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The 29th Rovenstine Lecture: Clinical Challenges for the Anesthesiologist

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I AM DEEPLY HONORED and privileged to be chosen to present the 29th annual Emery A. Rovenstine lecture. I am not of the generation of anesthesiologists who can describe personal memories of this giant in our specialty. Nevertheless, I, like all of you, continue to benefit from his early vision and dedication to our specialty. Perhaps I can claim some indirect influence from Dr. Rovenstine, as both my father and I trained under Dr. Stuart C. Cullen, who was one of Dr. Rovenstine's early residents. I would also be remiss if I did not point out that Dr. Rovenstine was a native of my home state and a 1928 graduate of Indiana University School of Medicine, ranking third in a class of 92 students. It is also reassuring that Dr. Rovenstine earned a passing grade by examination for his anesthesia experience as a medical student.

We Hoosiers often brag about our basketball teams, but I doubt if many of you know the role this game played in Dr. Rovenstine's eventual pursuit of a career in anesthesiology. As described by Dr. Solomon G. Hershey in his 1982 Rovenstine lecture, Rovey was an outstanding high school athlete.[1] During his senior year in high school, young Rovenstine became exasperated with a referee whom he felt was always in his way when he had the ball. To show his displeasure, Rovey butted the referee in the stomach. According to legend, the referee, a large man, picked up the young athlete and spanked him. This referee was also a physician on the faculty of Indiana University; his name was Dr. Arthur E. Guedel, the distinguished anesthesiologist who first described the planes and stages of ether anesthesia.

This chance meeting during a high school basketball game led to a lasting friendship and might be considered the event that launched Emery A. Rovenstine on his brilliant career in anesthesiology. Indeed, Dr. Rovenstine became one of the first two anesthesia residents appointed by Dr. Ralph Waters when he arrived at the University of Wisconsin in 1930, and it was Dr. Guedel's recommendation that directed Dr. Rovenstine to Dr. Waters.

I view this lecture as an opportunity for me to describe to you how I perceive certain aspects of our specialty. It is a frightening and humbling experience, however, when one considers the challenge of such an opportunity. What could I possibly say that would merit your attention and at the end of my comments deserve a polite round of applause?

After much reflection, I concluded that my thoughts would be best directed toward my view of education in anesthesiology as it relates to clinical practice, and thus my chosen topic—Clinical Challenges for the Anesthesiologist. If I have made an impact on anesthesia education, I would hope it is in the area of condensing clinically relevant information into a textbook format that provides a rapid and accurate source of information for both the trainee and practitioner. The continuum of anesthesia education is a life-long process, and anesthesiologists must never lose their zeal to be students. We live in an era of information explosion, which has been characterized by some as information pollution. Some questions are dissected beyond recognition; others are virtually ignored. New knowledge must be incorporated into daily activities, as personal experience is not enough. Indeed, personal experience, which is often characterized as clinical impression, may be both invaluable and at the same time misleading—misleading because control observations are absent and memories are highly selective. Acceptance of new information or reinterpretation of old information may be resisted, as added benefits to currently accepted approaches may be difficult to document. It is almost trite to say that knowledge is endless and constantly changing.

With this in mind, I would like to propose the following four principles for those of us who consider ourselves to be life-long students of anesthesiology: seek cause-and-effect relationships in decision-making; periodically re-evaluate traditional but unproven concepts; establish realistic priorities in dealing with available information; and be receptive to new information and technology. These four principles should apply equally to those who are in residency training, those who consider themselves educators, and most important, that largest group, those who are in the active practice of delivering anesthesia care to patients on a daily basis.

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I am going to discuss various issues in current anesthetic practice that emphasize these four principles and thus reflect clinical challenges for the anesthesiologist. Specifically, I will use as examples of clinical challenges the following issues: 1) anesthetic-related hepatotoxicity, 2) perioperative myocardial ischemia, 3) nothing by mouth (NPO) after midnight, 4) side effects of muscle relaxants, 5) premature drug obituaries, and 6) standards of monitoring.

Anesthetic-related Hepatotoxicity

With respect to the four principles cited above, the controversy surrounding anesthetic-related hepatotoxicity illustrates the importance of insistence upon documentation of cause-and-effect relationships in decision-making as well as receptivity to new information and technology.

The rarity of severe hepatic dysfunction after anesthesia with currently used inhaled anesthetics makes a prospective randomized investigation of a true cause-and-effect relationship between anesthetic drugs and liver damage impractical.[2] For example, if the incidence of injury is extremely rare (1 per 100,000 cases), the demonstration of a doubling of such an incidence secondary to the use of the anesthetic could require the collection of data on more than one million patients. As a result, the rare injury some drugs may produce becomes identifiable only by anecdotal reports of injury that are related in time to the administration of the drug in question. The existence of a large number of such reports may suggest a causal relationship, particularly if the associated findings are considered to be unique. In this regard, chills, fever, nausea, and eosinophilia occurring postoperatively in a middle-aged obese woman previously exposed to halothane have been proposed as a unique picture of halothane-induced hepatitis.[3] An unproven assertion is that enflurane and isoflurane, because they are also halogenated hydrocarbons, would predictably produce a syndrome similar to that attributed to halothane.

