noma sentinel lymph nodes by enhanced pathology: recommendations for standardizing pathologic analysis. Am J Surg Pathol 2005;29:305-17.

THE AUTHORS REPLY: The false negative rate of sentinel-lymph-node biopsy has been variably defined with the use of two approaches. In early studies, complete lymph-node dissection was performed immediately after sentinel-lymph-node biopsy to identify microscopic metastases in "nonsentinel lymph nodes" within the same basin; with the use of these data, an "immediate false negative rate" was determined. An alternative approach is based on later identification of nodal metastases after sentinel-node biopsy following an interval of observation (the "delayed false negative rate"). The letters by Thomas and by Nieweg and Veenstra suggest that this latter assessment better reflects the accuracy of sentinel-lymph-node biopsy and that the former approach (described in the article) paints a more favorable picture; we submit that the first method, which reflects sentinel-node status at the time of the procedure, is most relevant.

Sources of nodal failure after a negative sentinel-lymph-node biopsy may be classified as technical (there was failure to remove a sentinel node containing disease), pathological (a sentinel node containing metastasis was removed, but the metastasis was not detected by means of routine histologic techniques), or biologic (there was synchronous microscopic in-transit disease or subsequent metastasis from a clinical locoregional recurrence).[1] Pathological failure, which probably represents the bulk of nodal failures in many early studies, has been largely resolved by the use of enhanced pathological analysis. The relatively high "false negative" rates cited by Thomas probably reflect such early studies.

The concept of microscopic "false positivity" is promulgated by Thomas and by de Giorgi et al. to explain why patients with positive sentinel-node-biopsy specimens fare better than those in whom palpable nodal disease develops and why the comparison of such cohorts in the MSLT-1 trial should be invalid.[2] Data providing support for this concept, however, are limited. In contrast, data from MSLT-1 provide support for the clinical relevance of microscopic disease. Specifically, among patients randomly assigned to nodal observation, the incidence of clinical nodal failure and distribution of relevant prognostic factors for primary tumors were identical to the incidence and distribution in the combined group of patients with positive sentinel-lymph-node biopsy specimens and those patients with negative sentinel-lymph-node biopsy specimens in whom nodal disease subsequently developed.[2,3]

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The Tumor Lysis Syndrome

TO THE EDITOR: We recently admitted a patient to our intensive care unit with methemoglobinemia and severe hemolytic anemia after he received a single dose of rasburicase. The patient was a 55-year-old black man with chronic lymphocytic leukemia in whom the tumor lysis syndrome developed after rituximab and bendamustine treatment despite saline and allopurinol prophylaxis. Within 6 hours after receiving rasburicase at a dose of 0.2 mg per kilogram of body weight, he became hypoxic, with a methemoglobin concentration of 12.2% (Table 1). He subsequently had acute intravascular hemolysis, with the hemoglobin level decreasing from 13.1 to 4.5 g per deciliter, the lactate dehydrogenase level increasing from 158 to 1229 U per liter, and the haptoglobin level decreasing from 130 to 10 mg per deciliter. An elevated plasma oxyhemoglobin level (30.9 mg per deciliter [4.8 μmol per liter]; reference range, 0.0 to 12.4 mg per deciliter [0.0 to 1.9 μmol per liter]) was accompanied by acute pulmonary hypertension (tricuspid regurgitant jet velocity of 3.5 m per second; reference range, 1.7 to 2.8).[1,2] He was found to have a glucose-6-phosphate de-

Table 1. Biochemical Evidence of Methemoglobinemia and Intravascular Hemolysis after Rasburicase Administration.*

Variable	Reference Range	Rasburicase Administration		
		Before	6–18 Hr After	48–96 Hr After
Uric acid (mg/dl)	3.7–8.6	9.0	2.2	3.3
Hemoglobin (g/dl)	13.7–17.5	13.1	10.7	4.5
Methemoglobin (%)	0.0–1.9		12.2	6.9
Oxyhemoglobin (%)	94–97		86	
Haptoglobin (mg/dl)	30–200		130	10
Lactate dehydrogenase (U/liter)	113–226	158	1166	1229
Bilirubin, indirect (mg/dl)	0.1–0.8	0.3	0.3	3.0
Plasma oxyhemoglobin (mg/dl)	0.0–12.4			30.9
Tricuspid regurgitant jet velocity (m/sec)	1.7–2.8	2.9		3.5

* To convert the values for uric acid to millimoles per liter, multiply by 0.059. To convert the values for plasma oxyhemoglobin to micromoles per liter, multiply by 0.155. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

hydrogenase (G6PD) deficiency. Rasburicase causes oxidative stress by releasing hydrogen peroxide during the conversion of uric acid to allantoin.[3] Although not specifically mentioned in the review by Howard et al. (May 12 issue),[4] the Food and Drug Administration recommends that patients from populations where G6PD deficiency is common undergo testing before treatment with rasburicase.[5]

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TO THE EDITOR: Howard and colleagues provide an excellent overview of the pathophysiology of the tumor lysis syndrome and the potential complications from this oncologic emergency. Several points, however, merit further discussion. The authors make multiple mentions of a patient's risk of the development of xanthine nephropathy, a seemingly very rare albeit perhaps underappreciated entity, as a consequence of allopurinol use. It may be important to note that allopurinol also prevents the formation of xanthine from hypoxanthine, a much more soluble compound.

Rasburicase is a powerful drug that can efficiently deplete circulating uric acid. Several analyses have concluded that single fixed doses of 3.0 to 7.5 mg are capable of adequately lowering the uric acid level, thus effectively reducing the risk of urate nephropathy in those patients at high risk for the development of clinical tumor lysis syndrome.[1-3] In their review, the authors do not address the controversial issue of dosing this expensive drug, which is highly relevant given the abundance of data supporting much lower doses than what is suggested in the product's labeling.

