Medicine

Do nothing out of selfishness or out of vainglory;
rather, humbly regard others as more important than yourselves,
each looking out not for his own interests,
but (also) everyone for those of others.— Phil. 2:3–4 (NAB)

As I prepared this column on recent progress in medicine and clinical research, I reflected on this familiar expression of the Gospel message, the Golden Rule: "Do to others whatever you would have them do to you" (Matt. 7:12, NIV).

The current biomedical paradigm too often favors research aimed at developing the next blockbuster drug or agent that will tap into the soaring profits associated with certain classes of medicines. Other studies at the boundaries of life purport to end present human suffering but by exacting a cost on future generations. Rather than focus on headline-grabbing articles, I hope the abstracts that follow will guide readers to corners of the medical literature where investigators have made important discoveries or are posing important ethical questions. I have decided to canvass five core areas: (1) vaccines and newborn screening, (2) adult and embryonic stem cell therapy, (3) organ donation and transplantation, (4) valid fertility procedures and natural family planning, and (5) end-of-life decisions, palliative care, and physician-assisted suicide. The reader may be challenged by the methods of discovery employed in some studies, especially when the equitable distribution of the risks and benefits of an investigation is not certain. Nevertheless, courageous efforts to improve the human condition are still being made on a daily basis, as reflected in some of the literature highlighted here.

Vaccines

On July 11, the *Lancet* reported online the results of the first of two phase III trials of a vaccine against dengue fever.[1] This mosquito-borne disease causes an

[1] Maria Rosario Capeding et al. and the CYD14 Study Group, "Clinical Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children in Asia: A Phase 3,

estimated one hundred million symptomatic infections every year. Dengue is endemic in many tropical regions and has had a resurgence in several nations, most notably Brazil, where it re-emerged in 1981 after an absence of more than twenty years.

The purpose of the *Lancet* study was to assess the protective efficacy of a vaccine against dengue. The trial was conducted in healthy children (aged two to fourteen years) enrolled by their parents in five countries in the Asia-Pacific region (Philippines, Indonesia, Malaysia, Thailand, and Vietnam). A sister trial in Latin and South America is expected to report results later this year. Together, the studies involve more than thirty-one thousand children. Participants were randomly assigned to receive, at six-month intervals, either three injections of a newly developed vaccine against dengue or three injections of a placebo. Participants were followed on average for just over two years. The trial was sponsored by Sanofi Pasteur, the vaccines division of the multinational pharmaceutical company Sanofi (Paris, France).

The vaccine reduced the incidence of the mosquito-borne disease overall by 56.5 percent and, even more importantly, cut cases of dengue hemorrhagic fever, a severe life-threatening form of the disease, by 88.5 percent. But the vaccine provided only limited protection against dengue type 2, one of the four viruses that cause the disease, reducing those infections by only 35 percent. It also worked best among people who had *already* recovered from one dengue infection (notably, a group most at risk from the antibody enhancement that leads to hemorrhagic dengue) and among older children. The trial did not include adults or elders, who are at a higher risk of hemorrhagic fever. Together these findings mean that for those who have never had dengue, including travelers and volunteer health workers, the vaccine is likely to have significantly less benefit.

For local public health officials in dengue-endemic countries, the challenge is whether to include the Sanofi Pasteur vaccine in national immunization programs or await the development of an alternative vaccine.

Newborn Screening

Primary immunodeficiencies are weaknesses of the immune system that make a patient susceptible to repeat infections. They include more than 180 inherited disorders that affect both the development and the function of the immune system.[2] Screening newborns for these disorders is important so that treatment can be started early and possibly fatal infections avoided. Treatment focuses on reconstituting an infant's immune system by bone marrow transplantation, gene therapy, or other means.

Few pediatricians have experience treating immunodeficient patients, although population-based research suggests that the overall prevalence of primary immunodeficiencies is higher than previously suspected, and is increasing.[3]

Randomised, Observer-Masked, Placebo-Controlled Trial," *Lancet*, e-pub July 11, 2014, doi:10.1016/s0140–6736(14)61060–6.

[2] Nima Parvaneh et al., "Primary Immunodeficiencies: A Rapidly Evolving Story," *Journal of Allied and Clinical Immunology* 131.2 (February 2013): 314–323.

