pose is to ensure a properly functioning catheter, a minimum of adverse effects, and appropriate analgesia. When parenteral opiates are managed with the same degree of vigilance, differences in pain scores disappear.[3]

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1. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA.* 2003;290:2455-2463.
2. Macintyre PE. Safety and efficacy of patient-controlled analgesia. *Br J Anaesth.* 2001;87:36-46.
3. Norris EJ, Beattie C, Perler BA, et al. Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. *Anesthesiology.* 2001;95:1054-1067.

In Reply: In response to Drs Jankowski and Warner, a statistically significant difference is more likley to be obtained when analyzing larger numbers of patients. In our case, the overall difference between opioid and epidural analgesia represented an approximate 30% difference. When assessed over the entire range (10%-75%) and compared with patient-derived measures of clinically important differences, an approximate 33% reduction in pain intensity appears to be the optimal and clinically meaningful cutoff.[1,2] In addition, another article published after ours also suggested that an approximately 35% decrease in acute pain scores is clinically meaningful.[3] As more studies are published, an updated analysis comparing the 2 regimens would be appropriate.

We agree that extremely aggressive pain management might diminish the differences in pain scores between parenteral opioids and epidural analgesia. This might be especially true for PCA. In fact, aggressive pain management has been reported to result in similar pain scores between PCA and intramuscular opioids.[4] This does not necessarily mean that intramuscular analgesia is better. The ideal level of service for intramuscular analgesia (eg, 3 visits daily from the acute pain service)[5] is most likely not observed or obtainable in routine clinical practice. Effectiveness data, which probably have stronger external validity than RCTs for "real world" practice, also suggest that epidural analgesia provides better analgesia compared with PCA and intramuscular opioids.[6]

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1. Farrar JT, Portenoy RK, Berlin JA, et al. Defining the clinically important difference in pain outcome measures. *Pain.* 2000;88:287-294.
2. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage.* 2003;25:406-411.
3. Cepeda MS, Africano JM, Polo R, et al. What decline in pain intensity is meaningful to patients with acute pain? *Pain.* 2003;105:151-157.
4. Choiniere M, Rittenhouse BE, Perreault S, et al. Efficacy and costs of patient-controlled analgesia versus regularly administered intramuscular opioid therapy. *Anesthesiology.* 1998;89:1377-1388.
5. Norris EJ, Beattie C, Perler BA, et al. Double-masked randomized trial comparing alternate combinations of intraoperative anesthesia and postoperative analgesia in abdominal aortic surgery. *Anesthesiology.* 2001;95:1054-1067.
6. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management, I: evidence from published studies. *Br J Anaesth.* 2002;89:409-423.

Optimal Control of Glycemia Among Critically Ill Patients

To the Editor: Based on their observational study, Dr Finney and colleagues[1] speculated that less-stringent control of blood glucose levels suffices to optimize survival among critically ill patients, and that infusing more insulin may actually be harmful. In contrast, our randomized, controlled, intervention study found that intensive insulin therapy to maintain blood glucose levels below 110 mg/dL reduced mortality among critically ill patients.[2]

We are concerned that the data of Finney et al do not support their speculations. The authors analyzed the relationship between mortality, the time a patient spent in different strata of blood glucose levels, and the amount of insulin infused in each stratum. The logistic regression model, which did not include age, Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores, or Sequential Organ failure Assessment (SOFA) scores, and thus did not correct for these known risk factors, revealed that more infused insulin was associated with increased risk of death. The authors concluded that glycemic control, rather than the infused insulin per se, explained the outcome benefit of intensive insulin therapy, corroborating previous observations.[3] The authors further speculated that the statistical association between infused insulin and mortality indicates that exogenous insulin can be harmful.

For several reasons, we do not think their data can support this speculation. First, observational data cannot prove causality. Second, the fact that intensive insulin therapy reduced, rather than increased, mortality argues against such an interpretation. Finney et al merely confirmed the link between insulin resistance (insulin requirement to achieve a certain level of blood glucose control) and severity of illness, which does not necessarily indicate detrimental effects of exogenous insulin. Instead, outcome is improved by a dose of insulin high enough to overcome the resistance and maintain normoglycemia.[1,3] Third, other metabolic (eg, normalization of lipids) and immunological (eg, anti-inflammatory and immune enhancing) effects of intensive insulin therapy in critical illness ac-

company glycemic control.[4-6] These effects may partly explain the clinical benefits of intensive insulin therapy on sepsis, organ failure, and death, overruling the impact of concomitant control of blood glucose levels. It is thus inappropriate to presume similarities between insulin and growth hormone therapy in the critically ill, as the latter increased and the former reduced morbidity and mortality.

