Behold, the wages you withheld from the workers who harvested your fields are crying aloud, and the cries of the harvesters have reached the ears of the Lord of hosts.

— James 5:4 (NABRE)

Concerns about rising inequality are increasingly in the headlines; for example, what is a fair or “living” wage, or what is the appropriate level for executive pay? In medicine, the political debate is often over the best way to create accessible forms of health care, especially for lower-income Americans who are uninsured. With the implementation of the Affordable Care Act (ACA) in 2014, the number of adults without health insurance in the United States reportedly fell to twenty-nine million (16 percent of the population) from a high in 2010 of thirty-seven million (20 percent).1 This government-sponsored program has broadly decreased the number of uninsured Americans. States that opted out of the program insofar as they chose not to expand Medicaid following a challenge presented to the US Supreme Court continue to host a larger share of the remaining uninsured. Despite this success, “a near majority of Americans still oppose the ACA, even though they approve of most of its features.”2

The goal of the ACA is to improve the health of Americans by increasing the number covered by health insurance. However, many lower-income Americans


continue to find cost a barrier to care under this system. Almost a third of those surveyed with incomes below 200 percent of the federal poverty level reported that they did not get care they needed within the last year because of its cost. This is further exacerbated by another problem: the acute rise in generic drug prices that has occurred as the fallout from a rule passed by the US Food and Drug Administration designed to encourage the testing of older drugs using modern safety standards.\(^3\) In many cases these drugs predate the agency, or at least the regulatory process it oversees. In return for successfully evaluating the safety of a specific formulation and dosing regimen, the manufacturer is given a period of near-exclusive production rights for the medication (three-year market exclusivity, seven years if the drug is for an orphan disease), as competing products are eliminated or eased off the market.

The rationale for this FDA rule is that new studies can improve the guidance given to physicians who prescribe older drugs, thereby protecting patients. However, exclusive production rights have allowed companies to dramatically raise prices for certain medications (in some cases 2,000 percent).\(^4\) This problem is compounded by recent mergers and acquisitions that have further reduced competition within the pharmaceutical market. Prescription drug coverage available to patients may obscure some of these price distortions, but many patients are left without recourse to affordable options when less expensive generic drugs are suddenly taken off the market. The cost of a generic drug is often 80 percent lower than the brand-name product, but not when these “new” monopolies are granted.\(^5\) Pharmaceutical companies defend their pricing as necessary to finance development of new innovative medicines, but raising prices on established and successful medications, especially for vintage medications, and even for those drugs still on-patent, is a concerning trend, especially given the wide variation of (re)investment into research and development among firms.\(^6\) Pope Francis observes in his encyclical *Laudato si’* that “today, it is the case that some economic sectors exercise more power than states themselves.”\(^7\) The Holy Father highlights the challenges posed by a system where resources, power, and privilege are increasingly concentrated not within the hands of individuals but in larger human enterprises. As with popes before him, the Holy Father calls for “a radical change

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\(^7\) Francis, *Laudato si’* (May 24, 2015), n. 196.
in the conduct of humanity.” I pray that his call for change is heeded as we address the complex interactions between government regulation, human health, and society.

**Vaccines**

In June, *JAMA* reported online the results of the routine vaccination against rotavirus for US children. This vaccine program was implemented in 2006, recommended for all children before the age of eight months. The two currently licensed versions of the rotavirus vaccine (Rotarix, GlaxoSmithKline, and RotaTeq, Merck) were the subject of the study. Both are administered orally, not as a shot, and can be given at the same time as other scheduled vaccinations.

Symptoms of the rotavirus infection include fever, nausea, vomiting, abdominal cramps, and frequent, watery diarrhea. Dehydration is responsible for the majority of hospitalizations (and deaths) associated with this disease. Following the widespread use of the vaccine, the rate of hospitalization among children younger than five years for acute gastroenteritis declined by nearly a third to half across all age groups, with the greatest reductions among children aged six months to under two years of age. Furthermore, an even greater decline occurred for rotavirus-coded hospitalizations, which dropped between 63 and 94 percent. (In the paper there is a figure illustrating this almost immediate and spectacular decline.)