[3] Lisa Kobrynski, Rachel Powell, and Scott Bowen, "Prevalence and Morbidity of Primary Immunodeficiency Diseases, United States 2001–2007," *Journal of Clinical Immunology*,

A noteworthy report evaluating the efficacy of newborn screening for severe combined immunodeficiency (SCID) was published on August 20 in *JAMA*.[4] The study was authored by Antonia Kwan from the Benioff Children's Hospital at the University of California San Francisco, and her colleagues.

More than three million newborns in ten states and the Navajo Area Indian Health Service were screened for low levels of T cells, the cells responsible for healthy immune function, using the TRECs (T cell receptor excision circles) test.[5] This test uses DNA isolated from the blood routinely obtained for newborn screening. Fifty-two cases of SCID were detected, a prevalence of one in fifty-eight thousand infants. Of those fifty-two infants, forty-nine received immunity-restoring therapies, and forty-five of those survived.

Population-based screening is the only means of detecting SCID prior to the onset of infections, since more than 80 percent of patients lack a positive family history. Early diagnosis afforded by newborn screening alerts physicians and parents to potentially serious problems and makes it possible both to institute effective treatments and to avoid giving affected children live viral or bacterial vaccines, which can be dangerous or even fatal in infants with seriously compromised immune systems.

Adult Stem Cell Therapy

Body fat, or adipose tissue, has become a promising source of adult stem cells. In July, the first safety and feasibility trial of adipose-derived regenerative cells (ADRCs) injected into the heart for the treatment of heart failure was reported in the *American Heart Journal*.[6] The placebo-controlled, double-blind study was conducted in patients with chronic ischemic cardiomyopathy (heart failure that stems from a dilated, weakened heart muscle, often due to long-standing poor coronary blood flow) who had no surgical options for restoring perfusion. Twenty-one ADRC-treated patients and six control patients were enrolled from four clinical sites in Spain, Denmark, and the Netherlands. The trial was sponsored by Cytori Therapeutics (San Diego, California).

Several earlier trials have demonstrated modest but significant improvements in patients with chronic myocardial ischemia following injection of the patient's own bone marrow cells into the heart muscle.[7] Like bone marrow, adipose tissue contains mesenchymal stem cells (MSCs), a type of adult stem cell that is considered

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e-pub September 26, 2014, doi:10.1007/s10875–014–0102–8.

[4] Antonia Kwan et al., "Newborn Screening for Severe Combined Immunodeficiency in 11 Screening Programs in the United States," *JAMA* 312.7 (August 20, 2014): 729–738. SCID was added to the national recommended uniform panel for newborn screened disorders in 2010.

[5] Lena Al-Harthi et al., "Detection of T Cell Receptor Circles (TRECs) as Biomarkers for De Novo T Cell Synthesis Using a Quantitative Polymerase Chain Reaction-Enzyme Linked Immunosorbent Assay (PCR-ELISA)," *Journal of Immunological Methods* 237.1–2 (April 3, 2000): 187–197.

[6] Emerson C. Perin et al., "Adipose-Derived Regenerative Cells in Patients with Ischemic Cardiomyopathy: The PRECISE Trial," *American Heart Journal* 168.1 (July 2014): 88–95.

[7] See, for example, Jan van Ramshorst et al., "Intramyocardial Bone Marrow Cell Injection for Chronic Myocardial Ischemia: A Randomized Controlled Trial," *JAMA* 301.19 (May 20, 2009): 1997–2004.

a promising tool in cardiac regenerative medicine. Adipose tissue contains five hundred times more MSCs than does adult bone marrow, and it can be obtained by liposuction and prepared for use immediately before transplantation.[8]

In the trial, the liposuction procedure was performed on all patients. Cell-treated patients then received ADRCs by injection directly into the affected wall of the heart, while control patients received a placebo injection. No complications of the liposuction procedure were reported. Although primarily a safety study, the ADRC-treated patients did show modest but significant improvements in total left ventricular mass and a slight reduction in inducible ischemia up to eighteen months. No major cardiac complications were reported. The safety of the overall procedure was comparable with that of delivering bone marrow cells, but with the added benefit that the regenerative cells could be harvested from and injected into the patient on the same day, at the same point of care. Future studies ought to include quality-of-life endpoints.

