“You shall not kill.” (Exod. 20:13)

Though written as a negative prohibition, the Decalogue includes positive duties; and even the prohibition against the unrighteous taking of life entails the duty to protect innocent human life. As I prepared this column on recent progress in medicine and clinical research, I could not help but reflect on this line from the first reading of the third Sunday of Lent.

**Physician-Assisted Suicide**

News abounds of the legal invalidation of the longstanding Canadian prohibition against assisted suicide.\(^1\) Though no new law has been written, this is an example of the continued pressure on the medical profession in many nations to accept physician-assisted dying and euthanasia. When the US Supreme Court took up physician-assisted suicide (PAS) in 1997, it recognized the interest of the government to preserve life, prevent suicide, and protect the integrity of the medical profession, while observing that states were engaged “in serious, thoughtful examinations of physician-assisted suicide.”\(^2\) Today, bills that promote PAS are being drafted or under consideration in several US state legislatures, and existing laws barring PAS are under review or already have been overturned by US state courts—currently, some form of assisted suicide is legal in five US states (Washington, Oregon, Vermont, New Mexico, and Montana).\(^3\)

Advocates for the practice of assisted suicide profess that only a select group of terminally ill patients would be subject to the practice and argue that physicians

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are among the best equipped to collaborate in the termination of human life, for anyone less competent could unjustly cause additional suffering. There is ample evidence that the effect of ending the lives of patients through PAS or other means of legally sanctioned euthanasia has hardly been restricted to such a select group of people as the terminally ill, but also “patients with chronic illnesses or disabilities, or even those who are vulnerable or marginalized in other ways,” especially those suffering from depression and other psychological ailments. PAS is also a threat to improved palliative care. Involving a physician licensed by the state may even lower the psychological threshold for some patients to request a hastened death. Two recent surveys shed light on a concerning trend: many in society are becoming more accommodating to the idea of PAS and euthanasia, including members of the medical profession.

Researchers at the University of Helsinki reported that “Finnish Physicians’ Attitudes towards Active Euthanasia Have Become More Positive over the Last 10 Years.” A random sample of more than one thousand Finnish physicians was asked to express the intensity of their feelings about statements concerning euthanasia by means of a survey, and the results were compared to similar questionnaires sent to groups of Finnish physicians in 1993 and 2003. Most physicians remained opposed to PAS even though there is no specific legal prohibition in Finland. However, in the last ten years the willingness of physicians to accept legalized euthanasia more than doubled, equally dividing respondents for and against it.

This study indicates that, in the absence of a change in the domestic legal landscape, there has been a substantial change in physician attitudes toward euthanasia across Finland. Studies in the United States have shown that physician attitudes toward PAS often reflect the religious and ethnic background from which the practitioner originates. In contrast to the United States, where fully one-quarter of all

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8 For example, in the United States, the Death with Dignity Act was passed in the state of Oregon, available at the Oregon Public Health Division, accessed March 2, 2015, http://public.health.oregon.gov/ProviderPartnerResources/EvaluationResearch/DeathwithDignityAct/Pages/index.aspx.

practicing physicians are foreign medical graduates, a relatively small number of Finnish physicians are trained abroad, and a majority of the working-age physicians in this Finnish survey are part of a national health care system. Their stance on euthanasia likely reflects a shifting national viewpoint.

What is driving this change in attitudes toward PAS and euthanasia? Another study conducted by researchers at the National University of Ireland examining data from the British Social Attitudes Survey (publicly available from the National Centre for Social Research in London) found a strong correlation between increasing support for the legalization of physician-provided euthanasia and the rise of the “secularization” of British society. Examining data collected over almost thirty years (1983–2012), the authors performed a multivariate analysis to determine the extent to which one variable, reported religious affiliation, correlated with another, attitudes toward euthanasia. The authors found that the decline in the frequency of religious institution attendance (a proxy for religiosity) and a parallel decline in religious affiliation (i.e., the rise of people with no religious affiliation, which increased from 31 to 45.4 percent) were strongly associated with the shift in attitudes over the study period; and the biggest change in attitudes occurred within the group with the least religious affiliation. In contrast, the strength of religious affiliation and the religious denomination (Roman Catholics were consistently more than twice as likely to oppose legalization) were the most important factors in defining attitudes toward euthanasia involving a physician.