The American Academy of Pediatrics recommends that the rotavirus vaccine be included as part of the routine immunizations given to infants. These live attenuated oral rotavirus vaccines are generally considered safe, although certain children, such as those with immunodeficiencies, should avoid this class of vaccine. Unlike the first vaccine against rotavirus (RotaShield, Wyeth), which was introduced in 1998 but was subsequently withdrawn because of a significant association with intussusception, a serious abdominal disorder where the intestine “telescopes” within the abdomen, the two currently licensed vaccines do not carry a significant risk based on data from two trials conducted in fewer than sixty thousand infants. More recent post-licensure surveillance studies indicate that a small number of cases of intussusception may occur even with the newest generation of these vaccines, most often shortly after the first dose of vaccine is administered; however, the absolute number of hospitalizations (and deaths) averted by routine vaccination favor vaccination in most populations.

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Newborn Screening

One of the most significant developments in newborn screening has come as a consequence of a last-minute amendment to the Newborn Screening Saves Lives Reauthorization Act, which was signed into law on December 18, 2014. This bill provides federal funding for state-run newborn screening programs aimed at identifying infants with certain genetic, metabolic, hematologic, infectious, or auditory disorders. Children with many of these conditions appear normal at birth but have an inherent condition that will, without early intervention, lead to disability (or even death). The new law leaves intact these screening programs, but now stipulates that parents must give written informed consent for the research that is typically performed on the leftover, de-identified dried blood spots from their newborns. Prior to this, these samples were exempt under the Department of Health and Human Services Common Rule on Human Subjects Research, because these discarded samples were not obtained through a direct interaction with the individual patients and were not linked to any individually identifiable personal information.12

In an opinion piece published in the July issue of JAMA, Benjamin Berkman, deputy director of the Bioethics Core at the National Human Genome Research Institute, and colleagues at the National Institutes of Health highlight the potential negative effects of this policy change: not only will a new layer of consent “reduce dried bloodspot samples available for research [on a] population level, which could hinder public health,” but it “could even negatively affect newborn screening participation overall.”13 Parents who withhold permission for research may also be more likely to decline standard of care testing, putting their newborns at risk. Some states already allow parents to opt out of newborn screening altogether for various reasons.

An alternative approach, more similar to the current system the new rule replaces, is one where parents may “opt out” of research, but only after the samples have been obtained for screening their newborn. In the era of genomic medicine, the value of these dried blood spots for improving newborn screening for a host of disorders is clear, but at the same time there is a heightened concern about the risk of “re-identification” of subjects from the genetic (DNA) information contained in these samples. “When parents attend meetings about the use of residual dried blood spots . . . they often express concerns about how the use of those samples will affect not only their children but other members of the family.”14 Sufficient safeguards

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14 Roundtable on Translating Genomic-Based Research for Health, Board on Health Sciences Policy, Institute of Medicine, Challenges and Opportunities in Using Residual Newborn Screening Samples for Translational Research: Workshop Summary, ed. Steve Olson and Adam C. Berger (Washington, DC: National Academies Press, 2010), 8.
need to be put into place to ensure privacy. Consent for research is only one step in a much more significant process.

**Adult Stem Cell Therapy**

Heart failure occurs when the heart muscle cannot pump blood as well as it should. Sometimes addressing high blood pressure or reversing coronary artery disease can improve cardiac performance, but not all conditions that lead to heart failure can be overcome, especially when the heart muscle itself is compromised. Patients with advanced heart failure continue to have a poor long-term prognosis and few therapeutic options; many ultimately require cardiac transplantation.

In the August issue of *Circulation Research*, the journal of the American Heart Association, Emerson Perin, MD, and colleagues reported a dose escalation study of transendocardial injections of allogeneic mesenchymal precursor cells (MPCs), a unique class of adult stem-like cells found in bone marrow, for advanced heart failure.15 In prior studies, MPCs injected into the wall of failing hearts demonstrated an ability to increase blood vessel formation, promote neighboring cardiomyocyte survival, and even differentiate into new cardiomyocytes.16 The forty-five patients recruited at six sites in this trial had New York Heart Association (NYHA) class II or III heart failure with a left ventricular ejection fraction (LVEF) less than 40 percent by echocardiography. Of note, the MPC-treated patients received a commercially processed cell product from the same donor, a healthy twenty-six-year-old male. Of note, Dr. Perin and several of the authors are listed as consultants for Mesoblast, Inc.

