Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

Perioperative Hyperglycemia Management

An Update

Elizabeth W. Duggan, M.D., Karen Carlson, M.D., M.B.A., Guillermo E. Umpierrez, M.D., C.D.E.

CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

A SUBSTANTIAL body of literature demonstrates a clear association between perioperative hyperglycemia and adverse clinical outcomes.[1–3] The risk for postoperative complications and increased mortality relates to both long-term glycemic control and to the severity of hyperglycemia on admission and during the hospital stay.[2] The underlying mechanism(s) relating hyperglycemia to poor outcomes is not completely understood. Past and current studies point to physiologic changes that occur in the hyperglycemic state that may contribute to poor outcomes. Elevated blood glucose (BG) levels impair neutrophil function and cause an overproduction of reactive oxygen species, free fatty acids (FFA), and inflammatory mediators. These pathophysiologic changes contribute to direct cellular damage and vascular and immune dysfunctions.[4] Substantial evidence indicates that correction of hyperglycemia with insulin administration reduces hospital complications and decreases mortality in cardiac[5] and general surgery[6] patients. However, optimal glucose management during the perioperative period is widely debated. Recent randomized controlled trials targeting conventional targets for glycemic control do not demonstrate the significant risk of hypoglycemia[7,8] as seen in previous studies using insulin to maintain tight BG control.[9] The pendulum of inpatient care has since moved toward more moderate and individualized glycemic targets.

This article reports on the prevalence, diagnosis, and pathophysiology of perioperative hyperglycemia and provides a practical outline for the management of surgical patients with diabetes and hyperglycemia.

Metabolic Consequences of Surgical Stress and Anesthesia

During the fasting state, normal subjects maintain plasma glucose levels between 60 and 100 mg/dl (3.3 to 5.5 mM). The stress of surgery and anesthesia alters the finely regulated balance between hepatic glucose production and glucose utilization in peripheral tissues. An increase in the secretion of counterregulatory hormones (catecholamines, cortisol, glucagon, and growth hormone) occurs, causing excessive release of inflammatory cytokines including tumor necrosis factor-α, interleukin-6, and interleukin-1β (fig. 1).[10] Cortisol increases hepatic glucose production, stimulates protein catabolism, and promotes gluconeogenesis, resulting in elevated BG levels.[11] Surging catecholamines increase glucagon secretion and inhibit insulin release by pancreatic β cells.[4] Additionally, the increase in stress hormones leads to enhanced lipolysis and high FFA concentrations. Increased FFAs have been shown to inhibit insulin-stimulated glucose uptake[12] and limit the intracellular signaling cascade in skeletal muscle responsible for glucose transport activity.[13] Evidence also suggests that tumor necrosis factor-α interferes with the synthesis and/or translocation of the glucose transporter-4 receptor, reducing glucose uptake in peripheral tissues.[14] These processes result in an altered state of insulin action, leading to a relative state of insulin resistance, which is most pronounced on the first postoperative day and may persist for 9 to 21 days after surgery.[15]

Preoperative carbohydrate loading is becoming a more frequent surgical practice because it may counteract the state of insulin resistance that occurs due to stress and starvation. The Enhanced Recovery After Surgery (ERAS) program advocates carbohydrate-rich drinks up to 2 h before surgery. This avoids the catabolic state associated with starvation and has been demonstrated to increase insulin sensitivity[16] and decrease the risk of postoperative hyperglycemia.[17] Particularly in patients undergoing major abdominal surgery, carbohydrate loading has been associated with a reduced hospital length of stay.[18]

The magnitude of the counterregulatory response relates to the severity of surgery and the type of anesthesia.[19]

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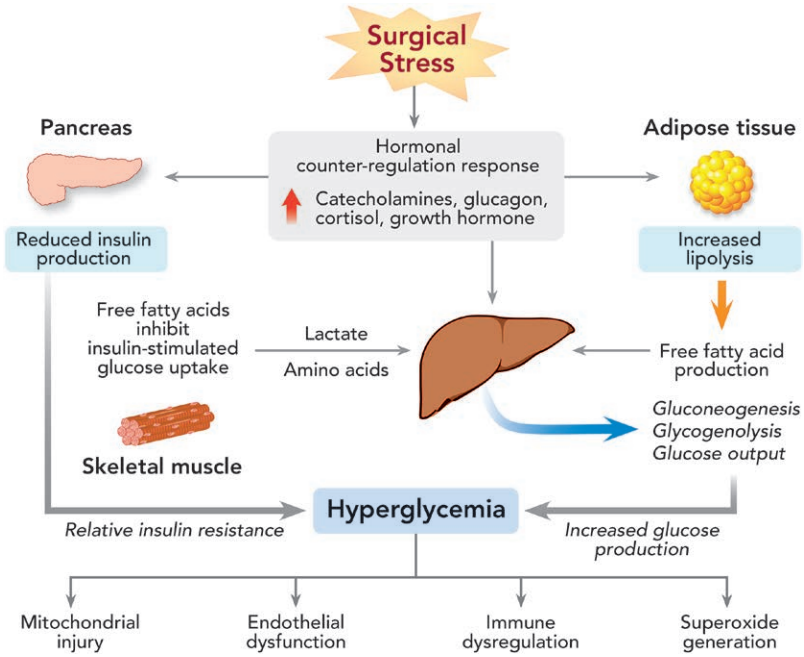

Fig. 1. The surgical stress response.

