JOURNALS IN MEDICINE

Annals of Internal Medicine

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Evidence-Based Therapies and Mortality in Patients Hospitalized in December with Acute Myocardial Infarction

Trip J. Meine et al.

Background: Previous studies suggest that patients hospitalized with acute myocardial infarction in December have poor outcomes, and some studies have hypothesized that the cause may be the infrequent use of evidence-based therapies during the December holiday season. *Objective:* To compare the care and outcomes of patients with acute MI hospitalized in December and patients hospitalized during other months. *Design:* Retrospective analysis of data from the Cooperative Cardiovascular Project. *Setting:* Nonfederal, acute-care hospitals in the United States. *Patients:* 127,959 Medicare beneficiaries hospitalized between January 1994 and February 1996 with confirmed acute myocardial infarction. *Measurements:* Use of aspirin, beta-blockers, and reperfusion therapy (thrombolytic therapy or percutaneous coronary intervention), and thirty-day mortality. *Results:* When the authors controlled for patient, hospital, and physician characteristics, the use of evidence-based therapies was not significantly lower, but thirty-day mortality was higher (21.7 vs. 20.1 percent; adjusted odds ratio, 1.07; 95 percent confidence interval, 1.02–1.12) among patients hospitalized in December. *Limitations:* This was a nonrandomized, observational study. Unmeasured characteristics may have contributed to outcome differences. *Conclusions:* Thirty-day mortality rates were higher for Medicare patients hospitalized with acute myocardial infarction in December than in other months, although the use of evidence-based therapies was not significantly lower.

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Clinical Decision Making during Public Health Emergencies: Ethical Considerations

Bernard Lo, Mitchell Katz

Recent public health emergencies involving anthrax, the severe acute respiratory syndrome (SARS), and shortages of influenza vaccine have dramatized the need for restrictive public health measures such as quarantine, isolation, and rationing. Front-line physicians will face ethical dilemmas during public health emergencies when patients disagree with these measures. Patients might request interventions that are not recommended or for which they are not eligible, or they might object to intrusive or restrictive measures. The physician's primary responsibility in such emergencies is to the public rather than to the individual patient. In public health emergencies, physicians need to address the patient's needs and concerns, recognize physicians' changed roles, and work closely with public health officials. Physicians can still work on behalf of patients by advocating for changes in policies and exceptions when warranted and by mitigating the adverse consequences of public health measures. Before an emergency occurs, physicians should think through how they will respond to foreseeable dilemmas arising when patients disagree with public health recommendations.

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Physical Abuse of Boys and Possible Associations with Poor Adult Outcomes

William C. Holmes, M.D., and Mary D. Sammel

Background: Men's childhood experiences of physical abuse are understudied. *Objec-*

tive: To obtain descriptions of men's personal childhood physical abuse histories and estimate their association with adult outcomes. *Design:* Population-based telephone survey. *Setting:* Urban areas with high frequency of domestic violence against girls and women. *Participants:* 298 men recruited through random-digit dialing. *Measurements:* Six Conflict Tactics Scale items and psychiatric, sexual, and legal history questions. *Results:* One hundred (51 percent) of 197 participants had a history of childhood physical abuse. Most participants (73 percent) were abused by a parent. Childhood physical abuse history was associated with depression symptoms (P=0.003), post-traumatic stress disorder symptoms (P<0.001), number of lifetime sexual partners (P=0.035), legal troubles (P= 0.002), and incarceration (P=0.007) in unadjusted analyses and with depression symptoms (P=0.015) and post-traumatic stress disorder symptoms (P=0.003) in adjusted analyses. *Limitations:* There may have been inaccurate recall of past events. Lack of exposure time data disallowed direct comparison of abuse perpetration by mothers versus fathers. Other unmeasured variables related to childhood physical abuse might better explain poor adult outcomes. *Conclusions:* The high frequency of childhood physical abuse histories in this population-based male sample, coupled with the high proportion of parent perpetrators and the association between childhood physical abuse and adult outcomes that are often associated with perpetration of violence, argues for more study of and clinical attentiveness to potential adult outcomes of men's own childhood physical abuse histories.

