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Senator Orrin Hatch (R-UT) urged President George W. Bush to sign the bill into law, in order to facilitate the advancement of the promising field of embryonic stem-cell research. In this audio interview conducted by Rachel Gotbaum, Senator Hatch discusses his support, the opposition by President Bush and other Republicans, and the future of U.S. . . .


In this issue of the Journal, Friis-Møller and colleagues (pages 1723–1735) report on results from a prospective observational study involving more than 23,000 patients infected with HIV. The study, called the Data Collection on Adverse Effects of Anti-HIV Drugs (DAD) trial, identified a possible increased risk of myocardial infarction associated with exposure to protease inhibitors but not to nonnucleoside reverse-transcriptase inhibitors. Because randomized studies are rarely well powered for evaluating adverse effects of treatment, well-designed observational studies are important. I However, such studies raise complex questions concerning both the potential confounding of risk associations and the mechanisms by which treatment . . .


During the 1950s, inmates at what was then called Holmesburg Prison, in Philadelphia, were inoculated with condylooma acuminatum, cutaneous moniliasis, and viruses causing rashes, peeling, and blisters on the scrotum as well as sexual difficulties. 2 Hundreds of such experiments induced . . .


Every 5 or 10 years, Congress enacts major legislation addressing pressing issues at the Food and Drug Administration (FDA). This year, the biggest reforms since at least 1997 are expected. A decade ago, reform was motivated by the perception that the agency wasn’t getting new medicines to patients as efficiently as possible. Today, a leading concern is that it isn’t protecting the public from drugs’ risks as effectively as it might. A key incident in raising such concern was the 2004 withdrawal by Merck of rofecoxib (Vioxx) because of an apparent increased risk of serious cardiovascular events. The withdrawal came . . .

PERSPECTIVES

(Since these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


Years ago, an administrator at a community hospital explained to me how well his institution’s grand-rounds program worked. “The drug companies find the speakers, pay their honoraria, and provide free food for the doctors, which helps a lot with attendance,” he said. “It works well for us, especially with our budgets so tight.” Yet those lunches were actually quite costly for the hospital: attendees at such events predictably go on to prescribe the products promoted there — which is precisely why the drug companies so willingly pay for these programs. This penetration of commerce into the province of science isn’t . . .


Mitochondria are subcellular organelles that coordinate numerous metabolic reactions, including those of the respiratory complexes that produce the ATP that powers cellular reactions. They have often been depicted as static, with a kidney-bean shape, but there is a growing appreciation of their dynamic nature.1,2 Moreover, they are strikingly varied in structure, ranging from small, spherical particles to long, interconnected filaments. Mitochondria are also highly motile and constantly move in a directed manner along cytoskeletal tracks within cells. An individual mitochondrion is not an autonomous organelle. The hundreds of mitochondria within a typical cell undergo continual cycles of . . .


Last December in Wuhan, China, two middle-aged rural women who had become infected with HIV in the 1990s struggled to describe to foreign visitors how China’s new HIV-treatment program had changed their lives. Suddenly, they said, had been too sick to get out of bed, and the girl had left school to help at home and on the farm. But when the HIV-treatment program had changed their lives. Suddenly, they said, had been too sick to get out of bed, and the girl had left school to help at home and on the farm. But when the . . .


On Wednesday, April 11, 2007, the U.S. Senate passed a bill that would loosen restrictions on federal funding of human embryonic stem-cell research. Entitled the Stem Cell Research Enhancement Act of 2007, the bill was supported by 63 senators, including 17 Republicans. During floor debate, Senator Orrin Hatch (R-UT) urged President George W. Bush to sign the bill into law, in order to facilitate the advancement of the promising field of embryonic stem-cell research. In this audio interview conducted by Rachel Gotbaum, Senator Hatch discusses his support, the opposition by President Bush and other Republicans, and the future of U.S. . . .
to the evolving understanding of risks and benefits of drugs.” So claims the September 2006 Institute of Medicine (IOM) report entitled The Future of Drug Safety, which paints a dismal picture of the U.S. system for ensuring the safety of drugs after they have been approved by the Food and Drug Administration (FDA).1 Among the more easily remediable shortcomings identified by the IOM are the severe underfunding of the FDA, the particularly poor funding for postapproval monitoring of safety, and the “troubling . . .