Anatomic location, invasiveness of the procedure, intraoperative fluids, and nutritional support have all been linked to glucose elevation and the duration of stress hyperglycemia. Surgeries involving the thorax and abdomen are associated with a more pronounced and prolonged duration of hyperglycemia when compared to peripheral procedures.[19] Laparoscopic procedures (*vs.* open) demonstrate a decreased incidence of insulin resistance and hyperglycemia.[15]

Type of anesthesia also influences the hyperglycemic response during surgery. General anesthesia is more frequently associated with hyperglycemia and higher levels of catecholamines, cortisol, and glucagon than local or epidural anesthesia.[20] Volatile anesthetic agents inhibit insulin secretion[21] and increase hepatic glucose production.[22]

Prevalence of Hyperglycemia and Diabetes in Surgical Patients

Perioperative hyperglycemia is reported in 20 to 40% of patients undergoing general surgery[2,23,24] and approximately 80% of patients after cardiac surgery.[5,25] A recent report examining point-of-care glucose testing in 3 million patients, across 575 American hospitals, reported a prevalence of hyperglycemia (BG greater than 180 mg/dl, 10 mM) as 32% in both intensive care unit (ICU) patients and non-ICU patients.[26] Most patients with hyperglycemia have a known diagnosis of diabetes. However, 12 to 30% of patients who experience intra- and/or postoperative hyperglycemia do not have a history of diabetes before surgery,[2] a state often described as "stress hyperglycemia."[27] Stress hyperglycemia typically resolves as the acute illness or surgical stress abates. However, cross-sectional and longitudinal studies show that between 30 and 60% of these patients have impaired carbohydrate intolerance when assessed by oral glucose tolerance testing after hospital discharge.[28] Furthermore, 60% of patients admitted with new hyperglycemia had confirmed diabetes at 1 yr.[28] Measurement of hemoglobin A1c (HbA1c) in patients with hyperglycemia during hospitalization provides the opportunity to differentiate patients with stress hyperglycemia from those with diabetes who were previously undiagnosed.[29] The Endocrine Society guidelines indicate that patients with hyperglycemia and HbA1C of 6.5% or higher can be identified as having diabetes.[30]

Preoperative Period

Few studies have examined the effects of preoperative BG levels on outcomes, and there is a paucity of data for best preoperative glucose management. A retrospective analysis of 61,000 patients undergoing elective noncardiac surgery demonstrated that 1-yr mortality was significantly related to preoperative BG. Crude incidence of mortality was 3 to 5% at 1 yr in patients with preoperative BG between 60 and 100 mg/dl (3.3 to 5.5 mM) *versus* 12% in patients with BG greater than 216 mg/dl (12 mM).[31] Han and Kang[32] reported that a preoperative HbA1c level greater than 8% was an independent risk factor for wound complications (odds ratio, 6.07; 95% CI, 1.12 to 33.0) in patients with type 2 diabetes undergoing total knee arthroplasty. Similarly, Dronge *et al.*[33] reported that among 490 diabetic patients who underwent major noncardiac surgery, HbA1c level greater than 7% was significantly associated with increased infectious complications with an adjusted odds ratio of 2.13 (95% CI, 1.23 to 3.70) compared to patients with HbA1c less than 7%. The relationship between peripheral BG and cerebral glucose (as measured by intracerebral microdialysis catheters) is complicated in injured brain tissue and

uncoupling can occur in the linear relationship. However, a review of the data does suggest that perioperative hyperglycemia in neurosurgical patients is a marker of poor outcomes.[34] A recent study of 918 craniotomy or neurosurgical procedures for spine cases demonstrated increasing number of postoperative complications with increasing BG.[35] Halkos *et al.*[36] reported that preoperative HbA1c levels greater than 7% in patients undergoing primary, elective coronary artery bypass graft (CABG) had a higher unadjusted 5-yr mortality compared with patients with HbA1c less than 7%. These studies indicate that poor preoperative glycemic control is associated with an increased rate of complications and reduced long-term survival after surgery. Optimizing preoperative glucose management may improve outcomes; however, no prospective randomized studies have determined the importance of preoperative control and clinical outcome.

Diabetes, Fasting, and Feeding

The Joint Commission recommends a nutritional assessment occur within 24 h of admission for all surgical patients. This is an important component of the preoperative evaluation. Most patients with and without diabetes tolerate fasting for several hours up to a few days without increased risk of malnutrition or perioperative complications. Nutritional support, with dextrose containing solutions, is not indicated in diabetic patients fasting for periods less than 24 to 48 h.

Prolonged fasting is avoided in patients with diabetes. Low carbohydrate diets facilitate insulin dosing and result in improved glucose control.[37] The metabolic needs for most hospitalized patients can be supported by providing 25 to 35 calories · kg^{-1}· day^{-1}. Critically ill patients require decreased caloric intake approximating 15 to 25 calories · kg^{-1}· day^{-1}.[37] A diet between 1,800 and 2,000 calories/day is appropriate for most patients.[37] A meta-analysis examining diabetic enteric feeding formulas demonstrated that low-carbohydrate high-monounsaturated fatty acid formulas are preferable to the standard high-carbohydrate formulas in hospitalized patients with type 1 and type 2 diabetes.[38] The postprandial rise in BG was reduced by 18 to 29 mg/dl with these formulations, demonstrating improved glucose control in diabetics.[38]

Intraoperative Period

Most investigations into the effects of intraoperative glucose control and outcomes have focused on the cardiac surgery population. In a retrospective study of 409 patients undergoing cardiac surgery, Gandhi *et al.*[39] reported that for each incremental change in intraoperative BG by 20 mg/dl (1.1 mM) above 100 mg/dl (5.5 mM), there was a 30% increase in occurrence of adverse events including pulmonary and renal complications and death. Another study correlated glucose levels with the risk of infection, atrial fibrillation, heart failure, myocardial infarction, pericarditis, neurologic complications, and pulmonary complications.[40] Thirteen percent of patients with BG levels less than 200 mg/dl (11.1 mM) experience complications, *versus* 36% with glucose greater than 200 mg/dl (11.1 mM) and 63% of patients with glucose greater than or equal to 250 (13.9 mM) mg/dl. In contrast to these observational studies, a randomized controlled trial of 400 diabetic and nondiabetic surgery patients assigned to receive continuous insulin infusion to maintain intraoperative glucose level between 80 and 100 mg/dl (4.4 to 5.6 mM), *versus* those treated only for glucose levels greater than 200 mg/dl (11.1 mM) reported more deaths and strokes in the intensive treatment group.[41] A meta-analysis of five randomized controlled trials in 706 cardiac surgery patients reported that rigorous intraoperative glycemic control decreased the infection rate compared to the conventional therapy but did not decrease mortality.[42]

Postoperative Period

Studies in cardiac, general surgery, and ICU patients have shown a clear association between inpatient hyperglycemia (greater than 180 mg/dl, 10 mM) and adverse clinical outcomes including surgical site infections, delayed wound healing, and increased length of stay.[1–3,24] Treating elevated BG has been reported to decrease morbidity.[5,9] Numerous well-designed multicenter trials have shown that intensive insulin treatment results in a higher incidence of hypoglycemia and increased mortality compared to moderate glucose control.[7,43,44]

