Unexpected Hypoglycemia in a Critically Ill Patient

David W. Bates, MD, MSc*

Administration of the wrong medication is a serious and under-studied problem. Because physicians are not directly involved in the drug administration process, they tend to overlook the possibility of adverse drug events and medication errors in their differential diagnoses of patient illnesses or acute deterioration. This article analyzes the case of a patient with iatrogenic hypoglycemia due to administration of the wrong medication: Insulin instead of heparin was used to flush the patient’s arterial line. In addition to assessing the results of the institution’s “root-cause analysis” of the factors contributing to this particular adverse event and the institution’s response, this article reviews the literature on preventing medication errors. Key strategies that might have been helpful in this case include using checklists for common emergency conditions (such as altered level of consciousness) and automated paging for “panic laboratory values,” as well as instituting protocols for medication administration. Changing the system of administering medications by bar coding drugs, with checks of the medication, patient, and provider, could have prevented this accident. Finally, organizations need to strive for a “culture of safety” by providing opportunities to discuss errors and adverse events in constructive, supportive environments and by resisting pressure to find a scapegoat.

SUMMARY OF EVENTS

Two weeks following surgery, Ms. Grant (a pseudonym), a 68-year-old nondiabetic woman, became unresponsive and was found to have profound hypoglycemia. The patient had undergone elective cardiac bypass surgery. Complications that developed during the postoperative period were ventilator-acquired pneumonia, a right-hemispheric stroke, clinically significant gastrointestinal bleeding, and acute tubular necrosis that required hemodialysis. Although Ms. Grant remained in the intensive care unit (ICU) because of these complications, her condition stabilized considerably. In fact, her primary physician recalled that on the day of the adverse event, “The patient actually told us that she was comfortable and felt good for the first time. She looked wonderful during rounds.”

At approximately 8:15 a.m., Ms. Grant’s ICU nurse heard coughing, entered her room, and found her moving her head and extremities in an uncontrolled manner. The nurse administered labetalol because the patient’s systolic blood pressure was greater than 200 mm Hg. The ICU team arrived almost immediately, diagnosed a generalized seizure, administered intravenous lorazepam followed by midazolam, and emergently intubated the patient for airway protection. Serum electrolyte and arterial blood gas levels were measured, and computed tomography (CT) was done to rule out intracranial hemorrhage. Approximately 30 minutes after initiation of these diagnostic and therapeutic maneuvers, the laboratory no-tified the ICU team that the patient’s serum glucose level was undetectable.

NOSOCOMIAL HYPOGLYCEMIA

Faced with an abrupt change in their patient’s neurologic status, the ICU team considered the possibilities of severe electrolyte disorders, hypoxemia, hypoglycemia, infection, or a severe intracranial event (such as a massive hemorrhagic stroke). In a critically ill patient who is probably receiving many medications, drug effects and medication withdrawal (for example, from benzodiazepines) should also be high on the list of considerations.

Possible causes that quickly respond to treatment should be addressed early. If this patient had been seen in the emergency department, she would have immediately received intravenous thiamine and 50 mL of 50% dextrose in water, even before the results of the laboratory analysis were available. Empirical administration of hypertonic dextrose has been standard practice in emergency assessment of altered level of consciousness. Some controversy surrounds possible adverse effects of this practice (1) because of the deleterious consequences in patients with cerebral ischemia (2). Thus, checking blood glucose levels immediately is ideal, but when this is not possible, rapid administration of hypertonic dextrose is still recommended (3). In hospitalized, nondiabetic patients, on the other hand, empirical management of possible hypoglycemia is not routine, although some authorities recommend it (4). In one study, failure to consider hypoglycemia as a cause of altered level of consciousness was the most frequent error in emergent scenarios (5). Timely diagnosis of hypoglycemia is especially important, because it is usually reversible and the degree of injury depends on how quickly treatment is started. In these situations, checklists can be very useful and should be more widely used.

