Top Medical Stories of 2007

Each year, the editors of Journal Watch *choose the year's top stories. We try to strike a balance between relevance to primary care, recognition of landmark studies, and media publicity and public awareness. Some of our top stories emerge from one important study, and others come from several studies on a single topic. All citations are from 2007 unless otherwise noted (a few were published in late 2006, too late to include in last year's top stories). Finally, these stories are arranged in no particular order; their sequence is not intended to reflect their relative importance.*

— Allan S. Brett, MD, Editor-in-Chief

Medical vs. Invasive Approaches in Patients with Stable Angina

Early invasive strategies, which include angiography, are associated with favorable outcomes in patients with acute coronary syndromes such as myocardial infarction or unstable angina. But do these benefits carry over to patients with stable angina? In 2007, the widely publicized COURAGE trial provided some answers. In this trial, 2287 patients (mean age, 62) were randomized to percutaneous coronary intervention (PCI) plus optimal medical therapy or to optimal medical therapy alone. Subjects had either ≥70% stenosis identified by angiography with objective evidence of ischemia or classic angina with ≥80% stenosis. High-risk patients, such as those with class IV angina, substantially reduced left ventricular ejection fractions (<30%), or markedly positive stress tests, were excluded (*JW* Apr 15, p. 61, and *N Engl J Med* Apr 12; 356:1503).

In the PCI group, 94% received stents (97% were bare metal). Adherence to optimal medical therapy was excellent in both groups. During a median follow-up of 4.6 years, the incidence of the primary outcome — death or MI — was similar in the two groups (about 19%); hospitalization and stroke rates were also similar in the two groups. However, the PCI group had a significantly lower rate of revascularization during follow-up (21% vs. 33%) and better angina-free survival at 1 year (66% vs. 58%) and 3 years (72% vs.67%) although not at 5 years (74% vs. 72%).

What do cardiologists think about PCI versus medical management in patients with stable angina? Investigators conducted focus groups, consisting of 20 cardiologists, to elicit their opinions on this question. During these interviews, conducted in 2006, researchers described hypothetical case scenarios. Despite acknowledging a lack of proof that PCI lengthens survival or lowers MI rates, these cardiologists expressed belief that PCI benefited stable-angina patients. Rationales included better treatment of ischemia, belief that an "open artery" was beneficial, potential regret if patients suffered cardiac events after receiving only medication, medicolegal concerns, and improvements in patients' well-being and anxiety levels (*Arch Intern Med* Aug 13/27; 167:1604).

The COURAGE trial suggests that, in patients with stable angina, an initial invasive approach is associated with somewhat better early control of symptoms but with mortality and infarction rates that are similar to those seen with medical therapy. Critics point out that <10% of screened patients were eligible for enrollment, which raises questions about the generalizability of the findings. Although these data support current guidelines that allow for deferring angiography in selected patients with stable angina, they should not be extended to higher-risk patients, such as those who present with acute coronary syndromes. The data from the focus groups suggest that difficulties will arise in preventing the "oculostenotic reflex" of performing PCI on anatomically significant lesions once the decision to pursue angiography is made.

— Kirsten E. Fleischmann, MD, MPH

This ACC/AHA guideline on chronic stable angina is available at http://www.guideline.gov/summary/summary.aspx?doc_id=3788&nbr=003... free of charge.

Surgery or Watchful Waiting for Lumbar Disk Herniation?

The best approach to a patient with acute lumbar disk herniation is unclear, to some extent because strictly randomized trials in this area are difficult to conduct. Three studies suggest that patient choice might be the most important factor.

In one study, 472 U.S. patients with acute lumbar radicular pain and corresponding positive imaging results were randomized to diskectomy or conservative care. Crossover to the alternate intervention was relatively common (40%–45%). Both groups improved substantially after 2 years of follow-up, with no difference noted by an intent-to-treat analysis. In an accompanying observational study of 743 patients who declined randomization, 528 chose surgery and improved somewhat more in pain and physical function than did those who chose conservative therapy. Surgery recipients tended to be younger and to have more severe symptoms at baseline than did those who chose conservative management (*JW* Dec 15 2006, p. 189, and *JAMA* 2006 Nov 22/29; 296:2441, 2451).