The primary objective of the trial was safety, including looking for an immune reaction against the donor cells. No clinical signs or symptoms were linked to a donor-specific immune response, although five of the forty-five MPC-treated patients (11 percent) developed donor-specific antibodies. Secondary endpoints looking for efficacy focused on the avoidance of major adverse cardiac events, as well as left ventricular function. Although conceived of as a therapy to replace cardiac cells within the failing heart, MPC therapy may also act to modulate the cascade of event in the failing heart that lead to inflammation and fibrosis, causing the heart muscle to stiffen and lose contractile function over time.17 A post hoc analysis suggests that the group of patients that received the highest MPC dose (150 million cells) fared better than the control groups (or those patients that received fewer cells). A Kaplan–Meier survival analysis (time to event) showed that heart-failure-associated major adverse cardiac events (e.g., cardiac death, myocardial infarction, or need for revascularization) differed significantly from all groups (P < 0.05 for 150 million MPC group versus


16 Ramesh Mazhari and Joshua M. Hare, “Advances in Cell-Based Therapy for Structural Heart Disease,” *Progress in Cardiovascular Disease* 49.6 (May–June 2007): 387–395.

control). The highest MPC dose also had improved cardiac volume measurements by means of echocardiography, but no significant change in either ejection fraction or exercise capacity. However, the tendency of these patients to develop immunologic sensitization to the transplanted tissue is concerning in light of the fact that these patients may ultimately require heart transplantation.

Another promising trial involving adult stem cell therapy for heart failure was reported in the European Heart Journal, the journal of the European Society of Cardiology. The trial was conducted in sixty patients with very serious dilated cardiomyopathy (DCM), the leading cause of heart failure and the most common indication for transplantation. All patients had left ventricular ejection fraction less than or equal to 45 percent and an NYHA classification of II or less. Patients were recruited from sites within the National Health Service in the United Kingdom, and all trial procedures were carried out at the London Chest Hospital. The study examined the delivery of autologous bone-marrow-derived cells (BMCs) with or without peripheral granulocyte-colony stimulating factor (G-CSF) administration. This is the first placebo-controlled trial of patients with DCM assessing the combination of cell and cytokine therapy.

The basis of this work comes from preclinical trials in models of heart failure where mobilized BMCs have been shown to repair infarcted myocardium with an associated improvement in cardiac structure and function, as well as survival. Although trials of G-CSF have not proved beneficial by themselves to enhance cardiac function, cytokine treatment may have important implications for the success of stem cell therapy, including the ability to enhance the survival, mobilization, and engraftment of BMCs. The use of BMCs delivers a more heterogeneous population of cells compared to MPCs employed in the US-based trial, but avoids the immunologic risks from a donor. On the other hand, patients must be healthy enough to undergo collection as well as treatment with the cell-based therapy, versus using a “product” available off the shelf.

Promising results for patients with DCM were reported from this trial. At three months, peripheral G-CSF combined with the direct transplantation of BMCs into the failing myocardium was associated with a 5.37 percent point increase in LVEF (38.30 percent ± 12.97 from 32.93 percent ± 16.46 P < 0.05), which was maintained out to one year. This was associated with a decrease in NYHA classification, reduced

NT-proBNP,\textsuperscript{21} and improved exercise capacity and self-reported quality of life. In contrast, this trial did not find a benefit from G-CSF treatment alone, necessitating the more invasive techniques. Perhaps someday, endogenous stem cells will be able to be mobilized or peripherally infused, thereby avoiding the risks associated with bone marrow aspiration and repeated cardiac catheterization.