Finney et al also speculated that a higher target for control of blood glucose levels, ie, below 145 mg/dL rather than 110 mg/dL, can be advised. The results of their observational study, however, do not support such a statement. Indeed, logistic regression analysis for glycemic threshold did not provide statistically significant results. In contrast, our previous intervention study showed that glycemic control below 110 mg/dL significantly further reduced the risk of mortality and morbidity compared with an intermediate level of 110 to 150 mg/dL.[3]

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1. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA*. 2003;290:2041-2047.
2. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367.
3. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med*. 2003;31:359-366.
4. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients, as indicated by circulating mannan-binding lectin and C-reactive protein levels. *J Clin Endocrinol Metab*. 2003;88:1082-1088.
5. Weekers F, Giuletti A-P, Michalaki M, et al. Metabolic, endocrine and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. *Endocrinology*. 2003;144:5329-5338.
6. Mesotten D, Swinnen J, Vanderhoydonc F, Wouters PJ, Van den Berghe G. Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. *J Clin Endocrinol Metab*. 2004;89:219-226.

In Reply: In response to Drs Van den Berghe and Bouillon, we indicated that APACHE II scores, SOFA scores, and reason for admission were all included in the logistic regression analysis. Age was removed as it did not improve the model fit, possibly because it is already contained within the APACHE II instrument. Consequently, we believe our model did examine the relationship between insulin administration, glycemia, and mortality, and was not confounded by severity of illness. Furthermore, because the predicted odds ratios of death attributable to insulin administration were the same in each glycemic band examined, it is highly unlikely that our results simply reflect insulin resistance.

Second, we do not dispute that insulin administered with the aim of lowering blood glucose levels reduces mortality, as reported by Van den Berghe et al.[1] Rather, we propose that although insulin may itself be harmful, in high glycemic bands its administration obviates the (even more) negative effects of hyperglycemia; the balance at low and intermediate glucose levels is less clear. Furthermore, we agree that association does not imply causation and applaud the efforts of Van den Berghe et al to elucidate the underlying mechanisms. It may be that glucose level is a surrogate marker of another metabolic parameter. However, because glucose level can be measured easily at the bedside, it remains the most appropriate variable to target in the clinical setting.

Finally, we concur that results from an observational study should not be used to direct therapy. Indeed, we were careful only to speculate that a moderate target for glucose control (ie, <145 mg/dL) may be sufficient. Nevertheless, we believe that our own data and that of Van den Berghe et al[1] demonstrate that glycemia between 180 and 200 mg/dL should be avoided in critically ill patients: such a control population may be inappropriate for future investigations. The data of Van den Berghe et al demonstrated significant benefit at glucose levels of 80 to 110 mg/dL. Our observational data suggest, but do not prove, that a similar benefit may be achieved by somewhat less stringent control of glucose levels.

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1. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367.

RESEARCH LETTER

Coffee Consumption and Insulin Sensitivity

To the Editor: Coffee consumption has been associated with a substantially lower risk of developing type 2 diabetes.[1] However, despite the widespread use of coffee, there are few data on the specific effects of coffee on the 2 main causes of diabetes, ie, insulin resistance and defective insulin secretion. We investigated the association between coffee consumption and both insulin sensitivity and insulin secretion in a sample of elderly Swedish men without diabetes.

Methods. We reanalyzed cross-sectional data collected between 1990 and 1994 from the Uppsala Longitudinal Study of Adult Men (ULSAM). A dietitian instructed all participants to record their dietary intake using a 7-day precoded food diary. Coffee and tea consumption were recorded 6 times daily (breakfast, lunch, supper, between meals, and in the evening). Amounts of sugar, cream, and milk used in coffee, as well as of cookies, cakes, and biscuits consumed with coffee, were also recorded at these occasions. Daily intakes were calculated using a computer program and the Swedish National Food Administration database (SLV Database, 1990). Participants also reported their leisure-time physical activity on a standardized questionnaire.

Insulin sensitivity index was determined by hyperinsulinemic euglycemic clamp.[2] Insulin secretion was measured as the