In another study, 283 Dutch patients, similar to those described above, were randomized to surgery or conservative treatment. Crossover rates were lower (11%–39%) than in the previous study. Surgical patients improved more initially than conservatively managed patients, but the groups were similar by 1 year (*JW* Jul 1, p. 102, and *N Engl J Med* May 31; 356:2245).

Patient preference is a huge factor in our approach to acute disk herniation, both in initial clinical decision making and in subsequent decisions to try other therapies, as in these quasi-controlled trials. Based on these studies, we reasonably can tell patients that most of them are likely to get better by 1 year, whether or not they undergo surgery. For those who are impatient with the conservative approach, who have minimal medical comorbidity, and who are at low risk for surgical complications, or for those whose pain is unbearable, early surgery is reasonable. For those who would like to try

conservative management (or eventually opt for surgery, depending on their degree of pain resolution), outcomes are comparable to those of early surgery. An editorialist notes that the uncertainty here will be resolved only with a trial that includes a sham-surgery control, which he believes would be justified ethically; however, recruitment for such a trial likely would be very difficult (*JW* Dec 15 2006, p. 189, and *JAMA* 2006 Nov 22/29; 296:2483).

— Thomas L. Schwenk, MD

Rosiglitazone: Unclear Evidence, Uncertain Practice

In May 2007, the FDA recommended that patients who were taking rosiglitazone (Avandia) speak with their doctors about data from controlled trials that showed a "potentially significant increase in the risk of heart attack and heart-related deaths." This recommendation was based, in large part, on the results of a meta-analysis of 42 randomized trials (*JW* Jun 15, p. 93, and *N Engl J Med* Jun 14; 356: 2457) that showed rosiglitazone use was associated with significantly higher risk (odds ratio, 1.4) for myocardial infarction than the baseline rate (0.6%). Risk for cardiovascular death (baseline, 0.3%) also was higher (OR, 1.6), although this finding was of borderline significance. A reanalysis, which addressed some of the methodologic concerns about that meta-analysis, demonstrated that the increased risks for cardiovascular death or MI were smaller and not statistically significant (*JW* Sep 15, p. 144, and *Ann Intern Med* Oct 16; 147:578). Another meta-analysis of seven randomized trials showed that thiazolidinediones (both rosiglitazone and pioglitazone) increased risk for heart failure, a known complication (2.3% vs. 1.4%), but did not increase risk for cardiovascular death (*JW* Nov 1, p. 168, and *Lancet* Sep 29; 370:1129).

Because of the controversy, investigators performed an interim analysis of a randomized trial in which patients received either metformin plus a sulfonylurea or rosiglitazone plus one of the other two medications. Risk for cardiovascular death or hospitalization was not significantly higher with rosiglitazone (hazard ratio, 1.08); the rosiglitazone group experienced slightly more MIs (43 vs. 37; P=0.5; *JW* Jul 1, p. 101, and *N Engl J Med* Jul 5; 357:28).

In November 2007, the FDA added a boxed warning to Avandia's label. The warning includes this statement: "In their entirety, the available data on the risk of myocardial ischemia are inconclusive."

We need large prospective studies that include relevant clinical outcomes beyond glycemic control; only such studies will show whether the rosiglitazone controversy has been much ado about nothing or about something. In the meantime, expert opinion has ranged from "the jury is still out" to "clinicians should no longer feel comfortable prescribing rosiglitazone." Because alternatives to thiazolidinediones exist, one approach to the evidence and warnings would be to not prescribe any of them. Another approach would be to substitute pioglitazone for rosiglitazone, because pioglitazone has not been associated with myocardial infarction (*JW* Oct 1, p. 152, and *JAMA* Sep 12; 298:1180, 1189). However, for some patients with good glycemic control on rosiglitazone, uncertain risks might not outweigh practical complexities associated with changing medical regimens.