End-of-Life Decisions and Palliative Care

An increasing proportion of patients with advanced cancer are receiving aggressive treatments within their last month of life, such as chemotherapy or invasive procedures, or are being admitted to the hospital intensive care unit. The benefits of aggressive treatments must be carefully balanced with the expected impact on quality of life, especially in vulnerable patients such as those diagnosed with a...
terminal illness. A paper published by surgeon Alvin Kwok and colleagues focused on the utilization of surgical care in patients being treated for metastatic cancer. The group examined the number and timing of invasive procedures relative to the time of cancer diagnosis through the time of death. Data was drawn from the National Cancer Institute’s Surveillance Epidemiology and End Results database, which allows inpatient, outpatient, and physician-billed Medicare claims to be assessed over the continuum of cancer care. The study found that nearly all patients with stage IV cancer (96 percent) underwent an invasive surgical procedure, including nearly two-thirds after the diagnostic period and one-quarter within the last month of life. Importantly, the longitudinal study showed that for the period between 1996 and 2006 there was a 20 percent rise in the utilization of invasive procedures within the last month of life. However, procedures consistent with primary tumor resection decreased, while “those with probable palliative intent and those unrelated to cancer increased,” such as gastrostomy and jejunostomy tube placements. The inability of physicians to anticipate death, particularly in the last month of life, should not limit the provision of life-sustaining procedures that have the potential for enhancing the quality of life, even when they are invasive.

Understanding and respecting patient preferences at the end of life often involves family members in what can be a difficult decision-making process. This is especially true for children and adolescents. Before the age of reason, parents are responsible for most if not all treatment decisions. However, as children and adolescents mature, a process that may accelerate in the setting of a terminal illness, shared decision making may increase. A group writing from the Children’s National Medical Center in Washington, DC, reports on the degree to which family members accurately represent the end-of-life preferences of adolescents with terminal cancer.

Though the total sample size was small, consisting of seventeen adolescent/family dyads, substantial areas of agreement existed between parents and their children. There was 80 percent agreement on the importance of “attending religious services, fulfilling personal goals . . . , saying everything I want to say to people in my family, understanding treatment choices, being . . . free from pain, and being at peace spiritually.” And this was despite a majority of the adolescents having never completed a formal advance directive. What parents were unaware of was the importance that adolescents placed on “dying a natural death and of dying at home,” and “wanting to know if I were dying,” which a majority felt were important to discuss early in care not only “if dying.” In the study, these differences were specifically addressed by an intervention, which lead to increased harmony between families and patients. Interestingly, less than half of the doctors and nurses caring for these patients believed that it was important for adolescents to complete an advance directive, whereas 80 percent believed it important for patients over the age of eighteen. The take-home

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15 Ibid., 754.
17 Ibid., 712.
message from this study is that facilitated conversations surrounding end-of-life issues are both effective and desired by adolescents (and their families) facing end-of-life decisions.

Vaccines

Nearly eighty million Americans are presently infected with human papilloma virus (HPV), and around fourteen million new infections occur each year.\textsuperscript{18} Persistent infection with one of the high-risk serotypes of HPV is a key step in the pathogenesis of cervical cancer; and at least 70 percent of cervical cancer cases are caused by HPV types 16 and 18.\textsuperscript{19} With this knowledge, HPV-vaccination programs have been implemented in many countries and more than 175 million doses have been administered worldwide.\textsuperscript{20} Almost ten years of data exist indicating that the vaccines are highly effective at preventing high-risk HPV infections.\textsuperscript{21} If prophylactic vaccination confers lasting immunity, many cases of cervical cancer could be prevented, thereby saving the lives of many women.

The vaccines are given as a three-dose series recommended in children (both girls and boys) as young as nine years of age.\textsuperscript{22} The early age of vaccination is an effort to protect against what is primarily a sexually transmitted infection before exposure to the virus. From a public health standpoint, this makes sense because it is impossible to identify which adolescents are going to engage in practices that place them (or their future partners) at risk. Delaying the decision to vaccinate until the age of majority or before marriage would leave many women vulnerable to exposures that may result in cancer later in life. Parents must therefore weigh the risks and benefits of vaccination on behalf of their children and decide how to present the vaccine in an age-appropriate fashion to their children.


