

In marked contrast to the *Riegel* decision and to the FDA's new position on preemption, a Supreme Court ruling this month in a drug preemption case, *Wyeth v. Levine*,⁷ dismissed Wyeth's argument that failure-to-warn suits against drug companies are preempted by FDA approval of the drug's label. The Food, Drug, and Cosmetic Act contains no explicit preemption clause with regard to prescription drugs. The drug company argued that even though preemption is not specifically mentioned in the Act, it is "implied" by virtue of the supremacy clause of Article IV of the U.S. Constitution, which states that federal law is supreme to state law. In its 6-to-3 ruling, the Supreme Court rejected this argument and found, as well, that the position put forth by the FDA in 2006 "does not merit deference."

As the law now stands, failure-to-warn and design-defect lawsuits are preempted for medical devices but not for drugs. This perplexing state of affairs defies all logic. To address the inconsistency and to improve the safety of medical products, Congressmen Henry Waxman (D-CA), chair of the House Committee on Energy and Commerce, and Frank Pallone (D-NJ), chair of the Health Subcommittee, recently introduced the Medical Device Safety Act.⁸ This bill, along with a companion bill introduced by Senators Edward Kennedy (D-MA) and Patrick Leahy (D-VT), would nullify the Court's ruling in *Riegel* by adding language to the Medical Device Amendments to make explicit that the law does not preempt suits against device companies, and thereby to place medical devices and drugs on a level playing field with respect to patient lawsuits.

Patients and physicians deserve to be fully informed about the benefits and risks of medical devices, and the companies making the devices should be held accountable if they fail to achieve this standard. We urge Congress to swiftly pass this legislation and to allow lawsuits by injured patients, which have been an important part of the regulatory framework and very effective in keeping medical devices safe, to proceed in the courts. The critical issue of preemption, which directly affects the disclosure of risks and thus the safety of the nation's supply of medical devices and drugs, should properly be decided by officials elected by the people, with whom the responsibility for the health of the public rightfully resides.

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Silent Acid Reflux and Asthma Control

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There are some patients with asthma who have a good response to standard therapy, but there are always some whose symptoms are not well controlled despite treatment with standard asthma medications. Guidelines for the treatment of asthma recommend that patients who have asthma that is difficult to control be evaluated for the presence of coexisting conditions such as gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis or sinusitis, and chronic stress or depres-

sion, since these conditions could be contributing to the lack of response to therapy. Previously published controlled trials have suggested that treatment with a proton-pump inhibitor alleviates asthma that is associated with symptomatic gastroesophageal reflux.^{1,2} Does this treatment benefit patients with asthma who may have asymptomatic gastroesophageal reflux?

Gastroesophageal reflux is a common syndrome, with 10 to 20% of the population in

Western countries and 5% of Asians having typical symptoms, such as heartburn. Its prevalence is higher in people with asthma. Furthermore, a large proportion of patients have multiple episodes of acid reflux but report few, if any, episodes of heartburn; it is estimated that no more than 5% of all acid-reflux events produce symptoms.³ The prevalence of asymptomatic acid reflux in patients with asthma varies between 10% and 62% according to the underlying severity of the asthma and the measure used to identify symptoms.⁴⁻⁶ Given the established benefit of treatment with proton-pump inhibitors in patients with asthma and symptomatic gastroesophageal reflux, it has been recommended that patients with poorly controlled asthma, especially those who have frequent episodes of nocturnal respiratory symptoms, be evaluated for acid reflux even when they do not have typical symptoms of reflux.

In this issue of the *Journal*, Mastronarde and colleagues⁷ report on a randomized, placebo-controlled, double-blind trial of treatment with esomeprazole, 40 mg twice daily, in adult patients who presented with uncontrolled asthma and no symptoms of gastroesophageal reflux. Patients who had a low quality of life or acute episodes of asthma during the previous year despite treatment with a moderate-to-high dose of inhaled corticosteroids were randomly assigned to either esomeprazole or placebo. Over the next 24 weeks, the rate of episodes of poor asthma control, defined as a decrease of 30% or more in the morning peak expiratory flow rate on 2 consecutive days, an unscheduled health care visit for asthma, or the need for a course of oral corticosteroids for asthma, was recorded. Esophageal pH monitoring was performed before the initiation of the study drugs in three quarters of the participants, and approximately 40% of patients in both groups had recordings consistent with acid reflux. Esomeprazole treatment did not improve asthma control, even in the presence of acid reflux as documented with the use of pH monitoring. The authors' conclusions that, among patients with asthma and no symptoms of acid reflux, treatment with proton-pump inhibitors does not improve asthma control in general and that 24-hour esophageal pH monitoring does not predict the response to proton-pump inhibitors are well justified.

