lower. The European Prospective Investigation into Cancer and Nutrition study recently reported a similarly strong inverse association. A prospective study from the Japan Public Health Center did not find an inverse relation between plasma 25-hydroxyvitamin D levels and the occurrence of colon cancer, although an inverse association with rectal cancer was apparent. Randomized trial evidence is limited. In a British trial comparing vitamin D_3 with placebo, the intervention was not associated with a change in colorectal-cancer incidence (relative risk, 1.02; 95% CI, 0.60 to 1.74). Similarly, in the WHI trial, calcium plus vitamin D_3 did not reduce the incidence of colorectal cancer (relative risk, 1.08; 95% CI, 0.86 to 1.34) or related mortality (relative risk, 0.82; 95% CI, 0.52 to 1.29).

Although ecologic studies suggest that mortality due to prostate cancer is inversely related to sun exposure, observational analytic studies of serum 25-hydroxyvitamin D and prostate cancer haven't supported this conclusion.[1-3] Eight of 12 nested case–control studies showed no association between baseline serum 25-hydroxyvitamin D levels and prostate-cancer risk, and just 1 showed a significant inverse association; a more recent nested case–control analysis of data from the α-Tocopherol, β-Carotene Cancer Prevention Study showed no association. Moreover, a meta-analysis of 45 observational studies of dairy-product intake and prostate-cancer risk showed no significant association with dietary intake of vitamin D. No relevant randomized clinical trials were identified.

The large-scale Cohort Consortium Vitamin D Pooling Project of Rarer Cancers showed no evidence linking higher serum 25-hydroxyvitamin D concentrations to reduced risk of less common cancers, including endometrial, esophageal, gastric, kidney, pancreatic, and ovarian cancers and non-Hodgkin's lymphoma[5] (which together account for approximately half of all cancers worldwide). Moreover, the report provided evidence suggestive of a significantly increased risk of pancreatic cancer at high 25-hydroxyvitamin D levels (≥40 ng per milliliter).[5] An increased risk of esophageal cancer at higher 25-hydroxyvitamin D levels has also been reported.

Despite biologic plausibility and widespread enthusiasm, the IOM committee found that the evidence that vitamin D reduces cancer incidence and related mortality was inconsistent and inconclusive as to causality. New trials assessing moderate-to-high-dose vitamin D supplementation for cancer prevention are in progress and should provide additional information within 5 to 6 years. Although future research may demonstrate clear benefits of vitamin D related to cancer and other nonskeletal health outcomes, and possibly support higher intake requirements, the existing evidence falls short.

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1. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academies Press, 2011.
2. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. Evidence report no. 183. Rockville, MD: Agency for Healthcare Research and Quality, 2009. (AHRQ publication no. 09-E015.)
3. International Agency for Research on Cancer. Vitamin D and cancer — a report of the IARC working group on vitamin D. Lyon, France: World Health Organization Press, 2008.
4. Byers T. Anticancer vitamins du jour — the ABCED's so far. Am J Epidemiol 2010; 172:1-3.
5. Helzlsouer KJ. Overview of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Am J Epidemiol 2010;172:4-9.

Defining Safe Use of Anesthesia in Children

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Anesthetic agents are commonly used for a variety of medical procedures in infants and children, but little is known about their effects on the developing brain. A growing body of data from studies in animals suggests that under certain circumstances, such as prolonged anesthesia, these drugs could adversely affect neurologic, cognitive, and social development of neonates

Ongoing Clinical Trials Assessing the Effects of Anesthetics on Neurocognitive Development

Odense University Hospital (Denmark) and the Danish Registry Study Group	A nationwide epidemiologic study comparing the educational achievement of all children who have undergone a surgical procedure before the age of 1 year with that of a general-population control group.
Columbia University	A prospective cohort study of children who had exposure to an anesthetic before the age of 3 years and their siblings who were not exposed. The two groups will be followed for neurodevelopmental outcomes.
International collaboration of institutions from Australia, the United States, Canada, Italy, the United Kingdom, and the Netherlands	Prospective, randomized, investigator-blinded, controlled clinical trial to assess the effects of general anesthesia using sevoflurane versus neuraxial anesthesia using bupivacaine on neurocognitive function in infants over 26 weeks' gestational age. Children will be followed with evaluations of neurocognitive development at 2 and 5 years of age.

and young children. We believe that these findings should be of concern to the scientific and medical communities.