Arguably the most successful application of stem cells has been in the area of BMC transplants in patients with leukemia. A review of the improved survival in adult patients with acute lymphoblastic leukemia in the Netherlands was recently published in the journal \textit{Leukemia}.\textsuperscript{22} The report noted that many lessons in adult cancer have come from adopting pediatric-based regimens, particularly enhancing the survival observed among younger patients aged eighteen to thirty-nine years. For older adults, the use of allogeneic stem cell transplantation with a reduced-intensity conditioning regimen contributed significantly to the observed improvement in survival. The study notes, however, that outcome for patients aged seventy and over remains unsatisfactory, and advocates for specific trials for the elderly.

\textbf{End-of-Life Decisions}

It has been over a decade since the Dutch made newborn euthanasia legal in 2005. In that time, continuous improvements to neonatal care have raised the outlook for many premature babies and those with other serious medical conditions—some of the very patients for whom the law was intended. How have Dutch physicians changed their end-of-life practices as a result? A retrospective study of fetal and neonatal outcomes for those babies born at or before twenty-two weeks that died in the delivery room or in the neonatal intensive care unit (NICU) reveals that the number of terminations in the delivery room increased substantially. The law may have contributed to this trend, but what may be even more significant is the decision by the Dutch government to routinely offer all pregnant women an ultrasound examination at twenty weeks of pregnancy, which led to an increase in the detection of congenital malformations of the fetuses.

At the same time, the duration of hospital care prior to the death of a neonate increased substantially, by nearly 50 percent over the period (from 11.5 to 18.4 days in the NICU).\textsuperscript{23} This shows that Dutch neonatologists, like their US counterparts, have adopted new and more successful interventions to prolong the survival of babies once they reach the NICU. Furthermore, “infants that died in the delivery room received no comfort medication, whereas most infants who were due to die imminently in the NICU did receive some form of comfort medication.” When babies died in the

\textsuperscript{21} N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a biochemical marker of heart failure. This laboratory test is used in patients primarily to help detect, diagnose, and evaluate the severity of heart failure.

\textsuperscript{22} Avinash G. Dinmohamed, “Improved Survival in Adult Patients with Acute Lymphoblastic Leukemia in the Netherlands: A Population-Based Study on Treatment, Trial Participation and Survival,” \textit{Leukemia} 30.2 (February 2016): 310–317.

NICU, withdrawal of life-sustaining therapy was the most common cause, rather than active euthanasia. In fact, at the tertiary-care hospital at which the study was conducted, no cases of euthanasia of neonates were noted during the study period. Even though euthanasia in this age group may be exceptionally rare, it is hard not to see the increase in delivery room terminations as a result of a law that makes it permissible to end a newborn’s life.

**Palliative Care**

Ethnic and racial disparities in health care persist despite efforts to improve access and equality of treatment between groups. A recent study in *Neurocritical Care* identifies a significant difference in the rate at which black or Hispanic surrogates elect for “comfort measures only” following subarachnoid hemorrhage, a serious type of bleeding that occurs within the covering of the brain and is often fatal. “It is common for patients who die from subarachnoid hemorrhage to have a focus on comfort measures at the end of life.”24 White patients were significantly more likely to have supportive care withheld or withdrawn and died under conditions that maximized comfort, compared to Hispanic and black patients—this despite equal mortality between the groups despite continued treatment. Understanding the reason behind differences in treatment choices is critical for ensuring that the difference is driven by cultural preferences rather than a lack of knowledge or mistrust of the health system. A number of interrelated factors have been suggested to account for these differences, including a lack of communication (especially in the face of a language barrier), mistrust across socioeconomic or educational lines, and differences in religious and cultural beliefs. It is possible that authors overestimate the difference between the groups, because the choice to maintain hydration and nutrition was not separated out from other “aggressive” treatment measures. Future research would benefit from a more detailed assessment of the rationale used by health care surrogates, as well as assessment of the degree to which families engaged in end-of-life discussions in advance.

**Addiction Medicine**

In recent years there has been an alarming rise in the abuse of prescription pain medications containing opioids—substances that are potent at blocking pain, but have a high potential for misuse and abuse. Some opioids, such as morphine, occur naturally in the opium poppy, but many others are synthetically manufactured. Other opioid derivatives, like heroin, are now only encountered as drugs of abuse, though at one time they were widely available in prescription pain medicines.25 There have been several important public health efforts designed to improve the safety of opioid prescribing and to reduce diversion, such as revised prescribing guidelines, the introduction of abuse-deterrent formulations, the withdrawal of medications with


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high abuse potential, and the recent implementation of prescription-drug monitoring programs at the state level.

