Science

Down Syndrome (*Trisomy 21*) *and the Legacy of Jérôme Lejeune*

In 1958, Jérôme Lejeune discovered that Down syndrome is linked to the presence of an additional copy of chromosome 21. In 1996, Dr. Lejeune's family established the Jérôme Lejeune Foundation in Paris to provide research, care, and advocacy for people with genetic intellectual disabilities. Since then, the foundation has funded over forty research groups in the United States to improve the lives of those with genetic intellectual disabilities.[1] Two reports published this past quarter highlight the type of work that could radically improve the lives of individuals with Down syndrome.

In a striking discovery, a research team from the Johns Hopkins University discovered that a single dose of a newly identified molecular compound called SAG could reverse many of the cognitive and behavioral defects associated with trisomy 21 in mice.[2] The new drug was able to stimulate the development of the cerebellum, a region of the brain involved in a wide range of complex functions, which is often significantly smaller in persons with Down syndrome than in their non-affected siblings. A single injection of the drug at birth resulted in adult mice with cerebellums of normal size. Although the drug has not yet been tested in human subjects, the positive results seen in mouse models point to a possible therapeutic intervention to improve cognitive function for people with Down syndrome.

At a more basic level, another research team, this time from the University of Massachusetts School of Medicine in Worcester, Massachusetts, and Sangamo

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[1] More information about Jérôme Lejeune and the Lejeune Foundation is available at http://lejeuneusa.org/about/. A list of Lejeune Foundation grant recipients is available at http://lejeuneusa.org/research/grant-recipients.

[2] Ishita Das et al., "Hedgehog Agonist Therapy Corrects Structural and Cognitive Deficits in a Down Syndrome Mouse Model," *Science Translational Medicine* 5.201 (September 4, 2013): 201ra120.

BioSciences in Richmond, California, was able to shut down one of the chromosomes in iPS cells taken from a boy with Down syndrome.[3] Intriguingly, the scientists did this by taking advantage of molecules found in women that are able to shut down one of their X chromosomes. Recall that women have two X chromosomes while men have only one. This double dose of X chromosomes in women can cause problems, so women inactivate one copy in every single one of their cells using RNA molecules called XIST (pronounced "exist"). The scientists were able to introduce the *XIST* gene into one of the copies of chromosome 21, and the gene was able to silence the duplicate chromosome, condensing it into an inactive state. Cells containing the silenced chromosome began to grow more quickly and divide into neuron-making cells. The next step will be to test this technique in the context of an animal, say a Down syndrome model in a mouse that has been genetically engineered so that each of its cells contains an extra chromosome 21.

Numerous studies have revealed that, of all pregnancies in which Down syndrome is detected, between 61 and 93 percent end in abortion.[4] In time, however, as Dr. Lejeune hoped, science should be able to find a cure to alleviate the suffering of persons with Down syndrome. As Dr. Lejeune once said, "I see only one way left to save them, and that is to cure them. The task is immense—but so is hope."[5]

Evolutionary Teleology, Monogamy, and the Origins of Homo sapiens

Like many others, I am convinced that the major disagreements and debates in bioethics today happen because our society has fractured into communities of belief that hold incommensurable first principles. Nonetheless, each of these communities has to deal with science and its discoveries. And science, especially evolutionary biology, has much to say about what constitutes reality and the human person. In our society, science explicitly, and more often implicitly, shapes human self-understanding.

Several papers published this past quarter will affect the way we think of ourselves. It is a common belief, for instance, that evolutionary theory undermines the teleological conception of the world that the ancients and the medievals took for granted. Take evolutionary biologist Stephen Jay Gould's famous thought experiment comparing evolution to a tape of life. His expectation was that "any replay of the tape would lead evolution down a pathway radically different from the road actually taken."[6] Contrary to Gould's predictions, however, a recent paper describing the evolution of the anoles—small, color-changing lizards that are abundant in the

[3] Jun Jiang et al., "Translating Dosage Compensation to Trisomy 21," *Nature* 500.7462 (August 15, 2013): 296–300.

