining giant pores, but they also pose many questions. At which pore size do nanoporous solids with ordered walls give way to "mesoporous" compounds with disordered walls? The previous barrier at 20 Å is surpassed in ASU-31. A related question regards the size limit for clusters used as SBUs. Polyoxometalates and the giant molybdenum wheels described by Muller (*7*) may be thought of as very large potential SBUs, and three-dimensional networks of these building units could result in even larger cavities than those described here.

The metallo-organic synthesis route seems to be particularly versatile, because the nature and coordination of the inorganic species, the shape, dimensions, and the composition of the linkers, and the choice of their terminal ligands can all be varied. Here, the main difficulty probably lies in controlling the dimensionality of the resulting structures. Depending on the temperature and the nature of the solvent, the reaction products can span molecular, chain, lamellar and three dimensional architectures for the same species. To understand this, the species that exist under reaction conditions in the hydrothermal solution must be identified, and the mechanisms by which they form the final structure elucidated. In situ experiments, mainly by nuclear magnetic resonance spectroscopy and synchrotron x-ray diffraction, have provided significant insights into the formation of microporous compounds with small SBUs (*8*). Recent experiments have resulted in materials with larger and larger pores, but further insights into the formation process are essential if we are to design such materials. A knowledge of the species involved in the formation process could be combined with computer simulations to tune the topologies of porous solids.

Well-ordered crystalline solids with giant pores remain quite rare. The discovery of such materials in two quite different chemical systems (*3, 4*) illustrates the scope of this rapidly expanding area. The possibilities that they offer, the different synthesis strategies that they use, and the modulation of the sizes and chemistries of the pores that they imply underline the potential for further exciting results in this important field.

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PERSPECTIVES: NEUROBIOLOGY

Brain, Heal Thyself

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In 1913, the great Spanish neuroscientist Santiago Ramón y Cajal concluded a treatise entitled *Degeneration and Regeneration of the Nervous System* by declaring, "In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated" (*1*). This assertion, based on Cajal's meticulous study of changes in brain anatomy after injury, has been the prevailing dogma for nearly a century. We are still taught that the fully mature brain lacks the intrinsic mechanisms needed to replenish neurons and reestablish neuronal networks after acute injury or in response to the insidious loss of neurons seen in neurodegenerative diseases.

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It is time to lay to rest the dogmatic assumption that the central nervous system (CNS) of adult mammals cannot repair itself. Obviously, CNS injuries such as stroke, trauma, or neurodegenerative processes do not fully reverse themselves spontaneously. Recent work suggests, however, that the mammalian CNS has a much greater potential for producing new neurons and repairing damaged regions than previously thought.

First and foremost, the mature CNS is not as hostile an environment for the regeneration of neuronal networks as once believed. It has been known for decades that, in a variety of mammalian species, specific populations of CNS neural progenitors normally proliferate well into adulthood (*2*). In rodents, for example, progenitor cells adjacent to the cerebral ventricles give rise to neurons that migrate rostrally to reside within the olfactory bulb (see the figure) (*3*). Similarly, a pool of progenitor cells within the dentate gyrus of the hippocampus, a structure important for learning and memory, continues to produce new dentate granule cells throughout life. This phenomenon even occurs in the brains of primates, including humans (*4*).

Not only does this neuronal birth continue into adulthood, but the newly born cells are able to migrate throughout the granule cell layer, and they can extend intricate axon arbors hundreds of micrometers away into the farthest reaches of their normal targets (*5*). Neural progenitors transplanted into the CNS of an adult recipient have the ability to survive, differentiate, and become incorporated (*6*). Furthermore, the mature CNS continues to express a variety of molecules that are required for the formation of neuronal networks during embryonic development. These include growth fac-