Over the past decade, studies in rodents have found that exposure to anesthetic agents during sensitive periods of brain development (i.e., the brain growth spurt) results in widespread neuronal apoptosis and functional deficits later in development. So far, agents that either antagonize *N*-methyl-D-aspartate (NMDA) receptors or potentiate the neurotransmission of γ-aminobutyric acid (GABAergic agents) have been implicated, and no safe doses of these agents or safe durations of administration have been defined.

More recent investigations in nonhuman primates have extended these findings. Studies conducted by the National Center for Toxicology Research (NCTR) of the Food and Drug Administration (FDA) have demonstrated that exposure to ketamine — the prototypical NMDA-receptor antagonist — resulted in increased neuronal cell death in nonhuman primates. Specifically, a dose of ketamine sufficient to produce a light surgical plane of anesthesia for either 9 or 24 hours resulted in neuroapoptosis in 5-day-old rhesus monkeys. No similar effect was seen when ketamine was administered for only 3 hours. Neuroapoptosis in the brain of the fetus was also evident when pregnant rhesus monkeys were exposed to ketamine for 24 hours on day 122 of gestation (equivalent to the third trimester of human pregnancy), but no neuroapoptosis was noted following administration of ketamine on postnatal day 35.[1] Neuroapoptosis has also been demonstrated in primates who were given isoflurane (predominantly a GABAergic agent) on postnatal day 6.[2]

Although the functional consequences of these histopathologic changes can only be inferred at this time, the FDA and others are currently conducting studies in animals to address the neurocognitive and neurobehavioral effects of anesthetic-induced apoptosis. At the NCTR, the FDA is using a so-called operant test battery to evaluate the cognitive function of rhesus monkeys exposed to a dose of ketamine sufficient to produce a light surgical plane of anesthesia for 24 hours on postnatal day 5 or 6. This battery consists of a number of tasks that evaluate short-term memory and attention, learning, time perception, motivation, and color and position discrimination. The results to date indicate that, as compared with controls, ketamine-treated animals have lower training scores — and continue to score lower than controls for at least 10 months after the administration of ketamine.[3] Similar studies of isoflurane in primates are ongoing.

Nonhuman primates are believed to offer the most appropriate model for assessing neurodevelopmental risk to humans; however, such cognitive testing in primates is expensive and requires many years to complete. Therefore, limited data exist to date. More rapid progress can be made using rodent models. Additional data from animal studies may help to define the window of vulnerability and the extent of anesthesia-induced neuronal alterations and provide insights both into the functional end points that should be assessed in clinical studies and into ways of blocking or ameliorating potential adverse effects. It is not known how the data from rodents or primates translate to humans, but such findings raise questions that require further scientific investigation.

Studies in children have attempted to assess the effects of anesthetics on the developing human brain. For instance, a retrospective cohort analysis followed a birth cohort of 383 children who underwent inguinal hernia repair during the first 3 years of life and compared them with

5050 children in a control sample who had undergone no hernia repair before the age of 3.[4] The children who underwent hernia repair were twice as likely as those who did not to be given a diagnosis of a developmental or behavioral disorder (adjusted hazard ratio, 2.3; 95% confidence interval [CI], 1.3 to 4.1). A population-based, retrospective, birth-cohort study examined the educational and medical records of children who were exposed to a single anesthetic (n=449), two anesthetics (n=100), or more (n=44). In contrast to the hernia-repair study, this study reported no increased risk of learning disabilities with a single anesthetic (hazard ratio, 1.0; 95% CI, 0.79 to 1.27). However, an increasing risk of learning disabilities was associated with two or more anesthetics (hazard ratio, 1.59; 95% CI, 1.06 to 2.37; and hazard ratio, 2.60; 95% CI, 1.60 to 4.24, respectively). The risk of learning disabilities also increased with greater cumulative exposure to anesthesia.[5]

No conclusions about causality can be drawn on the basis of these nonrandomized studies in humans because of the substantial potential for confounding. Indeed, there are conflicting findings between the two cited studies regarding a single exposure to anesthetics. It is not possible to discern from the published study reports whether or how differences in surgical procedures, anesthetic drugs, patient monitoring, or anesthesia techniques affected the outcomes. It is possible that the children undergoing surgery also differed from the nonexposed children in ways that were not discernible. At present, there is not enough information to draw any firm conclusions regarding an association between anesthetic exposure and subsequent learning disabilities, and additional studies such as those that are ongoing (see box) are warranted.

Generating definitive data about the effects of anesthetics on the developing brain will most likely take numerous studies in animals and humans spanning many years. Planning, conducting, and interpreting these studies will pose enormous challenges to the medical and scientific community. It seems unlikely that any single individual or organization will be able to muster the resources to take on this project.

