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PERSPECTIVES
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It seemed impossible at first. But in 2004, Ireland made history as the first country to implement a comprehensive smoking ban in indoor workplaces, including restaurants and bars. Defying dire predictions, Ireland’s policy has proved to be both popular and enforceable, with ready compliance,1 no decline in business, and improved health outcomes for hospitality workers. Overwhelming public support for the ban has come from smokers and nonsmokers alike, dispelling the belief that restaurants and bars should represent bastions of smoking and socialization. For a country traditionally known for its smoke-filled pubs, the new societal standard represents a breathtaking…


Three years ago, the Food and Drug Administration (FDA) approved the drug Ketek (telithromycin), lauding it as the first of a new class of antimicrobial agents that circumvent antibiotic resistance. Since then, Ketek has been linked to dozens of cases of severe liver injury, been the subject of a series of increasingly urgent safety warnings, and sparked two Congressional investigations of the FDA’s acceptance of fraudulent safety data and inappropriate trial methods when it reviewed the drug for approval. As a former FDA physician who was involved in the Ketek review, I believe there are lessons to be learned …


In the simplest terms, diabetes mellitus results when pancreatic beta cells are unable to maintain adequate insulin secretion to prevent hyperglycemia. A combination of genetic and environmental factors causes the underlying beta-cell failure. In type 1 diabetes, a T-cell–mediated autoimmune response against beta cells appears to be the main disease mechanism, whereas insulin resistance is the key metabolic abnormality in type 2 diabetes. Yet the way in which insulin resistance triggers beta-cell failure remains obscure. The report by Larsen et al. in this issue of the Journal (pages 1517–1526) provides insight into a shared mechanism of beta-cell dysfunction in type …


The vagus-nerve stimulator (VNS), a device that is implanted by a neurosurgeon and sends intermittent electrical pulses to the brain, has been marketed in the United States since 1997 as an adjunctive therapy for the control of epilepsy. Debate is ongoing, however, over the use of the device in patients with refractory depression. Though the key clinical questions (Does it work? Is it safe?) seem straightforward, answering them is proving rather complicated. The Food and Drug Administration (FDA) approved the use of the VNS for depression in 2005, but in February 2007, the Centers for Medicare and Medicaid Services …


During the past 20 years, as smoking rates have fallen in high-income countries, the tobacco industry has found new and bigger markets in the developing world. One third of current smokers live in China — more than in the United States and all European countries combined. The World Health Organization (WHO) predicts that 70% of the deaths from smoking-related illnesses will occur in low- and middle-income countries by 2020. Smoking is likely to have a particularly devastating effect on China, where the annual death toll from smoking-related diseases already exceeds 1 million — 2.5 times that in the United States…

ORIGINAL ARTICLES


Disrupted binding of the transcription factor Sp1 to the mutated promoter region of the mannosyl transferase--encoding gene PIGM causes inherited glycosylphosphatidylinositol (GPI) deficiency characterized by splanchnic vein thrombosis and epilepsy. We show that this results in histone hypoacetylation at the promoter of PIGM. The histone deacetylase inhibitor butyrate increases PIGM transcription and surface GPI expression in vitro as well as in vivo through enhanced histone acetylation in an Sp1-dependent manner. More important, the drug caused complete cessation of intractable seizures in a child with inherited GPI deficiency.


In patients with stable coronary artery disease, it remains unclear whether an initial management strategy of percutaneous coronary intervention (PCI) with intensive pharmacologic therapy and lifestyle intervention (optimal medical therapy) is superior to optimal medical therapy alone in reducing the risk
of cardiovascular events. We conducted a randomized trial involving 2287 patients who had objective evidence of myocardial ischemia and significant coronary artery disease at 50 U.S. and Canadian centers. Between 1999 and 2004, we assigned 1149 patients to undergo PCI with optimal medical therapy (PCI group) and 1138 to receive optimal medical therapy alone (medical-therapy group). The primary outcome was death from any cause and nonfatal myocardial infarction during a follow-up period of 2.5 to 7.0 years (median, 4.6). There were 211 primary events in the PCI group and 202 events in the medical-therapy group. The 4.6-year cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (hazard ratio for the PCI group, 1.05; 95% confidence interval [CI], 0.87 to 1.27; P=0.62). There were no significant differences between the PCI group and the medical-therapy group in the composite of death, myocardial infarction, and stroke (20.0% vs. 19.5%; hazard ratio, 1.05; 95% CI, 0.87 to 1.27; P=0.62); hospitalization for acute coronary syndrome (12.4% vs. 11.8%; hazard ratio, 1.07; 95% CI, 0.84 to 1.37; P=0.56); or myocardial infarction (13.2% vs. 12.3%; hazard ratio, 1.13; 95% CI, 0.89 to 1.43; P=0.33). As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy.


