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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)


Only 30 or 40 years ago, rheumatic fever was a common topic in the Journal. A PubMed search for articles on rheumatic fever published between 1967 and 1976 returned 55 New England Journal of Medicine articles — fewer than for endocarditis (77) but more than for stroke and syphilis (24 entries each). A similar PubMed search for the decade 1997 through 2006 yielded just eight entries for rheumatic fever. This trend holds for all Medline-indexed journals: an average of 516 articles on rheumatic fever per year from 1967 through 1976, but only 172 per year from 1997 through . . .


The past 3 months have seen the publication of a series of studies examining the inherited genetic underpinnings of common diseases such as prostate cancer, breast cancer, diabetes, and in this issue of the Journal, coronary artery disease (reported by Samani et al., pages 443–453). These genomewide association studies have been able to examine interpatient differences in inherited genetic variability at an unprecedented level of resolution, thanks to the development of microarrays, or chips, capable of assessing more than 500,000 single-nucleotide polymorphisms (SNPs) in a single sample. This “SNP-chip” technology capitalizes on a catalogue of common human genetic variations that . . .


“Old wine in a new bottle.” “A financial gamble.” “An early glimpse of the next generation of pay for performance.” All these appraisals have been applied to Geisinger Health System’s new approach to elective coronary-artery bypass grafting (CABG), which has been described with words rarely invoked in health care, such as “promise” and “guarantee.” Geisinger, an integrated health care delivery system in northeastern Pennsylvania, promises that 40 key processes will be completed for every patient who undergoes elective CABG — even though several of the “benchmarks” are to be reached before or after hospitalization. And although Geisinger cannot guarantee good . . .


At a primary care clinic in Montgomery County, Maryland, where I volunteer, the patients are uninsured immigrants from Latin America or West Africa. Many are day laborers, house cleaners, or construction workers; most do not speak English. Several months ago, I saw a middle-aged Hispanic baker with profound weakness, fatigue, limb swelling, and severe muscle pain, who had to be hospitalized for myxedema. Fortunately, a local charity agreed to pay most of her hospital costs, and she’s now receiving thyroid hormone–replacement therapy — but with regular care, her hypothyroidism could have been diagnosed earlier and hospitalization averted. Another day, I . . .


The recent case of Atlanta attorney Andrew Speaker has focused attention on the role of compulsory isolation and quarantine in tuberculosis control. In May, after being diagnosed with a drug-resistant form of tuberculosis, Speaker flew to Europe for his wedding and honeymoon. While he was there, laboratory tests at the Centers for Disease Control and Prevention (CDC) indicated that Speaker’s infection was extensively drug-resistant (XDR). Although accounts of what followed vary, it is known that the CDC contacted Speaker and asked him to stay in Italy while they tried to determine what to do. Fearing isolation in an Italian hospital, . . .


“You will spend the rest of your life working in the fields,” my cousin told me when I arrived in the United States in the mid-1980s. This fate indeed appeared likely: a 19-year-old illegal migrant farm worker, I had no English language skills and no dependable means of support. I had grown up in a small Mexican farming community, where I began working at my father’s gas station at the age of 5. Our family was poor, and we were subject to the diseases of poverty: my earliest memory is of my infant sister’s death from diarrhea when I was . . .

ARTICLES


The free-radical–trapping agent NXY-059 showed promise as a neuroprotectant in the Stroke–Acute Ischemic XNY Treatment I (SAINT I) trial, reducing disability when given to patients who had acute ischemic stroke. We sought confirmation of efficacy in a second, larger trial. We enrolled 3306 patients with acute ischemic stroke in a randomized, double-blind trial to receive a 72-hour infusion of intravenous NXY-059 or placebo within 6 hours after the onset of stroke symptoms. Our primary end point was the distribution of disability scores on the modified Rankin scale at 90 days. We examined scores on neurologic and activities-of-daily-living scales as secondary end points. We also tested the hypothesis that NXY-059 would reduce alteplase–related intracranial hemorrhages. The efficacy analysis was