Archives of Internal Medicine

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The Terri Schiavo Case: Legal, Ethical, and Medical Perspectives

Joshua E. Perry, Larry R. Churchill, and Howard S. Kirschner, M.D.

Although tragic, the plight of Terri Schiavo provides a valuable case study. The conflicts and misunderstandings surrounding her situation offer important lessons in medicine, law, and ethics. Despite media saturation and intense public interest, widespread confusion lingers regarding the diagnosis of persistent vegetative state, the judicial processes involved, and the appropriateness of the ethical framework used by those entrusted with Terri Schiavo's care. First, the authors review the current medical understanding of persistent vegetative state, including the requirements for patient examination, the differential diagnosis, and the practice guidelines of the American Academy of Neurology regarding artificial nutrition and hydration for patients with this diagnosis. Second, they examine the legal history, including the 2000 trial, the 2002 evidentiary hearing, and the subsequent appeals. The authors argue that the law did not fail Terri Schiavo, but produced the highest-quality evidence and provided the most judicial review of any end-of-life guardianship case in U.S. history. Third, they review alternative ethical frameworks for understanding the Terri Schiavo case and contend that the principle of respect for autonomy is paramount in this case and in similar cases. Far from being unusual, the manner in which Terri Schiavo's case was reviewed and the basis for the decision reflect a broad medical, legal, and ethical consensus. Greater clarity regarding the persistent vegetative state, less apprehension of the presumed mysteries of legal proceedings, and greater appreciation of the ethical principles at work are the chief benefits obtained from studying this provocative case.

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Discomfort in Nursing Home Patients with Severe Dementia in Whom Artificial Nutrition and Hydration is Forgone

H. Roeline W. Pasman et al.

Background: While there is debate about whether it may be better to forgo than to initiate artificial nutrition and hydration (ANH) in nursing home patients with severe demen-

tia, the consequences of forgoing ANH in these patients, in particular their discomfort, have not yet been investigated. *Methods:* In this prospective, longitudinal, observational study of 178 patients in Dutch nursing homes, discomfort was measured at all measurement times according to the observational Discomfort Scale–Dementia of Alzheimer Type. Furthermore, at all measurement times, plausible determinants of discomfort were registered. Data were analyzed with the statistical technique of generalized estimated equations. *Results:* Decisions to forgo ANH were made most often in severely demented, female patients with an acute illness as the most important diagnosis at that time. The mean level of discomfort was highest at the time of the decision and decreased in the days thereafter. There were substantial differences in level of discomfort between patients. Dyspnea, restlessness, and physicians' observations of pain and dehydration were associated with higher levels of discomfort. Furthermore, patients who were awake had higher levels of observed discomfort than patients who were asleep. *Conclusions:* Forgoing ANH in patients with severe dementia who scarcely or no longer eat or drink seems, in general, not to be associated with high levels of discomfort. The individual differences emphasize the need for constant attention for possible discomfort.

Volume 165, Number 19
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Justice at Work and Reduced Risk of Coronary Heart Disease among Employees: The Whitehall II Study

Mika Kivimäki et al.

Background: Justice is a fundamental value in human societies, but its effect on health is poorly described. The authors examined justice at work as a predictor of coronary heart disease (CHD). *Methods:* Prospective occupational cohort study of 6,442 male British civil servants aged thirty-five to fifty-five years without prevalent CHD at baseline in phase 1 (1985–1988). Baseline screening included measurements of conventional risk factors. Perceived justice at work and other work-related psychosocial factors were determined by means of questionnaire at phases 1 and 2 (1989–1990). Follow-up for CHD death, first nonfatal myocardial infarction, or definite angina occurring from phase 2 through 1999 was based on medical records (mean follow-up, 8.7 years). *Results:* Cox proportional hazard models adjusted for age and employment grade showed that employees who experienced a high level of justice at work had a lower risk of incident CHD than employees with a low or an intermediate level of justice (hazard ratio, 0.65; 95 percent confidence interval, 0.47–0.89). The hazard ratio did not materially change after additional adjustment for baseline cholesterol concentration, body mass index, hypertension, smoking, alcohol consumption, and physical activity. Although other psychosocial models such as job strain and effort-reward imbalance predicted CHD in these data, the level of justice remained an independent predictor of incident CHD after adjustment for these factors. *Conclusion:* Justice at work may have benefits for heart health among employees.