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

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TO THE EDITOR: I take issue with two opinions stated by Howard et al. in their otherwise informative review of the tumor lysis syndrome. First, they recommend that Cairo and Bishop's definition[1] of clinical tumor lysis syndrome, which includes a 25% decrease in the glomerular filtration rate as a criterion, be dropped, because such increases are rarely clinically significant. This view directly contradicts the RIFLE (risk, injury, loss, and end-stage renal disease) consensus classification of acute kidney injury.[2] This definition has been well validated and has shown strong correlation with clinical outcomes in critically ill patients.

Second, on the basis of a rat model of urate nephropathy, they recommend the use of loop diuretics such as furosemide to prevent acute kidney injury when urine flow is low. Although loop agents improve urine flow, in human studies of prevention of acute kidney injury, their use has often led to worse outcome.[3,4] It would therefore seem premature to recommend the use of loop diuretics to prevent acute kidney injury in the tumor lysis syndrome until this is proved in randomized, controlled human studies.

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

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THE AUTHORS REPLY: We thank Elinoff and colleagues for highlighting the potential for disastrous hemolysis when rasburicase is administered to patients with G6PD deficiency, which affects 400 million people worldwide, especially in regions with endemic malaria.[1] As mentioned in our review, patients with G6PD deficiency should avoid rasburicase because hydrogen peroxide, a breakdown product of uric acid, can cause methemoglobinemia and, in severe cases, hemolytic anemia (see Fig. 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Since most G6PD-deficient persons have no history of hemolysis, testing before the administration of potent oxidizing agents (e.g., rasburicase) is warranted for patients at risk for G6PD deficiency, including those of African, Mediterranean, or Southeast Asian ancestry. Indeed, among blacks, 10% of men and 1% of women are affected. When immediate G6PD testing is not possible, the benefits of rasburicase therapy must be weighed against potential risks.

Two unproven, mitigating strategies can be used when urgent rasburicase therapy is needed for high-risk patients with unknown G6PD status. A small "test dose" (e.g., 1.5 mg) may be given and could be effective[2,3] and produce less hydrogen peroxide, thus decreasing the oxidizing stress. If no hemolysis occurs after a few hours, additional doses can be given if needed. Alternatively, administration of *N*-acetyl-L-cysteine promotes glutathione production even in the absence of G6PD and may protect patients from an oxidizing stress.[4]

Mathisen raises two important issues. Although allopurinol decreases xanthine formation from hypoxanthine, this does not affect the conversion of guanosine to xanthine (see Fig. 1 of our article), which may explain the accumulation of xanthine. In our review article, we mentioned that low doses of rasburicase have been used effectively in some intermediate-risk patients, but we would caution against this approach in high-risk patients. The use of lower doses of rasburicase to reduce costs must be accompanied by frequent measurement of uric acid concentration, with samples placed immediately on ice, to reduce ex vivo breakdown of uric acid, with resulting spuriously low concentrations. The safety and cost-effectiveness of this approach await prospective evaluation.

We agree with Nzerue's assertion that a 25%

decrease in the glomerular filtration rate would constitute clinical tumor lysis syndrome (see Table 1 of our article). Removal of a 25% change from the definition by Cairo and Bishop applies only to uric acid, phosphorus, potassium, and calcium. The lack of randomized studies precludes definitive recommendation of a specific diuretic. For now, the rat model provides the only available data, and furosemide has proved effective in our practice.

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Fiberoptic Intubation

TO THE EDITOR: In his video on fiberoptic intubation (May 19 issue),[1] Heidegger provides excellent points for patients with a known or suspected difficult airway. Some readers may infer that there is a single way of preparing the patient and performing a fiberoptic intubation, yet multiple methods may be used for these procedures. The sizes of the endotracheal tube and the fiberoptic scope can vary according to several clinical factors (e.g., a smaller tube for suspected airway edema or subglottic narrowing). Also, I would suggest that it is preferable to have the patient in a sitting position with the laryngoscopist facing the patient, since this position optimizes airway anatomy. To prepare the patient, local anesthetics other than cocaine (e.g., lidocaine and tetracaine) are routinely used, and other vasoconstrictors (e.g., phenylephrine and oxymetazoline) can minimize the risk of intranasal bleeding. The administration of intravenous fentanyl (at a dose of 2 μg per kilogram of body weight) may be hazardous to some patients, and sedation often is not required or not safe. The intratracheal injection of local anesthetic is not necessary in many patients and, in those with a tenuous airway, could result in violent coughing and loss of the airway.

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1. Heidegger T. Fiberoptic intubation. N Engl J Med 2011;364(20):e42. (Available at NEJM.org.)

TO THE EDITOR: In patients who are undergoing fiberoptic intubation, we believe that it is essential to distinguish between awake and asleep techniques. The indications for an awake procedure, as presented by Heidegger, are too broad and, as described, might put the patient in unnecessary danger. Poor dentition, a beard, or obesity are not common indications for awake fiberoptic intubation and reflect what we consider to be an outdated approach to the management of a difficult airway. According to our practice, awake fiberoptic intubation is appropriate only when the patient is at risk for being in a "cannot intubate, cannot ventilate" situation (e.g., in cases of stridor secondary to airway cancer or neck mass).[1] The primary objective is to maintain patency of the upper airway until it is secured by the orotracheal tube. To avoid oversedation and upper-airway obstruction, any long-acting drug, such as clonidine or fentanyl, which may produce an alteration of consciousness, should not be used, especially not in combination. In our judgment, an ultrashort-acting opioid, such as remifentanil, which overcomes this problem, is preferable.[2]