Several randomized controlled trials (all in cardiac surgery) have attempted to evaluate the ideal BG target in the postoperative period to optimize outcomes and minimize harm.[25,45–47] Desai *et al.*[45] randomized 189 patients to intensive insulin therapy (target 90 to 120 mg/dl, 5 to 6.7 mM) or to conventional control (target 121 to 180 mg/dl, 6.7 to 10 mM), testing the hypothesis that a liberal BG target is noninferior to intensive control for outcomes after the first-time CABG surgery. There were no differences in deep sternal wound infection, pneumonia, perioperative renal failure, or mortality. However, the strict glucose control group took longer to reach the target range, had a greater number of measurements outside of the target range, and more patients with hypoglycemic events. Pezzella *et al.*[46] assessed the long-term mortality in diabetics and nondiabetics randomized to intensive *versus* conventional control. There was no difference in health-related quality of life or survival between groups during a 40-month follow-up period, demonstrating that long-term outcomes were not worse when BG was maintained in liberal target range. Lazar *et al.*[47] investigated the effects of a target glucose of 90 to 120 mg/dl (5 to 6.7 mM) *versus* 120 to 180 mg/dl (6.7 to 10 mM) on clinical outcomes in 82 diabetic patients undergoing CABG. The study reported no differences in perioperative complications, hospital length of stay, and mortality between the groups. The GLUCO-CABG trial[25] randomized both diabetic and nondiabetic patients to intensive control (100 to 140 mg/dl, 5.5 to 7.8 mM) or conventional glucose control (141 to 180 mg/dl, 7.8 to 10 mM) after coronary bypass surgery.

A significant difference was not detected between groups when evaluating a composite of complications including mortality, wound infection, pneumonia, bacteremia, respiratory failure, acute kidney injury, and major cardiovascular events. However, we observed heterogeneity in treatment effect according to diabetes status, with no differences in complications among patients with diabetes, but lower rates of complications in subjects without diabetes treated with intensive compared with conservative regimen. In agreement with these findings, a recent study by Blaha *et al.*[48] in 2,383 cardiac surgery patients treated to a target glucose range between 80 and 110 mg/dl (4.4 to 6.1 mM) reported a reduction in postoperative complications only in nondiabetic patients (21 *vs.* 33%; relative risk, 0.63; 95% CI, 0.54 to 0.74) without significant benefit of intensive therapy in patients with diabetes. These results indicate that at this time, institutions should target postoperative BG levels between 140 and 180 mg/dl for cardiac surgery patients.

In general surgery patients, observational and prospective randomized studies have shown that hyperglycemia is associated with increased rates of morbidity and mortality.[1–3,6,24] Improved glycemic control reduces the rate of hospital complications.[3,6] In a cross-sectional study, patients with glucose levels between 110 and 200 mg/dl (6.1 to 11.1 mM) *versus* patients with glucose levels greater than 200 mg/dl (11.1 mM) had, respectively, a 1.7- and 2.1-fold increased mortality compared to those with glucose levels less than 110 mg/dl (6.1 mM).[49] The risk of postoperative complications in general surgery patients relates to the severity of hyperglycemia, with a higher risk observed in patients without a history of diabetes (stress-induced hyperglycemia) compared to those with a known diagnosis of diabetes.[1–3]

Glycemic Targets

Glycemic targets recommended by several organizations are shown in Table 1. The Society for Ambulatory Anesthesia (SAMBA; Chicago, Illinois) recommends intraoperative BG levels less than 180 mg/dl (10 mM).[50] The American Association of Clinical Endocrinologists (AACE; Jacksonville, Florida) Task Force and the American Diabetes Association (Arlington, Virginia) recommend target glucose levels between 140 and 180 mg/dl (7.7 to 10 mM) in critically ill patients.[51] The Society of Critical Care Medicine (SCCM; Mount Prospect, Illinois) advises treatment be triggered at BG levels greater than or equal to 150 mg/dl (8.3 mM with a goal to maintain BG below that level, and absolutely less than 180 mg/dl [10 mM]).[52] The Society of Thoracic Surgeons (STS; Chicago, Illinois) Practice Guidelines recommend maintaining serum glucose levels less than or equal to 180 mg/dl (10 mM) for at least 24 h after cardiac surgery.[53] The American College of Physicians (ACP; Philadelphia, Pennsylvania) advocates against intensive insulin therapy in patients with or without diabetes in surgical and medical ICUs. The ACP target BG range is 140 to 200 mg/dl (7.7 to 11.1 mM) for patients with or without diabetes.[54]

For patients in non-ICU settings, the Endocrine Society and the American Diabetes Association/AACE Practice Guidelines recommended a target premeal glucose of less than 140 mg/dl (7.7 mM) and a random BG of less than 180 mg/dl (10 mM) for patients treated with insulin.[30,51] The Joint British Diabetes Societies guideline, for the perioperative management of adult patients, recommends to start insulin treatment when glucose levels are greater than 10 mM (180 mg/dl). The societies target a glucose range between 6 and 10 mM (108 to 180 mg/dl) but with acceptable values 4 to 12 mM (72 to 216 mg/dl).[55]

Preoperative Glycemic Management

Treatment recommendations for type 2 diabetics using home medications are based on numerous factors. Type of diabetes, nature and extent of the surgical procedure, length of pre- and postoperative fasting, type and frequency of daily medication, and state of metabolic control preceding surgery are taken into consideration when determining preoperative medication use and dose.

There is a lack of randomized controlled trials demonstrating the role of oral medication before surgery. Generally, based on pharmacology and small studies, the use of most oral antidiabetic agents is recommended up to the day before surgery. Certain medications may be safely continued on the day of surgery (table 2). It has been recommended that sulfonylurea and insulin secretagogues be discontinued the day of surgery as means to limit the risk of hypoglycemia.[30,50] The SAMBA consensus statement on perioperative BG management in diabetic patients recommends that metformin may be taken the day before surgery and restarted on the day of surgery when normal diet is resumed.[50] However, the Joint British Diabetes Societies guideline allows metformin to be continued on the day of surgery for patients undergoing only a short starvation period (one missed meal).[55] In patients undergoing procedures with use of intravenous (IV) contrast dye or with long expected surgical times, metformin is stopped when the preoperative fast begins and restarted postoperatively with normal diet resumption. Should renal dysfunction (glomerular filtration rate less than 45 ml/min)[56] be discovered during preoperative evaluation or develop after surgery, metformin is discontinued until renal function normalizes. If discontinued preoperatively, notice should be provided to the patient's primary care physician or endocrinologist. Alternative oral hypoglycemic therapy may be considered as appropriate.

