

and phrases that may be considered “more scientific” but merely lead to vagueness, ambiguity, or nonsense. For example, “Cohesiveness is the thread-forming ability of mucus under the influence of large amplitude deformation,” probably means, “Cohesiveness refers to mucus forming threads when mucus is stretched.” This practice is clearly becoming more common in medical writing.

Reviewers should be encouraged to review manuscripts not only for scientific content but also for sound rules and principles of composition. Authors who wish to publish in medical journals should be encouraged to spend as much time and effort on their writing as they do on other aspects of research. Editors can effect change by making a distinction between good writing and bad writing and using the ultimate sanction, which is to accept or reject.

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1. Anzueto A, Jubran A, Ohar JA, et al. Effects of aerosolized surfactant in patients with stable chronic bronchitis: a prospective randomized controlled trial. *JAMA*. 1997;278:1426-1431.

In Reply.—Dr Kissoon reminds us that clarity in writing is critically important for effective communication. I too have lampooned the use of jargon in medical writing,¹ and I appreciate his observations. It is important to clarify when a neologism is essential for clarity and when it obscures meaning. In our article on aerosolized surfactant, the terms *mucociliary clearability* and *cough transportability* mean something very different from mucociliary clearance and cough clearance. The former refers to a property of the secretion that is measured in vitro using expectorated sputum and provides us with specific information about a characteristic of the secretion. Mucociliary clearance and cough transport refer to the in vivo removal of tracer particles from the airway. This function tells us about the epithelium and secretory apparatus and not about the secretion. Thus, the terminology used clarifies what is being measured.

The term *spinnability* is a translation of the German *spinnbarkeit* and, until recently, was the accepted term used to describe secretion cohesiveness. The measurement of cohesiveness requires large amplitude elastic deformation. Small amplitude deformation is used to measure the stress-strain relationship (viscoelasticity), whereas large amplitude elastic deformation permits the measurement of secretion cohesiveness. Both the amplitude and type of deformation are critical to the validity and reproducibility of the measurement.

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1. Rubin BK. Cephalomalacia obfuscat. *Pediatr Infect Dis*. 1984;3:283.

Thiamine Before Glucose to Prevent Wernicke Encephalopathy: Examining the Conventional Wisdom

To the Editor.—In his letter, Dr Marinella¹ claims, “Thiamine should be administered prior to a glucose load because cases of Wernicke encephalopathy have been reported after glucose administration in thiamine-deficient patients.” The reference that supports this statement describes only 4 patients.² The first was a 27-year-old woman with weight loss for more than 6 months, gastrointestinal symptoms for 3 days, and the onset of dizziness and blurring of her vision. She had tachycardia, confusion, ataxia, absent deep tendon reflexes, and horizontal nystagmus. After treatment with 3 L of 5% dextrose for more than 24 hours, her symptoms worsened. The second patient was a 79-year-old woman with schizophrenia, anorexia, weight loss, horizontal nystagmus, absent deep tendon reflexes, and a temperature of 33°C; the diagnosis was septicemia. After

2 L of dextrose, she developed bilateral sixth nerve palsies, disorientation, and coma. The third patient was a 45-year-old woman with end-stage renal failure who began peritoneal dialysis and lost 6.3 kg in 6 months. Her peritoneal dialysis fluid was switched to hypertonic glucose 48 hours prior to the development of disorientation, nystagmus, and a sixth nerve palsy. The fourth patient, a 36-year-old alcoholic man, developed renal failure secondary to rhabdomyolysis and required hemodialysis. Five days after the initiation of a 20% dextrose infusion he developed nystagmus, bilateral sixth nerve palsies, areflexia, hypotension, and disorientation. All patients improved with thiamine administration.

Another report³ (cited in Watson et al²) describes a 35-year-old morbidly obese man admitted for prolonged starvation. After 30 days, refeeding was begun with daily glucose, 90 g by mouth. The patient complained of dizziness for the next 5 days and was treated with orange juice. Seven days later, he complained of double vision and developed nystagmus, bilateral partial sixth nerve palsies, and confusion.

Clearly, none of these 5 patients developed acute Wernicke encephalopathy after a single dose of glucose. Physical findings consistent with Wernicke encephalopathy were present prior to glucose administration in some and developed or worsened over days of glucose administration.