ARTICLES


A single infusion of intravenous zoledronic acid decreases bone turnover and improves bone density at 12 months in postmenopausal women with osteoporosis. We assessed the effects of annual infusions of zoledronic acid on fracture risk during a 3-year period. In this double-blind, placebo-controlled trial, 3889 patients (mean age, 73 years) were randomly assigned to receive a single 15-minute infusion of zoledronic acid (5 mg) and 3876 were assigned to receive placebo at baseline, at 12 months, and at 24 months; the patients were followed until 36 months. Primary end points were new vertebral fracture (in patients not taking concomitant osteoporosis medications) and hip fracture (in all patients). Secondary end points included bone mineral density, bone turnover markers, and safety outcomes. Treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% during a 3-year period, as compared with placebo (3.3% in the zoledronic-acid group vs. 10.9% in the placebo group; relative risk, 0.30; 95% confidence interval [CI], 0.24 to 0.38) and reduced the risk of hip fracture by 41% (1.4% in the zoledronic-acid group vs. 2.5% in the placebo group; hazard ratio, 0.59; 95% CI, 0.42 to 0.83). Nonvertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively (P<0.001 for all comparisons). Zoledronic acid was also associated with a significant improvement in bone mineral density and bone metabolism markers. Adverse events, including change in renal function, were similar in the two study groups. However, serious atrial fibrillation occurred more frequently in the zoledronic acid group (in 50 vs. 20 patients, P<0.001). A once-yearly infusion of zoledronic acid during a 3-year period significantly reduced the risk of vertebral, hip, and other fractures.


Undescended testis, which is a risk factor for testicular cancer, is usually treated surgically, but whether the age at treatment has any effect on the risk is unclear. We studied the relation between the age at treatment for undescended testis and the risk of testicular cancer. We identified men who underwent orchiopexy for undescended testis in Sweden between 1964 and 1999. Cohort subjects were identified in the Swedish Hospital Discharge Register and followed for the occurrence of testicular cancer through the Swedish Cancer Registry. Vital statistics and data on migration status were taken from the Register of Population and Population Changes for the years 1965 through 2000. We estimated the relative risk of testicular cancer using Poisson regression of standardized incidence ratios, comparing the risk in the cohort with that in the general population. We also analyzed the data by means of Cox regression, using internal comparison groups. The cohort consisted of 16,983 men who were surgically treated for undescended testis and followed for a total of 209,984 person-years. We identified 56 cases of testicular cancer during follow-up. The relative risk of testicular cancer among those who underwent orchiopexy before reaching 13 years of age was 2.23 (95% confidence interval [CI], 1.58 to 3.06), as compared with the Swedish general population; for those treated at 13 years of age or older, the relative risk was 5.40 (95% CI, 3.20 to 8.53). The effect of age at orchiopexy on the risk of testicular cancer was similar in comparisons within the cohort. Treatment for undescended testis before puberty decreases the risk of testicular cancer.


Episodes of depression are the most frequent cause of disability among patients with bipolar disorder. The effectiveness and safety of standard antidepressant agents for depressive episodes associated with bipolar disorder (bipolar depression) have not been well studied. Our study was designed to determine whether adjunctive antidepressant therapy reduces symptoms of bipolar depression without increasing the risk of mania. In this double-blind, placebo-controlled study, we randomly assigned subjects with bipolar depression to receive up to 26 weeks of treatment with a mood stabilizer plus adjunctive antidepressant therapy or a mood stabilizer plus matching placebo, under conditions generalizable to routine clinical care. A standardized clinical monitoring form adapted from the mood-disorder modules of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, was used at all follow-up visits. The primary outcome was the percentage of subjects in each treatment group meeting the criterion for a durable recovery (8 consecutive weeks of euthymia). Secondary effectiveness outcomes and rates of treatment-emergent affective switch (a switch to mania or
We have previously demonstrated an association between reperfusion but not long-term left ventricular size or function. In our pilot trial, the evidence of a difference between the two study groups in landmark) at 2 days. At 6 months, however, there was no evidence of such an association for nonnucleoside reverse-transcriptase inhibitors with the risk of myocardial infarction. We analyzed data collected through February 2005 from our prospective observational study of 23,437 patients infected with the human immunodeficiency virus. The incidence rates of myocardial infarction during the follow-up period were calculated, and the associations between myocardial infarction and exposure to protease Three hundred forty-five patients had a myocardial infarction during 94,469 person-years of observation. The incidence of myocardial infarction increased from 1.53 per 1000 person-years in those not exposed to protease inhibitors to 6.01 per 1000 person-years in those exposed to protease inhibitors for more than 6 years. After adjustment for exposure to the other drug class and established cardiovascular risk factors (excluding lipid levels), the relative rate of myocardial infarction per year of protease-inhibitor exposure was 1.16 (95% confidence interval [CI], 1.10 to 1.23), whereas the relative rate per year of exposure to nonnucleoside reverse-transcriptase inhibitors was 1.05 (95% CI, 0.98 to 1.13). Adjustment for serum lipid levels further reduced the effect of exposure to each drug class to 1.10 (95% CI, 1.04 to 1.18) and 1.00 (95% CI, 0.93 to 1.09), respectively. Increased exposure to protease inhibitors is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidemia. We found no evidence of such an association for nonnucleoside reverse-transcriptase inhibitors; however, the number of person-years of observation for exposure to this class of drug was less than that for exposure to protease inhibitors.