Torcetrapib, an inhibitor of cholesteryl ester transfer protein, may reduce atherosclerotic vascular disease by increasing levels of high-density lipoprotein (HDL) cholesterol. A total of 850 patients with heterozygous familial hypercholesterolemia underwent B-mode ultrasonography at baseline and at follow-up to measure changes in carotid intima–media thickness. The patients completed an atorvastatin run-in period and were subsequently randomly assigned to receive either atorvastatin monotherapy or atorvastatin combined with 60 mg of torcetrapib for 2 years. After 24 months, in the atorvastatin–only group, the mean (±SD) HDL cholesterol level was 52.4±13.5 mg per deciliter and the mean low-density lipoprotein (LDL) cholesterol level was 143.2±42.2 mg per deciliter, as compared with 81.5±22.6 mg per deciliter and 115.1±48.5 mg per deciliter, respectively, in the torcetrapib–atorvastatin group. During the study, average systolic blood pressure increased by 2.8 mm Hg in the torcetrapib–atorvastatin group, as compared with the atorvastatin–only group. The increase in maximum carotid intima–media thickness, the primary measure of efficacy, was 0.0053±0.0028 mm per year in the atorvastatin–only group and 0.0047±0.0028 mm per year in the torcetrapib–atorvastatin group (P=0.87). The secondary efficacy measure, annualized change in mean carotid intima–media thickness for the common carotid artery, indicated a decrease of 0.0014 mm per year in the atorvastatin–only group, as compared with an increase of 0.0038 mm per year in the torcetrapib–atorvastatin group (P=0.005). In patients with familial hypercholesterolemia, the use of torcetrapib with atorvastatin, as compared with atorvastatin alone, did not result in further reduction of progression of atherosclerosis, as assessed by a combined measure of carotid arterial-wall thickness, and was associated with progression of disease in the common carotid segment. These effects occurred despite a large increase in HDL cholesterol levels and a substantial decrease in levels of LDL cholesterol and triglycerides.


There is no community standard for the treatment of glioblastoma in patients 70 years of age or older. We conducted a randomized trial that compared radiotherapy and supportive care with supportive care alone in such patients. Patients 70 years of age or older with a newly diagnosed anaplastic astrocytoma or glioblastoma and a Karnofsky performance score of 70 or higher were randomly assigned to receive supportive care only or supportive care plus radiotherapy (focal radiation in daily fractions of 1.8 Gy given 5 days per week, for a total dose of 50 Gy). The primary end point was overall survival; secondary end points were progression-free survival, tolerance of radiotherapy, health-related quality of life, and cognition. We randomly assigned 85 patients from 10 centers to receive either radiotherapy and supportive care or supportive care alone. The trial was discontinued at the first interim analysis, which showed that with a preset boundary of efficacy, radiotherapy and supportive care were superior to supportive care alone. A final analysis was carried out for the 81 patients with glioblastoma (median age, 73 years; range, 70 to 85). At a median follow-up of 21 weeks, the median survival for the 39 patients who received radiotherapy plus supportive care was 29.1 weeks, as compared with 16.9 weeks for the 42 patients who received supportive care alone. The hazard ratio for death in the radiotherapy group was 0.47 (95% confidence interval, 0.29 to 0.76; P=0.002). There were no severe adverse events related to radiotherapy. The results of quality-of-life and cognitive evaluations over time did not differ significantly between the treatment groups. Radiotherapy results in a modest improvement in survival, without reducing the quality of life or cognition, in elderly patients with glioblastoma.

The body-mass index were similar in the two study groups. Insulin resistance, insulin-regulated gene expression in skeletal muscle, serum adipokine levels, and C-peptide secretion was enhanced (P=0.05), and there were percentage point lower than in the placebo group (P=0.03); in the anakinra group, the glycated hemoglobin level was 0.46 lower in the restrictive-strategy group than in the liberal-strategy group. Hemoglobin concentrations were maintained at a mean (±SD) level that was 2.1±0.2 g per deciliter lower in the restrictive-strategy group than in the liberal-strategy group (lowest average levels, 8.7±0.4 and 10.8±0.5 g per deciliter, respectively; P<0.001). Patients in the restrictive-strategy group received 44% fewer transfusions; 174 patients (54%) in that group did not receive any transfusions, as compared with 7 patients (2%) in the liberal-strategy group (P<0.001). New or progressive multiple-organ dysfunction syndrome (the primary outcome) developed in 38 patients in the restrictive-strategy group, as compared with 39 in the liberal-strategy group (12% in both groups) (absolute risk reduction with the restrictive strategy, 0.4%; 95% confidence interval, –4.6 to 5.4). There were 14 deaths in each group within 28 days after randomization. No significant differences were found in other outcomes, including adverse events. In stable, critically ill children a hemoglobin threshold of 7 g per deciliter for red-cell transfusion can decrease transfusion requirements without increasing adverse outcomes.