In singleton gestations, 17 alpha-hydroxyprogesterone caproate (17P) has been shown to reduce the rate of recurrent preterm birth. This study was undertaken to evaluate whether 17P would reduce the rate of preterm birth in twin gestations. We performed a randomized, double-blind, placebo-controlled trial in 14 centers. Healthy women with twin gestations were assigned to weekly intramuscular injections of 250 mg of 17P or matching placebo, starting at 16 to 20 weeks of gestation and ending at 35 weeks. The primary study outcome was delivery or fetal death before 35 weeks of gestation. Six hundred sixty-one women were randomly assigned to treatment. Baseline demographic data were similar in the two study groups. Six women were lost to follow-up; data from 655 were analyzed (325 in the 17P group and 330 in the placebo group). Delivery or fetal death before 35 weeks occurred in 41.5% of pregnancies in the 17P group and 37.3% of those in the placebo group (relative risk, 1.1; 95% confidence interval [CI], 0.9 to 1.3). The rate of the prespecified composite outcome of serious adverse fetal or neonatal events was 20.2% in the 17P group and 18.0% in the placebo group (relative risk, 1.1; 95% CI, 0.9 to 1.5). Side effects of the injections were frequent in both groups, occurring in 65.9% and 64.4% of subjects, respectively (P=0.69), but were generally mild and limited to the injection site. Treatment with 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with twin gestations.


Epidemiologic studies of the prevalence of rheumatic heart disease have used clinical screening with echocardiographic confirmation of suspected cases. We hypothesized that echocardiographic screening of all surveyed children would show a significantly higher prevalence of rheumatic heart disease. Randomly selected schoolchildren from 6 through 17 years of age in Cambodia and Mozambique were screened for rheumatic heart disease according to standard clinical and echocardiographic criteria. Clinical examination detected rheumatic heart disease that was confirmed by echocardiography in 8 of 3677 children in Cambodia and 5 of 2170 children in Mozambique; the corresponding prevalence rates and 95% confidence intervals (CIs) were 2.2 cases per 1000 (95% CI, 0.7 to 3.7) for Cambodia and 2.3 cases per 1000 (95% CI, 0.3 to 4.3) for Mozambique. In contrast, echocardiographic screening detected 79 cases of rheumatic heart disease in Cambodia and 66 cases in Mozambique, corresponding to prevalence rates of 21.5 cases per 1000 (95% CI, 16.8 to 26.2) and 30.4 cases per 1000 (95% CI, 23.2 to 37.6), respectively. The mitral valve was involved in the great majority of...
cases (87.3% in Cambodia and 98.4% in Mozambique). Systematic screening with echocardiography, as compared with clinical screening, reveals a much higher prevalence of rheumatic heart disease (approximately 10 times as great). Since rheumatic heart disease frequently has devastating clinical consequences and secondary prevention may be effective after accurate identification of early cases, these results have important public health implications.


Effective ways to prevent arthropathy in severe hemophilia are unknown. We randomly assigned young boys with severe hemophilia A to regular infusions of recombinant factor VIII (prophylaxis) or to an enhanced episodic infusion schedule of at least three doses totaling a minimum of 80 IU of factor VIII per kilogram of body weight at the time of a joint hemorrhage. The primary outcome was the incidence of bone or cartilage damage as detected in index joints (ankles, knees, and elbows) by radiography or magnetic resonance imaging (MRI). Sixty-five boys younger than 30 months of age were randomly assigned to prophylaxis (32 boys) or enhanced episodic therapy (33 boys). When the boys reached 6 years of age, 93% of those in the prophylaxis group and 55% of those in the episodic-therapy group were considered to have normal index-joint structure on MRI (P=0.006). The relative risk of MRI-detected joint damage with episodic therapy as compared with prophylaxis was 6.1 (95% confidence interval, 1.5 to 24.4). The mean annual numbers of joint and total hemorrhages were higher at study exit in the episodic-therapy group than in the prophylaxis group (P<0.001 for both comparisons). High titers of inhibitors of factor VIII developed in two boys who received prophylaxis; three boys in the episodic-therapy group had a life-threatening hemorrhage. Hospitalizations and infections associated with central-catheter placement did not differ significantly between the two groups. Prophylaxis with recombinant factor VIII can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A.


Modern genotyping platforms permit a systematic search for inherited components of complex diseases. We performed a joint analysis of two genomewide association studies of coronary artery disease. We first identified chromosomal loci that were strongly associated with coronary artery disease in the Wellcome Trust Case Control Consortium (WTCCC) study (which involved 1926 case subjects with coronary artery disease and 2938 controls) and looked for replication in the German MI (Myocardial Infarction) Family Study (which involved 875 case subjects with myocardial infarction and 1644 controls). Data on other single-nucleotide polymorphisms (SNPs) that were significantly associated with coronary artery disease in either study (P<0.001) were then combined to identify additional loci with a high probability of true association. Genotyping in both studies was performed with the use of the GeneChip Human Mapping 500K Array Set (Affymetrix). Results Of thousands of chromosomal loci studied, the same locus had the strongest association with coronary artery disease in both the WTCCC and the German studies: chromosome 9p21.3 (SNP, rs1333049) (P=1.80x10–14 and P=3.40x10–6, respectively). Overall, the WTCCC study revealed nine loci that were strongly associated with coronary artery disease in either study (P<0.001) and a high probability of being falsely positive. In addition to chromosome 9p21.3, two of these loci were successfully replicated (adjusted P<0.05) in the German study: chromosome 6q25.1 (rs6922269) and chromosome 2q36.3 (rs2943634). The combined analysis of the two studies identified four additional loci significantly associated with coronary artery disease (P<1.3x10–5 and less than a 50% chance of being falsely positive). In addition to chromosome 9p21.3, two of these loci were successfully replicated (adjusted P<0.05) in the German study: chromosomes 1p13.3 (rs599839), 1q41 (rs17465637), 10q11.21 (rs501120), and 15q22.33 (rs17228212). We identified several genetic loci that, individually and in aggregate, substantially affect the risk of development of coronary artery disease.