— Richard Saitz, MD, MPH, FACP, FASAM

This latest FDA alert on Avandia is available at http://www.fda.gov/bbs/topics/NEWS/2007/NEW01743.html free of charge.

Effects of Inhaled Therapy on Mortality in COPD

Do inhaled corticosteroids and long-acting β-agonists lower mortality in patients with chronic obstructive pulmonary disease (COPD)? To answer this question, industry-sponsored researchers conducted the TORCH study, which included 6000 COPD patients (FEV_1 <60% of predicted; and reversibility with albuterol <10% of predicted FEV_1). Patients were randomized to receive twice-daily inhaled therapy with salmeterol plus fluticasone (Advair 50/500), salmeterol (Serevent) alone, fluticasone (Flovent) alone, or placebo (*JW* Mar 15, p. 45, and *N Engl J Med* Feb 22; 356:775).

The primary endpoint, 3-year all-cause mortality, was lower with combined therapy than with placebo (12.6% vs. 15.2%), but the difference was of borderline statistical significance (P=0.052). Mortality with salmeterol alone (13.5%) was midway between rates seen with combined therapy and placebo, but mortality with fluticasone alone (16%) was slightly higher than mortality with placebo. Similarly, combined therapy and salmeterol alone — but not fluticasone alone — lowered hospitalization rates for COPD exacerbation. All three active therapies fared better than placebo for preventing COPD exacerbations, with combined therapy performing best. An unexpected outcome was a higher incidence of pneumonia in the steroid groups than in the salmeterol-alone and placebo groups.

Unfortunately, these findings don't yield a simple conclusion. The steroid-plus-β-agonist combination came close to lowering mortality significantly and did lower rates of exacerbation and hospitalization. For monotherapies, the overall balance of benefits and harm was more favorable for salmeterol than for fluticasone; a noteworthy finding in COPD patients, because it's the opposite of generally accepted dogma in asthma, where monotherapy with long-acting β-agonists is not recommended. Finally, TORCH did not include a long-acting anticholinergic drug (e.g., tiotropium [Spiriva]), which can lower exacerbation rates but has not been evaluated in a long-term mortality study.

According to a new COPD guideline recently published by the American College of Physicians, clinicians should prescribe a maintenance monotherapy — long-acting β-agonist, long-acting anticholinergic, or inhaled corticosteroid — for patients with COPD and FEV_1 <60% of predicted (*JW* Jan 1 2008, p. 11, and *Ann Intern Med* Nov 6; 147:633, 639). However, the TORCH findings suggest that steroid monotherapy should be dropped from this recommendation. The guideline authors also state that clinicians "may consider" combination steroid and β-agonist therapy, and they cite the TORCH study to support this recommendation. However, clinicians should think about long-term side effects when they consider prolonged inhaled-steroid therapy for COPD patients.

— Allan S. Brett, MD

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ew Guidelines for revention of Endocarditis

The focus of *Journal Watch* "Top Stories" generally is original research, not practice guidelines. This year, we make an exception with the American Heart Association's new guidelines on prevention of endocarditis, which represent a major shift in practice. For many clinical entities, multiple organizations elaborate competing clinical guidelines in the U.S., but for prevention of endocarditis, the AHA's guideline — last updated in 1997 — essentially stands alone (*JW* Jul 1, p. 101, and *Circulation* Oct 9; 116:1736).

Prophylaxis is now recommended for only four high-risk conditions — prosthetic valves, previous endocarditis, certain types of congenital heart disease, and cardiac transplantation with valvulopathy. For patients with these conditions, prophylaxis should be given before only the following procedures: dental procedures that involve manipulation of gingival tissue or periapical regions of the teeth or that involve perforation of oral mucosa, incision or biopsy of respiratory-tract mucosa, and surgery on infected skin or musculoskeletal structures. Amoxicillin (2 g, given orally 30–60 minutes before the procedure) is recommended; alternatives are listed for patients with penicillin allergy or those who cannot tolerate oral medications.