Organ Donation and Transplantation

In the United States alone, more than one hundred names are added to the national waiting list for transplant organs every day.[9] Many patients become seriously ill or die while waiting for a donor. Efforts to increase the number of donors include live donation, split-organ donation, and the use of paired-donor exchanges.

Another way to increase donations is to expand the criteria for acceptable donors. For example, certain subjects, such as those with a history of cancer, are routinely excluded from the pool of potential donors because they have been classified as carrying a high or unacceptable risk to transplant recipients.

In the June issue of the *British Journal of Surgery*, a team led by Rajeev Desai of NHS Blood and Transplant—a special authority within the UK National Health Service—reported on the risk of cancer transmission from donors who had a prior malignancy.[10] Using transplant and cancer registries to identify donors and recipients and to classify cancer details, the researchers identified 202 donors who had a history of cancer. Of these, sixty-one donors had cancers that were believed to carry an unacceptable or high risk of transmission. Organs from these sixty-one donors were transplanted into 133 recipients. According to data from the registries, no cancer transmission occurred in the recipients.

For each of the 133 recipients, the mean additional-survival benefit gained from the "risky" transplantation was calculated to be 7.1 years. These findings suggest that organs from some donors with "unacceptable" or "high risk" cancers can be used safely. Present guidelines that prohibit organ donation from potential donors

[8] John K. Fraser et al., "Plasticity of Human Adipose Stem Cells toward Endothelial Cells and Cardiomyocytes," *Nature Clinical Practice: Cardiovascular Medicine* 3 suppl 1 (March 2006): S33–S37.

[9] According to Donate Life America, another name is added every ten minutes (http://donatelife.net/statistics/, accessed September 22, 2014).

[10] Rajeev Desai et al., "Estimated Risk of Cancer Transmission from Organ Donor to Graft Recipient in a National Transplantation Registry," *British Journal of Surgery* 101.7 (June 2014): 768–774.

who have a history of certain prior malignancies may be unnecessarily restricting the supply of badly needed organs.

Fertility and Reproduction

Epididymitis, inflammation of the epididymis (the tube that connects the testicle with the vas deferens), is frequent in sexually active men in their reproductive years. It usually presents with mild unilateral scrotal pain and swelling. More than half the time, the testis is also involved (epididymo-orchitis).[11] Appropriate antibiotic therapy usually leads to resolution of symptoms; however, the effects of these infections on the male reproductive system and fertility have not been systematically investigated. In the June issue of *Fertility and Sterility*, Adrian Pilatz and colleagues reported on alterations in sperm protein composition following acute epididymitis.[12] The researchers performed proteome analysis of sperm samples from eight patients with acute epididymitis and from ten healthy fertile men requesting vasectomies. While conventional laboratory analysis showed normal semen parameters, the proteomic analysis revealed thirty-five abnormally regulated proteins in the semen of the patients with epididymitis. The role that these changes may play in reduced fertility or infertility in men after episodes of epididymitis and the length of time that the changes may persist were not addressed by this study.

Cesarean deliveries are the most common inpatient surgical procedure performed in the United States and account for almost a third of births.[13] In the July issue of *Obstetrics and Gynecology*, Lisa Masinter and colleagues reported on the likelihood of continued childbearing after cesarean delivery.[14] For a number of reasons, fewer than 10 percent of women deliver vaginally after a cesarean delivery;[15]—nearly every cesarean delivery will be followed by another cesarean delivery. Furthermore, it is well established that the risk of obstetric complications increases with each subsequent pregnancy and cesarean delivery.[16] The aim of this study was to determine whether increasing numbers of cesarean, as compared with vaginal, deliveries are associated with reduced childbearing. The data were extracted from the National Survey of Family Growth (2006–2010).

The study found that women in the United States who have cesarean deliveries are less likely to continue childbearing. For example, women who had two successive

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[11] Praveen Bilagi et al., "Clinical and Ultrasound Features of Segmental Testicular Infarction: Six-Year Experience from a Single Centre," *European Radiology* 17.11 (November 2007): 2810–2818.

[12] Adrian Pilatz et al., "Acute Epididymitis Induces Alterations in Sperm Protein Composition," *Fertility and Sterility* 101.6 (June 2014): 1609–1617.e1–5.

