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PERSPECTIVES
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More than any other cancer, cervical cancer reflects striking global health inequity. It is the second most common cancer among women worldwide, with about 493,000 new cases diagnosed annually (see map). Of 274,000 deaths due to cervical cancer each year, more than 80% occur in developing countries, and this proportion is expected to increase to 90% by 2020.1 Affecting relatively young women, it is the largest single cause of years of life lost to cancer in the developing world. The deaths of women who are in their most productive years have a devastating effect on the well-being of . . .


Cancer prevention has fallen victim to the culture wars. Throughout the United States, state legislatures are scrambling to respond to the availability of Merck’s human papillomavirus (HPV) vaccine, Gardasil, and to the likely introduction of GlaxoSmithKline’s not-yet-approved HPV vaccine, Cervarix, which have been shown to be effective in preventing infection with HPV strains that cause about 70% of cases of cervical cancer. At the Centers for Disease Control and Prevention (CDC), the Advisory Committee on Immunization Practices (ACIP) has voted unanimously to recommend that girls 11 and 12 years of age receive the vaccine, and the CDC has added Gardasil...


In the early decades of the 20th century, most Americans considered cosmetic surgery to be just a few steps removed from quackery. Many observers saw the desire for cosmetic surgery as a mark of vanity, and physicians tended to believe that such surgery violated their ethical injunction to do no harm. Yet by the end of the century, cosmetic surgery had become a multibillion-dollar business, and it is now an accepted part of mainstream medicine, with its own professional journals and associations. Cosmetic-surgery clinics are sponsored by elite academic centers such as Stanford, Johns Hopkins, and the Mayo Clinic. Even . . .


Even before the sequencing of the human genome began in earnest, Americans started worrying about how information about their genetic makeup might be used in harmful ways, and policymakers began considering legislation to prevent misuses of genetic information. The Genetic Information Nondiscrimination Act, which would prohibit health insurers and employers from asking or requiring a person to take a genetic test and from using genetic information in setting insurance rates or making employment decisions, passed unanimously in the Senate in 2003 and again in 2005. The bill remained stalled in the House of Representatives, however, apparently because the House leadership . . .


Ferrara Café in Manhattan’s Little Italy is a century-old bakery steeped in tradition, but executive pastry chef Dennis Canciello has recently been tinkering with the recipes of two of the café’s signature pastries: cheesecake and cannoli. Like other cooks in the city’s restaurants, bakeries, and fast-food outlets, Canciello faces an impending deadline for conforming to an unusual mandate from the New York City Board of Health. Beginning July 1, 2007, most foods prepared in the city’s 22,000 restaurants will no longer be permitted to contain more than half a gram per serving of artificial trans fats — a type of . . .


In 2002, the government of the Netherlands explicitly legalized euthanasia and physician-assisted suicide. These controversial end-of-life practices had been openly tolerated and studied for many years before legalization, and Dutch physicians were expected to voluntarily report their participation in these acts, trusting that they would be acquitted of any legal wrongdoing provided that they had met the accepted criteria for “careful practice.” Not surprisingly, the reporting rates have increased since the law was passed — from 18% in 1990 to approximately 80% in 2005, as reported by van der Heide and colleagues in this issue of the Journal (pages 1957–1965). . . .
ARTICLES


In 2002, an act regulating the ending of life by a physician at the request of a patient with unbearable suffering came into effect in the Netherlands. In 2005, we performed a follow-up study of euthanasia, physician-assisted suicide, and other end-of-life practices. We mailed questionnaires to physicians attending 6860 deaths that were identified from death certificates. The response rate was 77.8%. In 2005, of all deaths in the Netherlands, 1.7% were the result of euthanasia and 0.1% were the result of physician-assisted suicide. These percentages were significantly lower than those in 2001, when 2.6% of all deaths resulted from euthanasia and 0.2% from assisted suicide. Of all deaths, 0.4% were the result of the ending of life without an explicit request by the patient. Continuous deep sedation was used in conjunction with possible hastening of death in 7.1% of all deaths in 2005, significantly increased from 5.6% in 2001. In 73.9% of all cases of euthanasia or assisted suicide in 2005, life was ended with the use of neuromuscular relaxants or barbiturates; opioids were used in 16.2% of cases. In 2005, 80.2% of all cases of euthanasia or assisted suicide were reported. Physicians were most likely to report their end-of-life practices if they considered them to be an act of euthanasia or assisted suicide, which was rarely true when opioids were used. The Dutch Euthanasia Act was followed by a modest decrease in the rates of euthanasia and physician-assisted suicide. The decrease may have resulted from the increased application of other end-of-life care interventions, such as palliative sedation.