The combination of multiple cycles of rituximab and intravenous immune globulins has been reported to be effective in patients with severe pemphigus. The aim of this study was to assess the efficacy of a single cycle of rituximab in severe types of pemphigus. We studied 21 patients with pemphigus whose disease had not responded to an 8-week course of 1.5 mg of prednisone per kilogram of body weight per day (corticosteroid-refractory disease), who had had at least two relapses despite doses of prednisone higher than 20 mg per day (corticosteroid-dependent disease), or who had severe contraindications to corticosteroids. The patients were treated with four weekly infusions of 375 mg of rituximab per square meter of body-surface area. The primary end point was complete remission 3 months after the end of rituximab treatment; complete remission was defined as epithelialization of all skin and mucosal lesions. Eighteen of 21 patients (86%; 95% confidence interval, 64 to 97%) had a complete remission at 3 months. The disease relapsed in nine patients after a mean of 18.9±7.9 months. After a median follow-up of 34 months, 18 patients (86%) were free of disease, including 8 who were not receiving corticosteroids; the mean prednisone dose decreased from 94.0±10.2 to 12.0±7.5 mg per day (P=0.04) in patients with corticosteroid-refractory disease and from 29.1±12.4 to 10.9±16.5 mg per day (P=0.007) in patients with corticosteroid-dependent disease. Pyelonephritis developed in one patient 12 months after rituximab treatment, and one patient died of septicemia 18 months after rituximab treatment. These patients had a profound decrease in the number of circulating B lymphocytes but normal serum levels of IgG. A single cycle of rituximab is an effective treatment for pemphigus. Because of its potentially severe side effects, its use should be limited to the most severe types of the disease.

Rouse, D.J., Steve N. Caritis, Alan M. Peaceman, Anthony Sciscione, Elizabeth A. Thom, Catherine Y. Spong, Michael Varner, Fergal Malone, Jay D. Iams, Brian M. Mercer, John Thorp, Yoram Sorokin, Marshall Carpenter, Julie Lo, Susan Ramin, Fonseca, E. B., Ebru Celik, Mauro Parra, Mandeep Singh, and Julie Lo, Susan Ramin. (2007). Premature delivery. Asymptomatic women found at midgestation to have a short cervix are at greatly increased risk for spontaneous early preterm delivery, and it is unknown whether. Cervical length was measured by transvaginal ultrasonography at a median of 22 weeks of gestation (range, 20 to 25) in 24,620 pregnant women seen for routine prenatal care. Cervical length was 15 mm or less in 413 of the women (1.7%), and 250 (60.5%) of these 413 women were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. The primary outcome was spontaneous delivery before 34 weeks. Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group (19.2% vs. 34.4%; relative risk, 0.56; 95% confidence interval [CI], 0.36 to 0.86). Progesterone was associated with a nonsignificant reduction in neonatal morbidity (8.1% vs. 13.8%; relative risk, 0.59; 95% CI, 0.26 to 1.25; P=0.17). There were no serious adverse events associated with the use of progesterone. In women with a short cervix, treatment with progesterone reduces the rate of spontaneous early preterm delivery.

**REVIEW ARTICLES**


Drug-induced thrombocytopenia can be caused by dozens, perhaps hundreds, of medications. Because thrombocytopenia can have many other causes, the diagnosis of drug-induced thrombocytopenia can easily be overlooked. On occasion, outpatient patients with drug-induced thrombocytopenia are treated for autoimmune thrombocytopenia and can have two or three recurrences before the drug causing the disorder is identified.1 In acutely ill, hospitalized patients, drug-induced thrombocytopenia can be overlooked because thrombocytopenia is attributed to sepsis, the effect of coronary-artery bypass surgery, or some other underlying condition. . .