In the case of Ms. Grant, the diagnosis of profound

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Recently, advances in communication technology permit critical laboratory results to be obtained rapidly. However, an emergency department physician might not be notified of a critically abnormal laboratory finding, in conjunction with the patient’s clinical appearance, until the critical abnormality has become apparent to the team. Physicians can report the key abnormality and provide concurrent supporting data for decision making. In a controlled trial at Brigham and Women’s Hospital that evaluated a direct-paging approach (7), the intervention group had a median time to therapy that was reduced by 38% (P = 0.003) and a trend toward a lower mortality rate (7.4% vs. 13.3% in the control group) (P = 0.19).

What are the possible causes of Ms. Grant’s hypoglycemia? One review of hypoglycemia (8) organized the diagnostic approaches in terms of the patient’s clinical appearance and the clinical setting—patients without apparent illness, ill-appearing patients, and hospitalized patients. In hospitalized patients, major causes of hypoglycemia in nondiabetic patients are drug effects, renal insufficiency, liver failure, sepsis, malnutrition, and shock (9). Adrenal insufficiency can also occasionally present as severe hypoglycemia (10–13). However, the abrupt and profound hypoglycemia in Ms. Grant’s case strongly suggested a drug effect.

Medications that can cause hypoglycemia include quinidine (14) and its derivatives (14, 15), salicylates, pentamidine (16, 17), and trimethoprim–sulfamethoxazole (18). However, the predominant causes of drug-induced hypoglycemia, even in nondiabetic patients, are the drugs used to treat diabetes (14, 19). The patient’s undetectable blood glucose level strongly suggested inadvertent or excessive administration of a hypoglycemic agent.

### CHRONOLOGY OF EVENTS

When the patient was being returned to the ICU after the CT scan, the laboratory alerted the ICU to the undetectable serum glucose level. (The CT scan had revealed no evidence of intracranial hemorrhage, mass, or mass effect.) The patient immediately received one ampule of 50% dextrose in water, after which the serum glucose level reached 1.0 mmol/L (18 mg/dL). Administration of a second ampule of 50% dextrose in water produced a serum glucose level of 1.3 mmol/L (24 mg/dL).

At 9:15 a.m., a nearly empty 10-mL vial of regular human insulin (100 U/mL) was found on the medication cart outside the patient’s room. This finding, in conjunction with the persistent hypoglycemia despite aggressive glucose replacement, suggested that the patient’s sudden deterioration had resulted from inadvertent administration of insulin.

### THE WRONG DRUG

Nondiabetic persons can receive diabetic medications as a result of inadvertent ingestion or an error at some stage in the medication ordering, dispensing, or administering processes. Such errors have been well documented for oral hypoglycemic agents (20–28). Similar errors have also been reported for insulin (29). Errors in the administration of intravenous medications are more common than many physicians realize (30). The literature on anesthesia (31,