Marinella also states that patients “should receive oral or parenteral thiamine.” While we agree that thiamine replacement is essential, we believe there is compelling evidence favoring parenteral thiamine replacement. Patients requiring thiamine repletion absorb significantly less thiamine from the gastrointestinal tract compared with healthy controls.⁴ Additionally, a 50% reduction of thiamine absorption can be demonstrated following ethanol loading.⁴

Thus, the evidence supports neither the need to precede glucose administration with thiamine nor the use of oral thiamine. The established biochemical link between the 2 substances reminds clinicians that their contemporaneous administration is desirable. It is our experience that if the first provider fails to give parenteral thiamine at the time of glucose administration, thiamine is often forgotten. We cannot advocate any delay in glucose delivery while awaiting thiamine administration.

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1. Marinella M. Pharmacologic treatment of alcohol withdrawal. *JAMA*. 1997;278:1317.

2. Watson AJS, Walker JF, Tomkin OH, Finn MMR, Keogh JAB. Acute Wernicke's encephalopathy precipitated by glucose loading. *Ir J Med Sci*. 1981;150:301-303.

3. Drenick EJ, Joven CB, Swendseid ME. Occurrence of acute Wernicke's encephalopathy during prolonged starvation for the treatment of obesity. *N Engl J Med*. 1966;274:937-939.

4. Thomson AD, Baker H, Leevy CM. Patterns of ³⁵S-thiamine hydrochloride absorption in the malnourished alcoholic patient. *J Lab Clin Med*. 1970;76:34-45.

In Reply.—I agree with Drs Hack and Hoffman that patients with suspected Wernicke encephalopathy should receive parenteral rather than oral thiamine. They correctly note that patients who consume significant quantities of alcohol often do not adequately absorb oral thiamine from their intestinal tract.¹ Since the classic clinical triad of ophthalmoplegia, confusion, and ataxia is uncommon (less than 10% of patients), Wernicke encephalopathy should be considered in any patient presenting with a confusional state, and parenteral thiamine should be administered.² Patients with marginal thiamine reserves may develop overt Wernicke encephalopathy if administered a glucose load; hence, I agree with the traditional recommendation that, if possible, thiamine should be given prior to a glucose load.^{2,3} I agree with Hack and Hoffman that glucose should not be withheld from a patient while awaiting

thiamine. However, if a fingerstick glucose test reveals no hypoglycemia, thiamine should be administered before glucose, if possible. In addition, patients with suspected thiamine deficiency should also receive concurrent magnesium as this acts as a cofactor for transketolase activity.²

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1. Thomson AD, Ryle PR, Shaw GK. Ethanol, thiamine, and brain damage. *Alcohol*. 1983;18:27-43.
2. Charness ME, Simon RP, Greenberg DA. Ethanol and the nervous system. *N Engl J Med*. 1989;321:442-454.
3. Diamond I. Nutritional disorders of the nervous system. In: Wyngaarden JB, Smith LH, eds. *Cecil's Textbook of Medicine*. Philadelphia, Pa: WB Saunders; 1988:2137-2141.

Clinical Trials Comparing Surgical vs Nonsurgical Therapy

To The Editor.—Dr Howard and colleagues¹ correctly emphasize that studies comparing surgical vs nonsurgical therapy pose distinctive statistical challenges because the complications of surgery usually occur early, whereas the complications of nonsurgical therapy generally occur at a constant rate over time. However, other inherent differences between surgical and nonsurgical therapies can invalidate comparisons between them despite the most careful statistical adjustments.²

Drug therapy is constant throughout the duration of a study since the chemical compound does not change, whereas surgical technique evolves continuously. The operation being used by the end of a study can differ markedly from the one with which the study began. Thus, increased experience with surgery improves results and decreases complication rates, whereas increased use of drugs usually unveils more complications. In one study, the mortality of coronary bypass surgery decreased from 3 (12%) of 25 patients in 1968 to 2 (1.5%) of 134 patients in 1973.³ Furthermore, drug therapy in collaborative studies is standardized among all participants and is unrelated to physician skill, whereas the quality of surgical therapy varies unavoidably. Crossovers occur from medical to surgical therapy, but the reverse cannot occur. Drugs also usually have an indistinguishable placebo. Moreover, when surgery is an alternative, imperceptible bias often occurs before randomization. Physicians are likely to refer their sickest patients for the therapy they feel is best, while allowing lower-risk patients to be randomized.⁴ This tendency probably explains why randomized studies that compare nonsurgical with surgical therapy frequently enroll low-risk subsets that usually fare better than historical controls in both arms of treatment.