Treatment guidelines recommend the use of inhaled corticosteroids in patients with asthma who have persistent symptoms and the “stepping down” of therapy to the minimum needed to maintain control of asthma. Whether patients with asthma that is well controlled with the use of inhaled corticosteroids twice daily can receive a step-down treatment with once-daily montelukast (our primary hypothesis) or once-daily fluticasone propionate plus salmeterol (our secondary hypothesis) has not yet been determined. We randomly assigned 500 patients with asthma that was well controlled by inhaled fluticasone (100 µg twice daily) to receive continued fluticasone (100 µg twice daily) (169 patients), montelukast (5 or 10 mg each night) (166 patients), or fluticasone (100 µg) plus salmeterol (50 µg) each night (165 patients). Treatment was administered for 16 weeks in a double-blind manner. The primary outcome was the time to treatment failure. Approximately 20% of patients assigned to receive continued fluticasone or switched to treatment with fluticasone plus salmeterol had treatment failure, as compared with 30.3% of subjects switched to montelukast. The hazard ratio for both comparisons was 1.6 (95% confidence interval, 1.1 to 2.6; P=0.03). The percentage of days on which patients were free of asthma symptoms (78.7 to 85.8%) was similar across the three groups. Patients with asthma that is well controlled with the use of twice-daily inhaled fluticasone can be switched to once-daily fluticasone plus salmeterol without increased rates of treatment failure. A switch to montelukast results in an increased rate of treatment failure and decreased asthma control; however, patients taking montelukast remained free of symptoms on 78.7% of treatment days.


Human papillomavirus types 16 (HPV-16) and 18 (HPV-18) cause approximately 70% of cervical cancers worldwide. A phase 3 trial was conducted to evaluate a quadrivalent vaccine against HPV types 6, 11, 16, and 18 (HPV-6/11/16/18) for the prevention of high-grade cervical lesions associated with HPV-16 and HPV-18. In this randomized, double-blind trial, we assigned 12,167 women between the ages of 15 and 26 years to receive three doses of either HPV-6/11/16/18 vaccine or placebo, administered at day 1, month 2, and month 6. The primary analysis was performed for a per-protocol susceptible population that included 5305 women in the vaccine group and 5260 in the placebo group who had no virologic evidence of infection with HPV-16 or HPV-18 through 1 month after the third dose (month 7). The primary composite end point was cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer.
related to HPV-16 or HPV-18. Subjects were followed for an average of 3 years after receiving the first dose of vaccine or placebo. Vaccine efficacy for the prevention of the primary composite end point was 98% (95.89% confidence interval [CI], 86 to 100) in the per-protocol susceptible population and 44% (95% CI, 26 to 58) in an intention-to-treat population of all women who had undergone randomization (those with or without previous infection). The estimated vaccine efficacy against all high-grade cervical lesions, regardless of causal HPV type, in this intention-to-treat population was 17% (95% CI, 1 to 31). In young women who had not been previously infected with HPV-16 or HPV-18, those in the vaccine group had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18 than did those in the placebo group.


The association between small size at birth and impaired glucose regulation later in life is well established in persons born at term. Preterm birth with very low birth weight (<1500 g) is also associated with insulin resistance in childhood. If insulin resistance persists into adulthood, preterm birth with very low birth weight also may be associated with an increased risk of disease in adulthood. We assessed glucose tolerance and insulin sensitivity and measured serum lipid levels and blood pressure in young adults with very low birth weight. We performed a standard 75-g oral glucose-tolerance test, measuring insulin and glucose concentrations at baseline and at 120 minutes in 163 young adults (age range, 18 to 27 years) with very low birth weight and in 169 subjects who had been born at term and were not small for gestational age. The two groups were similar with regard to age, sex, and birth hospital. We measured blood pressure and serum lipid levels, and in 150 very-low-birth-weight subjects and 136 subjects born at term, we also measured body composition by means of dual-energy x-ray absorptiometry. As compared with the subjects born at term, the very-low-birth-weight subjects had a 6.7% increase in the 2-hour glucose concentration (95% confidence interval [CI], 0.8 to 12.9), a 16.7% increase in the fasting insulin concentration (95% CI, 4.6 to 30.2), a 40.0% increase in the 2-hour insulin concentration (95% CI, 17.5 to 66.8), an 18.9% increase in the insulin-resistance index determined by homeostatic model assessment (95% CI, 5.7 to 33.7), and an increase of 4.8 mm Hg in systolic blood pressure (95% CI, 2.1 to 7.4). Adjustment for the lower lean body mass in the very-low-birth-weight subjects did not attenuate these relationships. Young adults with a very low birth weight have higher indexes of insulin resistance and glucose intolerance and higher blood pressure than those born at term.

REVIEW ARTICLES


Hypertension affects approximately 25% of the adult population worldwide, and its prevalence is predicted to increase by 60% by 2025, when a total of 1.56 billion people may be affected. It is the major risk factor for cardiovascular disease and is responsible for most deaths worldwide. Primary hypertension, also known as essential or idiopathic hypertension, accounts for as many as 95% of all cases of hypertension. Primary hypertension results from the interplay of internal derangements (primarily in the kidney) and the external environment. Sodium, the main extracellular cation, has long been considered the pivotal environmental factor in . . .