[13] Brady E. Hamilton, Joyce A. Martin, and Stephanie J. Ventura, "Births: Preliminary Data for 2012," *National Vital Statistics Reports* 62.3 (September 6, 2013): 1–20.

[14] Lisa M. Masinter et al., "Likelihood of Continued Childbearing after Cesarean Delivery in the United States," *Obstetrics and Gynecology* 124.1 (July 2014): 111–119.

[15] Hamilton et al., "Births."

[16] Serena Wu, Masha Kocherginsky, and Judith U. Hibbard, "Abnormal Placentation: Twenty-Year Analysis," *American Journal of Obstetrics and Gynecology* 192.5 (May 2005): 1458–1461.

cesarean deliveries were 27 percent less likely to have a third birth, compared with women who had two consecutive vaginal deliveries. For women who had three births, the likelihood of a fourth birth was even lower. Interestingly, this relationship was somewhat attenuated among lower-income women. The authors suggest that this socioeconomic difference may be due to a "volitional etiology" rather than an infertility phenomenon. However, the reason for the dissimilar childbearing patterns remains to be elucidated. Bringing every child into the world is an act of courage. Rather than focus on higher rates of unintended pregnancies and births, abortions, teen pregnancies, and "contraceptive" failures among women from lower socioeconomic backgrounds, one might instead view positively the resilience of women in continuing to bear children in the face of adversity.

Another recent article that deals with female fertility is "Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome," published in the July issue of the *New England Journal of Medicine*.[17] This study is aimed at improving pregnancy outcomes, especially reducing the number of multiple gestations induced by "fertility" treatments. The Reproductive Medicine Network of the National Institute of Child Health and Human Development sponsored the study. Although several of the authors report consulting and other financial interests, none appear to be directly related to the study.

Polycystic ovary syndrome is a complex reproductive–metabolic disorder in which a woman has an imbalance of female sex hormones, leading to hyperandrogenism (increased "male" hormone levels), reduced ovulation, and polycystic ovaries on ultrasound, as well as other health changes. Polycystic ovary syndrome affects 5 to 10 percent of reproductive-age women and is the most common cause of anovulatory infertility.[18] The hypothalamic–pituitary axis is the target of most methods of ovulation-induction in this disorder. This double-blind, multicenter trial sought to compare clomiphene citrate (Clomid), a selective estrogen-receptor modulator, with letrozole (Femara), an oral nonsteroidal aromatase inhibitor. Both drugs have drawbacks. Clomiphene has an overall poor efficacy: in a previous study by the same group, women who received clomiphene had only a 22 percent rate of live birth with up to six cycles of treatment, a relatively high multiple-gestation rate (3 to 8 percent), and an undesirable side-effect profile that included mood changes and hot flashes.[19] In contrast, letrozole and other aromatase inhibitors act to block estrogen synthesis, thereby directly affecting hypothalamic–pituitary–ovarian function, and should theoretically provide more physiologic hormonal stimulation of the endometrium, a

[17] Richard S. Legro et al. for the NICHD Reproductive Medicine Network, "Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome," *New England Journal of Medicine* 371.2 (July 10, 2014): 119–129.

[18] Wendy A. March et al., "The Prevalence of Polycystic Ovary Syndrome in a Community Sample Assessed under Contrasting Diagnostic Criteria," *Human Reproduction* 25.2 (February 2010): 544–551.

[19] Richard S. Legro et al. for the Cooperative Multicenter Reproductive Medicine Network, "Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome," *New England Journal of Medicine* 356.6 (February 8, 2007): 551–566.

lower multiple-pregnancy rate, and fewer vasomotor side effects. However, potential fetal teratogenicity remains a concern with both drugs.

In the study, 750 women aged eighteen to forty years with polycystic ovary syndrome were randomly assigned to receive either letrozole or clomiphene for up to five treatment cycles. They and their partners agreed to have regular intercourse during the study with the intent of conceiving. Visits were scheduled to determine ovulation, and pregnancies that resulted were tracked. The women who received letrozole had more cumulative live births than those who received clomiphene (103 vs. 72). Although there were no significant differences between the groups in congenital anomalies among the babies born, four babies in the letrozole group had major congenital anomalies and one in the clomiphene group had major anomalies (P=0.65). There were no statistical differences in twin pregnancies (3.4 vs. 7.4 percent, respectively). Unfortunately, lifestyle modifications to improve both women's health and their chances of conception were not included in the study intervention.