Long-standing concern about the effects of type 1 diabetes on cognitive ability has increased with the use of therapies designed to bring glucose levels close to the nondiabetic range and the attendant increased risk of severe hypoglycemia. A total of 1144 patients with type 1 diabetes enrolled in the Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study were examined on entry to the DCCT (at mean age 27 years) and a mean of 18 years later with the same comprehensive battery of cognitive tests. Glycated hemoglobin levels were measured and the frequency of severe hypoglycemic events leading to coma or seizures was recorded during the follow-up period. We assessed the effects of original DCCT-treatment-group assignment, mean glycated hemoglobin values, and frequency of hypoglycemic events on measures of cognitive ability, with adjustment for age at baseline, sex, years of education, length of follow-up, visual acuity, self-reported sensory loss due to peripheral neuropathy, and (to control for the effects of practice) the number of cognitive tests taken in the interval since the start of the DCCT. Forty percent of the cohort reported having had at least one hypoglycemic coma or hypomania early in the course of treatment) were also examined. Forty-two of the 179 subjects (23.5%) receiving a mood stabilizer plus adjunctive antidepressant therapy had a durable recovery, as did 51 of the 187 subjects (27.3%) receiving a mood stabilizer plus a matching placebo (P=0.40). Modest nonsignificant trends favoring the group receiving a mood stabilizer plus placebo were observed across the secondary outcomes. Rates of treatment-emergent affective switch were similar in the two groups. The use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch.


Microvascular perfusion is often impaired after primary percutaneous coronary intervention (PCI). We proposed that in situ thrombosis might contribute to poor myocardial perfusion in this setting. To test this hypothesis, we evaluated the effect of low-dose intracoronary streptokinase administered immediately after primary PCI. Forty-one patients undergoing primary PCI were randomly assigned to receive intracoronary streptokinase (250 kU) or no additional therapy. Two days later, cardiac catheterization was repeated, and coronary hemodynamic end points were measured with the use of a guidewire tipped with pressure and temperature sensors. In patients with anterior myocardial infarction, the deceleration time of coronary diastolic flow was measured with transthoracic echocardiography. At 6 months, angiography, echocardiography, and technetium-99m single-photon-emission computed tomography were performed. Two days after PCI, all measures of microvascular function (means ±SD) were significantly better in the streptokinase group than in the control group, including coronary flow reserve (2.01±0.57 vs. 1.39±0.31), the index of microvascular resistance (16.29±5.06 U vs. 32.49±11.04 U), the collateral-flow index (0.08±0.05 vs. 0.17±0.07), mean coronary wedge pressure (10.81±5.46 mm Hg vs. 17.20±7.93 mm Hg), systolic coronary wedge pressure (18.24±6.07 mm Hg vs. 33.80±11.00 mm Hg), and diastolic deceleration time (828±258 msec vs. 360±292 msec). The administration of intracoronary streptokinase was also associated with a significantly lower corrected Thrombolysis in Myocardial Infarction frame count (the number of cine frames required for dye to travel from the ostium of a coronary artery to a standardized distal coronary landmark) at 2 days. At 6 months, however, there was no evidence of a difference between the two study groups in left ventricular size or function. In our pilot trial, the administration of low-dose intracoronary streptokinase immediately after primary PCI improved myocardial reperfusion but not long-term left ventricular size or function.