Classic preventive vaccines are designed to mimic the effects of natural exposure to microbes. They provide a high level of long-lasting protection against infection in the vast majority of recipients and serve as free-standing preventive measures. Although a classic preventive vaccine remains the ultimate goal of efforts to develop a vaccine for protection against the human immunodeficiency virus (HIV), the enormous genetic diversity and other unique features of the HIV envelope protein have thus far thwarted attempts to identify an effective candidate. However, we have learned from studies of HIV pathogenesis in humans and from animal models that a vaccine . . .

IMAGES IN CLINICAL MEDICINE


A healthy 70-year-old man presented with a 2-month history of painless swelling of his right upper and lower eyelids. The swelling had been treated with antibiotics, with no improvement. He had no
history of ocular trauma and felt well. On examination, there was rubbery, painless thickening of the right eyelids (Panel A) with associated right preauricular lymphadenopathy. There was full range of ocular movement, and the right globe was unremarkable. The patient was afebrile, and the levels of inflammatory markers and the results of other blood tests were normal. Computed tomography of the orbit showed preseptal thickening of the right . . .


A 51-year-old woman with a history of childhood asthma presented with a sensation of food impaction. Upper gastrointestinal endoscopy revealed classic “feline” esophagus, with mucosal rings (Panel A) and an esophageal stricture near the gastroesophageal junction. Biopsy specimens of the proximal and distal esophagus showed extensive mucosal eosinophilic infiltrates (Panel B, hematoxylin and eosin). The distal esophageal stricture was dilated with the use of a balloon dilator. The patient was treated with a fluticasone inhaler (four 220-µg puffs twice daily), with instructions to swallow and to rinse her mouth. During the next 2 months, her symptoms diminished, and the histologic . . .


A 15-year-old boy was receiving chemotherapy for osteogenic sarcoma of the left femur. A routine chest radiograph incidentally showed an azygous lobe of the lung (Panel A) with a thin fissure (arrows) separating it from the rest of the right upper lobe. As part of an evaluation for lung metastases, computed tomography of the chest was performed 2 weeks later (Panels B and C). In addition to the fissure (Panel B, white arrows) and the contrast-enhanced azygos vein (Panel C, asterisk), a small nodule, 1 cm in diameter (Panel B, black arrow) was seen in the posterior right upper lobe. . . .


A 44-year-old woman with a 20-year history of type 1 diabetes mellitus presented with progressive visual loss over a period of 3 months in both eyes. She had no prior eye examinations, and on examination at our hospital her corrected visual acuity was 20/400 in the right eye and 20/40 in the left eye. She reported arterial hypertension, heavy smoking, and foot ulcers. Dilated ophthalmoscopy, performed at the first visit (Panels A and B), and red-free photographs (Panels C and D) and fluorescein angiography (Panels E and F), performed a week later, revealed severe, bilateral proliferative diabetic retinopathy with significant . . .

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL


Dr. David T. Ting (Medicine): A 59-year-old man was admitted to this hospital because of fever as well as pain and swelling of both eyes, which was worse in the left, and the right ear. The patient had been well until 6 weeks before admission, when headache and fever developed; he saw his physician, who sent him to the emergency department of another hospital, where a diagnosis of a viral syndrome and sinusitis was made. A 5-day course of azithromycin was prescribed. Symptoms persisted, and neck pain and sinus congestion developed; the patient returned to the other hospital and was . . .

CLINICAL IMPLICATIONS OF BASIC RESEARCH


Three recent reports1,2,3 have shown that cancers in mice can be eliminated through the activation of a single gene, Tp53, which encodes the protein p53. The power of p53 with respect to killing cancer cells had been suspected for decades, but the elimination of malignant tumors by the activation of p53 had not been observed. The p53 protein is arguably the most important sensor of stress that mammals possess. Under normal, basal conditions, this protein is inconsequential, because of the rapidity of its degradation. But almost any type of stress, including damage to DNA . . .


A 20-year-old woman with asthma was taken to the emergency room of another hospital because of cardiorespiratory arrest. The patient had had severe asthma since childhood. She was born after a normal pregnancy and delivery to a
teenaged, single mother, who smoked three packs of cigarettes per day during pregnancy and during the patient’s childhood. Asthma developed at the age of 4 years, and exacerbations occurred frequently thereafter, triggered by cold air, hot humid air, physical activity, respiratory infections, anxiety, and exposures to paint and to cats and birds that were kept in her home or the homes of relatives. . . .

**CLINICAL PRACTICE**


This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations. A 62-year-old woman noted an unpleasant, sweet taste in her mouth. She otherwise felt well and was taking no medications. Because dysgeusia is a rare manifestation of hyponatremia, her serum sodium level was tested and was 122 mmol per liter. The serum osmolality was 250 mOsm per kilogram of water, the urinary osmolality 635 mOsm per kilogram of water, the urinary sodium . . .