Two important changes are particularly relevant to everyday practice. First, endocarditis prophylaxis is no longer recommended before gastrointestinal (GI) and genitourinary (GU) procedures; however, for patients with high-risk cardiac conditions who have established GI or GU infections (e.g., enterococcal urinary infection), one should attempt to eradicate the infection prior to any invasive procedure. Second, prophylaxis is no longer recommended for patients with acquired cardiac valvular disease or mitral valve prolapse, even if mitral regurgitation is present.

What prompted these changes? Researchers have long noted limitations in the evidence supporting endocarditis prophylaxis. No randomized trials have been conducted, and retrospective studies have yielded mixed results. Moreover, cumulative exposure to bacteremia from daily oral activities (e.g., chewing, flossing, brushing) is far greater than exposure from occasional dental procedures. Experts now believe that the potential harms from millions of antibiotic courses in low-risk patients outweigh any benefits.

This new guideline should dramatically lower antibiotic prescribing for endocarditis prophylaxis. In fact, many patients who shouldn't have qualified for endocarditis prophylaxis even under the 1997 version (e.g., those with innocent systolic murmurs) have been receiving prophylaxis. The new guideline affords an opportunity for primary care physicians to educate such patients. Finally, resistance from dentists should be eased by the American Dental Association's approval of this guideline.

*— **Allan S. Brett, MD***

Benefits and Risks of Long-Term Alendronate

Alendronate (and the related biphosphonates, risedronate and zoledronic acid), when taken for 3 to 5 years, increases bone density and reduces both vertebral and nonvertebral fracture rates in postmenopausal women. However, some experts have voiced concern that prolonged exposure to these drugs eventually might decrease bone strength by suppressing bone turnover (*JW* May 1 2005, p. 69, and *J Clin Endocrinol Metab* 2005 Mar; 90:1294). This apprehension led researchers to ask whether a "holiday" from alendronate after 5 years of therapy might be reasonable.

In the Fracture Intervention Trial Long-term Extension (FLEX), a multiinstitutional team began with 1099 women who previously had been randomized to alendronate therapy for a median of 5 years. These participants were randomized again to either daily alendronate (5–10 mg) or placebo for 5 additional years (*JW* Feb 1, p. 21, and *JAMA* 2006 Dec 27; 296:2927). Women who took placebo showed declines in bone-mineral density (BMD) at the hip and spine during the next 5 years, as well as increased serum markers of bone turnover. In contrast, women who received alendronate did not have these findings.

Relative risk for symptomatic vertebral fractures in women taking alendronate (now for 10 consecutive years) was considerably lower than that in subjects taking alendronate for 5 years and then placebo for 5 years. However, no significant differences were noted in the rates of nonsymptomatic vertebral fractures or nonvertebral fractures. Subgroup analysis revealed that the greatest benefit from an additional 5 years of alendronate therapy was in women with baseline BMD T scores of –2.5 or lower or those who already had experienced vertebral fractures at the time of enrollment in the FLEX study.

No significant difference was seen between the alendronate and placebo groups in serious adverse events or discontinuations of drug because of suspected adverse events. In particular, not a single case of osteonecrosis of the jaw occurred — an adverse effect that got a lot of media attention but that has been seen primarily in patients with cancer who are treated with high-dose intravenous bisphosphonates, not in typical patients taking oral bisphosphonates (*JW* Aug 15, p. 126, and *J Natl Cancer Inst* Jul 4; 99:1016).

The FLEX study results help us determine for whom long-term alendronate therapy (as long as 10 years) is beneficial. For women with low T scores or previous fractures, continued alendronate therapy conferred benefits. For women with better BMD scores and no vertebral fractures at baseline, however, one could make a case for discontinuing alendronate after 5 years and monitoring BMD closely. The same could be true for women who are at low 5-year risk of hip fracture; based on a large, recently published observational study (*JW* Jan 1 2008, p. 1, and *JAMA* Nov 28; 298:2389) risk can be determined using a Web-based interactive calculator.

