Notes on Bioethics

Science

The Nature of Human Nature

In a groundbreaking paper published in *Science*, A. Clark et al. ("Inferring Nonneutral Evolution from Human-Chimp-Mouse Orthologous Gene Trios" *Science* 302.5652 [December 12, 2003]) compared the genomes of the human being and the chimp, our closest living relative on the evolutionary tree. Since the genomes of the two primate species are nearly 99 percent identical, sequence differences could single out key biological functions that contribute to the biological essence of what makes us human. The study identified a partial list of genes that bear significant sequence differences unique to our species. Intriguingly, the list includes genes involved in hearing, speech, smell, and brain development. Two genes stand out. The first gene called FOX2P was identified several years ago because it was mutated in a London family with barely intelligible speech. This gene is probably important for the proper development of speech, a trait that is uniquely associated with our species. How a single gene could be a critical component for such a complex behavior as human speech is still not clear. The second gene called SEMA3B helps growing nerves target and reach their proper regions of the brain. The human version of this gene may account for the differences in the wiring between human and chimp brains. Though this study raises more questions than it answers, it is only the first in what surely will be a hot field, the study of comparative primate genomics. It is an area of research that will help us identify the biological basis for our distinctive human nature.

Human Gene Therapy

In recent years, scientists working on somatic gene therapy to treat congenitally inherited genetic defects have reported limited successes. One of the most dramatic involves the cure of young patients suffering from X-linked severe combined immunodeficiency (SCID-X1). These patients—one young boy with SCID became famous as the bubble boy—are unable to develop an intact immune system. In one clinical trial, ten children received their own bone-marrow-derived stem cells that had been genetically engineered so that they now carried a normal copy of the interleukin-2 receptor, the gene that is defective in SCID-X1. Of the ten patients, nine showed clinically significant, long-term improvements in their immune response. In a recent setback, however, S. Hacein-Bey-Abina and colleagues ("*LMO2*-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1," *Science* 302.5644 [October 17, 2003]), report that the two youngest SCID-X1 patients receiving gene therapy have developed leukemia. The study showed that

the DNA vector used to introduce the normal copy of the interleukin-2 receptor gene selectively inserted itself next to the *LMO2* gene, a gene known to be involved in the development of blood. The mutagenic insertion and the aberrant activation of the *LMO2* gene that resulted was the apparent cause of the leukemia. This unfortunate side effect of the gene therapy protocol highlights the risk involved with gene-transfer methods that lead to the integration of DNA into the patient's chromosomes. Hopefully, this study will accelerate efforts to find alternative forms of gene therapy that do not lead to the aberrant activation of cancer-causing genes.

Embryonic Stem-Cell Research

Not surprisingly, stem-cell research with both embryonic stem (ES) cells and adult stem (AS) cells continued to advance this past quarter. With embryonic stem cells, several groups report a variety of discoveries. First, T. Barberi and colleagues ("Neural Subtype Specification of Fertilization and Nuclear Transfer Embryonic Stem Cells and Application in Parkinsonian Mice," *Nature Biotechnology* 21.10 [October 2003]) have developed a fast and efficient way to transform murine ES cells into different types of nerve cells. Transplantation of dopaminergic neurons derived from ES cells into mice was able to successfully treat a condition similar to Parkinson's disease in humans. Though this achievement has been reported before, this study is the first to use ES cells from cloned embryos derived from the recipient mice using somatic cell nuclear transfer. Thus, there was a perfect genetic match for the transplant recipient, removing the need for extra treatments to suppress the immune system. Significantly, the research team noted that they observed neither aberrant differentiation of the transplanted cells nor tumor formation in the recipient mice, detrimental side effects often associated with transplanted ES cells.

Next, two independent laboratories have now published specific culture conditions that can be used to consistently transform mammalian ES cells into germ cells, the cells that give rise to egg and sperm cells of the animal. This is a significant advance from the discovery noted in this column last August (*NCBQ* 3.3 [Autumn 2003]) which reported that scientists were able to isolate egg cells from mouse ES cells. In the earlier report, the egg and sperm cells arose spontaneously in a culture of ES cells over the course of fifty days. In contrast, Y. Toyooka et al. ("Embryonic Stem Cells Can Form Germ Cells in Vitro," *Proceedings of the National Academy of Sciences USA* 100.20 [September 30, 2003]) have now developed an in vitro system that allowed them to systematically visualize the development of mouse ES cells into germ cells in tissue culture dishes. These germ cells were able to produce sperm when they were transplanted into artificially reconstituted testicular tubules. In a similar discovery, N. Geijsen et al. ("Derivation of Embryonic Germ Cells and Male Gametes from Embryonic Stem Cells," *Nature*, published online December 10, 2003) have independently derived germ cells from cell clusters (technically called embryoid bodies) formed by ES cells. These germ cells were able to produce sperm, which when injected into egg cells resulted in embryo-like structures that developed into blastocysts.