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**Table. Timeline of Events**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:30 a.m.</td>
<td>Nurse draws blood for routine morning laboratory tests; serum glucose level is 6.72 mmol/L (121 mg/dL).</td>
</tr>
<tr>
<td>6:00 a.m.</td>
<td>Medical student visits patient before team rounds. Patient is stable.</td>
</tr>
<tr>
<td>6:10 a.m.</td>
<td>Cardiothoracic ICU team visits; no new issues are noted. Patient is showing much improvement; team has every expectation that she will make a complete recovery.</td>
</tr>
<tr>
<td>6:20 a.m.</td>
<td>Patient drinks small amount of orange juice; note in chart indicates that patient is stable.</td>
</tr>
<tr>
<td>6:35 a.m.</td>
<td>Nurse uses a straight urinary catheter to drain patient’s bladder per a standing order. Patient appears well but tired; expresses desire to nap.</td>
</tr>
<tr>
<td>6:45 a.m.</td>
<td>Alarm goes off, alerting nurse to occlusion of the patient’s arterial line; nurse flushes line with 1 to 2 mL of what he believes is heparin lock flush.</td>
</tr>
<tr>
<td>7:35 a.m.</td>
<td>Day nurse receives shift change report from night nurse; day nurse assumes care of patient.</td>
</tr>
<tr>
<td>7:45 a.m.–8:00 a.m.</td>
<td>Night nurse completes shift. Patient is reported to be sleeping soundly.</td>
</tr>
<tr>
<td>8:15 a.m.</td>
<td>Day nurse discovers patient having seizure activity. Labelotil is given by day nurse for systolic blood pressure &gt;200 mm Hg; patient’s physician is called.</td>
</tr>
<tr>
<td>8:20 a.m.</td>
<td>1 mg lorazepam is given intravenously by nurse for apparent seizure.</td>
</tr>
<tr>
<td>8:35 a.m.</td>
<td>Neurology service is called to see patient immediately for abrupt decrease in consciousness.</td>
</tr>
<tr>
<td>8:42 a.m.</td>
<td>Emergent CT head scan is performed; no evidence of intracranial hemorrhage, mass, or mass effect is noted. Laboratory notifies ICU that serum glucose level is undetectable; 1 ampule 50% dextrose in water is given intravenously.</td>
</tr>
<tr>
<td>8:55 a.m.</td>
<td>1 mg lorazepam is given intravenously by nurse.</td>
</tr>
<tr>
<td>9:05 a.m.</td>
<td>1 mg midazolam is given as IV push by nurse, and patient is intubated.</td>
</tr>
<tr>
<td>9:15 a.m.</td>
<td>Day nurse finds bottle of regular human insulin on the medication cart immediately outside patient’s room.</td>
</tr>
<tr>
<td>9:20 a.m.</td>
<td>1 mg midazolam is given again as IV push by nurse.</td>
</tr>
<tr>
<td>9:45 a.m.</td>
<td>10 mg chlorpromazine, 6 mg morphine, and 2 mg midazolam are given as IV push by nurse.</td>
</tr>
<tr>
<td>9:50 a.m.</td>
<td>1 ampule 50% dextrose in water is given.</td>
</tr>
<tr>
<td>10:05 a.m.</td>
<td>Laboratory repeats glucose test and reports glucose level of 13 mmol/L (24 mg/dL).</td>
</tr>
<tr>
<td>10:15 a.m.</td>
<td>1 ampule 50% dextrose in water is given.</td>
</tr>
<tr>
<td>11:00 a.m.</td>
<td>2 ampules 50% dextrose in water is given.</td>
</tr>
<tr>
<td>12:45 p.m.</td>
<td>5 mg labelotil is given as IV push by day nurse for systolic blood pressure of 195 mm Hg.</td>
</tr>
<tr>
<td>1:15 p.m.</td>
<td>1 ampule 50% dextrose in water is given by day nurse for serum glucose level of 3.1 mmol/L (55 mg/dL).</td>
</tr>
<tr>
<td>Remainder of day</td>
<td>Blood glucose level is difficult to maintain; patient remains comatose.</td>
</tr>
</tbody>
</table>

* CT = computed tomography; ICU = intensive care unit; IV = intravenous.
and respond rapidly to serious deviations. In this case, the deficiencies in the system that made an error more likely included the failure to store medications properly, the lack of checks in medication administration, and the less-than-optimal response to the patient’s deterioration. The primary error appears to have occurred at 6:45 a.m., when insulin was used to flush the arterial line, although no change in the patient’s condition was detected until 8:15 a.m. The time sequence (Table, available at www.annals.org) and additional information (Appendix, available at www.annals.org) help reconstruct the events. Both heparin flush solution and insulin were taken from multidose vials that were on the top of the cart at the time of the error. Both types of vials hold 10 mL of solution, and the vials look somewhat similar (Figure). Although the insulin should have been kept in the refrigerator, it was often left on the top of the cart after being taken out of the refrigerator, a practice that psychologist James Reason (37) would term an unsafe act—something that violates a policy or procedure but is often done to save time.

**THE EPIDEMIOLOGY OF MEDICATION ERRORS AND ADVERSE DRUG EVENTS**

Medication errors occur much more frequently than do adverse drug events, although most have little potential for harm (34, 38). Adverse drug events occur when a drug causes injury; if an adverse drug event is associated with an error, it is considered preventable. Medication errors with potential for harm that do not cause injury are considered potential adverse drug events. Thus, the case described here represents a preventable adverse drug event. One study (34) found approximately 100 medication errors for every preventable adverse drug event and seven potential adverse drug events (or near-misses) for every preventable adverse drug event. In another large study (38), the rate of occurrence of adverse drug events was 6.5 per 100 admissions, of which 28% were preventable. In that study, the stage at which serious medication errors (potential adverse drug events and preventable adverse drug events) occurred was broken down as follows: 49% at the ordering stage, 26% at the administration stage, 14% at the dispensing stage, and 11% at the transcription stage. Errors were much more likely to be intercepted if they occurred at an early stage of the medication use process.