In this double-blind, parallel-group trial involving 70 patients with type 2 diabetes, we randomly assigned 34 patients to receive 100 mg of anakinra (a recombinant human interleukin-1–receptor antagonist) subcutaneously once daily for 13 weeks and 36 patients to receive placebo. At baseline and at 13 weeks, all patients underwent an oral glucose-tolerance test, followed by an intravenous bolus of 0.3 g of glucose per kilogram of body weight, 0.5 mg of glucagon, and 5 g of arginine. In addition, 35 patients underwent a hyperinsulinemic–euglycemic clamp study. The primary end point was a change in the level of glycated hemoglobin, and secondary end points were changes in beta-cell function, insulin sensitivity, and inflammatory markers. At 13 weeks, in the anakinra group, the glycated hemoglobin level was 0.46 percentage point lower than in the placebo group (P=0.03); C-peptide secretion was enhanced (P=0.05), and there were reductions in the ratio of proinsulin to insulin (P=0.005) and in levels of interleukin-6 (P<0.001) and C-reactive protein (P=0.002). Insulin resistance, insulin-regulated gene expression in skeletal muscle, serum adipokine levels, and the body-mass index were similar in the two study groups. Symptomatic hypoglycemia was not observed, and there were no apparent drug-related serious adverse events. The blockade of interleukin-1 with anakinra improved glycemia and beta-cell secretory function and reduced markers of systemic inflammation.


A neutral gastric pH is critical for the stability of clots over bleeding arteries. We investigated the effect of preemptive infusion of omeprazole before endoscopy on the need for endoscopic therapy. Consecutive patients admitted with upper gastrointestinal bleeding underwent stabilization and were then randomly assigned to receive either omeprazole or placebo (each as an 80-mg intravenous bolus followed by an 8-mg infusion per hour) before endoscopy the next morning. Over a 17-month period, 638 patients were enrolled and randomly assigned to omeprazole or placebo (319 in each group). The need for endoscopic treatment was lower in the omeprazole group than in the placebo group (60 of the 314 patients included in the analysis [19.1%] vs. 90 of 317 patients [28.4%], P=0.007). There were no significant differences between the omeprazole group and the placebo group in the mean amount of blood transfused (1.54 and 1.88 units, respectively; P=0.12). Sixty-three patients underwent emergency surgery (3 and 4, P=1.00), or who died within 30 days (8 and 7, P=0.78). The hospital stay was less than 3 days in 60.5% of patients in the omeprazole group, as compared with 49.2% in the placebo group (P=0.005). On endoscopy, fewer patients in the omeprazole group had actively bleeding ulcers (12 of 187, vs. 28 of 190 in the placebo group; P=0.01) and more omeprazole-treated patients had ulcers with clean bases (120 vs. 90, P=0.001). Infusion of high-dose omeprazole before endoscopy accelerated the resolution of signs of bleeding in ulcers and reduced the need for endoscopic therapy.


After poliomyelitis has been eradicated, access to live polioviruses will be highly restricted and the use of oral poliovirus vaccine (OPV) will probably be discontinued. Countries using OPV must decide whether to switch to inactivated poliovirus vaccine (IPV) or stop polio vaccination. Because data on the immunogenicity of IPV in tropical developing countries are limited, we conducted a randomized, controlled trial of IPV in Cuba. The study population consisted of healthy infants born in Havana. A total of 166 infants were randomly assigned to two groups. Group A received a combination of the diphtheria–pertussis–tetanus (DPT) vaccine, the Haemophilus influenzae type b (Hib) vaccine, and IPV (DPT-Hib-IPV) at 6, 10, and 14 weeks of age. Group B, the
An 83-year-old healthy woman was admitted with episodes of
incontinence. There is no history of gastrointestinal or rectal surgery
has occasional urinary incontinence when she coughs or
precipitates an episode, and she wears absorbent pads. She
incontinence. Because of embarrassment, she has curtailed her
occurrence and professional activities. Physical activity often
precipitates an episode, and she wears absorbent pads. She
has occasional urinary incontinence when she coughs or
sneezes. There is no history of gastrointestinal or rectal surgery
and no neurologic symptoms. Physical examination reveals . . .