We have previously demonstrated an association between combination antiretroviral therapy and the risk of myocardial infarction. It is not clear whether this association differs according to the class of antiretroviral drugs. We conducted a study to investigate the association of cumulative exposure to protease inhibitors and nonnucleoside reverse-transcriptase inhibitors with the risk of myocardial infarction. We analyzed data collected through February 2005 from our prospective observational study of 23,437 patients infected with the human immunodeficiency virus. The incidence rates of myocardial infarction during the follow-up period were calculated, and the associations between myocardial infarction and exposure to protease Three hundred forty-five patients had a myocardial infarction during 94,469 person-years of observation. The incidence of myocardial infarction increased from 1.53 per 1000 person-years in those not exposed to protease inhibitors to 6.01 per 1000 person-years in those exposed to protease inhibitors for more than 6 years. After adjustment for exposure to the other drug class and established cardiovascular risk factors (excluding lipid levels), the relative rate of myocardial infarction per year of protease-inhibitor exposure was 1.16 (95% confidence interval [CI], 1.10 to 1.23), whereas the relative rate per year of exposure to nonnucleoside reverse-transcriptase inhibitors was 1.05 (95% CI, 0.98 to 1.13). Adjustment for serum lipid levels further reduced the effect of exposure to each drug class to 1.10 (95% CI, 1.04 to 1.18) and 1.00 (95% CI, 0.93 to 1.09), respectively. Increased exposure to protease inhibitors is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidemia. We found no evidence of such an association for nonnucleoside reverse-transcriptase inhibitors; however, the number of person-years of observation for exposure to this class of drug was less than that for exposure to protease inhibitors.
seizure. Neither frequency of severe hypoglycemia nor previous treatment-group assignment was associated with decline in any cognitive domain. Higher glycated hemoglobin values were associated with moderate declines in motor speed (P=0.001) and psychomotor efficiency (P<0.001), but no other cognitive domain was affected. No evidence of substantial long-term declines in cognitive function was found in a large group of patients with type 1 diabetes who were carefully followed for an average of 18 years, despite relatively high rates of recurrent severe hypoglycemia.


We report on a newborn girl with microcephaly, abnormal brain development, optic atrophy and hypoplasia, persistent lactic acidemia, and a mildly elevated plasma concentration of very-long-chain fatty acids. We found a defect of the fission of both mitochondria and peroxisomes, as well as a heterozygous, dominant-negative mutation in the dynamin-like protein 1 gene (DLP1). The DLP1 protein has previously been implicated, in vitro, in the fission of both these organelles. Overexpression of the mutant DLP1 in control cells reproduced the fission defect. Our findings are representative of a class of disease characterized by defects in both mitochondria and peroxisomes.

**SPECIAL ARTICLES**


Relationships between physicians and pharmaceutical, medical device, and other medically related industries have received considerable attention in recent years. We surveyed physicians to collect information about their financial associations with industry and the factors that predict those associations. We conducted a national survey of 3167 physicians in six specialties (anesthesiology, cardiology, family practice, general surgery, internal medicine, and pediatrics) in late 2003 and early 2004. The raw response rate for this probability sample was 52%, and the weighted response rate was 58%. Most physicians (94%) reported some type of relationship with the pharmaceutical industry and the factors that predict those associations. We examined this growth with respect to the quantity and mix of services, revisions in the valuation of RVUs, and new service codes. Between 1992 and 2002, the volume of physicians’ work per Medicare beneficiary grew by 50%, and the total RVUs per Medicare beneficiary grew by 45%. The quantity and mix of services were the largest sources of growth, increasing by 19% for RVUs for physicians’ work and by 22% for total RVUs. Our findings varied among services and specialties. Revised valuation of RVUs was a key source of the growth in RVUs for physicians’ work and total RVUs for evaluation and management and for tests. New service codes were the largest drivers of growth for major procedures (accounting for 36% of the growth in the total RVUs). The increase in RVUs was greatest in cardiology (114%) and gastroenterology (72%). The total growth in RVUs was greatest in cardiology (99%) and dermatology (105%). In the first 10 years after the implementation of the resource-based relative-value scale, RVUs per Medicare beneficiary grew substantially. The leading sources of growth varied among service types and specialties. An understanding of these sources of growth can inform policies to control Medicare spending.