*— **Anthony L. Komaroff, MD***

The risk calculator is available at http://riskcalculator.fore.org free of charge.

A Bad Year for Pharmaceutical Erythropoietins

Pharmaceutical erythropoietins, such as epoetin α (Epogen and Procrit) and darbepoetin α (Aranesp), are FDA approved to treat symptomatic anemia caused by chronic kidney disease (CKD) and cancer chemotherapy. However, several recent trials have heightened concerns about the safety

of these agents, particularly when they are used to induce hemoglobin (Hb) levels >12 g/dL.

In an international trial, 603 non-dialyzed CKD patients with Hb levels of 11–12.5 g/dL were randomized to receive epoetin β (unavailable in the U.S.) to correct anemia completely (target Hb level, 13–15 g/dL) or to receive epoetin β only when Hb levels fell below 10.5 mg/dL (target Hb level, 10.5–11.5 g/dL). The likelihood of first cardiovascular events was the same in both groups. However, patients in the complete-correction group were significantly more likely to experience headaches and hypertension and to require hemodialysis (*JW* Dec 15 2006, p. 190, and *N Engl J Med* 2006 Nov 16; 355:2071).

In a U.S. trial, 1432 nondialyzed CKD patients with Hb levels <11 g/dL were randomized to receive epoetin α to achieve target Hb levels of 13.5 g/dL or 11.3 mg/dL. The trial was stopped early, because patients in the high-target group experienced significantly more endpoint events (death, myocardial infarction, heart failure, and stroke) than did patients in the low-target group (*JW* Dec 15 2006, p. 190, and *N Engl J Med* 2006 Nov 16; 355: 2085). A meta-analysis of nine randomized trials (including the two described above) confirmed poorer outcomes in CKD patients who were treated to achieve high Hb targets than in similar patients whose targets were lower (*JW* Mar 1 2007, p. 38, and *Lancet* Feb 3; 369:381).

The results of recent trials also have raised concerns about the safety of pharmaceutical erythropoietins in cancer patients. For example, in one trial, patients with advanced non-small cell lung cancer and hemoglobin levels ≤12 g/dL were randomized to receive epoetin α (target Hb level, 12–14 g/dL) or placebo. The trial was stopped early, because an interim data analysis revealed significantly shorter median survival in the epoetin group than in the placebo group (*JW* May 15, p. 80, and *J Clin Oncol* Mar 20; 25:1027).

These and other findings prompted the FDA to issue advisories in 2007 about pharmaceutical erythropoietins. The FDA warns that these drugs can stimulate tumor growth and shorten survival in patients with various cancers and that they can increase risk for death and adverse cardiovascular events when they are dosed to achieve Hb levels >12 g/dL. The FDA recommends using the lowest effective dose of pharmaceutical erythropoietin to avoid blood transfusions and withholding these drugs if Hb levels are >12 g/dL.

As if the results of recent trials and the FDA warnings weren't troubling enough, the *New York Times* reported that the manufacturers of pharmaceutical erythropoietins have paid physicians hundreds of millions of dollars in rebates for prescribing these agents. Obviously, this practice raises ethical concerns about inappropriate prescribing practices (*The New York Times* May 9).

— ***Paul S. Mueller, MD, MPH, FACP***

Dr. Mueller is an Associate Professor of Medicine at Mayo Clinic College of Medicine in Rochester, Minnesota.

The latest FDA alert on epoetin is available at http://www.fda.gov/cder/drug/InfoSheets/HCP/RHE2007HCP.pdf free of charge.

Circumcision to Prevent HIV: A Promising Strategy Raises Provocative Questions

As access to antiretroviral therapy for HIV-infected people slowly penetrates the developing world, preventing new HIV infections remains a high priority. Unfortunately, efforts to lower transmission rates through behavior change and use of vaginal microbicides generally have been disappointing, and an HIV vaccine remains only a distant hope.

