aberrant gene expression when their nuclei were transferred to enucleated oocytes. Obata *et al.* (*4*) have shown that the pattern of DNA methylation is altered in donor cells cultured in vitro and that the original methylation pattern cannot be restored by transferring the donor nucleus to recipient oocyte cytoplasm. For successful reprogramming of the donor nucleus, the entire methylation pattern must be faithfully recapitulated from the beginning. Thus, for cells to be useful as donors for nuclear transfer, it is imperative that their genes retain their correct methylation pattern during manipulation in vitro.

Another important area that needs further research to improve cloning efficiency is the development of defined culture conditions—for example, culture medium lacking serum proteins, the quality of which varies between serum batches. Defined culture medium should allow successful maturation of pig oocytes in vitro as well as early development of embryos before their transfer to the uterus of pregnant sows. Although the Onishi and Polejaeva groups used mature pig oocytes that did not need to be cultured to become competent, the best way to obtain large numbers of fully mature oocytes (which will be required if cloning is to be scaled up) is to culture immature oocytes in vitro. Recently, such a highly efficient, well-defined culture system has been developed, which has resulted in the successful maturation and fertilization of immature pig oocytes and the birth of seven live piglets per litter (a large number for pigs) (*5*).

Currently, the most useful application of nuclear transfer technology is to produce transgenic domestic animals for research, because embryonic stem cells for these animals are not available. In terms of the food industry, one goal is to clone pigs that, for example, do not have the protein myostatin (a negative regulator of muscle growth) in order to produce animals with increased muscle mass. There will certainly be bureaucratic hurdles to jump through in order for transgenic pork to become a supermarket reality.

From the perspective of pig-to-human xenotransplantation, cloning pigs without the porcine cell surface antigen α-1,3-galactosyl transferase will provide a source of pig organs for transplantation that should not be rejected by the human immune system. One major problem with transplanting pig organs to humans is the danger of transferring pig endogenous retroviruses (PERVs) into human patients, which raises the possibility of another retrovirus pandemic if the viruses mutate to adapt to their human hosts. A paper accompanying the Polejaeva work describes the infection of a human cultured cell line with PERV from pig pancreatic islet cells (*6*). When the pig islets were grown in immunodeficient mice, they continued to produce PERV, which then infected several mouse tissues. The potential for PERV transmission needs to be fully addressed if therapeutic xenotransplantation—for example, the transplant of pig islets into immunosuppressed human diabetic patients—is ever to become an acceptable treatment. It is possible that certain breeds of pig carry PERVs but do not transmit them to human tissue, which would make such animals particularly valuable as organ donors.

Nuclear transfer will remain the method of choice for creating transgenic domestic animals until embryonic stem cell lines for them become available. To make nuclear transfer efficient, we need to learn much more about the molecular events that control cellular differentiation and how these events can be reversed to reprogram a somatic cell nucleus so that it can drive embryonic development.

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PERSPECTIVES: NEUROSCIENCE

Regional Differences in Cortical Organization

Michael S. Gazzaniga

Understanding how the microstructure of each region of the cerebral cortex relates to its particular function is still in its infancy. Why is it that some cortical areas of the human brain handle the processing of language and speech, whereas others carry out higher order perceptual processes such as face recognition? Are the signals carried by afferent neurons to these various cortical regions processed in different ways? Are the neurons in each cortical area organized differently?

To answer some of these questions, traditional anatomists have given us their cytoarchitectural maps depicting differences in the density and size of neuron clusters in various regions of the brain. And thanks to modern neuroscience we now have maps that profile neurotransmitter release within specific cortical regions when they are activated by incoming signals (*1*). But a map that depicts the cellular and structural differences between corresponding cortical regions in the right and left brain hemispheres—which look identical anatomically but carry out totally different functions—has not yet been made. Enter Galuske and colleagues on page 1946 of this issue to remedy this oversight (*2*).

Using a carbocyanine dye in postmortem human brain tissue, these investigators examined differences in the neuronal organization of Brodmann's area 22—involved in the processing of auditory signals associated with human speech—between the two hemispheres (*2*). During language processing, area 22 in the left hemisphere, which is crucial for word detection and generation, is preferentially activated; area 22 in the right hemisphere, which helps to discriminate between melody, pitch, and sound intensity, is activated to a much smaller degree. The authors find that area 22 in both the left and right hemisphere is sprinkled with clusters of neurons, all of the clusters having the same size. However, neuronal clusters in area 22 of the left brain are spaced about 20% further apart and are "cabled together" (*3*) with longer interconnecting axons than clusters in area 22 of the right brain. Consistent with these dramatic findings are the recent results of Hutsler and colleagues (*4*). They show that in area 22 and other language regions in the left hemisphere, pyramidal cells in the 90th to 100th percentile for size were larger than the biggest pyramidal cells in area 22 of the right hemisphere. Here, too, the authors argue that the biggest cells have the longest axons and that these axons are able to convey information between critical language zones spread out through the left hemisphere.

