

We agree with Jerrett and Burnett that the sources and components of particulate matter are likely to be important for determining toxicity and that much variation within cities is attributable to traffic sources. Our study, like prior work, does not provide specific guidance on sources and components.

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## Inhaled Insulin for Diabetes Mellitus

**TO THE EDITOR:** An important uncertainty about treatment with inhaled insulin is the potentially increased risk of lung cancer. In their *Clinical Therapeutics* article on inhaled insulin for diabetes mellitus, McMahon and Arky (Feb. 1 issue)<sup>1</sup> report that short-term studies in animals have not shown a substantial effect on cell-proliferation indexes in the alveolar or bronchiolar areas of the lung. This is not quite correct. One of the short-term studies reports an increased rate of mitosis induced by inhaled insulin in rats.<sup>2</sup>

Presumably in response to this finding, Pfizer, the manufacturer of a dry-powder formulation of human insulin, proposed to conduct a 12-year prospective study “to compare lung cancer mortality between INH [inhaled insulin]–treated and non–INH-treated patients.”<sup>3</sup> However, the rate of lung cancer depends on the rate of smoking 20 years earlier. It is therefore highly unlikely that we can expect a reliable result within 12 years.

McMahon and Arky report that “insulin acts as a weak growth factor when it binds to the type 1 insulin-like growth factor receptor.”<sup>1</sup> It also can have a mitogenic effect mediated by its own receptors, especially if — like the insulin used for inhalation — it has a long average residence time at the receptor.<sup>4</sup> Only 25% of the dose deposited in the lung is absorbed.<sup>1</sup> This necessarily leads to high insulin concentrations in the alveolar and bronchiolar tissue. Studies of human bronchial epithelial cells suggest that insulin-receptor activation is in itself insufficient for malignant transformation. The insulin-receptor pathway, however, is thought to promote malignant progression of these cells

once malignant transformation has been induced by other agents.<sup>5</sup>

Informing patients about the “unknown long-term adverse effects of this form of therapy”<sup>1</sup> is not sufficient. One should point out that lung cancer has not been ruled out as one of the possible side effects. Only with this information do patients have the opportunity to make an informed choice of treatment.

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Dr. E. von Kriegstein reports receiving consulting fees from Berlin-Chemie. No other potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** McMahon and Arky do not recommend inhaled insulin in patients with asthma

or chronic obstructive pulmonary disease because of unpredictable absorption. More important concerns may be an increased risk of airway smooth-muscle contraction that is dependent on the insulin concentration and significantly increased production of prostaglandin, especially prostaglandin  $F_{2\alpha}$ .<sup>1</sup> Whether such contraction precipitates or exacerbates chronic obstructive pulmonary disease or episodes of asthma is not known, but it represents a potential risk.

Another possible factor that eventually modifies the pharmacokinetics of inhaled insulin is the change in tidal-volume ventilation. In one experimental model,<sup>2</sup> an increase in insulin absorption oscillating between 106 and 149% was observed when ventilation was achieved with use of different tidal volumes. For these reasons, the use of subcutaneous insulin is more prudent in these patients.

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**TO THE EDITOR:** In regard to the case vignette in the article by McMahon and Arky: using basal insulin at bedtime to manage an elevated fasting blood glucose concentration is not necessarily the most appropriate decision. The relative contribution of postprandial hyperglycemia is about 50% in patients with a glycated hemoglobin value of 8.6%.<sup>1</sup> As compared with basal insulin, preprandial lispro has a greater effect on metabolic control.<sup>2</sup> One study showed that in patients in whom two oral agents were not effective, inhaled insulin resulted in a 1.7 percentage point mean reduction in glycated hemoglobin,<sup>3</sup> which is similar to the reduction reported after the addition of basal insulin in patients in whom one or two oral agents were not effective.<sup>4</sup> Furthermore, inhaled insulin induces a greater decrease in fasting plasma glucose concentrations than does short-acting insulin administered subcutaneously before meals.<sup>5</sup> Finally, I would be concerned about keeping the thiazolidinedione because of an increased risk of fluid retention and heart failure in association with insulin and because there are no data providing support for this approach. The addition of inhaled

insulin before meals with continued use of metformin and sulfonylurea seems to be a more rational and scientifically based decision and would be more acceptable to the patient.

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**TO THE EDITOR:** Although much effort has been devoted to understanding the use of oral inhalation of insulin in diabetes mellitus, the presence of insulin<sup>1</sup> and insulin receptors<sup>2</sup> in nasal mucus and their relationship to insulin in other body fluids in diabetes mellitus has only recently been discovered. Although my colleagues and I can offer no therapeutic data, our studies suggest that nasal inhalation of insulin may be a useful alternative to oral inhalation of the drug. This technique does not simply involve a change of orifice. It may offer a more effective delivery system. Our studies suggest that a complex feedback system exists between insulin in nasal mucus and the blood-brain barrier,<sup>2</sup> such that nasal inhalation of insulin can affect insulin metabolism in the brain.

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**THE AUTHORS REPLY:** The comments of von Kriegstein and von Kriegstein remind us of the need to offer our patients a balanced presentation of the possible risks and benefits before initiating treatment with inhaled insulin. We acknowledge that it is premature to be confident that there is no association between inhaled insulin and bronchial cancer. We agree with Guevara that patients with obstructive airway disease or asthma should not be treated with inhaled insulin until its safety has been demonstrated in clinical trials. For these reasons, prescribers will need to carefully examine the suitability of inhaled insulin for each patient.

Further research will be required before the safety of the approach suggested by Gross can be ensured. Basal insulin once daily and inhaled insulin thrice daily may be equally efficacious in reducing glycated hemoglobin concentrations; however, inhaled insulin is associated with a substantially higher risk of hypoglycemia.<sup>1,2</sup> Current standards of care reserve preprandial insulin for patients with type 2 diabetes who do not reach their glycemic goal while being treated with a basal insulin.<sup>3</sup>

For a patient who is receiving a basal insulin, a decision to prescribe inhaled insulin rather than a subcutaneous short-acting insulin must be considered in the context of the paucity of long-term safety data and an awareness of the additional

cost. Evidence provides support for the combination of basal insulin with a thiazolidinedione.<sup>4</sup>

We hope that researchers such as Henkin will continue to develop oral, buccal, transcutaneous, and nasal insulin formulations; other inhaled insulin preparations are being evaluated in advanced clinical trials. It is possible that these and other developments will ultimately help improve the management of diabetes for a growing population of patients who deserve the best evidence-based medicine available.

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## Assessment in Medical Education

**TO THE EDITOR:** I am disappointed that Epstein's review of assessment in medical education (Jan. 25 issue)<sup>1</sup> does not include the short case, which is an excellent instrument used in many educational settings.<sup>2</sup> In the short case, the student is asked to perform a supervised focused physical examination (e.g., of only the abdomen) of a real patient, with little knowledge of the patient's history, and is then assessed on the basis of the technique of the examination and the ability to elicit physical signs and interpret these findings correctly. Several cases are used to improve validity and reliability.

By making physical examination an integral part of trainee evaluation, the short case represents a tool for curtailing the decline in physical-examination skills.<sup>3</sup> Furthermore, the short case uniquely prepares a trainee to perform an accurate assessment and place physical findings in context. These skills are especially valuable in the current era of

duty-hour restrictions and increasing shift work,<sup>4</sup> since a house officer is likely to be called to evaluate a patient he or she hardly knows.

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**TO THE EDITOR:** In his review of assessment methods, Epstein misses an opportunity to discuss the importance of providing constructive feedback to