\textsuperscript{22} The vaccine is available as a bivalent (bHPV [types 16, 18]; Cervarix, GlaxoSmithKline) and quadrivalent (qHPV [types 6, 11, 16, 18]; Gardasil, Merck, Sharp and Dohme Corp.) formulation, each composed of unique noninfectious subunits—\textit{virus-like particles}—which prime the immune system to resist infection from the related virus subtype. After the first dose, a second dose is ordinarily recommended to follow between one to two months and a third dose beyond six months.
Apart from common side effects including pain or redness at the injection site, mild fever, or headache, a number of cases of women developing multiple sclerosis (MS) and other demyelinating diseases shortly after HPV vaccination have been reported. In the January issue of the JAMA, researchers in Denmark and Sweden published a comprehensive survey of the rate of these devastating diseases in the two years following vaccination against HPV. Nearly 400,000 women ages ten to forty-four were included in the study. Preexisting cases of MS or demyelinating diseases of the central nervous system were excluded. Using the comprehensive national vaccination and prescription registers in these two Scandinavian countries, the group found that no excess risk existed within the two years following vaccination in this cohort. Post-marketing surveillance is an important part of drug and vaccine safety protocols, and countries with national health systems are better equipped than those like the United States that rely largely on voluntary reporting.

**Adult Stem Cell Therapy**

Multiple sclerosis is an autoimmune inflammatory disease that often progresses toward severe disability despite therapies aimed at suppressing the immune system. A novel treatment recently pioneered for MS is the transplantation of autologous hematopoietic stem cells (HSCs). These adult stem cells are isolated from the patient’s own blood and then re-infused following a regimen that ablates the patient’s existing immune system. The hope is that by doing this procedure the immune system will be reset, thereby reducing the number of MS recurrences and their severity. A group led by Richard Burt, the Chief of the Division of Immunotherapy and Autoimmune Diseases at Northwestern University in Chicago, published in the January issue of the JAMA an observational case series that included 145 patients treated with HSC transplantation over ten years. The patients who received this sophisticated therapy had the severest forms of the disease, known as relapsing-remitting MS or secondary progressive MS with progression toward disability, and all were unsuccessfully treated with one or more currently available FDA-approved drugs. Many of these patients, if untreated, were at risk of increasingly severe forms of disability such as para- or quadriplegia and progressive loss of vision or cognition.

An unexpected and welcome outcome following HSC transplantation in patients with the relapsing-remitting disease subtype was not just a stabilization of the patients, but a measurable decrease in disability score. The expected course for these patients is a relentless progression of neurological impairments. Patients with secondary progressive MS and those with disease durations longer than ten years did not show

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a similar benefit. It is well known that patient selection is important in determining outcomes in medicine. Although this is a large case series, there is no control group and it is possible that the improvement represents recovery from acute episodes of MS that may have taken place even in the absence of HSC transplantation. However, no study to date has reported a significant and sustained improvement in disability and quality of life among these types of MS patients. This study gives hope that HSCs may be of aid in MS and other demyelinating diseases of the central nervous system, but randomized and controlled trials are needed before this approach will become a part of standard care.

Organ Donation and Transplantation

The first human birth following the transplantation of a uterus was reported in the February issue of the *Lancet.*26 The patient was one of nine enrolled in a trial for patients with absolute uterine infertility. The subject of the report possessed a rare developmental disorder known as Mayer-Rokitansky-Küster-Hauser syndrome, leading the vagina and uterus to be underdeveloped; this condition affects about 1 in 4,500 newborn girls.27 However, the condition of absolute uterine infertility affects millions of women of reproductive age who may have a non-functional or absent uterus from a variety of causes, for example, because of a hysterectomy.28 Uterine transplantation is the only potential treatment for this condition and advances have taken place in both transplantation science and reproductive medicine to only recently make this possible. To put this advance in perspective, the first uterus transplant took place in Saudi Arabia in 2000, but did not result in a functional organ and was removed after only three months; however, just over a decade later, a group in Turkey demonstrated that a transplanted uterus could become physiologically functional (capable of menstruation), but unlike the present case, no pregnancy resulted.29 The present case has the added complexities that the donor of the uterus was a sixty-one-year-old “family friend” (the patient’s first choice was reportedly her mother) and the conception resulted from the implantation of a cryopreserved embryo. Although antirejection drugs were needed throughout the pregnancy, and several bouts of early rejection had to be treated with steroids, it was otherwise uncomplicated. Uterine transplantation is a restorative rather than life-sustaining medical intervention. Although the current procedure did not connect the transplanted uterus to the fallopian tubes, future research may make such an advance possible, thereby granting women with absolute uterine infertility the ability to get pregnant naturally.