Archives of Neurology

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Prognosis of Parkinson Disease: Risk of Dementia and Mortality: The Rotterdam Study

Lonneke M. L. de Lau, M.D., et al.

Background: Most prognostic studies on Parkinson disease have been hospital based or have applied register-based case-finding methods. Potential under-representation of mild cases may have given biased results. *Objective:* To evaluate whether Parkinson disease is associated with an increased risk of dementia and death. *Design:* Population-based cohort study. Parkinson disease and dementia were assessed through in-person examination at baseline (1990–1993) and twofollow-up visits (1993–1994 and 1997–1999). Computerized linkage to medical and municipality records provided additional in-

formation on disease outcomes and mortality. *Setting:* General population. *Participants:* A total of 6,969 participants, including ninety-nine prevalent and sixty-seven incident cases of Parkinson disease. *Main outcome measures:* Incident dementia and death. Adjusted hazard ratios were calculated through Cox proportional hazards regression analysis. *Results:* Patients with Parkinson disease had an increased risk of dementia (hazard ratio, 2.8; 95 percent confidence interval, 1.8–4.4), which was especially pronounced in participants carrying at least one apolipoprotein E gene (*APOE*) epsilon2 allele (13.5; 4.5–40.6). Parkinson disease was associated with an increased mortality risk (1.8; 1.5–2.3). The association consistently diminished when analyses were sequentially restricted to patients with shorter disease duration and after adjustment for the occurrence of dementia. *Conclusions:* Especially patients with Parkinson disease who carry an *APOE* epsilon2 allele have an increased risk of developing dementia. Increased mortality risk in Parkinson disease is dependent on disease duration and is only modest in the absence of dementia.

Circulation

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Effect Size Estimates of Lifestyle and Dietary Changes on All-Cause Mortality in Coronary Artery Disease Patients: A Systematic Review

J. A. Iestra et al.

Background: Guidelines for lifestyle and dietary modification in patients with coronary artery disease (CAD) are mainly supported by evidence from general population studies. CAD patients, however, differ from the general population in age (older) and treatment with preventive drugs. This review seeks to provide evidence for a prognostic benefit of lifestyle and dietary recommendations from studies in CAD patients. *Methods and results:* A literature search was performed on the effect of lifestyle and dietary changes on mortality in CAD patients. Prospective cohort studies and randomized controlled trials of patients with established CAD were included if they reported all-causes mortality and had at least six months of follow-up. The effect estimates of smoking cessation (relative risk [RR], 0.64; 95 percent confidence interval [95%CI], 0.58–0.71), increased physical activity (RR, 0.76; 95%CI, 0.59–0.98), and moderate alcohol use (RR, 0.80; 95%CI, 0.78–0.83) were studied most extensively. For the six dietary goals, data were too limited to provide reliable effect size estimates. Combinations of dietary changes were associated with reduced mortality (RR, 0.56; 95%CI, 0.42–0.74). *Conclusions:* Available studies show convincingly the health benefits of lifestyle changes in CAD patients. Effect estimates of combined dietary changes look promising. Future studies should confirm these findings and assess the contribution of the individual dietary factors.

Cleveland Clinic Journal of Medicine

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Influenza 2005–2006: Vaccine Supplies Adequate, but Bird Flu Looms

Sherif B. Mossad, M.D.

Influenza vaccine supplies appear to be adequate for the 2005–2006 season, though delivery has been somewhat delayed. However, in the event of a pandemic of avian flu—considered inevitable by most experts, although no one knows when it will happen—the United States would be woefully unprepared.

Hypertension

Volume 46, Number 2
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Cocoa Reduces Blood Pressure and Insulin Resistance and Improves Endothelium-Dependent Vasodilation in Hypertensives

Davide Grassi et al.