Finally, a review of cancer and pregnancy was published in the July issue of the *American Journal of Obstetrics and Gynecology*.[20] Although at first blush this would seem a rare occurrence, cancer actually affects approximately one in every thousand pregnancies, and its incidence is rising as the average maternal age advances and cancer rates increase. The article provides an overview of the current literature regarding concurrent pregnancy and cancer diagnoses, management options, and maternal and neonatal outcomes. The effects of treatments on future fertility, as well as fertility "preservation" techniques, are also addressed. The article does a good job of discussing strategies for optimizing treatment of cancer while minimizing harm to the fetus. However, the risks of many chemotherapeutics are not fully known, which the authors of a companion letter to the editor point out.[21] As clinical trials rarely include pregnant patients, and even less commonly those with cancer, expert opinion remains the most important source of guidance in these difficult situations.

End-of-Life Decisions and Palliative Care

Two important articles on palliative care were recently published. The American Heart Association and American Stroke Association issued a combined statement on the palliative care and end-of-life needs of patients and families with stroke.[22] Severe disability remains an all-too-common outcome for many of the nearly eight

[20] Ritu Salani, Caroline C. Billingsley, and Sarah M. Crafton, "Cancer and Pregnancy: An Overview for Obstetricians and Gynecologists," *American Journal of Obstetrics and Gynecology* 211.1 (July 2014): 7–14.

[21] Paul Berveiller, Bruno Carbonne, and Olivier Mir, letter, "Cancer and Pregnancy: An Overview for Obstetricians and Gynecologists," *American Journal of Obstetrics and Gynecology* 211.1 (July 2014): 82.

[22] Robert G. Holloway et al. for the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology, "Palliative and End-of-Life Care in Stroke: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association," *Stroke* 45.6 (June 2014): 1887–1916.

hundred thousand individuals who suffer stroke each year.[23] Palliative care works throughout the course of an individual's illness to address physical, intellectual, emotional, social, and spiritual needs. The AHA/ASA statement is to be applauded for identifying family-centered care as a way to optimize a person's quality of life. The statement reminds care providers that "it is reasonable for providers caring for stroke patients and their families to consider asking their patients about possible spiritual or religious beliefs and to offer referral to a chaplain or spiritual care provider." Perhaps a stronger mandate should be placed on health care providers to ensure that patients' spiritual needs are met.

Finally, there is a well-acknowledged shortage of palliative care specialists across the United States, compared with the growing number of patients who are facing serious and life-threatening illnesses. A national survey of expert palliative care physician educators was recently conducted with the goal of defining competencies for medical students and internal medicine and family medicine (IM/FM) residents.[24] The authors make clear that doctors in training need to be better versed in the five domains of palliative care: (1) pain and symptom management; (2) communication; (3) psychosocial, spiritual, and cultural aspects of care; (4) terminal care and bereavement; and (5) palliative care principles and practice. The number-one-ranked competency for medical students was the ability to describe ethical principles that inform decision making at the end of life. The most important competency for IM/FM residents was related to patient-centered communication and shared decision making: to explore patient and family understanding of illness, concerns, goals, and values, and identify treatment plans that respect and align with these priorities. This was closely followed by demonstrating effective patient-centered communication when giving bad news or prognostic information, discussing resuscitation preferences, and coaching patients through the dying process. Identifying learning objectives is an important first step. The difficult work remaining is to train providers, especially those who are not dedicated palliative care specialists, to care for patients throughout the continuum of illness in ways that uphold the dignity of the person and the family.

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[23] Jacob S. Elkins and S. Claiborne Johnston, "Thirty-Year Projections for Deaths from Ischemic Stroke in the United States," *Stroke* 34.9 (September 2003): 2109–2012.

[24] Kristen G. Schaefer et al., "Raising the Bar for the Care of Seriously Ill Patients: Results of a National Survey to Define Essential Palliative Care Competencies for Medical Students and Residents," *Academic Medicine* 89.7 (July 2014): 1024–1031.