“Wrong drug” or “wrong patient” errors represented 4% of all medication errors in hospitalized medical patients in a study that used various approaches to review records of such errors (34). The most sensitive approach for detecting medication administration errors is probably direct observation (39). Barker and Allan (33) developed an approach in which a trained observer watches a health care professional, notes what he or she does when administering drugs, and watches the patient receive the medication. This approach is now widely used in health care organizations, most notably in long-term care facilities; federal inspectors use the
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ACADEmia AND CLINIC

The Role of Individual Errors in Causing This Adverse Event

This case represents a common error—almost certainly a “slip.” A “slip” is one of the two primary classes of errors. Slips occur during low-level, semiautomatic everyday functions. They are distinct from the other primary class of error, “mistakes,” which involve higher cognitive function and occur in new or nonstereotypical situations.

In this case, the nurse clearly intended to give heparin, but because both types of vials were on the top of the cart, he “slipped” and inadvertently selected the wrong one. Poor systems design increases the likelihood of slips resulting in catastrophic harm. A classic medical example is giving a gas other than oxygen to a patient receiving anesthesia, often with disastrous consequences (43). This error has been largely “engineered out” of anesthesia, using what is termed a forcing function. Anesthesia machines are now built with a unique oxygen yoke that prevents attachment of any other type of gas.

In this case, which is similar to many preventable adverse events in medicine, an individual made a clear-cut error. The nurse should have checked the vial to ensure that it contained heparin before giving the medication. However, such slips are inevitable, especially given increasing time pressures and workloads: Humans are not “perfectible” (44). If one person exhibits a pattern of poor performance, appropriate action should be taken. However, most errors are made by competent providers. In a report from the Adverse Drug Event Prevention Study Group that evaluated more than 250 serious errors (45), no one person showed a recurring pattern of error.

The Role of Systems in This Adverse Event

The systems and processes of care clearly played a major role in this adverse drug event. In the ICU, it was routine practice to have heparin and insulin accessible at the same time and to use multidose vials. In addition, there was no system of second checks (by another person) before high-risk drugs were administered. Also, the institution did not have a system of bar code checking. In responding to the adverse event, it is not clear whether physicians had a protocol for responding to hypoglycemia. The patient probably should have received glucose earlier and should have been treated more aggressively, because the dangers of overadministration of glucose are lower than the risk from prolonged hypoglycemia.

Prevention Strategies

A variety of approaches may have prevented this adverse event, although it is important to note that the strength of evidence for safety practices overall varies substantially and is generally weak (46). Multidose vials of insulin, in particular, should not be kept on top of medication carts and probably should not be used at all. Insulin should be drawn up at one site in the nursing unit or, even better, prepared in the pharmacy. After insulin is drawn up, a second provider should independently check the original order. Bar coding, if strictly adhered to, could also have prevented this type of drug-substitution error (47).

It is important to note that applying the criteria of evidence-based medicine to safety practices has been challenging for a variety of reasons (46). Because adverse events occur rarely, trials are expensive; because many practices (for example, sponge counts) have become accepted, it would be difficult to subject them to trials; and because many practices are systems- and culture-oriented, they are not especially amenable to randomized trials. It is not clear whether trials are appropriate for many safety-related issues, especially given that other industries, such as aviation, have substantially improved safety without randomized trials (48).

Chronology of Events, Continued

The physicians caring for the patient and the medical center’s physician-in-chief met with the family within hours after the adverse event. The error and the immediate actions were explained, and the prognosis and need for supportive treatment and watchful waiting were discussed. The physicians and staff expressed profound regret and sorrow for the medical error. The family was understandably upset but appreciated the acknowledgment that a mistake had occurred.