Preterm birth is defined as birth before the completion of 37 weeks of gestation. The frequency of preterm birth in the United States increased from 10.7% in 1992 to 12.3% in 2003.1 Preterm births can be categorized as those undertaken because of a specific indication or as spontaneous preterm births. Indicated preterm births occur as a consequence of spontaneous preterm labor or preterm rupture of fetal membranes before the onset of . . .

**IMAGES IN CLINICAL MEDICINE**


A 50-year-old woman presented with abdominal tenderness, fever, and vaginal bleeding. Physical examination showed a periumbilical mass and
necrosis of the upper wall of the vagina. Laboratory data were notable for a leukocyte count of 14,600 per cubic millimeter, without eosinophilia. Computed tomography showed a large intraabdominal cystic lesion with variable density and a thick wall (Panel A, arrow). Fine-needle aspiration revealed no signs of cancer or parasitic infection. Diagnostic considerations included an infected pseudocyst and a mesenteric or dermoid cyst. Antibiotic therapy was started, and the patient recovered quickly. Explorative laparotomy revealed an intraabdominal plastic bag containing 80 g . . .


A healthy 26-year-old driver had routine laboratory tests performed to renew his driver's license. Hematuria (3+) was incidentally noted. He reported having had no urinary tract symptoms. Abdominal radiography of the kidneys, ureters, and bladder showed large bladder stones (Panel A, with a Foley catheter tube visible). During cystotomy, two large stones, measuring 8 cm and 3 cm in diameter, were removed (Panel B). These stones were found to contain both calcium phosphate and uric acid and were infected with Proteus mirabilis. No structural bladder-outlet obstruction or other anatomical abnormalities were identified. The patient recovered quickly from the surgery . . .


An 82-year-old woman presented with abdominal colic. She had a 20-year history of type 2 diabetes and a 2-year history of recurrent urinary tract infections despite many courses of antimicrobial therapy. She lived in a long-term care facility. An abdominal radiograph showed a large stone in her bladder, with a foreign body in the center of the stone (Panel A). On cystotomy (Panel B), an infected bladder stone measuring 6 by 2 by 0.5 cm was removed (Panel C), and a pen cap was found at the center (Panel D). The patient was discharged 2 days later and had a . . .


A 54-year-old woman presented with a sudden onset of fever (temperature, 39.3°C) and erythema on the right breast and right arm (Panel A) and on the right side of the back (Panel B). There was no history of trauma. Eleven months earlier, she had undergone a wide local excision with axillary lymph-node dissection for an invasive ductal carcinoma (T2N0, 2.5 cm in diameter) of the ipsilateral breast. The postoperative course was uneventful, and she did not receive perioperative antibiotics. Surgery was followed by six courses of chemotherapy and 50 Gy of radiotherapy on the right breast. Examination of the breast . . .

**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 36-year-old pregnant woman at 21 weeks of gestation presented with a 4-week history of a dry, nonproductive cough. Acute onset of cough in the patient’s age group is most commonly due to a respiratory tract infection, typically viral. However, in the absence of other clinical findings suggesting an infectious cause, the most common causes of cough are postnasal drip (also called . . .

**CLINICAL IMPLICATIONS OF BASIC RESEARCH**


Delaying the onset of cognitive decline and reducing cognitive decline once it has begun have become increasingly important with the aging of the population. Age-related changes in cognitive functions such as memory occur even among healthy persons and have been seen in humans, nonhuman primates, and rodents. Moreover, several neurodegenerative disorders that cause cognitive decline are increasingly prevalent with age. The most common neurodegenerative disorder is Alzheimer’s disease: about 5 million people in the United States have Alzheimer’s disease, and current estimates indicate that about 16 million people will have the disease in 40 years. Delaying the onset of Alzheimer’s . . .

**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 man has sudden weakness of the left arm and leg and slurred speech. Except for untreated hypertension, his medical history is unremarkable. He is a current smoker with a smoking history of 45 pack-years. On arrival at the emergency department 1 hour 15 minutes after the onset of symptoms, he reports no headache or vomiting. His blood pressure is 180/100 . . .
A 20-year-old pregnant woman was admitted to this hospital at 26 weeks of gestation because of dizziness, confusion, and difficulty walking. Ten weeks before admission, the patient had a positive result on a home pregnancy test and presented to a neighborhood health center for prenatal screening. Tests for sickle cell trait, syphilis, and human immunodeficiency virus (HIV) and hepatitis B and C virus antibodies were negative. Serologic tests for varicella–zoster virus and rubella IgG were positive. Two weeks later, an endocervical specimen was positive for Chlamydia trachomatis infection and negative for gonorrhea. The patient missed follow-up appointments, and treatment with . . .