The great classical anatomist Brodmann argued for the existence of cortical specialization in 1909 when he wrote: "The specific histological differentiation

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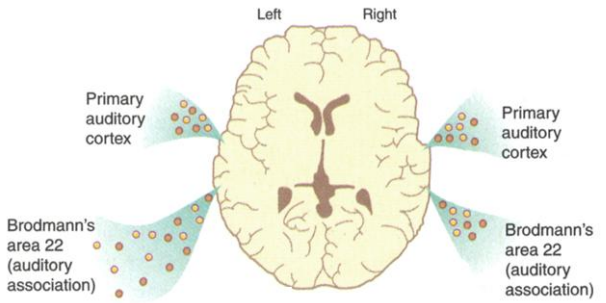

Cable connections. An axial section through the human brain showing Brodmann's area 22 and the primary auditory cortex in both the left and right hemisphere. In area 22 of the left hemisphere (which is preferentially activated during language processing) clusters of neurons are spaced further apart and are cabled together with longer axons than the neuronal clusters in area 22 of the right hemisphere. This asymmetry is not apparent in the primary auditory cortex where the neuronal clusters in both hemispheres have the same spacing. (The neuronal clusters in area 22 and in the primary auditory cortex are the same size in both hemispheres.)

of the cortical areas proves irrefutably their specific functional differentiation—for it rests as we have seen on the division of labor—the large number of specially built structural regions points to a spatial separation of many functions and from the sharp delineation of some fields there follows finally the sharply delimited localization of the physiological processes which correspond to it" (*5*).

In studying the human brain, basic researchers have the advantage of calling upon a vast neuropsychological literature to help them interpret their results. For example, Galuske and co-workers speculate that because the right brain hemisphere is capable of taking over crucial language and speech activities if the left hemisphere is injured (*6*), the differences in cellular architecture that they observed between the two hemispheres of their normal adult brain samples may be the result of differential activation during development (*7*). They predict that the essential framework for a particular cortical zone to develop language and speech capabilities is laid down in both hemispheres, but it is only through use and practice that the structural arrangement of neurons becomes different. It will be fascinating to see whether these asymmetries in cellular microstructure between the two hemispheres are absent in the brains of newborns. One possible way such subtle microstructural differences might be detected is through analysis of gene expression in various cortical regions of both hemispheres with cDNA microchip arrays. Such work is now under way in mice (*8*).

Despite the Galuske work, we remain ignorant of what additional crucial differences might exist in the cellular organization of the two hemispheres. As there seem to be more clusters of neurons interconnected in language areas of the left hemisphere, it could be argued that these better connected clusters permit greater information exchange with a putative cortical processing center that is shared by both hemispheres. Alternatively, the particular way the clusters are arranged and interconnected may provide a unique architecture that is capable of specifically processing incoming language signals.

Recently, it has been proposed that because the brain evolved from a very simple structure into a very complex one, there cannot be a universal learning system, but rather, there are different areas of the brain that oversee the learning of separate activities (*9*). For example, the area of the human brain involved in learning to recognize faces is completely different from that involved in learning to navigate a tricky maze. These areas or signal processing centers probably have different local connections both within and between the myriad neuronal clusters that compose the cortex. Seeking subtle differences in the local connections between neuronal clusters should help us to understand how a unique cellular architecture can direct human behavior.

The elegant work of Galuske *et al.* demonstrates that the melding of neuropsychology, brain anatomy, and the cellular and molecular biology of neurons is under way. It is no longer a dream—the exciting reality is here.

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PERSPECTIVES: ASTRONOMY

Don't We Already Know Everything About Polaris?

Nancy Remage Evans

Recent developments in ground-based and satellite instruments are providing unprecedented levels of quantitative precision in stellar studies. Measurements of Cepheids, a group of variable stars used as an astronomical yardstick, illustrate this new precision with which stellar parameters can now be measured and show that even groups of stars that we thought we understood well are good for surprises.

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Classical Cepheids are stars that are several time as massive as the sun and have exhausted the hydrogen fuel in their cores. They generate their luminosity by a more complicated mix of nuclear burning and are therefore considered evolved stars. For certain combinations of mass, luminosity, and temperature, Cepheids pulsate (expand and contract) with a very regular period. During pulsation, basic properties such as mass and luminosity of the stars are unchanged; it is only the envelope of the star that pulsates. The period of pulsation is tightly correlated with their intrinsic luminosity. The resulting period-luminosity relation can be used to determine the intrinsic luminosity of the star. Comparison with the apparent brightness of the star then gives an accurate distance from Earth. This is why Cepheids are important "primary extragalactic distance indicators" for galaxies that are relatively close but external to our own Milky Way.

Polaris is a Cepheid with a very low amplitude of pulsation. Recently, its diameter was measured (*1*, *2*) with a new ground-based interferometer. The diameter confirms a recent result (*3*) from the Hipparcos satellite (the first of several satellites that measure stellar distances with increasingly high precision) that Polaris is pulsating not in the fundamental mode, but in the first

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