For these reasons, it is often impossible to make enough statistical adjustments in studies that compare surgical with nonsurgical therapy. The implications are substantial because an increasing number of invasive procedures (comparable to surgical therapy) are being carried out by nonsurgeons, which leads to the possibility of more randomized studies that are unavoidably flawed.

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1. Howard G, Chambless LE, Kronmal RA. Assessing differences in clinical trials comparing surgical vs nonsurgical therapy: using common (statistical) sense. *JAMA*. 1997;278:1432-1436.
2. Bonchek LI. Are randomized trials appropriate for evaluating new operations? *N Engl J Med*. 1979;301:44-45.
3. Anderson RP, Rahimtoola SH, Bonchek LI, et al. The prognosis of patients with coronary artery disease after coronary bypass operations. *Circulation*. 1974;50:274-282.
4. Bonchek LI. The role of the randomized clinical trial in the evaluation of new operations. *Surg Clin North Am*. 1982;62:761-769.

In Reply.—We agree that the comparison of medical vs surgical treatments is complex. However, Dr Bonchek's overall conclusion that "it is often impossible to make enough statis-

tical adjustments in studies that compare surgical with nonsurgical therapy" seems to be suggesting that randomized clinical trials (RCTs) may be inappropriate to establish the relative efficacy in challenging clinical situations. We suggest that while RCTs of medical vs surgical trials present challenges, the objective comparison of treatments by RCTs remains central to the scientific advancement of medicine.

Many of the concerns raised by Bonchek to discount the value of RCTs may be overstated. For example, he suggests that improvement in surgical technique may imply a differential efficacy at the beginning and end of a study. We agree. However, any investigator would agree that it is likely inappropriate to conduct an RCT if the surgical procedure is rapidly evolving. Furthermore, most medical vs surgical clinical trials have an implicit or explicit 1-sided hypothesis in which surgery will not be performed unless it is clearly superior to medical management. For studies such as the Asymptomatic Carotid Atherosclerosis Study,¹ in which surgery was found superior, an improving efficacy of surgery will only strengthen the findings as surgery continues to improve. Bonchek's suggestion that drug therapy is standardized whereas surgery varies from surgeon to surgeon seems to show a lack of appreciation for variations in medical practice and patient compliance. His concerns regarding crossovers fail to acknowledge that any crossover will only serve to bias results toward the null hypothesis. As such, in RCTs that find a significant result, the relative superiority of a treatment is understated. That drugs have a placebo effect and that patients participating in clinical trials may not be completely generalizable are problems common to any RCT.

Although Bonchek raises some valid concerns, these concerns represent relatively minor issues when compared with the great benefit gained by objectively contrasting the relative merit of alternative treatments. While there are flaws in any study that should be reflected by the cautious interpretation of the results, the RCT remains the "gold standard" approach for contrasting alternative treatments. The careful planning of a study focuses on minimizing potential biases. However, even in the presence of these concerns, surely the scientific community is not ready to base important medical decisions on subjective clinical impressions.

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1. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421-1428.

CORRECTIONS

Incorrect Figure Key.—In the Special Communication entitled "Assessing Differences in Clinical Trials Comparing Surgical vs Nonsurgical Therapy: Using Common (Statistical) Sense" published in the November 5, 1997, issue of THE JOURNAL (1997;278:1432-1436), the key to Figure 2 was reversed. The dotted line should have indicated "Surgically Treated"; the solid line should have indicated "Medically Treated."

Incorrect Wording.—In The Rational Clinical Examination entitled "Does This Dizzy Patient Have a Serious Form of Vertigo?" published in the February 2, 1994, issue of THE JOURNAL (1994;271:385-388), the wording in a table was incorrect. On page 387, Table 3, the sentence that reads, "Presence of vertigo or age \leq 69 y or no neurological deficit," should read, "Presence of vertigo and age \leq 69 y and no neurological deficit."