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Guinea worm disease, or dracunculiasis — Latin for “affliction with little dragons” — is a plague so ancient that it has been found in Egyptian mummies and has been proposed by some to have been the “fiery serpent” described in the Old Testament as torturing the Israelites in the desert. The global Dracunculiasis Eradication Program spearheaded by former President Jimmy Carter and the Carter Center has now reached its final stages (see graph). This accomplishment is unprecedented — the only disease previously eradicated was smallpox, not a parasitic disease — and it has been achieved through grassroots public health . . .


It is hard to overstate the medical importance and burden of vector-transmitted infectious diseases. Whether the metric used is mortality (malaria, for example, kills 1 million to 2 million people annually, most of them children under 5 years of age), morbidity (more than 70 million years of healthy living are lost to malaria, Chagas’ disease, leishmaniasis, dengue fever, lymphatic filariasis, and the encephalitis viruses), or something as difficult to quantify as anxiety in a population (activities in outdoor playgrounds and high schools, for example, were moved or suspended along the south shore of Massachusetts this past fall because of concern . . .


Dr. Cyril Nkabinde, an intern at Prince Mshiyeni Memorial Hospital in Durban, South Africa, grew up dreaming of becoming a doctor — an ambition he inherited from his mother, whose own dream had been thwarted by apartheid. Nkabinde’s goal of working as a family physician in rural KwaZulu-Natal has kept him on track, even as he’s watched medical school classmates depart for business careers and superiors quit medicine because of a chronic lack of health care resources. Now, as he prepares to marry a fellow physician, Nkabinde realizes that his dream may not be achievable. “The hope is to go . . .


Four years after national limits on duty hours for medical residents took effect — and nearly two decades after similar limits were enacted by New York State — conversations with residency directors, attending physicians, health care researchers, and sleep-medicine experts suggest that neither patient care nor medical education is optimal under the current system and that further reforms are needed. But there is little agreement on what should be done or even on whether the work-hour limits should be tightened or relaxed. U.S. teaching hospitals are handling more admissions, treating older and sicker patients, and discharging patients more quickly than . . .


On July 1, 2003, prompted by the medical profession’s concerns about patient safety and the working conditions and education of resident physicians, the Accreditation Council for Graduate Medical Education (ACGME) instituted one of the most substantial redesigns of the country’s resident training system in more than a century. Among other changes, the duty hours of residents were tapered to 80 per week, averaged over 4 weeks, and shifts were limited to 30 hours, with a minimum 10-hour rest period between them. Welcomed or criticized, the ACGME rules were anything but ignored. ‘The hope is to go . . .

ARTICLES


Information regarding the safety of selective serotonin-reuptake inhibitors (SSRIs) in human pregnancy is sparse. Concern has been raised about the risk of congenital heart defects associated with the use of SSRIs in pregnancy. We obtained data on 9622 case infants with major birth defects and 4092 control infants born from 1997 through 2002 from the National Birth Defects Prevention Study. Case infants were ascertained through birth-defects surveillance systems in eight U.S. states; controls were selected randomly from the same . . .
geographic areas. Mothers completed a standardized telephone interview regarding exposure to potential risk factors, including medications, before and during pregnancy. Exposure to SSRIs was defined as treatment with any SSRI from 1 month before to 3 months after conception. Birth defects were assigned to 26 categories and subcategories. There were no significant associations between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories of birth defects. Maternal use of SSRIs during early pregnancy was associated with significantly increased risks of craniosynostosis (432 infants, 24 exposed; adjusted odds ratio, 2.5; 95% CI, 1.5 to 4.0), and omphalocele (181 infants, 11 exposed; adjusted odds ratio, 2.8; 95% CI, 1.3 to 5.7).

Maternal use of SSRIs during early pregnancy was not associated with significantly increased risks of congenital heart defects or of most other categories of birth defects. Associations were observed between SSRI use and three types of birth defects, but the absolute risks were small, and these observations require confirmation by other studies.