The FDA is continuing efforts to address the pediatric safety of anesthetics. On March 29, 2007, the FDA's Anesthetic and Life Support Drugs Advisory Committee met to discuss the data from animal studies suggesting that exposure to anesthetic agents during the period of rapid brain growth produces widespread neuronal apoptosis with possible long-term functional consequences. The committee members agreed that additional research was essential to understanding the implications of the animal data for children who must be exposed to anesthetic and sedative drugs for necessary medical procedures. They also concluded that there was insufficient information to warrant changing the practice of pediatric anesthesia, other than to forgo elective procedures in children less than 3 years of age. Since that time, numerous nonclinical and clinical studies have been undertaken (and published) in an attempt to further understand this challenging issue; therefore, a second advisory committee meeting on this issue is scheduled for March 10, 2011. The committee will evaluate the weight of existing scientific evidence and discuss the research agenda and potential risk-communication issues.

As part of its Critical Path Initiative, the FDA has entered into a public–private partnership with the International Anesthesia Research Society (IARS) called SmartTots (Strategies for Mitigating Anesthesia-Related Neurotoxicity in Tots). This partnership will seek to mobilize the scientific community, stimulate dialogue among thought leaders in the anesthesia community, and work to raise funding for the necessary research.

We need to definitively answer the questions of whether anesthetic use in children poses a risk to their development and, if so, under what circumstances.

But these activities are just the first step. We need to definitively answer the questions of whether anesthetic use in children poses a risk to their development and, if so, under what circumstances. Although withholding anesthesia from children who need surgery is unreasonable, obtaining more information about safe use is imperative. If anesthetic agents are found, in certain cases, to affect the developing brain, strategies for mitigating and managing such risks can be

implemented. The FDA is committed to pursuing these answers with the medical and scientific communities and will take the steps necessary to ensure that the benefits of anesthetic use in children continue to outweigh any potential risks.

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1. Slikker W Jr, Zou X, Hotchkiss CE, et al. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci 2007; 98:145-58.
2. Brambrink AM, Evers AS, Avidan MS, et al. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology 2010;112:834-41.
3. Paule MG, Li M, Allen RR, et al. Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. Neurotoxicol Teratol 2011 January 15 (Epub ahead of print).
4. DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G. A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. J Neurosurg Anesthesiol 2009;21:286-91.
5. Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 2009;110:796-804.

How CER Could Pay for Itself — Insights from Vertebral Fracture Treatments

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The pain and disability caused by osteoporotic vertebral fractures have long motivated the search for effective therapy. Two procedures designed to restore vertebral body height and function have been widely adopted: percutaneous vertebroplasty, in which cement is injected into the vertebral body to support the fractured bone; and kyphoplasty, a variant of vertebroplasty in which a balloon is inserted and inflated in a collapsed vertebral body, restoring the bone's height before the cement injection. Initial studies suggested that these procedures were superior to conventional symptomatic treatment. But when later studies cast doubt on those favorable findings, health care funding agencies sought to curb their use. The story of these procedures offers a glimpse of the ways in which comparative-effectiveness research (CER) may influence medical practice and health care expenditures.

Early studies of these procedures were neither randomized nor blinded, and because the symptoms of compression fractures often abated over time, the lack of adequate controls made it impossible to know whether improvements that followed treatment would have occurred even without surgery. Furthermore, neither procedure was risk-free; reported complications included compression fractures, cement leakage, pulmonary complications, paraplegia, and death.[1] In a scenario that's likely to be repeated frequently as CER gains greater acceptance and support, randomized trials eventually followed the observational studies that had fostered the initial enthusiasm.[2] If the full consequences of that research are not yet fully apparent, their potential importance is. Were the results of better-designed studies translated into practice, the reduction in U.S. health care expenditures would be considerable.

CER treats effectiveness as a balance of benefits and harms; when the risks associated with a procedure outweigh its clinical benefits, it is appropriate and ethical to limit its use. Both the clinical need and the desire to avoid wasteful expenditures were part of the rationale for subjecting these procedures to comparative studies. Furthermore, consensus that these procedures were promising but unproven led several countries to make them available on an interim-coverage basis. These arrangements, in effect from 2006 through 2010, allowed the procedures to be performed in everyday practice while further evidence was generated.

Trials conducted during that period suggested that kyphoplasty did not improve outcomes. The studies of vertebroplasty produced varying results, but the highest-quality trials cast doubt on the benefit and raised additional safety concerns. In a randomized but non-blinded trial by Kallmes et al.,[3] patients who underwent vertebroplasty and controls had similar reductions in disability and pain scores, with a trend toward a higher rate of clinically meaningful improvement in pain