Consumption of flavanol-rich dark chocolate has been shown to decrease blood pressure and insulin resistance in healthy subjects, suggesting similar benefits in patients with essential hypertension. Therefore, the authors tested the effect of dark chocolate on twenty-four-hour ambulatory blood pressure, flow-mediated dilation, and oral glucose tolerance tests (OGTTs) in patients with essential hypertension. After a seven-day chocolate-free run-in phase, twenty never-treated, grade I patients with essential hypertension (ten men, 43.7 ± 7.8 years) were randomized to receive either 100 g per day of dark chocolate (containing 88 mg flavanols) or 90 g per day flavanol-free white chocolate in an isocaloric manner for fifteen days. After a second seven-day chocolate-free period, patients were crossed over to the other treatment. Noninvasive twenty-four-hour ambulatory blood pressure, flow-mediated dilation, OGTT, serum cholesterol, and markers of vascular inflammation were evaluated at the end of each treatment. The homeostasis model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), and insulin sensitivity index (ISI) were calculated from OGTT values. Ambulatory blood pressure decreased after dark chocolate (24-hr systolic blood pressure -11.9 ± 7.7 mm Hg, P<.0001; 24-hr diastolic BP -8.5 ± 5.0 mm Hg, P<0.0001) but not white chocolate. Dark chocolate but not white chocolate decreased HOMA-IR (P<0.0001), but it improved QUICKI, ISI, and flow-mediated dilation. Dark chocolate also decreased serum LDL cholesterol (from 3.4 ± 0.5 to 3.0 ± 0.6 mmol/L; P<0.05). In summary, dark chocolate decreased blood pressure and serum LDL cholesterol, improved flow-mediated dilation, and ameliorated insulin sensitivity in hypertensives. These results suggest that, while balancing total calorie intake, flavanols from cocoa products may provide some cardiovascular benefit if included as part of a healthy diet for patients with essential hypertension.

JAMA: The Journal of the American Medical Association

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Hypertension in Adults across the Age Spectrum: Current Outcomes and Control in the Community

Donald M. Lloyd-Jones, M.D., Jane C. Evans, Daniel Levy, M.D.

Context: Data are sparse regarding current rates of hypertension treatment and control, and risks associated with hypertension, among persons older than eighty years. *Objective:* To determine the prevalence of blood pressure stages, hypertension treatment and control, and cardiovascular risk among older patients with hypertension. *Design, setting, and participants:* A community-based cohort study in which data were collected during all Framingham Heart Study examinations attended in the 1990s. Participants were pooled according to age: younger than sixty years, sixty to seventy-nine years, or eighty years or older. There were 5,296 participants who contributed 14,458 person-examinations of observation, including 7,135 hypertensive person-examinations (4,919 treated). *Main outcome measures:* Prevalence of hypertension, its treatment, and its control were compared across age groups. Risks for incident cardiovascular disease during follow-up of up to six years were estimated as multivariate-adjusted hazard ratios (HRs) and 95 percent confidence intervals (95%CIs) using Cox proportional hazards regression. *Results:* Prevalence of hypertension and drug treatment increased with advancing age, whereas control rates were markedly lower in older women

(systolic <140 and diastolic <90 mm Hg). For ages younger than sixty years, sixty to seventy-nine, and eighty years and older, respectively, control rates were 38, 36, and 38 percent in men (P=0.30) and 38, 28, and 23 percent in women (P<0.001). Relative risks for cardiovascular disease associated with increasing blood pressure stage did not decline with advancing age, and absolute risks increased markedly. Among participants eighty years of age or older, major cardiovascular events occurred in 9.5 percent of the normal blood pressure (referent) group, 19.8 percent of the prehyper-tension group (HR, 1.9; 95%CI, 0.9–3.9), 20.3 percent of the stage 1 hypertension group (HR, 1.8; 95%CI, 0.8–3.7), and 24.7 percent of the stage 2 or treated hypertension group (HR, 2.4; 95%CI, 1.2–4.6). *Conclusions:* Relative to current national guidelines, rates of blood pressure control in the community are low, especially among older women with hypertension. Short-term risks for cardiovascular disease are substantial, indicating the need for greater efforts at safe, effective risk reduction among the oldest patients with hypertension.

Volume 294, Number 8
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Fetal Pain: A Systematic Multidisciplinary Review of the Evidence

Susan J. Lee et al.