Smoldering (asymptomatic) multiple myeloma is an asymptomatic plasma-cell proliferative disorder associated with a high risk of progression to symptomatic multiple myeloma or amyloidosis. Prognostic factors for the progression and outcome of this disease are unclear. Methods We searched a computerized database and reviewed the medical records of all patients at Mayo Clinic who fulfilled the criteria of the International Myeloma Working Group for the diagnosis of smoldering multiple myeloma between 1970 and 1995. Bone marrow aspirate and biopsy specimens were studied, and patients were followed throughout the course of disease. During the 26-year period, 276 patients fulfilled the criteria for smoldering multiple myeloma. During 2131 cumulative person-years of follow-up, symptomatic multiple myeloma or amyloidosis developed in 163 persons (59%). The overall risk of progression was 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% per year for the last 10 years; the cumulative probability of progression was 73% at 15 years. At diagnosis, significant risk factors for progression included the serum level and type of monoclonal protein, the presence of urinary light chain, the extent and pattern of bone marrow involvement, and the reduction in uninvolved immunoglobulins. The proportion of plasma cells in the bone marrow and the serum monoclonal protein level were combined to create a risk-stratification model with three distinct prognostic groups. The risk of progression from smoldering multiple myeloma to symptomatic disease is related to the proportion of bone marrow plasma cells and the serum monoclonal protein level at diagnosis.


The risk of birth defects after antenatal exposure to selective serotonin-reuptake inhibitors (SSRIs) remains controversial. We assessed associations between first-trimester maternal use of SSRIs and the risk of birth defects among 9849 infants with and 5860 infants without birth defects participating in the Slone Epidemiology Center Birth Defects Study. In analyses of defects previously associated with SSRI use (involving 42 comparisons), overall use of SSRIs was not associated with significantly increased risks of craniosynostosis (115 subjects, 2 exposed to SSRIs; odds ratio, 0.8; 95% confidence interval [CI], 0.2 to 3.5), omphalocele (127 subjects, 3 exposed; odds ratio, 1.4; 95% CI, 0.4 to 4.5), or heart defects overall (3724 subjects, 100 exposed; odds ratio, 1.2; 95% CI, 0.9 to 1.6). Analyses of the associations between individual SSRIs and specific defects showed significant associations between the use of sertraline and omphalocele (odds ratio, 5.7; 95% CI, 1.6 to 20.7; 3 exposed subjects) and septal defects (odds ratio, 2.0; 95% CI, 1.2 to 4.0; 13 exposed subjects) and between the use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio, 3.3; 95% CI, 1.3 to 8.8; 6 exposed subjects). The risks were not appreciably or significantly increased for other defects or other SSRIs or non-SSRI antidepressants. Exploratory analyses involving 66 comparisons showed possible associations of paroxetine and sertraline with other specific defects. Our findings do not show that there are significantly increased risks of craniosynostosis, omphalocele, or heart defects associated with SSRI use overall. They suggest that individual SSRIs may confer increased risks for some specific defects, but it should be recognized that the specific defects implicated are rare and the absolute risks are small.


Surgeons in training are at high risk for needlestick injuries. The reporting of such injuries is a critical step in initiating early prophylaxis or treatment. Methods We surveyed surgeons in training at 17 medical centers about previous needlestick injuries. Survey items inquired about whether the most recent injury was reported to an employee health service or involved a “high-risk” patient (i.e., one with a history of infection with human immunodeficiency virus, hepatitis B or hepatitis C, or injection-drug use); we also asked about the perceived cause of the injury and the surrounding circumstances. The overall response rate was 95%. Of 699 respondents, 582 (83%) had had a needlestick injury during training; the mean number of needlestick injuries during residency increased according to the postgraduate year (PGY): PGY-1, 1.5 injuries; PGY-2, 3.7; PGY-3, 4.1; PGY-4,
5.3; and PGY-5, 7.7. By their final year of training, 99% of residents had had a needlestick injury; for 53%, the injury had involved a high-risk patient. Of the most recent injuries, 297 of 578 (51%) were not reported to an employee health service, and 15 of 91 of those involving high-risk patients (16%) were not reported. Lack of time was the most common reason given for not reporting such injuries among 126 of 297 respondents (42%). If someone other than the respondent knew about an unreported injury, that person was most frequently the attending physician (51%) and least frequently a “significant other” (13%). Needlestick injuries are common among surgeons in training and are often not reported. Improved prevention and reporting strategies are needed to increase occupational safety for surgical providers.