Due to reports of diabetic ketoacidosis (DKA) occurring in conjunction with sodium glucose-cotransporter 2 inhibitor therapy, the Food and Drug Administration released a safety statement in 2015.[57] In response to this statement, the American College of Endocrinology (ACE; Washington, DC) and AACE convened a conference of experts to evaluate and minimize the risk of DKA in patients using sodium glucose-cotransporter 2 inhibitors.[58] Recommendations from the

Table 1. Society Guideline Recommendations for Treatment of Perioperative Hyperglycemia and Diabetes

	Ambulatory Surgery	ICU	Non-ICU
SAMBA[50]	SC rapid-acting insulin analogs are preferred over IV or SC regular insulin Treatment goal: intraoperative blood glucose levels < 180 mg/dl (10 mM)		
ADA/AACE[51]		Initiate insulin therapy for glucose > 180 mg/dl (10 mM) Treatment goal: For most patients, target a glucose level between 140 and 180 mg/dl (7.7–10 mM). Glucose target between 110 and 140 mg/dl (6.1–7.7 mM) may be appropriate for select patients if achievable without significant risk for hypoglycemia	Treatment goal: If treated with insulin, premeal glucose targets should generally be < 140 mg/dl (< 7.7 mM), with random glucose levels < 180 mg/dl (10 mM)
ACP[54]		Recommends against intensive insulin therapy in patients with or without diabetes in surgical/medical ICUs Treatment goal: Target glucose is between 140 and 200 mg/dl (7.7–11.1 mM) in patients with or without diabetes	
Critical Care Society[52]		BG > 150 mg/dl (8.3 mM) should trigger insulin therapy Treatment goal: Maintain glucose < 150 mg/dl (8.3 mM) for most patients in ICU	
Endocrine Society[30]			Treatment goal: Target premeal blood glucose < 140 mg/dl (7.7 mM) and random glucose < 180 mg/dl (10 mM) Higher target glucose < 200 mg/dl (11.1 mM) is acceptable in patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia
Society of Thoracic Surgeons[53]		Continuous insulin infusion preferred over SC or intermittent IV boluses Treatment goal: Recommend glucose < 180 mg/dl (10 mM) during surgery, ≤ 110 mg/dl (6.1 mM) in fasting and premeal states	
Joint British Diabetes Societies[55]			Initiate insulin therapy for glucose > 10 mM (180 mg/dl) Target blood glucose levels in most patients are between 6 and 10 mM (108–180 mg/dl) with an acceptable range of between 4 and 12 mM (72–216 mg/dl)

ACP = American College of Physicians; ADA/AACE = American Diabetes Association/American Association of Endocrinologists; ICU = intensive care unit; IV = intravenous; SAMBA = Society for Ambulatory Anesthesia; SC = subcutaneous.

symposium's emerging guidelines include stopping the drug in patients undergoing emergency surgery and holding the medication 24 h before an elective surgery or invasive procedure.

There is growing interest in the incretin family (dipeptidyl peptidase-4 [DPP-4]) inhibitors and the glucagon-like peptide-1 receptor antagonists as agents to improve glycemic control without increasing the incidence of hypoglycemia. Currently, randomized placebo-controlled trials are underway examining sitagliptan for use in both cardiac and general surgery patients with type 2 diabetes. DPP-4 inhibitors were proven to be safe in a recent randomized trial of medical and noncardiac surgery patients with type 2 diabetes treated at home with diet, oral antidiabetic agents, or a low daily insulin dose (less than or equal to 0.4 U · kg^{-1} · day^{-1}).[59] DPP-4 inhibitors may be taken the day of surgery and continued through the perioperative period.

Table 2. Oral Medication Use the Day Before and Day of Surgery

Oral Medication for Elective Surgery	Day Before Surgery	Day of Surgery if Normal Oral Intake Anticipated Same Day and Minimally Invasive Surgery	Day of Surgery if Reduced Postoperative Oral Intake or Extensive Surgery, Anticipated HD Changes and/or Fluid Shifts
Secretagogues	Take	Hold	Hold
SGLT-2 Inhibitors	Hold	Hold	Hold
Thiazolidinediones	Take	Take	Hold
Metformin	Take*	Take*	Hold
DPP-4 Inhibitors	Take	Take	Take

*Hold if patient having a procedure with intravenous contrast dye administration, particularly in those with glomerular filtration rate < 45 ml/min.[56]
DPP = dipeptidyl peptidase-4; HD = hemodynamic; SGLT = sodium glucose cotransporter-2.

Table 3. Day Before Surgery Insulin Regimens Based on Oral Intake Status

Day Before Surgery Insulin Regimens	Glargine or Detemir		NPH or 70/30 Insulin		Lispro, Aspart, Glulisine, Regular		Noninsulin Injectables	
	AM Dose	PM Dose	AM Dose	PM Dose	AM Dose	PM Dose	AM Dose	PM Dose
Normal diet until midnight (includes those permitted clear liquids until 2 h before surgery)	Usual dose	80% of usual dose	80% of usual dose	80% of usual dose	Usual dose	Usual dose	Usual dose	Usual dose
Bowel prep (and/or clear liquids only 12–24 h before surgery)	Usual dose	80% of usual dose	80% of usual dose	80% of usual dose	Usual dose	Usual dose	Hold when starting clear liquid diet/bowel prep	Hold when starting clear liquid diet/bowel prep

NPH = neutral protamine Hagedorn.

Patients with type 2 diabetes treated with insulin should continue their insulin therapy (table 3). It has been suggested that the patient's basal insulin (glargine or detemir) dose be reduced by approximately 25% of normal dose the evening before[60] or morning of surgery if twice daily dosing. Neutral protamine Hagedorn (NPH) insulin and premixed formulations are reduced by 20% the evening before surgery and by 50% the morning of surgery.[61] In addition, we recommend holding the dose of NPH or premixed insulin the morning of surgery in patients with type 2 diabetes and fasting glucose less than 120 mg/dl. Day of surgery regimens are outlined in table 4.