Finally, K. Vrana et al. from Advanced Cell Technology in Massachusetts, report that they have successfully obtained pluripotent stem cells derived from the parthenogenetic activation of a monkey egg ("Nonhuman Primate Parthenogenetic

Stem Cells," *Proceedings of the National Academy of Sciences USA* 100.S1 [September 30, 2003]). Parthenogenesis is the process whereby an egg is activated to begin what appears to be embryonic development in the absence of sperm. In this study, the activated eggs were able to develop into blastocyst-like structures, which could then be destroyed to harvest pluripotent cells that have characteristics typically associated with embryonic stem cells. The authors point out that their research may provide a source for embryonic stem cells that bypasses the need for creating competent embryos. Of course, this presupposes that parthenogenesis in mammals does not generate a "competent" embryo. However, as I have argued in this journal before ("On Static Eggs and Dynamic Embryos," *NCBQ* 2.4 [Winter 2002]: 659–683), present methods to activate mammalian eggs in the absence of sperm do not appear to generate bona fide embryos because the data suggests that they are unable to effect the cell-to-organism transition. Thus, experiments with mammalian parthenotes generated with current protocols should be morally permissible.

Adult Stem Cell Research

One thing often forgotten in the ES-cell versus AS-cell debate is the fact that regenerative medicine involving ES cells necessarily involves the transformation of ES cells into AS cells. For instance, in the study described above by Barberi et al., ES cells had to be transformed into neural AS cells in order for them to replace tissue lost in Parkinson's disease. Thus, studies that lead to the identification of unique AS cell populations in the intact organism are important for regenerative medicine protocols that involve both ES and AS cells.

This quarter, two laboratories reported the identification of distinct AS cell populations in the heart and in the inner ear. H. Oh et al. ("Cardiac Progenitor Cells from Adult Myocardium: Homing, Differentiation, and Fusion after Infarction," *Proceedings of the National Academy of Sciences USA* 100.21 [October 14, 2003]) describe their successful attempt to identify stem cells in the adult mammalian heart. Given intravenously after a simulated heart attack in recipient mice, these stem cells were able to home to the injured myocardium and to contribute to the formation of new heart tissue.

Next, in mammals, acquired hearing loss often results from the inability of the inner ear to replace lost hair cells. H. Li and his colleagues have purified AS cells in the mouse inner ear that are able to give rise to a variety of cell types including the hair cells that are important for hearing ["Pluripotent Stem Cells from the Adult Mouse Inner Ear," *Nature Medicine* 9.10 [October 2003]). This research could lead to regenerative therapies that correct deafness by restoring hair cells in patients who have lost them.

Like ES cells, AS cells hold great promise for regenerative medicine. This past quarter, M. Kanatsu-Shinohara and colleagues transplanted frozen sperm stem cells into infertile male mice that allowed them to father live pups by normal sex ["Restoration of Fertility in Infertile Mice by Transplantation of Cryopreserved Male Germline Stem Cells," *Human Reproduction* 18.12 [December 2003]). This work may eventually lead to new treatments for male infertility caused either by disease or by medical treatment. For instance, sperm stem cells could be collected from men about to undergo cancer chemotherapy so that they can be transplanted back into

the testes after treatment. This would be a moral alternative for patients who want to procreate without recourse either to sperm collection via masturbation or to IVF. It would also work with men with sperm that cannot withstand freezing and thawing and for boys who have not yet started producing sperm. Significantly, with this technology, germline stem cells could also be transplanted from one man to another. However, this would clearly raise moral questions since every recipient of heterologous germline stem-cell transplantation would not produce his own gametes but the gametes of the donor. In effect, the recipient would be procreating with another man's sperm. This would lead to a rupture between genetic parenthood and gestational parenthood similar to the one condemned with heterologous artificial fertilization (see Congregation for the Doctrine of the Faith, *Donum vitae*, II, A, n. 2).

Finally, we should note the work of I. Abuljadayel et al. ("SCID Repopulating Cells Derived from Unmobilised Adult Human Peripheral Blood," *Current Medical Research and Opinion* 20.1 [January 2004]), who claim that they have developed a technique that can turn ordinary blood into AS cells capable of regenerating damaged or diseased tissues. In this published work, the authors used their technique to turn human white blood cells into the blood-generating stem cells found in bone marrow. When injected into SCID mice lacking an immune system, these cells migrated to the bone marrow and generated nearly all the different types of human blood cells. Amazingly, the paper reports that this technique can take human blood and transform them into human stem cells *in a matter of hours*. If confirmed and developed, this method could lead to regenerative therapies that do not involve the destruction of embryos or the cloning of persons. Instead, immunocompatible stem cells would be derived from a patient's own blood so that they can be returned to him to treat a variety of diseases. It would be a fantastic result.

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MEDICINE

The fall of 2003 saw the largest hepatitis A epidemic ever in the U.S., with over five hundred cases and three deaths among those who ate raw onions in a fast-food restaurant in Pennsylvania (V. Dato, M.D., et al., "Hepatitis A Outbreak Associated with Green Onions at a Restaurant—Monaca, Pennsylvania, 2003" *MMWR Dispatch* 52 [November 21, 2003]), a cruel early beginning to the annual influenza season, and—at long last—the passage of the partial-birth abortion ban, and Medicare reform and prescription-drug coverage for seniors and disabled Americans.

SARS and Quarantine Measures

Health workers throughout the world find themselves this winter facing the possible return of the SARS virus. Many community health systems are considering initiating isolation and quarantine systems in case SARS returns. These methods can be justified since no practical diagnostic or treatment strategies are yet available. Much of the burden of prevention will fall on health-care workers themselves, who were most affected by the illness as well as the prime agents of spreading the disease