Entecavir, a drug approved by the Food and Drug Administration for the treatment of chronic hepatitis B virus (HBV) infection, is not believed to inhibit replication of human immunodeficiency virus type 1 (HIV-1) at clinically relevant doses. We observed that entecavir led to a consistent 1-log10 decrease in HIV-1 RNA in three persons with HIV-1 and HBV coinfection, and we obtained supportive in vitro evidence that entecavir is a potent partial inhibitor of HIV-1 replication. Detailed analysis showed that in one of these patients, entecavir monotherapy led to an accumulation of HIV-1 variants with the lamivudine-resistant mutation, M184V. In vitro experiments showed that M184V confers resistance to entecavir. Until more is known about HIV-1 resistance patterns and their selection by entecavir, caution is needed in the use of entecavir in persons with HIV-1 and HBV coinfection who are not receiving fully suppressive antiretroviral regimens.


Calcified plaque in the coronary arteries is a marker for atheromatous-plaque burden and is predictive of future risk of cardiovascular events. We examined the relationship between estrogen therapy and coronary-artery calcium in the context of a randomized clinical trial. In our ancillary study of the Women’s Health Initiative trial of conjugated equine estrogens (0.625 mg per day) as compared with placebo in women who had undergone hysterectomy, we performed computed tomography of the heart in 1064 women aged 50 to 59 years at randomization. Imaging was conducted at 28 of 40 centers after a mean of 7.4 years of treatment and 1.3 years after the trial was completed (8.7 years after randomization). Coronary-artery calcium (or Agatston) scores were measured at a central reading center without knowledge of randomization status. The mean coronary-artery calcium score after trial completion was lower among women receiving estrogen (83.1) than among those receiving placebo (123.1) (P=0.02 by rank test). After adjustment for coronary risk factors, the multivariate odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared with placebo were 0.78 (95% confidence interval, 0.58 to 1.04), 0.74 (0.55 to 0.99), and 0.69 (0.48 to 0.98), respectively. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P=0.01), 0.55 (P=0.001), and 0.46 (P=0.001). For coronary-artery calcium scores of more than 300 (vs. <10), the multivariate odds ratio was 0.58 (P=0.03) in an intention-to-treat analysis and 0.39 (P=0.004) among women with at least 80% adherence. Among women 50 to 59 years old at enrollment, the calcified-plaque burden in the coronary arteries after trial completion was lower in women assigned to estrogen than in those assigned to placebo. However, estrogen has complex biologic effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways.


Mevalonic aciduria is a rare, inborn error of isoprene biosynthesis characterized by severe, periodic attacks of fever and inflammation, developmental delay, ataxia, and dysmorphic features. This autosomal recessive disease is caused by a mutation in the mevalonate kinase gene that severely reduces mevalonate kinase activity. A 3-year-old boy with mevalonic aciduria whose condition had failed to improve with antiinflammatory treatment underwent allogeneic bone marrow transplantation from an HLA-identical sibling who was a heterozygous carrier of the mutant gene. We observed sustained remission of febrile attacks and inflammation during a 15-month follow-up period.