Patients with type 1 diabetes undergoing surgical procedures require insulin during the perioperative period. The stress of surgery may result in severe hyperglycemia or ketoacidosis. These patients should receive 80% of basal insulin dose the evening before surgery and on the morning of surgery in order to prevent hypoglycemia.[62] Prandial insulin is stopped when the fasting state begins.

Intraoperative Glycemic Management

The target perioperative BG level depends upon the duration of surgery, invasiveness of surgical procedure, type of anesthetic technique, and expected time to resume oral intake and routine antidiabetic therapy. The Endocrine Society and SAMBA recommend that intraoperative BG levels be maintained less than 180 mg/dl.[30,50]

Hyperglycemia (greater than 180 mg/dl, 10 mM) is treated with subcutaneous rapid-acting insulin analogs or with an IV infusion of regular insulin. Patients undergoing ambulatory surgery or procedures of short duration (less than 4-h operating room time) are often appropriate candidates for SC insulin treatment. Additionally, SC rapid-acting insulin analogs may also be used to correct hyperglycemia during inpatient procedures that are minimally invasive, with expected hemodynamic stability, and allow early resumption of oral intake.[50,55] Onset time of rapid-acting insulin analogs is between 15 and 30 min with peak drug effect occurring between 1 and 1.5 hours. Advantages of subcutaneous rapid-acting insulin analogs include ease of administration, low rate of hypoglycemia, and efficacy in correcting hyperglycemia.[63]

When subcutaneous insulin is used in the preoperative period or operating room to treat hyperglycemia, BG testing should occur at least every 2 h. Correctional insulin is defined as the supplemental insulin provided for BG greater than 180 mg/dl (10 mM) after BG testing. Correctional dosing with a rapid-acting insulin can be calculated with the following formula: measured glucose minus 100/insulin sensitivity factor. Insulin sensitivity factor is equal to 1,800 divided by the patient's total daily dose (TDD) of insulin. The TDD is equivalent to the patient's daily amount of basal, prandial, and correctional insulin. Should TDD not be available or if a patient is using only oral medications at home, a sensitivity

Table 4. Day of Surgery Insulin Regimens

Day of Surgery Insulin Regimens	Glargine or Detemir	NPH or 70/30 Insulin	Lispro, Aspart, Glulisine, and Regular	Noninsulin Injectables
	80% of usual dose if patient uses morning only or twice daily basal therapy	50% of usual dose if BG 120 mg/dl* Hold for BG < 120 mg/dl	Hold	Hold

*6.6 mM.
BG = blood glucose; NPH = neutral protamine Hagedorn.

factor (denominator) of 40 provides a safe calculation for a correctional insulin dose. Rapid-acting insulin should not be dosed more frequently than every 2 h to minimize the risk of insulin stacking. Data comparing subcutaneous insulin to IV insulin infusion in the operative setting are lacking. The short duration of action of rapid-acting insulin analogs limits the risk of "insulin stacking" with repeat dosing. However, limiting the number of intraoperative subcutaneous insulin doses to two, within the 4-h operative time, may reduce the risk hypoglycemia.

Algorithms are available that recommend subcutaneous insulin dosing regimens to treat intraoperative hyperglycemia.[64] Table 5 provides a subcutaneous rapid-acting insulin correction scale that can be used intra- and postoperatively. To limit the risk of hypoglycemia, patient factors associated with insulin sensitivity (age greater than 70 yr, renal insufficiency) are identified, and a reduced correctional dose is provided for BG greater than 180 mg/dl (10 mM). Larger doses of correctional subcutaneous insulin are provided for BG greater than 180 mg/dl (10 mM) in patients with factors associated with insulin resistance (body mass index greater than 35 kg/m^2, TDD greater than 80 U/day, steroid equivalent greater than 20 mg prednisone daily). Should a patient have factors in multiple categories (insulin sensitive, insulin usual, and insulin resistant), the category with smallest correctional dose is chosen to minimize the risk of hypoglycemia.

An IV insulin infusion is recommended in patients undergoing procedures with anticipated hemodynamic changes, significant fluid shifts, expected changes in temperature (passive hypothermia or active cooling, hyperthermic intraperitoneal chemotherapy), use of inotropes, or lengthy operative times (greater than 4 h). These variables alter subcutaneous insulin absorption and distribution. Unreliable pharmacokinetics may result in persistent hyperglycemia or, conversely, sudden hypoglycemia. For these same reasons, an IV insulin infusion is used in critically ill patients or those undergoing cardiac surgery. The short half-life of IV insulin (less than 15 min) allows for rapid-adjustment in drug delivery and has limited lasting effect. The ideal protocol allows flexible rate adjustments that are based on both the current and previous glucose value. An example is provided in table 6. BG testing should occur hourly when using a variable rate insulin infusion. Given the frequency of monitoring, use of an electronic alert system in the operating room can increase provider adherence to testing and treatment of BG.[65] A pre- and intraoperative testing and treatment algorithm is outlined in figure 2.

Postoperative Glycemic Management for Non-ICU Patients

Glucose control in noncritically ill, non-ICU surgical patients is managed with subcutaneous insulin. While recovering in the postanesthesia care unit (PACU), BG checks need to continue at least every 2 h for all diabetic patients and for nondiabetics treated with insulin in the operating room. Correctional subcutaneous rapid-acting insulin doses are provided for BG greater than 180 mg/dl (10 mM; table 5). The anesthesiologist's assessment of the patient's level of consciousness, recovery condition, ability to swallow, and oral status determined by surgical team are used

Table 5. Correctional Subcutaneous Insulin Scale Day of Surgery and Postoperative Surgical Ward Care

Blood Glucose mg/dl (mM)	Insulin Sensitive* Age > 70 yr, GFR < 45 ml/min, No History of Diabetes	Usual Insulin	Insulin Resistant* BMI > 35 kg/m2, Home TDD Insulin > 80 U, Steroids > 20 mg Prednisone Daily
141–180 (7.7–10)	0	2	3
181–220 (10–12.2)	2	3	4
221–260 (12.2–14.4)	3	4	5
261–300 (14.4–16.6)	4	6	8
301–350 (16.6–19.4)	5	8	10
351–400 (19.4–22.2)	6	10	12
> 400 (> 22.2)	8	12	14

*If the patient falls into more than one insulin treatment group, choose the category with the lowest correctional dose to minimize the risk of hypoglycemia.
BMI = body mass index; GFR = glomerular filtration rate; TDD = total daily dose.