[4] Jaime L. Natoli et al., "Prenatal Diagnosis of Down Syndrome: A Systematic Review of Termination Rates (1995–2011)," *Prenatal Diagnosis* 32.2 (February 2012): 142–153.

[5] "Thoughts of Jerome Lejeune," no. 8, Association Les Amis du Professeur Jerome Lejeune, accessed January 16, 2014, http://amislejeune.org/index.php/en/jerome-lejeune/jerome-lejeunes-message/textes-and-quotations/thoughts.

[6] Stephen Jay Gould, *Wonderful Life: The Burgess Shale and the Nature of History* (New York: Norton, 1989), 51.

Caribbean—has demonstrated that lizard evolution is in fact repeatable.[7] Scientists at the Harvard Museum of Comparative Zoology compared the species of anoles on two different islands in the Greater Antilles. Despite living on different islands, islands that have similar climates and similar plants, the lizards on each island evolved in similar ways to occupy the same evolutionary niches, although there were a few instances of novelty, including one lizard species (*Anolis barbouri*) that lives entirely on the ground. It appears that evolution is a lot more deterministic than evolutionary biologists had thought. Replaying the tape of life leads both to similarity and difference. Teleology—at least extrinsic teleology, and maybe even intrinsic teleology—is back.

Is monogamy natural? There are some who have argued that lifelong human pair bonds are actually *contra natura*. Two papers published this past quarter suggest that there are evolutionary reasons to think that monogamy is an adaptive trait in primates and in mammals. First, Dr. Quentin Atkinson and his colleagues at the University of Auckland propose that social monogamy developed in primates as a way for males to protect their offspring from infanticide.[8] The researchers studied 230 different species of primates and discovered that the only thing common among the primate species with long-term pair bonds was the high level of infanticide that appeared just prior to the evolution of monogamy.

In contrast, a British team that studied the evolution of monogamy in mammals using data from more than twenty-five hundred mammalian species has come to a different conclusion.[9] According to their analysis, monogamy evolved in nonhuman mammals where males were unable to monopolize and defend access to multiple females. As one of the scientists, Tim Clutton-Brock, explained, "Where females are widely dispersed, the best strategy for a male is to stick with one female, defend her, and make sure that he sires all her offspring. In short, a male's best strategy is to be monogamous."[10] Although the correct explanation for monogamy remains unclear, and it is unclear whether there is only a single explanation for the phenomenon, these papers suggest that monogamy is adaptive. From the perspective of evolutionary biology, it is a genetically encoded trait. It is natural.

Finally, two research groups have independently sequenced and compared the Y chromosomes of numerous men scattered throughout the planet and have discovered that the most recent common ancestor for all these males—the individual some have called Y-chromosomal Adam—lived between one hundred twenty thousand

[7] D. Luke Mahler et al., "Exceptional Convergence on the Macroevolutionary Landscape in Island Lizard Radiations," *Science* 341.6143 (July 19, 2013): 292–295.

[8] Christopher Opie et al., "Male Infanticide Leads to Social Monogamy in Primates," *PNAS* 110.33 (August 13, 2013): 13328–13332.

[9] Dieter Lukas and Timothy H. Clutton-Brock, "The Evolution of Social Monogamy in Mammals," *Science* 341.6145 (August 2, 2013): 526–530.

[10] Genevieve Maul, "Monogamy Evolved as a Mating Strategy," University of Cambridge, news release, July 29, 2013, http://www.cam.ac.uk/research/news/monogamy-evolved-as-a-mating-strategy.

and two hundred thousand years ago.[11] What is significant is that this date agrees reasonably well with other data dating the most recent common female ancestor—the individual popularly named Mitochondrial Eve—to between one hundred and one hundred fifty thousand years ago. This resolves a long-standing conundrum in human genetics that suggested that "Adam" lived much more recently than "Eve." I predict that these results will influence the philosophical and theological debates surrounding the origins and self-understanding of our species.