In December 2006, the NIH announced the early termination of two randomized controlled studies of adult male circumcision in Kenya and Uganda after interim analyses showed that, in each trial, HIV incidence was halved among men who had been circumcised compared with those who had not. In both trials, researchers randomized uncircumcised, HIV-negative men to surgical circumcision either immediately or after a delay of 24 months; all participants were given risk-reduction counseling and condoms. No differences in risk behaviors were observed between groups in either study nor were severe complications of surgery seen (*JW* Apr 1, p. 55, and *Lancet* Feb 24; 369:643, 657).

Based on these studies, an editorialist called male circumcision "the most compelling evidence-based [HIV] prevention strategy to emerge since the results from mother-to-child transmission clinical trials." Epidemiologic modeling suggested that, in southern Africa alone, widespread male circumcision could prevent 2 million new HIV infections and 300,000 deaths in the next decade. The huge potential benefits of this strategy immediately brought forth new questions: What might be the direct and indirect effects on male-to-female transmission? What is the optimal age for circumcision? How can resources be deployed to maximize benefits and minimize risks? Will circumcision be accepted in different cultures? How can circumcision be promoted without undermining education about condom use and campaigns against female genital mutilation?

Finally, what are the implications of these findings for advice on newborn circumcision in developed countries? In a study published in 2006, uncircumcised men in a New Zealand birth cohort were more than three times as likely as circumcised men to have sexually transmitted infections between age 18 and age 25 (*JW* Jan 1, p. 10, and *Pediatrics* 2006 Nov; 118:1971). Other evidence suggests that circumcision lowers risk for urinary tract infections, genital ulcer disease, penile cancer, and, perhaps, transmission of human papillomavirus. The perceived benefits of newborn circumcision in any setting will depend on the perceived risks for these negative outcomes. The new data on HIV and sexually transmitted diseases could shift the discussion perceptibly toward advocacy for circumcision in the developed world, particularly among groups perceived to be at greatest risk for HIV infection.

— ***Bruce Soloway, MD***

Dietary Supplements Don't Prevent Cognitive Decline, CVD, or Infections

In 2006, sales of nutritional supplements exceeded $4.5 billion in the U.S. alone. This year, in several studies, researchers assessed whether supplements — especially with vitamins that are touted as antioxidants — are beneficial.

In one randomized trial, researchers assessed whether long-term vitamin E supplementation slowed cognitive decline among older women (age, ≥65 at

udy entry). At 10 years, global cognitive function did not differ in the vitamin E and placebo groups. In secondary analyses, statistically significant reductions in cognitive decline were seen in several subgroups of vitamin E recipients (i.e., women with low baseline vitamin E intake, women who exercised less than once weekly, and women without diabetes), but these reductions were small and of questionable clinical importance (*JW* Jan 15, p. 16, and *Arch Intern Med* 2006 Dec 11/25; 166:2462).

Another randomized supplement study involved women with histories of cardiovascular disease or three or more risk factors for cardiovascular disease (CVD). After a mean of 9 years, no reduction was observed in a combined cardiovascular endpoint with vitamin C, vitamin E, or β-carotene supplementation, when taken alone or in combination. In the subgroup of women with histories of CVD, vitamin E was associated with a marginally significant reduction in the endpoint (*JW* Oct 15, p: 157, and *Arch Intern Med* Aug 13/27; 167:1610).

In a study from Toronto, nursing home residents were randomized to receive either a multivitamin and mineral supplement or placebo. During 18 months of follow-up, the multivitamin and the placebo groups had similar numbers of infections per patient, infection-free patients, visits to the emergency department, and hospitalizations (*JW* Feb 15, p. 34, and *J Am Geriatr Soc* Jan; 55:35).