Table 6. Variable Rate Continuous Insulin Infusion

BG mg/dl (mM)	If BG Increased from Previous Measurement	BG Decreased from Previous Measurement by Less Than 30 mg/dl	BG Decreased from Previous Measurement by Greater Than 30 mg/dl
> 241 (13.4)	Increase rate by 3 U/h	Increase rate by 3 U/h	No change in rate
211–240 (11.7–13.4)	Increase rate by 2 U/h	Increase rate by 2 U/h	No change in rate
181–210 (10–11.7)	Increase rate by 1 U/h	Increase rate by 1 U/h	No change in rate
141–180 (7.8–10)	No change in rate	No change in rate	No change in rate
110–140 (6.1–7.8)	No change in rate	Decrease rate by ½ U/h	Hold insulin infusion
100–109 (5.5–6.1)	1. Hold insulin infusion 2. Recheck BG hourly 3. Restart infusion at ½ the previous infusion rate if BG > 180 mg/dl (10 mM)		
71–99 (3.9–5.5)	1. Hold insulin infusion 2. Check BG every 30 minutes until BG > 100 mg/dl (5.5 mM) 3. Resume BG checks every hour 4. Restart infusion at ½ the previous infusion rate if BG > 180 mg/dl (10 mM)		
70 (3.9) or lower	If BG = 50–70 (2.8–3.9 mM), 1. Give 25 ml D50 2. Repeat BG checks every 30 min until BG > 100 mg/dl (5.5 mM) If BG < 50 mg/dl (2.8 mM), 1. Give 50 ml D50 2. Repeat BG every 15 min until > 70 mg/dl (3.9 mM) 3. When BG > 70 mg/dl, check BG every 30 min until > 100 mg/dl (5.5 mM). Repeat 50 ml D50 dose if BG < 50 mg/dl a second time and start D10 infusion 4. After BG > 100 mg/dl (5.5 mM), resume hourly BG check Restart infusion at ½ the previous infusion rate if BG > 180 mg/dl (10 mM)		

Perioperative target blood glucose (BG) 140 to 180 mg/dl (7.8 to 10 mM).
1. If BG > 180 mg/dl (10 mM), start insulin infusion.
2. Consider bolus dose (BG = 100/40).
3. Start rate at BG/100 = U/h.
4. Check BG hourly and correct per table.
D10 = 10% dextrose solution; D50 = 50% dextrose solution.

to determine treatment of BG less than 70 mg/dl (3.9 mM). An oral glucose or IV dextrose solution is appropriate. If a PACU patient's condition deteriorates and there is need for ICU level care, all subcutaneous insulin is stopped and an IV insulin drip started for BG greater than 180 mg/dl (10 mM; table 6). For same-day surgery, the patient may resume their home medication regimen when he/she leaves the hospital.

When patients transition out of the PACU onto the surgical ward, use of sliding scale insulin alone is not acceptable as the single regimen in patients with diabetes, as it results in undesirable hypoglycemia and/or hyperglycemia.[66,67] The administration of once or twice daily basal insulin (glargine, detemir, or NPH) alone, or in combination with prandial insulin, is the recommended approach.[66–68] The use of a long-acting basal insulin plus prandial rapid-acting insulin is commonly referred to as a "basal bolus" insulin regimen. A randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT-2 Surgery) reported that in general medicine patients with type 2 diabetes, basal bolus treatment resulted in greater control of BG than regimens consisting only of sliding-scale insulin.[66] In general surgery patients, basal bolus regimens also significantly reduce the number of postoperative complications, primarily wound infections.[67] NPH and regular insulin, or premixed (70/30) formulations, demonstrate equivalent BG control when compared to basal bolus regimens, but are associated with higher rates of hypoglycemia in patients with poor oral intake.[69,70]

The "basal plus" regimen includes a long-acting basal insulin once daily plus a correctional rapid-acting insulin to treat BG greater than 180 mg/dl.[68] Although the correctional insulin appears similar to a sliding scale, it is intended to make small corrections in BG that occur despite basal therapy. Sliding scale insulin regimens do not supply basal insulin. In surgical patients with reduced total caloric intake, the Basal Plus trial[68] reported that a single daily dose of glargine plus correctional doses with rapid-acting insulin resulted in improved glycemic control compared to sliding scale insulin therapy alone. There was no difference in the frequency of hypoglycemia compared to a basal bolus regimen. These results indicate that in surgical patients, the basal plus correctional insulin regimen is preferred for patients with poor or no oral intake while an insulin regimen with basal, prandial, and correctional components (Basal Bolus) is preferred for patients with good nutritional intake.