REVIEW ARTICLES


The liver possesses the unique ability to regenerate within a short period.1,2,3 This feature has led to the development of innovative strategies in liver surgery and transplantation. The anatomy of the liver is paramount in considering advances in hepatic surgery. The liver is divided into segments (Figure 1). In healthy adults, the liver weighs about 1.5 kg (3.3 lb).4 The blood supply of the liver is carried through two major vessels, the hepatic artery and the portal vein. The portal vein carries a large volume of venous blood to the liver . . .

IMAGES IN CLINICAL MEDICINE


An 83-year-old healthy woman was admitted with episodes of
nausea and vertigo that had increased in frequency over
several months. Many of the episodes involved brief periods of unresponsiveness and staring spells. She did not report a
history of seizures, head trauma, headache, or vestibular
disease. The neurologic examination did not reveal papilledema or any other abnormalities. Computed
tomography of the head showed a large (5 by 5 cm), well
circumscribed, and highly calcified extra-axial mass overlying the right temporal lobe. Electroencephalography showed mild slowng and occasional sharp waves in the right temporal area. A diagnosis of temporal-lobse seizures due to . . .


A 32-year-old healthy woman, gravida 6 with two living children, presented at our clinic for the termination of pregnancy at 18 weeks of gestation. Her only previous abdominal surgeries had been two cesarean sections. The physical examination showed a gravid uterus; the rectus sheath was deficient in the midline infraumbilical area, a finding consistent with an incisional hernia. This defect had been present since the patient’s last cesarean section 2 years earlier. A medical termination of the pregnancy was performed with the use of a 0.1% solution of ethacridine lactate, which was instilled extra amniotically through a Foley catheter. The termination . . .


A 64-year-old woman with ulcerative colitis presented with abdominal pain. Plain radiography of the abdomen showed dilatation of the large bowel with a plug of barium (Panel A, arrow) and a second plug in the pelvis. The patient’s last barium study, performed 9 months earlier, had been normal. Abdominal computed tomographic examination for strictures and underlying masses showed a short segment of thick-walled left colon immediately distal to the plug of barium in the abdomen (Panel B, arrow). The plug in the pelvis was found to be in the cecum and was not associated with small-bowel obstruction. The patient underwent . . .


A 51-year-old woman with polycystic liver and kidney disease had undergone renal transplantation 21 years before presentation. She had no evidence of cerebrovascular malformations. Both her father and aunt also had polycystic kidney disease. After the renal transplantation, her liver had become progressively diseased and enlarged through cystic changes. Early satiety, malnutrition, and abdominal pain necessitated a liver transplantation. The recipient’s weight at transplantation was 59 kg. A 9.1-kg liver (white arrow) was removed and replaced with a whole graft that was one tenth the weight of the diseased liver (black arrowhead). A large cyst at the dome of the . . .
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL


A 56-year-old woman with a history of primary pulmonary hypertension and heart and lung transplantation was admitted to the hospital because of renal failure. When the patient was approximately 43 years old, a diagnosis of primary pulmonary hypertension was made at another institution; progressive hypoxemia and polycythemia developed, and 3 years later (10 years before admission), heart and lung transplantation was performed at another hospital. The patient’s symptoms improved, and oxygenation and hemoglobin levels returned to normal. Her medications included prednisone (10 mg daily), cyclosporine (225 mg twice daily), azathioprine (75 mg per day in divided doses), folic acid, hydralazine, furosemide, . . .


A 59-year-old man was admitted to this hospital in late summer because of back pain, weakness in the right arm, and cranial-nerve palsies. The patient was in his usual state of health until the first week in July, 5 weeks before admission, when fevers led to body temperatures up to 39.4°C and neck stiffness developed. He saw his primary care physician, who noted thrombocytopenia; a viral illness was diagnosed, and antibiotics were administered. The fevers resolved within 5 days after they started, and the platelet count returned to normal within 2 weeks. However, the discomfort in his neck gradually worsened. . . .

CLINICAL IMPLICATIONS OF BASIC RESEARCH


More than 10 million people in the United States are blind or visually impaired, and 50,000 more will become blind each year. The results of a survey conducted by the American Foundation for the Blind indicate that people with diabetes fear blindness even more than premature death.1 Retinal repair by means of the transplantation of photoreceptor precursors, recently described by MacLaren and colleagues,2 thus holds hope for many people. Blindness is often caused by degenerative conditions in which the sensory cells in the retina deteriorate and die. Such conditions include retinitis pigmentosa and age-related macular degeneration. Photoreceptors do . . .