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Fertility and Reproduction

Presently, more than 1 percent of all babies born in the United States are conceived with some form of assisted reproductive technology (ART), and nearly 2 to 5 percent of all babies born in Europe are conceived this way.30 Fertility treatments may be linked to certain forms of cancer because of hormone exposure. Utilizing data made available from the Medical Birth Registry of Norway and the Cancer Registry of Norway, a group of researchers lead by Marte Reigstad recently performed an analysis of the risk of breast cancer following ART.31 They found a significantly elevated risk of developing breast cancer among the cohort of women who underwent ART within the period of 1983 (when ART was introduced into Norway) to 2010. Stratified analyses indicated that the risk was greatest for women who were ten years or more beyond ART exposure and who specifically utilized in vitro fertilization. Unfortunately, ascertainment of the use of ART did not allow further separation of women by exposure to specific agents. The study was also unable to control for other important factors related to the development of breast cancer, such as family history of cancer, age at menarche, breastfeeding history, and obesity. Important caveats remain. Women who conceived following intracytoplasmic sperm injection, a technique ordinarily used when male infertility is the problem, did not have higher risk of breast cancer than controls in the study, though the follow up for patients subjected to this newer procedure was somewhat shorter. This finding leaves open the possibility that infertility itself may play a role in the risk of breast cancer. Finally, the study cohort was relatively young, which may underestimate the true lifetime risk of breast cancer, which increases as women age.

In the area of male fertility, an updated review was recently published by the Cochrane collaboration, summarizing the findings of forty-eight randomized clinical trials exploring the potential benefits of antioxidants on male subfertility.32 Although it is well established that a significant portion of male infertility is due to oxidative damage impairing the quality and quantity of sperm, it is unknown whether oral antioxidants improve fertility outcomes. The authors conducted a meta-analysis, which is a statistical approach that combines the results from multiple studies to increase their power, or likelihood, that a conclusion drawn from a line of research is indeed valid. Data was combined from forty-eight studies that included more than four thousand subfertile men and looked at whether varying durations of treatment with oral antioxidant supplements lead to a pregnancy and ultimately a live birth.

32 Marian G. Showell et al., “Antioxidants for Male Subfertility,” Cochrane Database of Systematic Reviews 12 (2014): CD007411. The Cochrane Collaboration is an international not-for-profit organization that is well-respected for their systematic reviews on all manner of health care topics.
Examples of some of the antioxidants tested alone or in combination included vitamin E, vitamin C, folate, zinc, selenium, carnitine, and carotenoids, many of which are highly enriched within normal semen. The duration of the interventions studied ranged from three to twenty-six weeks, and patients were followed for as long as two years. The authors conclude that “low quality evidence suggests that clinical pregnancy rates may increase . . . [as much as double] among men who were taking antioxidants,” but that “further large well-designed randomized placebo-controlled trials are needed to clarify these results.”

Finally, on an inspiring note, an article describing an internet-based fertility monitoring application (mobile app) was published in the January issue of the European Society of Contraception and Reproductive Health Journal. The program helps women to identify their ovulation day and fertile window. It was developed by a Swedish software company, NaturalCycles Nordic AB. A pilot study using the app was carried out with the aid of researchers at Karolinska Institutet and University Hospital in Stockholm, Sweden. A majority of the participants were recruited in Switzerland and Sweden, both through advertisements, as well as directly by clinics that gave advice on family planning. More than three hundred women aged eighteen to thirty-nine entered their basal body temperatures, ovulation test results (optional), and dates of menstruation into the application. All of the women using the software were sexually active, not pregnant, and not planning to get pregnant. A retrospective analysis performed on more than 1,500 cycles provided by these women yielded good agreement between temperature-based estimation of the ovulation day and the ovulation test results in the study. Only one unanticipated pregnancy was reported, resulting from intercourse on a day not recommended by the software, as it was the day before predicted ovulation. This implementation of a natural method of birth control provides an engaging solution to fertility monitoring and provides an opportunity for further research.

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34 Ibid., 2.