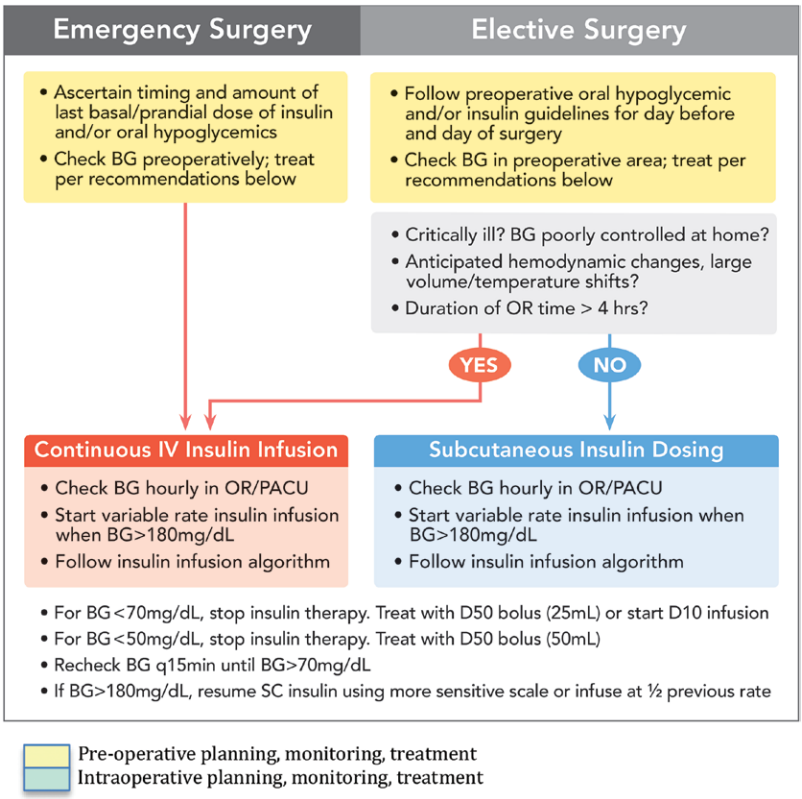

Fig. 2. Pre- and intraoperative testing and treatment algorithm (intravenous or subcutaneous insulin). BG = blood glucose; D10 = dextrose 10% solution; D50 = dextrose 50% solution; IV = intravenous; OR = operating room; PACU = postanesthesia care unit; q15min = every 15 min; SC = subcutaneous. BG 180 mg/dl = 10 mM; BG 70 mg/dl = 3.9 mM, BG 50 mg/dl = 2.8 mM.

Table 7. Postoperative Surgical Ward Insulin for Type 2 Diabetics on Oral Agents at Home

	Type of Insulin	Total Daily Dose Insulin Sensitive* Age > 70 yr, GFR < 45 ml/min	Total Daily Dose Insulin Usual	Total Daily Dose Insulin Resistant BMI > 35 kg/m^2, Steroids ≥ 20 mg Prednisone Daily
NPO/Poor Oral Intake/Clear Liquid Diet	Basal (glargine/detemir)	0.1–0.15 U · kg^{-1} · day^{-1}	0.2–0.25 U · kg^{-1} · day^{-1}	0.3 U · kg^{-1} · day^{-1}
USE BASAL PLUS REGIMEN	Correctional (rapid acting)	Treat BG > 180 mg/dl (10 mM) using correctional calculation or table 5		
Normal Oral Intake At Meals	Basal (glargine/detemir)	0.1–0.15 U · kg^{-1} · day^{-1}	0.2–0.25 U · kg^{-1} · day^{-1}	0.3 U · kg^{-1} · day^{-1}
USE BASAL BOLUS REGIMEN	Prandial (rapid acting)	0.1–0.15 U · kg^{-1} · day^{-1}	0.2–0.25 U · kg^{-1} · day^{-1}	0.3 U · kg^{-1} · day^{-1}
	Correctional (rapid acting)	Treat BG > 180 mg/dl (10mM) using correctional calculation or table 5		

*If the patient falls into more than one insulin treatment group, choose the category with the lowest insulin dose to minimize the risk of hypoglycemia.
BG = blood glucose; BMI = body mass index; GFR = glomerular filtration rate; NPO = nothing by mouth.

Insulin doses administered subcutaneously are calculated either based on weight or on home insulin doses (table 7). For insulin naive diabetic patients, an evaluation of oral intake determines basal daily dose. For patients who are nothing by mouth (NPO) or with poor oral intake, the starting daily dose of basal (glargine and detemir) insulin is 0.2 to 0.25 U · kg^{-1} · day^{-1}. As patients' diet orders are advanced and they tolerate a diet (regular, low carbohydrate, or diabetic), a basal bolus regimen is started. In elderly patients (age greater than 70 yr) and those with impaired renal function (glomerular filtration rate less than 45 ml/min), the daily basal insulin dose is reduced by approximately half of the normal recommended dose (0.1 to 0.15 U · kg^{-1} · day^{-1}) to reduce the risk of hypoglycemia. Insulin-resistant patients are provided higher doses of basal insulin (0.3 U · kg^{-1} · day^{-1}) to minimize hyperglycemia. A correctional scale (table 5) is included for all diabetic patients in the both basal plus and basal bolus regimen.

The home insulin regimen of a diabetic patient is used to calculate daily hospital dose. Reducing TDD by 20 to 25% yields the starting inpatient dose of basal insulin while the patient is NPO. The reduction in basal insulin reduces the risk of hypoglycemia, particularly in those with poor or uncertain caloric intake.[68] The dose of basal insulin is adjusted daily if the patient's BG is not within target range over the previous 24 h. In the absence of hypoglycemia (BG less than 70 mg/dl, 3.8 mM), the basal insulin dose is increased by 10 or 20%, respectively, for persistent BG greater than 180 mg/dl (10 mM) or 240 mg/dl (13 mM). As normal diet is resumed, insulin therapy can be transitioned to the patient's usual basal and prandial regimen. An endocrinology consult is recommended in diabetic patients if they are started, or placed on increasing doses of steroids or immunosuppressants, if parenteral or enteral feeding is initiated (or with formula change), for persistent hypoglycemia or hyperglycemia (despite dose adjustment) and before discharge if the patient's home regimen is not controlling their disease (HbA1C greater than 8%).

The use of oral antidiabetic agents is generally not recommended in hospitalized patients due to the limited data available on their safety and efficacy. Hospitalized patients frequently have contraindications to oral medications and the slow onset of action may preclude achieving rapid glycemic control. However, in recent years, the use of DPP-4 inhibitors has been proposed for the management of inpatient hyperglycemia.[59] A recent randomized study in medicine and surgery patients with type 2 diabetes reported that the use of sitagliptin alone, or in combination with a single basal insulin dose, resulted in similar mean daily glucose concentrations when compared to basal bolus insulin regimens.[59]

Transitioning from IV to Subcutaneous Insulin

Postoperatively, glycemic control in critically ill patients is managed with a continuous insulin infusion. When ICU patients are ready to be transferred to the general medical wards, appropriate transition orders from an IV insulin to scheduled subcutaneous insulin are needed to prevent rebound hyperglycemia.[71] This is imperative in patients with type 1 diabetes since stopping or delaying insulin for only a few hours can result in DKA.