Context: Proposed federal legislation would require physicians to inform women seeking abortions at twenty or more weeks after fertilization that the fetus feels pain, and to offer anesthesia administered directly to the fetus. This article examines whether a fetus feels pain and if so, whether safe and effective techniques exist for providing direct fetal anesthesia or analgesia in the context of therapeutic procedures or abortion. *Evidence acquisition:* Systematic search of PubMed for English-language articles focusing on human studies related to fetal pain, anesthesia, and analgesia. Included articles studied fetuses of less than thirty weeks' gestational age or specifically addressed fetal pain perception or nociception. Articles were reviewed for additional references. The search was performed without date limitations and was current as of June 6, 2005. *Evidence synthesis:* Pain perception requires conscious recognition or awareness of a noxious stimulus. Neither withdrawal reflexes nor hormonal stress responses to invasive procedures prove the existence of fetal pain, because they can be elicited by nonpainful stimuli and occur without conscious cortical processing. Fetal awareness of noxious stimuli requires functional thalamocortical connections. Thalamocortical fibers begin appearing between twenty-three and thirty weeks' gestational age, while electroencephalography suggests that the capacity for functional pain perception in preterm neonates probably does not exist before twenty-nine or thirty weeks. For fetal surgery, women may receive general anesthesia and/or analgesics intended for placental transfer, and parenteral opioids may be administered to the fetus under direct or sonographic visualization. In these circumstances, administration of anesthesia and analgesia serves purposes unrelated to reduction of fetal pain, including inhibition of fetal movement, prevention of fetal hormonal stress responses, and induction of uterine atony. *Conclusions:* Evidence regarding the capacity for fetal pain is limited but indicates that fetal perception of pain is unlikely before the third trimester. Little or no evidence addresses the effectiveness of direct fetal anesthetic or analgesic techniques. Similarly, limited or no data exist on the safety of such techniques for pregnant women in the context of abortion. Anesthetic techniques currently used during fetal surgery are not directly applicable to abortion procedures.

Volume 294, Number 15
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Early Mortality among Medicare Beneficiaries Undergoing Bariatric Surgical Procedures

David R. Flum, M.D., et al.

Context: Case series demonstrate that bariatric surgery can be performed with a

low rate of perioperative mortality (0.5 percent), but the rate among high-risk patients and the community at large is unknown. *Objectives:* To evaluate the risk of early mortality among Medicare beneficiaries and to determine the relative risk of death among older patients. *Design:* Retrospective cohort study. *Setting and patients:* All fee-for-service Medicare beneficiaries, 1997–2002. *Main outcome measures:* Thirty-day, ninety-day, and one-year postsurgical all-cause mortality among patients undergoing bariatric procedures. *Results:* A total of 16,155 patients underwent bariatric procedures (mean age, 47.7 years [SD, 11.3 years]; 75.8 percent women). The rates of thirty-day, ninety-day, and one-year mortality were 2.0, 2.8, and 4.6 percent, respectively. Men had higher rates of early death than women (3.7 vs 1.5 percent, 4.8 vs 2.1 percent, and 7.5 vs 3.7 percent at thirty days, ninety days, and one year, respectively; P<0.001). Mortality rates were greater for those aged sixty-five years or older compared with younger patients (4.8 vs 1.7 percent at thirty days, 6.9 vs 2.3 percent at ninety days, and 11.1 vs 3.9 percent at one year; P<0.001). After adjustment for sex and comorbidity index, the odds of death within ninety days were five-fold greater for older Medicare beneficiaries (aged seventy-five years or older; n=136) than for those aged sixty-five to seventy-four years (n=1,381; odds ratio, 5.0; 95 percent confidence interval, 3.1–8.0). The odds of death at ninety days were 1.6 times higher (95 percent confidence interval, 1.3–2.0) for patients of surgeons with less than the median surgical volume of bariatric procedures (among Medicare beneficiaries during the study period) after adjusting for age, sex, and comorbidity index. *Conclusions:* Among Medicare beneficiaries, the risk of early death after bariatric surgery is considerably higher than previously suggested and is associated with advancing age, male sex, and lower surgeon volume of bariatric procedures. Patients aged sixty-five years or older had a substantially higher risk of death within the early postoperative period than younger patients.