CLINICAL THERAPEUTICS

(Since these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy
follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author’s clinical recommendations. During an evaluation by his internist, a 48-year-old man reports that his wife tells him that he snores loudly. Further questioning reveals that he has been falling asleep whenever sedentary. His physical examination is notable for truncal obesity (body-mass . . .

**CLINICAL PRACTICE**

*(Since these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)*


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 58-year-old man presents with a 2-week history of progressive dyspnea on exertion, neck swelling, decreased appetite, and fatigue. There is no history of syncope or dysphagia. He smoked cigarettes until 5 years ago. The physical examination reveals a heart rate of 105 beats per minute, a respiratory rate of 20 breaths per minute, and superficial vascular distention over the neck, chest, . . .

**VIDEOS IN CLINICAL MEDICINE**

*(Since these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)*


Emergency orotracheal intubation is indicated in any situation in which definitive control of the airway is needed. Specific indications include cardiac or respiratory arrest, failure to protect the airway from aspiration, inadequate oxygenation or ventilation, and impending or existing airway obstruction. Orotracheal intubation is also commonly performed as part of the care of the critically ill patient with multisystem disease or injuries, and to facilitate control of the airway during surgical procedures requiring general anesthesia.

**IMAGES IN CLINICAL MEDICINE**

*(Since these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)*


67-year-old man receiving hemodialysis because of kidney failure resulting from renovascular disease was admitted to the hospital for revision of dialysis access. Six months earlier, a dual-chamber, permanent pacemaker had been implanted in the right side of the chest for the treatment of complete heart block. The dialysis catheter, inserted into the left internal jugular vein under fluoroscopic guidance, showed a left superior vena cava draining into the right atrium through a coronary sinus.


A 68-year-old man with hypertension presented with vague abdominal pain. Ultrasonography of the abdomen showed a renal mass in the left kidney. A computed tomographic scan of the abdomen showed a mass consistent with a renal-cell carcinoma in the upper pole of the left kidney (arrowhead) and a duplication of the inferior vena cava (arrow). The aorta, which has calcifications, can be seen between the duplicate inferior vena cavae. The inferior vena cava is formed between weeks 6 and 10 of gestation. Duplication occurs in 0.2 to 3.0% of the general population. The infrarenal portion of the inferior vena cava . . .


A 50-year-old man presented for a routine physical examination for the first time in 10 years. He reported having had no recent health problems. He had a 60 pack-year smoking history and did not drink alcohol. During the examination, a painless, firm mass was found on the hard palate. The remainder of the examination was unremarkable. The patient reported that this lesion had been present and without change since childhood. A torus palatinus, a benign overgrowth of bone, was diagnosed. Approximately 20% of the population has at least a small torus palatinus, which often goes unnoticed until middle age.


A 20-year-old man, who had long-standing end-stage renal disease and was receiving peritoneal dialysis, presented with fever and abdominal pain. The patient began peritoneal dialysis at the age of 4 years because of a nephropathy of uncertain origin and subsequently underwent a renal transplantation, which failed. He had hypertension, had had multiple previous episodes of peritonitis, and had undergone a partial parathyroidectomy. Extensive calcifications were noted on radiographic evaluation, including increased opacification of the pulmonary interstitium on chest radiography (Panel A). Extensive calcification within the interstitium on computed tomography (CT) of the chest (Panel B), and extensive peritoneal calcifications on . . .

**CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL**


A 46-year-old woman came to the Center for Cancer Risk Analysis at the Cancer Center of this hospital because of recent diagnoses of endometrial, ovarian, and colonic cancers. Fifteen
weeks earlier, a routine Papanicolaou smear showed an atypical glandular cell, and she was referred to a gynecologist at this hospital. Fifteen years earlier, the patient had had abnormal findings on a Pap smear performed elsewhere; the uterine cervix was treated with cryotherapy. Over the next 14 years, repeated Papanicolaou smears were normal. She had had four early miscarriages at 6 to 8 weeks’ gestation. Her menses were normal and regular. . . .

CLINICAL PROBLEM-SOLVING


In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows. A 55-year-old male physician was seen in August because of a 1-week history of fever and night sweats. The night sweats required at least one nightly change of his pajamas and pillowcase. The patient also noted a persistent cough, which had previously been ascribed to esophageal reflux. There was no sputum production, photophobia, rash, arthralgia, dysuria, or change in bowel function.