Calculation of subcutaneous insulin dose in those who have been on an IV insulin infusion is done by determining the TDD of insulin based on the patient's insulin infusion over the last 8 h. Seventy percent of this total is administered as basal insulin. Thirty percent is added as prandial insulin when the patient is tolerating a normal diet.[72] For diabetic patients on insulin therapy before admission, surgical ward insulin dose is based on home regimen.[68,71] Reducing the patient's home TDD of insulin by 20 to 25% provides the starting daily basal insulin dose for the patient while NPO or with limited oral intake. To prevent rebound hyperglycemia, basal insulin is given 2 h before discontinuation of the IV insulin infusion. Patients without a history of diabetes (HbA1c less than 6.5%) requiring insulin infusion at low doses (less than or equal to 2 U/h) can be transitioned to the surgical ward without basal insulin. Continued monitoring is necessary, and correctional insulin may be needed.[25]

Insulin Pump Therapy

The use of insulin pump therapy has increased significantly during the past decade with recent estimates of more than 400,000 pump users in the United States.[73] The majority of patients with an insulin pump have type 1 diabetes, but use is growing in type 2 diabetics. Patients with an insulin pump should continue insulin preoperatively and on the day of surgery. Depending on the provider's comfort level managing an insulin pump and its settings, as well the placement of the pump in relation to the surgical field, a patient's home device may be used in the operating room. Advanced preoperative planning to facilitate pump use in the operating room, especially for shorter cases or outpatient surgery, prevents interruption of the patient's normal insulin routine.

Intraoperatively, if the patient's own insulin pump is used, the basal rate is continued. Hourly monitoring of BG is initiated when the patient arrives to the preoperative area and continued until the patient is sufficiently alert to resume self-management. The pump is turned off when the BG is less than 110 mg/dl, 6.1 mM). Correctional insulin bolus therapy is provided to treat BG greater than 180 mg/dl (10 mM). Alternatively, if the pump cannot be used because placement interferes with the surgical field, the anesthesia team cannot access the pump due to positioning or, if turning off and/or changing basal rate is difficult for the anesthesiology team, an IV insulin infusion can be substituted for the pump. The pump is disconnected, and an insulin infusion is started at the same basal rate used by the patient.

Postoperatively, successful management of inpatient diabetes with the continuation of insulin pump therapy has been demonstrated in selected patients.[74] Current recommendations advocate for the establishment of clear policies and procedures to guide patients and hospital staff in the management of diabetes with the use of insulin pumps.[73] Patients who are sufficiently alert to aid in their BG testing, pump rate change, and bolus administration, can continue to use and manage their pump as an inpatient. In addition to the other previously mentioned reasons for consult, prompt involvement of inpatient diabetes specialists is recommended to assist with the assessment and management of critically ill or sedated/somnolent patients or if the patient has difficulty in controlling BG with typical rate adjustments and prandial doses.[75]

Hypoglycemia

Hypoglycemia (less than 70 mg/dl, 3.9 mM) is the most common event associated with insulin administration and has been demonstrated to be associated with poor clinical outcomes[10] and mortality.[7] Clear data demonstrate that the probability of hypoglycemia increases significantly when glycemic goals are aggressive.[44] Because hypoglycemia may go unrecognized under anesthesia,[76] providers can be reticent to use insulin in the operating room. Undoubtedly, care must

be taken to appropriately monitor patients in the perioperative setting to prevent dangerous drops in blood sugar. Conservative BG targets,[7] frequent monitoring, perioperative provider communication,[77] and treatment algorithms that base doses on insulin sensitivity[64] jointly reduce the risk of intra- and postoperative hypoglycemia.

Glucose Monitoring in the Perioperative Period

Options for testing BG include central laboratory testing, blood gas analysis, and capillary point-of-care testing (POC). Although central laboratory testing provides the most accurate BG measurement, the immediate turnaround time of POC glucometer devices enable anesthesia providers to make quick decisions to treat both hyper- and hypoglycemia. However, intensivists, anesthesiologists, and surgeons need to recognize the limitations of glucometer POC testing. In 2014, the Food and Drug Administration issued a draft guidance outlining that 99% of POC readings greater than 70 mg/dl (3.9 mg/dl) be within 10% of central laboratory reference values and that all BG readings less than 70 mg/dl be within 7 mg/dl (0.39 mM). Glucometers available in many hospitals do not meet these metrics and may be less accurate than providers recognize. The safety of these devices to monitor BG in critically ill patients has been extensively questioned. A recent review of 21 studies examining POC glucose testing in this population suggested that in the setting of hemodynamic instability or continuous insulin infusions, bedside glucometers may not be sufficiently precise or reliable for use.[78]

Conclusion

Hyperglycemia is common in surgical patients. Current data demonstrate an association between elevated BG and a risk of perioperative complications in diabetic and nondiabetic patients. Insulin administration intra- and post-operatively has been shown to improve clinical outcomes. Individual patient characteristics and surgical case factors are considered when choosing subcutaneous insulin or an insulin infusion. Both are appropriate options on the day of surgery. BG values of 180 mg/dl or higher (10 mM) are treated with insulin. Target range for the perioperative period is 140 to 180 mg/dl (7.7 to 10 mM; table 1).[50–54] Postoperatively, surgical ward patients with poor or uncertain oral intake are treated with once daily basal insulin. Prandial insulin is added when patients tolerate oral intake. Increasing evidence suggests a role for incretin therapy during the perioperative period in patients with type 2 diabetes.

Multiple teams care for a surgical patient during the hospital course (anesthesiology, surgery, critical care medicine, internal/hospital medicine, and endocrinology). Therefore, multidisciplinary groups within an institution should work together to create appropriate protocols for hyperglycemia screening, monitoring, and treatment to minimize errors and to better care for patients.

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Competing Interests

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Correspondence

Address correspondence to Dr. Duggan: Department of Anesthesiology, Emory University School of Medicine, 1364 Clifton Road, Office B-352, Atlanta, Georgia 30322. elizabeth.w.duggan@emory.edu.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

From Water to Ether: Oconee Hill Cemetery

In Athens in northeastern Georgia, Oconee Hill Cemetery stretches near East Campus Road, opposite Sanford Stadium, the home of the University of Georgia's Bulldogs. The cemetery's hill was named after part of the Oconee River, itself named after the Oconee tribe of Native Americans. Claiming southeastern Georgia's Okefenokee Swamp as their original homeland, the Oconees had their current name anglicized from the Itsati or Hitchiti-Creek word Okvni for "born from water." Many anesthesiologists treasure Oconee Hill Cemetery as the burial site for physician-pharmacist Crawford Williamson Long, M.D. (1815 to 1878), who etherized James Venable on March 30, 1842. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois; and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.