New England Journal of Medicine

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Normal Fasting Plasma Glucose Levels and Type 2 Diabetes in Young Men

Amir Tirosh, M.D., et al. for the Israeli Diabetes Research Group

Background: The normal fasting plasma glucose level was recently defined as less than 100 mg per deciliter (5.55 mmol per liter). Whether higher fasting plasma glucose levels within this range independently predict type 2 diabetes in young adults is unclear. *Methods:* The authors obtained blood measurements, data from physical examinations, and medical and lifestyle information from men in the Israel Defense Forces who were twenty-six to forty-five years of age. *Results:* A total of 208 incident cases of type 2 diabetes occurred during 74,309 person-years of follow-up (from 1992 through 2004) among 13,163 subjects who had baseline fasting plasma glucose levels of less than 100 mg per deciliter. A multivariate model, adjusted for age, family history of diabetes, body-mass index, physical-activity level, smoking status, and serum triglyceride levels, revealed a progressively increased risk of type 2 diabetes in men with fasting plasma glucose levels of 87 mg per deciliter (4.83 mmol per liter) or more, as compared with those whose levels were in the bottom quintile (less than 81 mg per deciliter [4.5 mmol per liter], P for trend <0.001). In multivariate models, men with serum triglyceride levels of 150 mg per deciliter (1.69 mmol per liter) or more, combined with fasting plasma glucose levels of 91 to 99 mg per deciliter (5.05 to 5.50 mmol per liter), had a hazard ratio of 8.23 (95 percent confidence interval, 3.6 to 19.0) for diabetes, as compared with men with a combined triglyceride level of less than 150 mg per deciliter and fasting glucose levels of less than 86 mg per deciliter (4.77 mmol per liter). The joint effect of a body-mass index (the weight in kilograms divided by the square

of the height in meters) of 30 or more and a fasting plasma glucose level of 91 to 99 mg per deciliter resulted in a hazard ratio of 8.29 (95 percent confidence interval, 3.8 to 17.8), as compared with a body-mass index of less than 25 and a fasting plasma glucose level of less than 86 mg per deciliter. CONCLUSIONS: Higher fasting plasma glucose levels within the normoglycemic range constitute an independent risk factor for type 2 diabetes among young men, and such levels may help, along with body-mass index and triglyceride levels, to identify apparently healthy men at increased risk for diabetes.

Volume 353, Number 15
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Efficacy of an Acellular Pertussis Vaccine among Adolescents and Adults

Joel I. Ward, M.D., et al. for the APERT Study Group

Background: Pertussis immunization of adults may be necessary to improve the control of a rising burden of disease and infection. This trial of an acellular pertussis vaccine among adolescents and adults evaluated the incidence of pertussis, vaccine safety, immunogenicity, and protective efficacy. *Methods: Bordetella pertussis* infections and illnesses were prospectively assessed in 2,781 healthy subjects between the ages of fifteen and sixty-five years who were enrolled in a national multicenter, randomized, double-blind trial of an acellular pertussis vaccine. Subjects received either a dose of a tricomponent acellular pertussis vaccine or a hepatitis A vaccine (control) and were monitored for 2.5 years for illnesses with cough that lasted for more than five days. Each illness was evaluated with use of a nasopharyngeal aspirate for culture and polymerase-chain-reaction assay, and serum samples from patients in both acute and convalescent stages of illness were analyzed for changes in antibodies to nine *B. pertussis* antigens. RESULTS: Of the 2,781 subjects, 1,391 received the acellular pertussis vaccine and 1,390 received the control vaccine. The groups had similar ages and demographic characteristics, and the median duration of follow-up was twenty-two months. The acellular pertussis vaccine was safe and immunogenic. There were 2,672 prolonged illnesses with cough, but the incidence of this nonspecific outcome did not vary between the groups, even when stratified according to age, season, and duration of cough. On the basis of the primary pertussis case definition, vaccine protection was 92 percent (95 percent confidence interval, 32–99 percent). Among unimmunized controls with illness, 0.7 to 5.7 percent had *B. pertussis* infection, and the percentage increased with the duration of cough. On the basis of other case definitions, the incidence of pertussis in the controls ranged from 370 to 450 cases per 100,000 person-years. *Conclusions:* The acellular pertussis vaccine was protective among adolescents and adults, and its routine use might reduce the overall disease burden and transmission to children.