False Memories and Laboratory-Grown Human "Mini-brains"

Memories are often unreliable. A laboratory at MIT has now discovered how to create false memories, a discovery that will undoubtedly make us doubt the accuracy of our memories even more. Nobel laureate Susumu Tonegawa and his colleagues were able to make a mouse fear a cage by shocking its feet while simultaneously reactivating neurons that had been associated with a memory of the cage.[12] In effect, they were able to make the animal fear an environment where technically it had never experienced anything fearful, simply by altering the original memory of that environment. To those who fear that the dystopian vision of the movie *Total Recall* has finally arrived, it is unlikely that this technology will be altering human memories anytime soon. To get their experiments to work, the MIT scientists had to identify the specific neurons in the mouse's brain that had been activated when the mouse had a specific memory. This technical feat has not been done with human subjects. When it has, we will have confront the numerous bioethical issues raised by the possible third-person manipulation of human memory.

Next, in an astonishing paper, a team from the Institute of Molecular Biotechnology at the Austrian Academy of Sciences in Vienna has discovered a way to grow human stem cells into structures called "cerebral organoids" that superficially resemble the brain of a nine-week-old human embryo.[13] The method involves introducing the stem cells into a gel-based scaffold and growing them in a spinning bioreactor for a month to allow them to self-organize into organoids that were 3 or 4 mm in diameter. These organoids contained many of the different cell types usually found in a human embryonic brain, though they were not spatially organized in the same way. Since brain organization is critical for brain function, properly speaking, these organoids are not human mini-brains. They are clumps of different types of cells usually found in the human brain. Any attempt to generate a functional human brain using a scaled-up version of this technique would raise grave ethical concerns.

[11] G. David Poznik et al., "Sequencing Y Chromosomes Resolves Discrepancy in Time to Common Ancestor of Males versus Females," *Science* 341.6145 (August 2, 2013): 562–565; and Paolo Francalacci et al., "Low-Pass DNA Sequencing of 1200 Sardinians Reconstructs European Y-Chromosome Phylogeny," *Science* 341.6145 (August 2, 2013): 565–569.

[12] Steve Ramirez et al., "Creating a False Memory in the Hippocampus," *Science* 341.6144 (July 26, 2013): 387–391.

[13] Madeline A. Lancaster et al., "Cerebral Organoids Model Human Brain Development and Microcephaly," *Nature* 501.7467 (September 19, 2013): 373–379.

Induced Pluripotent Stem Cells and
Very Small Embryonic-like Stem Cells

Induced pluripotent stem (iPS) cells—pluripotent embryonic-like stem cells generated from adult cells without the destruction of embryos—have now been made using just drugs, without the insertion of genes. Chinese scientists at Peking University screened ten thousand chemical compounds and identified a cocktail of seven compounds that were able to transform mouse adult cells into iPS cells at an appreciable frequency of 0.2 percent.[14] These pluripotent stem cells have been called chemically induced pluripotent stem cells. The paper describes several advantages of using this chemical-based approach, including cost-effectiveness, ease of use, and neutrality with regard to immune systems. Significantly, the chemical compounds can be washed away as soon as they have successfully reprogrammed the cells. Now the compounds have to be tried with human cells.

Most Catholic bioethicists are probably not aware of very small embryonic-like stem cells, referred to as VSELs. They were first reported to exist in mouse bone marrow by a team led by Mariusz Ratajczak at the University of Louisville in 2006.[15] Since then, the research group along with several others has published numerous papers that suggest that VSEL stem cells are able to become a diverse range of cells types, including bone, blood, and muscle. In 2007, the cell therapy company Neostem acquired exclusive licensing rights to these cells and promoted them as ethical alternatives to the embryonic stem cells obtained from the destruction of embryos. Two years ago, the Vatican donated one million dollars to Neostem's Stem for Life Foundation, which has hosted two international conferences in Vatican City. This past quarter, a paper in *Stem Cell Reports* from the Irving Weissman laboratory at Stanford University concluded that VSELs do not exist.[16] This is the fourth paper reporting data that refute the original discovery of VSELs.[17] However, recent data from another independent laboratory suggest that VSELs are real, are pluripotent, and are able to become lung cells.[18] Disagreements like this are common in science,

[14] Pingping Hou et al., "Pluripotent Stem Cells Induced from Mouse Somatic Cells by Small-Molecule Compounds," *Science* 341.6146 (August 9, 2013): 651–654.

