data strongly suggest that, in addition to recessively inherited syndromes such as the mosaic variegated aneuploidy syndrome, haploinsufficiency of spindle-assembly checkpoint components may underlie early-onset gastrointestinal cancers that may be prevented by surveillance.

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No potential conflict of interest relevant to this letter was reported.

1. Rio Frio T, Lavoie J, Hamel N, et al. Homozygous *BUB1B* mutation and susceptibility to gastrointestinal neoplasia. N Engl J Med 2010;363:2628-37.
2. Scully R. The spindle-assembly checkpoint, aneuploidy, and gastrointestinal cancer. N Engl J Med 2010;363:2665-6.
3. Rao CV, Yang YM, Swamy MV, et al. Colonic tumorigenesis in BubR1+/–ApcMin/+ compound mutant mice is linked to premature separation of sister chromatids and enhanced genomic instability. Proc Natl Acad Sci U S A 2005;102:4365-70.
4. Baker DJ, Jin F, Jeganathan KB, van Deursen JM. Whole chromosome instability caused by Bub1 insufficiency drives tumorigenesis through tumor suppressor gene loss of heterozygosity. Cancer Cell 2009;16:475-86.

Glycemic Control in the ICU

TO THE EDITOR: Kavanagh and McCowen (Dec. 23 issue)[1] recommend a glycemic target range of 140 to 180 mg per deciliter for a patient with pneumonia in an intensive care unit (ICU) who had an increase in the arterial glucose concentration from a level of 105 mg per deciliter to 195 mg per deciliter. This recommendation is surprising to us, given the evidence.

Until 2001, neglecting hyperglycemia was standard ICU care. The proof of concept for hyperglycemia-induced toxic effects came from a randomized, controlled trial involving patients in a surgical ICU,[2] in which normoglycemia (glucose level, 80 to 110 mg per deciliter) improved outcome, as compared with tolerating hyperglycemia to a level of 210 mg per deciliter. Studies documenting the transition from neglecting hyperglycemia to targeting normoglycemia showed similar benefits.[3] Confirmative data subsequently came from large, single-center, randomized, controlled trials, one involving adult patients in a medical ICU (which showed morbidity benefits)[4] and one involving patients in a pediatric ICU (which showed improved survival).[5] Studies in animals have elucidated the underlying mechanisms of this benefit. Multicenter studies that used different protocols and inaccurate glucose meters and that compared intermediate glycemia with normoglycemia argued against the generalizability of these findings.

But where is the randomized, controlled trial comparing the target of 140 to 180 mg per deciliter against neglecting hyperglycemia? Currently, no evidence supports this intermediate target, which might still evoke risks, such as hypoglycemia, glycemic fluctuations, and hypokalemia.[6] The current data support the choice between targeting normoglycemia or no treatment. Is not any target of 110 to 200 mg per deciliter rather a pragmatic choice driven by the unavailability of accurate tools to measure and stably control blood glucose? Also, would the recommendation imply that clinicians should infuse glucose to treat a spontaneous glucose concentration of less than 140 mg per deciliter?

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No potential conflict of interest relevant to this letter was reported.

1. Kavanagh BP, McCowen KC. Glycemic control in the ICU. N Engl J Med 2010;363:2540-6.
2. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
3. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004;79:992-1000. [Erratum, Mayo Clin Proc 2005;80:1101.]
4. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449-61.
5. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.
6. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. Crit Care Med 2010;38:1021-9.

THE AUTHORS REPLY: The original 2001 report[1] by Van den Berghe et al. provided important preliminary data. It was assumed that intensive insulin therapy provided benefit, but because of the design, it is also possible that the control management caused harm. Despite this uncertainty, intensive insulin therapy was prematurely and widely implemented. However, the authors' 2006 study[2] was not confirmatory, since intensive insulin therapy resulted in no benefit in the primary outcome of in-hospital mortality. Although a secondary analysis suggested reduced mortality in "long stay" patients, this finding implied that there was a reciprocally increased rate of death in the "short stay" group.[3] In addition, the reported morbidity benefits have not been replicated in subsequent studies.[4] The control management in the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study[5] constituted a moderate glycemic-control strategy (<180 mg per deciliter), necessitating substantial amounts of insulin.[5] Such a glucose target is not "neglect," and the strategy was associated with a lower mortality than was intensive insulin therapy. We recommend the infusion of glucose only to provide energy or to treat hypoglycemia. Our recommendations are not surprising; they are consistent with best estimates from available data and are reflected in those guidelines that have been updated.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
2. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449-61.
3. Malhotra A. Intensive insulin in intensive care. N Engl J Med 2006;354:516-8.
4. Marik PE, Preiser J-C. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. Chest 2010;137:544-51.
5. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-97.

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Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

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CORRECTIONS

Case 7-2011: A 52-Year-Old Man with Upper Respiratory Symptoms and Low Oxygen Saturation Levels (March 10, 2011;364:957-66). In the legend for Figure 2 (page 964), the penultimate sentence should have read, "The duodenal-biopsy specimen (Panel C, hematoxylin and eosin) shows blunted and atrophic villi (long arrow), crypt hyperplasia (short arrows) . . . ," rather than ". . . shows blunted and atrophic villi (short arrows), crypt hyperplasia (long arrow). . . ." The article is correct at NEJM.org.

Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death (March 3, 2011;364:829-41). In the Discussion (page 837), the second sentence should have ended, ". . . the reduction in life expectancy from long-term cigarette smoking is about 10 years," rather than ". . . about 7 years." The article is correct at NEJM.org.

Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia (March 3, 2011;364:842-51). In Figure 2 (page 847), the x-axis should have been labeled "Freedom from Hospitalization," rather than "Probability of Hospitalization." The article is correct at NEJM.org.