Dr. Marc Larochelle and colleagues report in the June issues of *JAMA Internal Medicine* a small but significant reversal in the “previously unrelenting increases in opioid dispensing on a national scale,” as well as a reduction in deaths from prescription opioid medications following two major changes in the pharmaceutical market in late 2010—the introduction of abuse-deterrent OxyContin (resistant to crushing or dissolving) on August 9, 2010, and the voluntary withdrawal of propoxyphene from the market on November 19, 2010.26 The research was based on claims from a large national US health insurer and showed that in the two years after these interventions the rate of overdoses due to prescription opioids decreased by 20 percent. An association between prescription opioid supply and prescription opioid overdose mortality at the state level has previously been shown.27 Despite these positive developments, reductions in nonprescription deaths continue to rise. It is possible that a reduced prescription opioid supply, at least in the short run, “may lead individuals already addicted to opioids to substitute alternative prescription opioids or heroin.” Tackling the public health crisis requires destigmatization of drug treatment and increasing accessibility—the article points out that less than one in five adults with opioid abuse problems are reported to be receiving any form of treatment.

**Fertility Procedures and Natural Family Planning**

Starting a family is a momentous decision. The chances of conception followed by a successful delivery are affected by many factors; one of the most important is the age of the couple. Another consideration may be the ability to achieve a desired family size. Dr. Dik Habbema et al. present an updated computer simulation model of fertility based on a large set of age-dependent data of monthly pregnancy chances in natural non-contraceptive populations. They report, “In order to have a chance of at least 90 percent to realize a one-child family … couples should start no later than age 32 years for a one-child family, at 27 years for a two-child family, and at 23 years for three children.” The study goes on to provide revised probabilities should assisted reproductive options be an “acceptable option” but does not differentiate between the different forms of reproductive treatment available. For some couples, ovulation monitoring may be a viable option, whereas other couples may opt for forms of hormonal support. Of course every couple has a unique situation influenced by factors that are not accounted for in the model. For example, a physician advising in the area of natural family planning may take into account family history or prior medical conditions. The decision to start a family is affected by many factors of modern life and marital development; however, the guidance provided by this

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26 Propoxyphene is a prescription opioid medication that was first approved by the FDA in 1957 for treatment of pain; however, poor efficacy and emerging data about cardiac toxicity led to its voluntary withdrawal from the US market on November 19, 2010.

model may nonetheless serve as a useful starting point for couples hoping to achieve a desired family size.

**The Environment and Health**

Finally, a thoughtful article on the health effects of radiation and other health problems in the aftermath of nuclear accidents was contributed to the August issue of the *Lancet* by Professor Arifumi Hasegawa in the Department of Radiation Disaster Medicine, Fukushima Medical University, Fukushima, Japan, and colleagues. The authors find that the problems attributable to radiation exposure following major nuclear accidents are less commonly “physical health problems directly attributable to radiation exposure, but rather psychological and social effects.” The evacuation process and long-term displacement in the face of a nuclear disaster pose special risks for vulnerable populations such as the elderly or those who are hospitalized. One can only imagine the consequences of a larger disaster or one in an even more populous area.

The increasing need for power, as well as the concern that carbon emissions are harming our environment, are among the reasons that more than four hundred nuclear power plants are in operation around the world, with additional plants either in the planning or construction stage. Pope Francis’s encyclical *Laudato si’*, On Care for Our Common Home, is an eloquent reflection on the natural world and its relationship to human health and society. He cautions, “We all know that it is not possible to sustain the present level of consumption in developed countries and wealthier sectors of society, where the habit of wasting and discarding has reached unprecedented levels.” Finding safer ways to produce power and with less pollution is mandated by the experience at Fukushima and by other man-made nuclear disasters.

**DAVID J. RAMSEY, MD**

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