[15] M. Kucia et al., "A Population of Very Small Embryonic-like (VSEL) CXCR4(+) SSEA-1(+)Oct-4+ Stem Cells Identified in Adult Bone Marrow," *Leukemia* 20.5 (May 2006): 857–869.

[16] Masanori Miyanishi et al., "Do Pluripotent Stem Cells Exist in Adult Mice as Very Small Embryonic Stem Cells?" *Stem Cell Reports* 1.2 (July 24, 2013): 198–208.

[17] The earlier papers were the following: Ralitza Danova-Alt et al., "Very Small Embryonic-like Stem Cells Purified from Umbilical Cord Blood Lack Stem Cell Characteristics," *PLoS One* 7.4 (April 2012): e34899; Krzysztof Szade et al., "Murine Bone Marrow $Lin^{-}Sca^{-}1^{+}CD45^{-}$ Very Small Embryonic-like (VSEL) Cells Are Heterogeneous Population Lacking Oct-4A Expression," *PLoS One* 8.5 (May 17, 2013): e63329; and Cesar Alvarez-Gonzalez et al., "Cord Blood $Lin^{-}CD45^{-}$ Embryonic-like Stem Cells Are a Heterogeneous Population That Lack Self-Renewal Capacity," *PLoS One* 8.6 (June 28, 2013): e67968.

[18] Susannah H. Kassmer et al., "Very Small Embryonic-like Stem Cells from the Murine Bone Marrow Differentiate into Epithelial Cells of the Lung," *Stem Cells* 31.12 (December 2013): 2759–2766.

and I am sure that future studies will resolve this controversy. Strikingly, however, this seemingly insignificant scientific dispute has become quite public precisely because of the Vatican's involvement in the commercial aspects of the science.[19]

The Length of Normal Human Pregnancies and the Function of the Placenta

How long is a human pregnancy? Most women are told to expect their child 280 days after the onset of their last menstrual period. However, a recent study has revealed that only 4 percent of women have their children at 280 days, and only 70 percent deliver within ten days of their official due dates.[20] For 125 naturally conceived pregnancies, researchers determined the precise time of ovulation and followed the pregnancy through to delivery. They ascertained that the average length of a human pregnancy from ovulation to birth was 268 days, which is 38 weeks and 2 days. However, the normal length of the pregnancies varied by as much as five weeks. Factors that influenced the duration of the pregnancy included the age of the mother (with each year of age adding one day to the pregnancy), the weight of the mother at her birth, and the duration of the mother's previous pregnancy, if she had had one. These data should guide clinicians who are trying to decide if they should intervene in a pregnancy to accelerate or delay birth.

For most people, the placenta functions as a fetal–maternal interface for the exchange of nutrients and wastes, including oxygen and nitrogen. New research in mice has revealed that the placenta is also involved in the long-term programming of emotional behavior, linking placental function and adult behavior for the first time.[21] Behavioral neuroscientists at Cardiff University in the United Kingdom disrupted the gene for a placenta-specific molecule called insulin-like growth factor-2-P0, which is found in both mice and humans. They discovered that knocking out this gene led to an imbalance in the nutrient supply controlled by the placenta. More strikingly, they also noticed that this imbalance led to symptoms later in life where the adult mice were more susceptible to anxiety-causing stimuli. This is the first report of what has been called placenta programming of adult behavior, suggesting that the placenta is a more complex fetal–maternal organ than is usually appreciated.

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[19] For commentary, see Alison Abbott, "Doubt Cast over Tiny Stem Cells: Studies Refute the Existence of Very Small Embryonic-like Cells Endorsed by the Vatican," *Nature* 499.7459 (July 25, 2013): 390, http://www.nature.com/polopoly_fs/1.13435!/menu/main/topColumns/topLeftColumn/pdf/499390a.pdf.

[20] A. M. Jukic et al., "Length of Human Pregnancy and Contributors to Its Natural Variation," *Human Reproduction* 28.10 (October 2013): 2848–2855.

[21] Mikael A. Mikaelsson et al., "Placental Programming of Anxiety in Adulthood Revealed by Igf2-Null Models," *Nature Communications* 4.8 (August 2013): art. 2311.