Finally, in a meta-analysis of 68 randomized clinical trials involving more than 230,000 patients, researchers assessed the effect of β-carotene, vitamin A, vitamin C, vitamin E, or selenium supplementation, in combination or individually, relative to placebo. Overall, no mortality benefit was seen. When only 47 trials with the highest methodologic quality were examined, a significant increase in mortality risk was noted with supplemental β-carotene, vitamin A, and vitamin E (relative risks, 1.05, 1.16, and 1.04, respectively; *JW* Apr 1, p. 57, and *JAMA* Feb 28; 297:842).

In total, these studies failed to show evidence of health benefit associated with vitamin supplementation across a broad set of clinical endpoints, and potential harm cannot be excluded. Patients should be told that little evidence supports the use of supplements other than for several specific indications (e.g., folic acid for pregnancy). The best advice is to return to mother's directive — eat your fruits and vegetables.

— Jamaluddin Moloo, MD, MPH

Pharmaceutical Influence Is Pervasive but Hard to Quantitate

The methods used by pharmaceutical companies to market their wares have undergone increasing scrutiny in recent years. This year, several research groups attempted to provide quantitative data on these controversial tactics.

Legislation proposed or recently passed in 16 states mandates public disclosure of pharmaceutical company payments to physicians. However, researchers who examined records in two of these states found it virtually impossible to assemble a complete database of per-physician payments. Some companies routinely withheld information on the grounds that such information constituted a "trade secret," and others provided information only erratically. Overall, the researchers concluded that existing laws are not stringent enough to provide the public with the full disclosure intended and, unless amended, will lead to substantial underestimates of the dollar amounts that are changing hands (*JW* Apr 15, p. 64, and *JAMA* Mar 21; 297:1216).

Researchers also approached the question from the opposite direction: Of more than 3000 U.S. physicians who were asked to report gifts or payments from industry during a single year, 52% responded. Almost all responders reported accepting some gifts, most commonly food or trinkets (83%) and drug samples (78%) from drug reps. More than a third were subsidized to attend continuing medical education seminars or medical conferences, and 28% were paid for consulting, speaking, or enrolling patients in trials (*JW* May 15, p. 83, and *N Engl J Med* Apr 26; 356:1742).

Meanwhile, the marketing of drugs directly to patients has escalated. In a recap of such advertising, researchers found that, from 1996 to 2005 in the U.S., total spending rose from $1 billion to $4 billion, consuming as much as a third of the marketing budget for some well-known brand-name drugs. Direct-to-consumer advertising elicited a disproportionate fraction of the violations that the FDA found in overall drug promotion, with ads generally cited for minimizing drug risks or exaggerating effectiveness (*JW* Sep 15, p. 141, and *N Engl J Med* Aug 16; 357:673).

Overall, the links between physicians and industry clearly are strong, but even our best data are likely to underestimate their extent. Industry also is reaching out to individual consumers with record amounts of advertising that is often rife with misinformation.

— Abigail Zuger, MD

Potpourri of Pediatric Research: 2007

Tympanostomy tubes for otitis: They don't improve outcomes

To improve hearing and developmental outcomes in children with otitis media, tympanostomy tubes often are used to reduce middle-ear effusions. In a long-term follow-up study, 391 children were randomized to either prompt or delayed insertion of tympanostomy

tubes before age 3 years. At ages 9 to 11 years, comprehensive assessments yielded no significant differences between groups in speech and language, intelligence, academic achievement, or parent and teacher ratings of behavior (*JW* Feb 15, p. 32, and *N Engl J Med* Jan 18; 356:248).

Liberal transfusion policies: No evidence of benefit

Randomized trials in critically ill adults have shown that restrictive transfusion policies are superior to liberal strategies. However, whether these data apply to children is unclear. In a randomized trial, 637 stable critically ill children with hemoglobin (Hb) concentrations of ≤9.5 g/dL were assigned to either restrictive transfusion (target Hb level, 8.5–9.5 g/dL) or liberal transfusion (target Hb level, 11–12 g/dL). During the study, the average difference in Hb levels between the two groups was 2.1 g/dL, and the restrictive group received 44% fewer transfusions. No differences between groups were observed in any primary outcome, including death or multiple organ dysfunction. This study suggests that, in stable critically ill children, a liberal transfusion policy confers no benefit (*JW* May 15, p. 77, and *N Engl J Med* Apr 19; 356:1609).