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Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

Martine J. Piccart-Gebhart, M.D., et al. for the Herceptin Adjuvant (HERA) Trial Study Team

Background: Trastuzumab, a recombinant monoclonal antibody against HER2, has clinical activity in advanced breast cancer that overexpresses HER2. The authors investigated its efficacy and safety after excision of early-stage breast cancer and completion of chemotherapy. *Methods:* This international, multicenter, randomized trial compared one or two years of trastuzumab given every three weeks with observation in patients with HER2-positive and either node-negative or node-positive breast cancer who had completed locoregional therapy and at least four cycles of neoadjuvant or adjuvant chemotherapy. *Results:* Data were available for 1,694 women randomly assigned to two years of treatment with trastuzumab, 1,694 women assigned to one year of trastuzumab, and 1,693 women assigned to observation. The authors report here the results only of treatment with trastuzumab for one year or obser-

vation. At the first planned interim analysis (median follow-up of one year), 347 events (recurrence of breast cancer, contralateral breast cancer, second nonbreast malignant disease, or death) were observed: 127 events in the trastuzumab group and 220 in the observation group. The unadjusted hazard ratio for an event in the trastuzumab group, as compared with the observation group, was 0.54 (95 percent confidence interval, 0.43–0.67; P<0.0001 by the log-rank test, crossing the interim analysis boundary), representing an absolute benefit in terms of disease-free survival at two years of 8.4 percentage points. Overall survival in the two groups was not significantly different (twenty-nine deaths with trastuzumab vs. thirty-seven with observation). Severe cardiotoxicity developed in 0.5 percent of the women who were treated with trastuzumab. *Conclusions:* One year of treatment with trastuzumab after adjuvant chemotherapy significantly improves disease-free survival among women with HER2-positive breast cancer. (ClinicalTrials.gov number, NCT00045032.)

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Obstructive Sleep Apnea as a Risk Factor for Stroke and Death

H. Klar Yaggi, M.D., et al.

Background: Previous studies have suggested that the obstructive sleep apnea syndrome may be an important risk factor for stroke. It has not been determined, however, whether the syndrome is independently related to the risk of stroke or death from any cause after adjustment for other risk factors, including hypertension. *Methods:* In this observational cohort study, consecutive patients underwent polysomnography, and subsequent events (strokes and deaths) were verified. The diagnosis of the obstructive sleep apnea syndrome was based on an apnea-hypopnea index of five or higher (five or more events per hour); patients with an apnea-hypopnea index of less than five served as the comparison group. Proportional-hazards analysis was used to determine the independent effect of the obstructive sleep apnea syndrome on the composite outcome of stroke or death from any cause. *Results:* Among 1,022 enrolled patients, 697 (68 percent) had the obstructive sleep apnea syndrome. At baseline, the mean apnea-hypopnea index in the patients with the syndrome was 35, as compared with a mean apnea-hypopnea index of 2 in the comparison group. In an unadjusted analysis, the obstructive sleep apnea syndrome was associated with stroke or death from any cause (hazard ratio, 2.24; 95 percent confidence interval, 1.30–3.86; P=0.004). After adjustment for age, sex, race, smoking status, alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension, the obstructive sleep apnea syndrome retained a statistically significant association with stroke or death (hazard ratio, 1.97; 95 percent confidence interval, 1.12–3.48; P=0.01). In a trend analysis, increased severity of sleep apnea at baseline was associated with an increased risk of the development of the composite end point (P=0.005). *Conclusions:* The obstructive sleep apnea syndrome significantly increases the risk of stroke or death from any cause, and the increase is independent of other risk factors, including hypertension.

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Fatal Toxic Shock Syndrome Associated with *Clostridium sordellii* after Medical Abortion

Marc Fischer, M.D., et al.

Endometritis and toxic shock syndrome associated with *Clostridium sordellii* have previously been reported after childbirth and, in one case, after medical abortion. The authors describe four deaths due to endometritis and toxic shock syndrome associated with *C. sordellii* that occurred within one week after medically induced abortions. Clinical findings included tachycardia, hypotension, edema, hemoconcentration, profound leukocytosis, and absence of fever. These cases indicate the need for physician awareness of this syndrome and for further study of its association with medical abortion.