The patient remained in a coma for 7 weeks. At that time...
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THE INSTITUTIONAL RESPONSE

The hospital implemented the following procedures and policies:

1. Insulin was added to the automated dispensing device.

2. All staff who obtain medications from ward stock were instructed to keep medications secured in authorized places.

3. All nurses were reminded to keep medication carts locked when not attended.

4. Use of multidose vials of insulin and of heparin was prohibited.

5. Use of normal saline flushes to restore patency to arterial lines (instead of heparin flushes) was required.

6. An interdisciplinary team, composed of a staff pharmacist, pharmacy manager for inpatient services, staff nurse, clinical coordinator, physician, and clinical risk manager, was established to examine how to expedite the delivery of medications to patients while maintaining optimum medication practices.

COMMENTS ON THE INSTITUTIONAL RESPONSE

How institutions respond to adverse events is vitally important if an organization is to build a culture of safety. With respect to patients and their families, a consensus has emerged that the most appropriate and ethical course is to immediately disclose an adverse event. Doing so is now required by new regulations from the Joint Commission on Accreditation of Healthcare Organizations (49). A report from the Department of Veterans Affairs argued persuasively for a full-disclosure policy and described one of its medical centers that had moderate liability payments since implementing this approach in 1987 (50).

The fear, of course, is that increased reporting, especially coupled with disclosure, could lead to skyrocketing malpractice litigation rates in the United States. A no-fault compensation approach for medical injuries (51) may alleviate this problem, but the obstacles are substantial. The current system strongly pressures providers to hide accidents rather than to bring them forward as a means to fuel quality improvement. Furthermore, persons who report adverse events may be punished (52). The tone set by administrators is crucial. Although remedial action should be taken, leadership must resist strong pressures to use individual workers as scapegoats, even when a serious error is found. Organizations that yield to these pressures will find it exceptionally difficult to develop a safety-oriented culture.

When given the opportunity to respond anonymously, individual providers recognize that error is a serious issue, but they harbor many counterproductive feelings that hinder development of a culture of safety. In an anonymous survey of internal medicine house officers regarding their most serious mistakes, Wu and colleagues (53) found serious adverse outcomes in 90% of the cases, including death in 31%. Only 24% of the responsible housestaff told the patients or families, and just 54% had even discussed the mistake with their attending physicians. House officers who accepted responsibility for and discussed the mistake made constructive changes more often. Those who attributed the mistake to job overload were less likely to respond positively. They reported defensive changes more often if they felt the institution was judgmental.

Providers involved in accidents feel guilty, tend to be overly self-critical, and need support (54, 55). Organizations should provide opportunities to discuss errors and adverse events in constructive, supportive environments. In general, hospitals have made a low overall investment in safety. One welcome response to the U.S. Institute of Medicine report on error (56) has been to increase this investment. Hospitals are increasingly providing support for a safety officer (often a physician) who, with staff and a budget, is charged with improving the safety of the organization. Historically, most of this function has been carried out by the risk management department, which in many organizations has focused primarily on dealing with potential lawsuits—a necessary role, but one that has been more reactive than proactive. This new and vital patient safety role should include close teaming of health care providers with risk management personnel. Safety officers should review the myriad suggestions being made by various groups (such as the Institute for Safe Medication Practices), evaluate their organization’s current practices, and encourage implementation of those procedures and policies that make sense. Only with more resources and support for safety will we develop a health care system that learns from the errors and accidents of others so that each site does not suffer its own disaster before procedures are improved.

Approaching patient safety problems is analogous to containing water in a sieve. In choosing how to apply resources to improve safety, institutions must decide whether to prioritize fixing “individual leaks” or overhauling the system (finding a container with fewer holes). A combination of approaches may often be appropriate. An evidence-based approach to prioritization of systems changes, especially their impact and costs, has begun but could be greatly expanded (46).

The approaches selected by the hospital in this case for preventing medication administration errors are reasonable, although some are stronger than others. Elimination of multidose insulin and heparin vials will probably be very effective; the educational measures will be less so (57). Moving insulin to the automated dispensing device is also desirable, although it may be more effective to prepare insulin in the pharmacy, at least for routine daily doses. Switching from heparin to saline flushes is a positive step that is supported by the available evidence (58). Develop-
ing a multidisciplinary team to evaluate the medication process on an ongoing basis is also a key step. With the exception of the elimination of heparin flushes, these changes amount to patching leaks rather than overhauling the system, which would involve fundamental redesign of the medication administration process and incorporating key systems changes (such as bar coding technology) (59).