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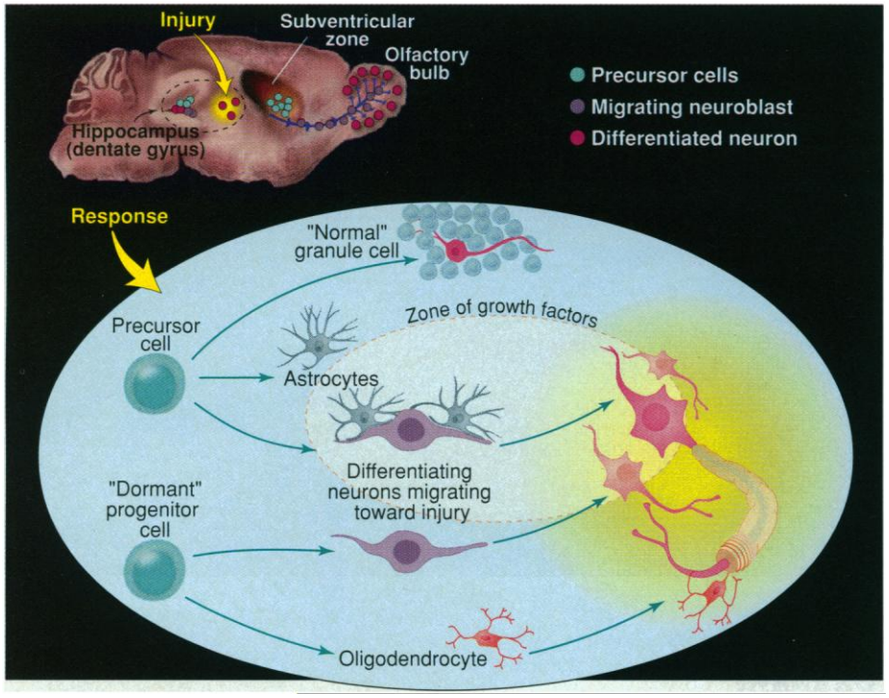

Intrinsic repair potential of the brain. Neurogenesis persists in the adult brain (upper left). After acute injury (yellow region, enlarged in lower panel) constitutively proliferating precursors may be attracted to the site and local, dormant progenitor cells induced to differentiate into neurons and glial cells.

tors, axon-guidance molecules, embryonic forms of cell adhesion molecules, and proteins that determine cell fate (*7*). Although the functional importance of most of these molecules in the adult is unknown, their expression pattern goes beyond the regions of known neurogenesis, suggesting that the degree of potential network remodeling in the mature CNS may be more extensive than generally thought.

Second, "dormant" progenitor cells persist in the CNS of adult mammals, and these progenitor cells have the capacity to give rise to a variety of CNS cells. This has been shown by culturing dispersed cells in vitro from small samples of mature CNS, such as the spinal cord or forebrain (*8, 9*). Under appropriate conditions, these cultures produce cells that are mitotically active and proliferate into the main cellular constituents of the CNS: neurons and various types of glia. The cell fate of these cultures can be controlled, in part, by growth factors normally expressed in the CNS, such as basic fibroblast growth factor and epidermal growth factor (*9*). Thus, although there is currently no evidence that the fully developed CNS continues to produce new neurons and glia everywhere, progenitor cells with this potential likely exist widely in the mature mammalian CNS.

Finally, the dynamics of network remodeling in the mature CNS are dramatically altered in the setting of injury and include modulation of neurogenesis and the activation of astrocytes, microglia, and other CNS constituents. For example, prolonged seizures cause a marked increase in dentate gyrus neurogenesis that persists for at least 2 weeks (*5*). The newly born cells survive and differentiate into mature neurons and are incorporated into the dentate granule cell layer. Other reports describe increased dentate gyrus neurogenesis after stroke, local injection of a toxin, and extremely brief seizure-like activity (*10*). No one has yet observed similar changes in other regions of the CNS. In particular, stimulation of dormant progenitors to differentiate into neurons after injury has not been demonstrated. Nevertheless, preliminary observations suggest that clones of neural progenitors transplanted into one side of the brain can migrate to the opposite side, and even home in to the site of local injury (*11*), suggesting that the "postdevelopment" environment of the mature CNS is permissive for long-distance migration and targeting of progenitor cells.

The contribution of glia to CNS repair is far from understood, but current evidence supports both antagonistic and facilitatory actions. Activation of astrocytes or their de novo generation from stem cells, for example, can lead to the formation of a "glial scar" that inhibits cell migration (*12*). Yet astrocytes also express growth factors and provide a surface that may augment the remodeling or "sprouting" of axons of neurons (*13*). Similarly, microglia, the cells that mediate the inflammatory response associated with CNS injury, are thought to initially produce toxic factors that exacerbate cell death, and later express growth factors that provide trophic support to surviving cells in the network.

Taken together, these observations point to the idea that the mature CNS is far from being fixed and immutable, as Cajal lamented. Many of the components of a system for regeneration after injury are present, but most brain regions do not normally utilize them. Understanding the mechanisms that control the latent state of progenitor cells and modulating the apparent adaptive and maladaptive components of glial cell activation will be critical elements in unlocking the brain's capacity for self-repair. This is not such a far-fetched idea. Cajal himself predicted this when he followed his remarks about the lack of regenerative capacity of the brain by stating that, "It is for the science of the future to change, if possible, this harsh decree. Inspired with high ideals, it must work to impede or moderate the gradual decay of the neurones, to overcome the almost invincible rigidity of their connections, and to re-establish normal nerve paths, when disease has severed centres that were intimately associated" (*1*). We are on the threshold of doing just that.

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