The course and prognosis of childhood-onset multiple sclerosis have not been well described. We used data from 13 adult neurology departments affiliated with the
Injectable paromomycin for visceral leishmaniasis


Visceral leishmaniasis (kala-azar) affects large, rural, resource-poor populations in South Asia, Africa, and Brazil. Safe, effective, and affordable new therapies are needed. We conducted a randomized, controlled, phase 3 open-label study comparing paromomycin, an aminoglycoside, with amphotericin B, the present standard of care in Bihar, India. In four treatment centers for visceral leishmaniasis, 667 patients between 5 and 55 years of age who were negative for the human immunodeficiency virus and had parasitologically confirmed visceral leishmaniasis were randomly assigned in a 3:1 ratio to receive paromomycin (502 patients) at a dose of 11 mg per kilogram of body weight intramuscularly daily for 21 days or amphotericin B (165 patients) at a dose of 1 mg per kilogram intravenously every other day for 30 days. Final cure was assessed 6 months after the end of treatment; safety assessments included daily clinical evaluations and weekly laboratory and audiometric evaluations. Noninferiority testing was used to compare 6-month cure rates, with a chosen margin of noninferiority of 10 percentage points. Paromomycin was shown to be noninferior to amphotericin B (final cure rate, 94.6% vs. 98.8%; difference, 4.2 percentage points; upper bound of the 97.5% confidence interval, 6.9; P<0.001). Mortality rates in the two groups were less than 1%. Adverse events, which were more common among patients receiving paromomycin than among those receiving amphotericin B (6% vs. 2%, P=0.02), included transient elevation of aspartate aminotransferase levels (>3 times the upper limit of the normal range); transient reversible ototoxicity (2% vs. 0, P=0.20); and injection-site pain (55% vs. 0, P<0.001), and in patients receiving amphotericin B, as compared with those receiving paromomycin, nephrotoxicity (4% vs. 0, P<0.001), fevers (57% vs. 3%), rigors (24% vs. 0, P<0.001), and vomiting (10% vs. <1%, P<0.001). Paromomycin was shown to be noninferior to amphotericin B for the treatment of visceral leishmaniasis in India.

CLINICAL THERAPEUTICS


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. A 30-year-old woman was evaluated for consideration of treatment options for multiple sclerosis. Two years earlier she had reported having vertigo. The diagnosis of multiple sclerosis was confirmed by clinical evaluation, examination of cerebrospinal fluid, and magnetic resonance imaging . . .

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 author's clinical recommendations. A 51-year-old woman presents with a generalized tonic-clonic seizure. After a brief postictal period, she recovers fully and does not report headache or other neurologic symptoms. She takes no medications and her medical history is unremarkable. Computed tomography of the head suggests a right occipital arteriovenous malformation, without evidence of hemorrhage. Computed tomographic angiography, magnetic resonance imaging, and magnetic resonance angiography of . . .

IMAGES IN CLINICAL MEDICINE


A 44-year-old man presented with intermittent epistaxis, fever, and polyarthralgias of 2 months’ duration. For the previous week, he had had puffiness of the face and reduced urinary output. On physical examination, the blood pressure was 180/100 mm Hg; he was pale and had pedal edema. A saddle nose deformity (Panel A) had developed during the previous...
4 months. There were no clinical signs of sinus involvement, but computed tomography (CT) showed bilateral mucosal thickening in the maxillary sinuses. Laboratory evaluation revealed the following values: hemoglobin, 7.5 g per deciliter; blood urea nitrogen, 163 mg per deciliter (58 mmol per liter). A 72-year-old woman presented for evaluation of dyspnea. Thirty-five years earlier, she had noticed a painless, slowly enlarging anterior neck mass. Since she was otherwise asymptomatic and many in her community had the same “problem,” she did not seek medical attention. For the past few years, however, she has had a sensation of suffocating a few minutes after falling asleep. Physical examination showed a goiter that was large, lobular, soft, and painless, with cyanosis and protrusion of the inferior lip (Panel A), which was probably related to chronic respiratory insufficiency. Serum thyrotropin and free thyroxine levels were normal. Computed tomography . . .

**CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL**


Dr. Margo McKenna Benoit (Otolaryngology): An 11-year-old boy was referred to a pediatric otolaryngologist at the Massachusetts Eye and Ear Infirmary because of headaches and a right nasal mass. Bifrontal headaches had started approximately 5 years earlier; in recent months, the pain had been predominantly in the right supraorbital area. The patient had chronic nasal congestion with occasional rhinorrhea. Approximately 2 years earlier, a neurologist had made a diagnosis of migraine headache. Magnetic resonance imaging (MRI) of the head at that time showed no intracranial abnormalities, but the findings were interpreted as being consistent with sinusitis. Two months before presentation, . . .


A healthy 28-year-old woman presented with a 1-year history of high blood pressure, which had been diagnosed during her first pregnancy and treated with amiloride and hydrochlorothiazide. Physical examination revealed a blood pressure of 200/100 mm Hg. She reported having no chest pain, shortness of breath, or headache. Radiography of the chest was performed. What is the diagnosis? *Editor’s note: We invite our readers to submit their answers at www.nejm.org/mystery. We will publish the diagnosis in the Correspondence section of the August 16, 2007, issue and e-mail it to everyone who submits an answer. All answers must be received . . .

**VIDEO IN CLINICAL MEDICINE**


This video will demonstrate how to perform a comprehensive pelvic examination, which includes an examination of the external genitalia, a Papanicolaou test, a bimanual examination, as well as a rectovaginal examination. Indications Women should undergo a pelvic examination when they have vulvar and/or vaginal complaints such as pain, discharge, abnormal bleeding, itching, and/or a mass. A pelvic examination is also indicated when pregnancy is suspected or proven, and in women who have been exposed to sexually transmitted infections. Pap testing is the main screening tool for detecting precancerous lesions of the cervix, we will now highlight the American Cancer Society . . . .


Dr. Maxwell T. Vergo (Department of Medicine): A 19-year-old woman was transferred to this hospital because of joint pain, fever, and hypotension. The patient, a freshman student at a local university, had been in good health until the late spring, approximately 11 days before admission, when sore throat and fatigue developed. She was evaluated at the university health service. A Monospot test was positive, and a rapid screening test for group A streptococcus was negative; a diagnosis of infectious mononucleosis was made. The results of laboratory tests are shown in Table 1. One week before admission, nasal congestion and . . .

**CLINICAL IMPLICATIONS OF BASIC RESEARCH**


The search for the basic mechanisms responsible for the development and progression of heart failure has been exhaustive. Despite the elucidation of several clinically relevant signal transduction pathways that can lead to disease progression (e.g., those that activate the angiotensin and adrenergic signaling pathways), the means by which these pathways are coordinated with respect to the development and progression of heart failure remain obscure. A recent study by van Rooij and colleagues is particularly welcome because it provides a new understanding of how stress responses are coordinated in the failing heart. The heart responds to cardiac injury or hemodynamic overload . . .
REVIEW ARTICLE


Studies from more than six countries report a high prevalence of harmful medical errors. Most providers and patients realize that health care services are potentially hazardous and that errors sometimes occur despite the best efforts of people and institutions. Patients expect to be informed promptly when they are injured by care, especially care that has gone wrong. However, a divide between these expectations and actual clinical practice is increasingly evident. Regulators, hospitals, accreditation organizations, and legislators in the United States and other countries are moving to bridge the gap by developing standards, programs, and laws that encourage transparent communication with . . .

HEALTH LAW, ETHICS, AND HUMAN RIGHT


Public unease about industry’s influence over clinical research has never been greater. Recent events have elevated concerns about financial ties among investigators, academic medical centers, and industry sponsors, and disquieting findings have emerged about the legal relationships these entities form to conduct clinical trials. Tort litigation brought by injured research subjects has accentuated the legal dimensions of clinical research relationships. These areas of focus converged in Abney v. Amgen, an important case decided in March 2006 by the U.S. Court of Appeals for the Sixth Circuit. The dispute centered on the legal obligation of an industry sponsor to provide . . .