Case reports as a mechanism to prove cause-and-effect relationships have many limitations. Proof by analogy is the weakest way of demonstrating an association, as the absence of a control group eliminates any scientific credibility concerning a cause-and-effect relationship. Examples of the hazards of basing cause-and-effect conclusions on the basis of chance or temporal association are abundant in the anesthesia literature. For example, in 1976, Schemel described the incidence of unexpected hepatic dysfunction after routine laboratory screening of asymptomatic adult patients admitted to the hospital for elective operations.[4] In this report, 11 of more than 7,000 patients manifested unsuspected liver disease. Surgery was cancelled in these patients, and 3 of the 11 subsequently developed jaundice in what would have been the postoperative period. Wataneeyaweeh *et al.*,[5] in a similar study, observed an incidence of unsuspected liver disease similar to that found in the study by Schemel.[4] Combining data from these two reports results in an incidence of unsuspected liver disease of about 1 in 700 previously asymptomatic adults and an incidence of unsuspected postoperative jaundice of about 1 in 2,100–2,500 adults.

A report published in 1977 described a case of hepatic necrosis after anesthesia with enflurane.[6] The only obvious cause appeared to be the anesthetic until a liver biopsy and electron microscopic examination revealed cytomegalovirus. One cannot help but wonder how many other cases of so-called anesthetic-related hepatotoxicity might have been attributed to other causes had more sophisticated testing been performed.

Why do we insist on better proof before a causal relationship is accepted? One obvious concern is that an assertion of a causal relationship impugns the reputation and may inappropriately decrease application of a useful drug. Patients who might benefit from the drug in question or in whom the drug would be the optimal selection are potentially deprived of the best care. Furthermore, the alternative drug may introduce its own unique side effects, such as depression of ventilation following opioid administration. Another concern is that acceptance of a causal relationship provides a reason to stop looking for other causes.

It is reassuring that hepatic dysfunction after administration of volatile anesthetics is so rare that its clinical significance can rightfully be questioned. Indeed, the incidence of alleged isoflurane-induced hepatic dysfunction, based on anecdotal case reports, is lower than the spontaneous incidence of viral hepatitis, leading some to question the need for dwelling on this topic.[7] Be aware, however, that there is new information that the clinical anesthesiologist must continue to assimilate. For example, recently developed and more sensitive technology demonstrates that patients with halothane hepatitis may generate antibodies toward a covalently bound metabolite of halothane.[8] These antibodies, formed in response to oxidative metabolites of halothane, are also produced to a lesser extent after administration of enflurane and isoflurane. Indeed, it has been demonstrated that enflurane metabolism produces covalently bound liver adducts that are recognized by antibodies from patients with halothane hepatitis.[9] The incidence of anesthetic-related hepatic dysfunction most likely parallels the magnitude of production of these antigenic metabolites, which is least with isoflurane, greatest with halothane, and intermediate with enflurane.

In view of this common mechanism for hepatotoxicity induced by volatile anesthetics and cross-sensitivity between these drugs, it is conceivable that changing halogenated anesthetics for patients requiring multiple exposures will not necessarily reduce the risk of anesthetic-

induced liver injury in the rare susceptible individual. One could also ask how many patients have been sensitized by virtue of a previous uneventful exposure to halothane. Perhaps the future will yield antibody assays for the detection of patients sensitized to volatile anesthetics as well as provide definitive proof when a diagnosis of exclusion is proposed as acceptable evidence for establishment of a cause-and-effect relationship between the anesthetic and liver dysfunction.[10] Clearly, the issue of anesthetic-induced hepatotoxicity must still be confronted by the clinical anesthesiologist even in this era of declining halothane usage.

Perioperative Myocardial Ischemia

One of the most sacred concepts of cardiac anesthesia teaching is the presumed role of the balance between myocardial oxygen delivery and myocardial oxygen requirements in the development of myocardial ischemia (fig. 1). The clinical anesthesiologist would seem to be following conventional wisdom in avoiding changes that adversely alter this delicate balance when caring for patients with coronary artery disease. I do not challenge the concept but suggest that a literal acceptance of this equation fails to give proper weight to that event or events most likely to increase myocardial oxygen requirements and produce myocardial ischemia in vulnerable patients. For example, Slogoff and Keats postulated that approximately 90% of new myocardial ischemia observed during anesthesia is the manifestation of asymptomatic or silent ischemia observed in patients before operation and that only 10% is related to anesthetic management.[11] Since silent ischemia occurs in the absence of hemodynamic abnormalities, it is likely that this form of myocardial ischemia, when it occurs, will not be preventable by the anesthesiologist.