Does the failure of treatment with proton-pump inhibitors mean that gastroesophageal re-

flux is not related to the worsening of asthma? Probably not. Even among the patients with reflux symptoms, treatment with proton-pump inhibitors twice daily for 4 to 8 weeks, a regimen that effectively suppresses acid reflux in more than 90% of people, fails to suppress symptoms in approximately 25% of patients.⁸ Response to standard acid-suppressive treatment is even lower among patients with nonerosive reflux disease, since, in up to 60% of these patients, there is no increased exposure to distal esophageal acid.⁹ Potential reasons for the failure of proton-pump inhibitors to elicit a response include a lack of compliance with the medication regimen, impaired gastric accommodation, delayed gastric emptying, nocturnal gastric-acid breakthrough, and rapid drug metabolism. In addition, reflux of nonacidic gastric contents (e.g., pepsin, bile acids, and pancreatic enzymes), mechanical distention of the esophagus, or sensory-nerve hyperalgesia may act as a predominant mechanism in eliciting symptoms in the patients with asthma that is resistant to proton-pump inhibitors. The improvement of asthma control in more than 80% of patients with asthma who undergo laparoscopic fundoplication further supports the notion that esophageal reflux plays a role in asthma¹⁰; however, these data are not that strong, and more objective assessment of the effects of the surgery on asthma control will be required.

Demonstration of the relationship between gastroesophageal reflux and asthma is even more difficult, given that there is no established method to examine the effect of esophageal reflux on esophageal or extraesophageal symptoms. Ambulatory 24-hour esophageal pH monitoring, which has been considered until now to be the reference standard for the diagnosis of gastroesophageal reflux, has many limitations. Acid reflux can be diagnosed when distal esophageal pH is less than 4 for at least 5% of the total study time; this diagnostic definition correlates well with endoscopically diagnosed erosive esophagitis.¹¹ Nevertheless, this method does not evaluate the volume and proximal extent of reflux, factors that may be important for the development of extraesophageal symptoms. Dual-probe esophageal pH monitoring in patients with upper airway symptoms showed that patients who had acid reflux detected at both the proximal and distal probe had a significantly higher incidence of nocturnal cough than those in whom acid reflux was detected only at the distal probe.¹² Methods such

as multichannel intraluminal impedance measurements with a pH sensor or the monitoring of bilirubin reflux are required to detect nonacidic reflux; it may be these events that are leading to asthma that is difficult to treat.

What Mastronarde and colleagues have shown is that neither esophageal pH monitoring nor the empirical treatment with proton-pump inhibitors identifies the patients in whom asthma is worse because of factors related to gastroesophageal reflux. We believe that a clinical trial should be undertaken in which the inclusion criteria include objective evidence of acidic and nonacidic esophageal reflux and patients are randomly assigned to treatment with medication or surgical repair of gastroesophageal reflux. Until such a trial is undertaken, empirical treatment with proton-pump inhibitors does not make sense.

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Brown Adipose Tissue — When It Pays to Be Inefficient

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Obesity has reached epidemic proportions, and complications related to obesity contribute substantially to health care costs and mortality. Since the accumulation of fat is the net result of a prolonged state of imbalance between energy intake and energy expenditure, one would think that an ideal fat mass in obese persons could be achieved relatively simply by either decreasing food intake or increasing energy expenditure, ultimately causing a sustained negative energy balance. Unfortunately, this is not so easy to achieve, because evolutionary pressure has rewarded those individuals and species able to store sufficient energy to survive famines; also, the unrestricted availability of food represents an unnatural condition.¹ Currently, most interventions, whether behavioral or pharmacologic, are aimed at the energy-intake side of the equation and result in only moderate, often temporary improvements, with the notable exception of bariatric surgery.

Interventions designed to increase energy expenditure are relatively limited. An increase in physical activity, although effective, is not easy to sustain. The pharmacologic approach has also been disappointing. Supraphysiologic doses of thyroid hormones or adrenergic agonists result in an increase in energy expenditure, but their systemic adverse events preclude their use for the treatment of obesity.

Brown adipose tissue represents a natural target for the modulation of energy expenditure. This tissue is far from being a fat depot. When activated, it requires the uptake of substrate from the circulation, mostly free fatty acids, but also glucose (Fig. 1). The physiologic role of brown adipose tissue in small mammals (and human newborns) is the maintenance of core temperature. In brown adipose tissue, mitochondria release chemical energy in the form of heat by means of the uncoupling of the oxidative phos-