Steroids for bronchiolitis: They don't work

Many different drugs are used to treat bronchiolitis in infants. In a multisite double-blind clinical trial, researchers randomized 600 infants with suspected bronchiolitis who had no past history of wheeze to either dexamethasone or placebo. Hospital admission rates were virtually identical in the steroid and placebo groups (39.7% and 41.0%, respectively). Length of stay for hospitalized infants and subsequent admissions in the 7 days after intervention also were similar in the two groups. For infants with bronchiolitis, steroids do not prevent hospitalization or speed recovery (*JW* Aug 15, p. 125, and *N Engl J Med* Jul 26; 357:331).

Caffeine for apnea of prematurity: Success story!

Caffeine often is administered for apnea of prematurity (AOP), despite a lack of safety data in infants. In an important randomized trial, 2006 infants with birth weights between 500 g and 1250 g received either caffeine citrate or placebo until AOP resolved. At a corrected age of 18 to 21 months, caffeine recipients were significantly more likely than placebo recipients to survive without neurodevelopmental disability, and caffeine significantly lowered the incidence of cerebral palsy and cognitive delay. Caffeine is safe and probably works primarily by improving ventilation (*JW* Dec 1, p. 185, and *N Engl J Med* Nov 8; 357:1893).

— Howard Bauchner, MD

Human Stem-Cell Breakthrough

In late 2007, two laboratories reported breakthroughs that one day could make possible all of the potential benefits of human embryonic stem cells (ESCs) with none of the ethical objections. How did this come about? First, some context:

In 1997, the famous cloned sheep, Dolly, was created by nuclear transfer (*JW* Apr 1 1997, p. 53, and *Nature* 1997 Feb 27; 385:810): The nucleus of a differentiated adult cell was placed into an egg from which the nucleus had been extracted. Signals in the egg cytoplasm then "reprogrammed" the adult nucleus to return to an embryonic state. The embryo was placed in a ewe's uterus and developed into Dolly. This same nuclear transfer technique was then used in various mammals to harvest ESCs from embryos. In 2005, a Korean team claimed (fraudulently) to have achieved the same feat in humans (*JW* Apr 1 2004, p. 53, and *Science Express* 2004 Feb 12). Even if the Korean team had succeeded, some would have regarded the feat as unethical, because it involved the creation and destruction of a human embryo.

In 2006, a Japanese team distinguished genes that are turned on in an embryonic stem cell from those activated in an adult cell and identified candidate genes that they hypothesized turned a cell into an ESC. In June 2007, the Japanese team, along with two American teams, reported that they had been able to trick fully differentiated mouse cells into becoming undifferentiated pluripotent cells with all the characteristics of mouse ESCs by introducing these genes (*JW* Jul 15, p. 115, and *Nature* Jul 19; 448:313).

In November 2007, the Japanese team and another American team reported the same feat with *human* cells (*JW* Dec 15, p. 196, and *Cell* Nov 20). Both teams introduced four genes into differentiated cells using retroviral vectors. Cells, with all the properties of human ESCs, now can be made that contain the genome of a specific patient; such cells should not engender immune rejection. Moreover, such cells can be made without creating (and destroying) a human embryo — the primary ethical concern about ESC therapy. However, manipulated cells can become cancerous with the techniques used now, so more work is needed to optimize this approach. Finally, in December 2007, scientists used ESC-like cells that were made from mouse skin cells to cure sickle cell anemia in mice (*JW* Jan 1 2008, p. 12, and *Science* Dec 6). Because of all of these landmark studies, 2007 likely will be regarded as a turning point in the history of human stem-cell therapy.

— Anthony L. Komaroff, MD