**CONCLUSIONS**

As is generally the situation when preventable adverse events are assessed, several opportunities for improvement could be found. In Ms. Grant’s case, although the nurse made an error, he was “set up” to do so by poorly designed systems. The organization in this instance made appropriate short-term changes to its drug administration system, but its future course in this domain is unclear. In particular, bar coding would probably have prevented this accident. In addition, the team’s response to the patient’s altered level of consciousness could have been more effective and use of a checklist to prompt a systematic approach to altered mentation might have been helpful. Finally, all organizations need better ways to prioritize and implement key systems changes before accidents occur.

**APPENDIX**

**Additional Background Information About the Heparin and Insulin Vials from the Institution’s Root-Cause Analysis**

*Heparin lock flush solution.* This is one of the most frequently used pharmaceutical items in the intensive care setting where the adverse event occurred. It had been standard practice to keep heparin flush solution on top of the medication cart as a convenience for a busy unit with frequent emergent situations. In the past, both labeled and unlabeled syringes of the solution had been prepared in advance by the nursing staff and left on top of the cart. The practice of preparing syringes in advance had been abandoned recently because of safety concerns. Nevertheless, because of the inconvenience of entering the locked cart multiple times during each shift, once a vial was removed from inside of the medication cart, it was stored on top of the cart.

*Storage of insulin vials.* At the time of this adverse event, nurses did not generally store multidose insulin vials on top of the cart. Instead, stock insulin was usually kept in a refrigerator in a locked room located approximately 20 feet from the intensive care unit nursing station. When a multidose vial was removed, it was supposed to be returned to that location immediately after use. It is unclear who left the insulin vial on top of the cart at the time of the adverse event. However, staff agreed that insulin vials were frequently left on top of the cart.

*How the vials were confused by the nurse.* Routine practice at the time of this event was to administer both heparin flush solution and insulin from multidose vials. There were two medication vials on the top of the cart at the time the flush solution was (presumably) drawn. Heparin lock flush and insulin vials have some similarities. Each holds 10 mL of solution. Also, the label colors are similar (that is, blue and red for heparin; black and red for insulin). The medications should have been in their appropriate places—specifically, an appropriate drawer of the medication cart for the heparin flush or in the medication refrigerator for insulin.

**QUESTIONS AND ANSWERS FROM THE CONFERENCE**

*An Emergency Medicine Physician:* Did the team consider using a point-of-care blood glucose test rather than relying on sending the blood sample to the laboratory for evaluation?

*Dr. Bates:* Using a bedside glucose test may have provided the information sooner and possibly improved the patient’s outcome. However, our institution has decreased its use of bedside blood glucose monitoring because of both financial incentives and increased regulatory requirements related to the quality of point-of-care monitoring systems.

*Dr. Saint:* The providers in this case probably thought that hypoglycemia was an extremely unlikely cause of this patient’s confusion, so they did not consider obtaining a bedside glucose value. The low glucose level was obtained as a part of a “grope-a-gram” evaluation of blood tests routinely ordered whenever a patient experiences acute confusion.

*Dr. Bates:* Since hypoglycemia was not considered initially, this case highlights a reason to use checklists and other standard methods for evaluating differential diagnoses, especially during emergencies. It also points out the importance of maintaining an expansive differential diagnosis. As I think back, many of the errors that I’ve made in clinical medicine relate to narrowing the differential diagnosis too severely or prematurely.

*A Conference Attendee:* How important is it to notify risk management prior to discussing an error with family members of a patient?

*Dr. Bates:* This depends on the circumstances. In part to prevent such errors in the future.

*A Risk Manager in the Audience:* Providers in our hospital are encouraged to contact risk management prior to discussing cases with families. These situations can be incredibly charged, and risk management makes an effort to guide the provider on how to have a constructive discussion with the family about the error. Many patients’ families want to ensure that similar errors do not occur with other patients, while some are looking for an award of damages—in part to “send a message” to large institutions to prevent such errors in the future.

*Dr. Bates:* I would underscore the important role of risk management in helping to guide providers toward doing the right thing in response to an error.

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The Table, Appendix, and excerpts of the question-and-answer session are available at www.annals.org.

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