During anesthesia, increases in heart rate seem to be the single most predictable event resulting in reversible causes of myocardial ischemia. Indeed, in anesthetized patients the incidence of myocardial ischemia sharply increases in patients in whom the heart rate increases to

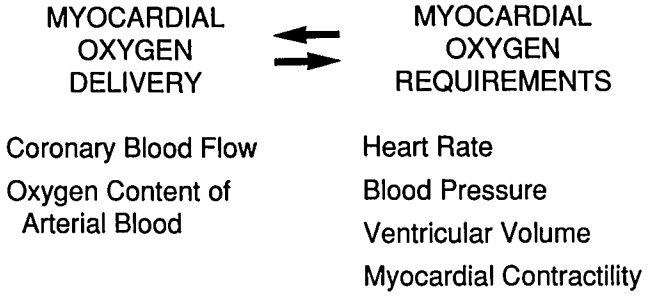

FIG. 1. The balance between myocardial oxygen delivery and myocardial oxygen requirements. Below each are listed events that determine oxygen delivery or requirements.

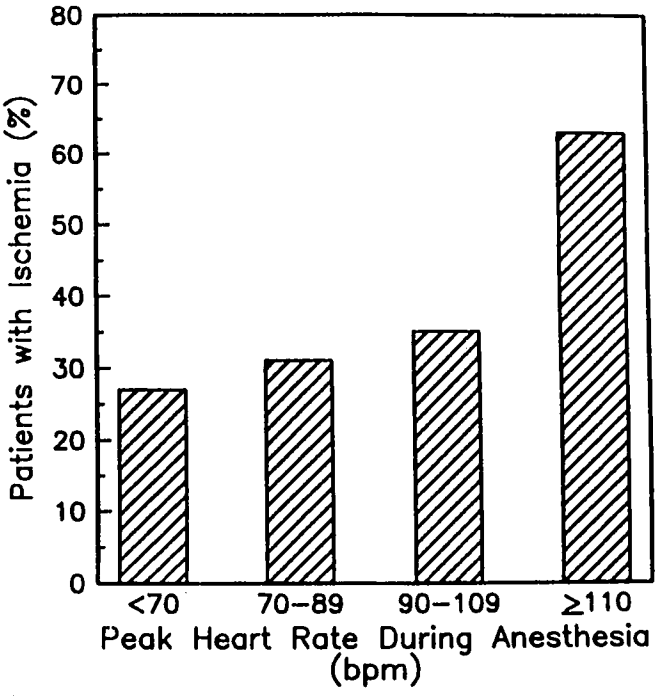

FIG. 2. The incidence of myocardial ischemia increases in anesthetized patients who experience peak heart rates greater than 110 beats per min. When peak heart rates are less than 110 beats per min, the incidence of myocardial ischemia is unrelated to heart rate. (Reproduced with permission.[12])

greater than 110 beats per min (fig. 2).[12] When heart rate is less than 110 beats per min[12] (fig. 2), the incidence of myocardial ischemia is random and silent, being unrelated to heart rate. The fact that most myocardial ischemia occurs in the absence of hemodynamic alterations suggests caution in endorsing routine use of expensive and complex monitors solely to detect myocardial ischemia in vulnerable patients. While increased sensitivity is attractive there are no data to confirm that ischemia detected with these devices will improve outcome. Likewise, there are no data to show outcome benefit from pharmacologic reversal of hemodynamically unrelated (*i.e.*, silent) myocardial ischemia.

The issue of anesthetic-induced coronary artery steal syndrome and perioperative myocardial ischemia in patients with coronary artery disease can trace its origin to a report in 1983 by Reiz *et al.*[13] At first glance, the title of this paper, "Isoflurane: A powerful coronary vasodilator in patients with coronary artery disease," suggests goodness for isoflurane, an inhaled nitroglycerin that also produces anesthesia. However, careful reading reveals a different picture. Ten of 21 patients studied by Reiz *et al.* receiving 1% end-tidal isoflurane manifested electrocardiographic evidence of myocardial ischemia. Patients receiving halothane did not show evidence of myocardial ischemia. The authors speculated that isoflurane, but not

halothane, produced redistribution of coronary blood flow in the majority of the 10 patients, resulting in regional myocardial ischemia—the so called coronary artery steal syndrome.[13] This report stimulated a flurry of investigative activity culminating in four reports of the results of laboratory research and an editorial entitled "Is isoflurane dangerous for the patient with coronary artery disease," all of which were published in the March 1987 issue of ANESTHESIOLOGY.[14–18]

Some anesthesiologists became reluctant to administer isoflurane to patients with coronary artery disease out of concern that myocardial ischemia might result. Nevertheless, clinical experience as well as observations in many published studies fails to show that isoflurane is dangerous for use in patients with coronary artery disease.[19,20] Indeed, in 1989, Slogoff and Keats reported the results of a randomized trial of primary anesthetic agents on the outcome of coronary artery bypass graft operations.[11] These authors concluded that the incidence of perioperative myocardial ischemia and subsequent outcome following coronary artery bypass graft operations were not different in patients anesthetized with halothane, enflurane, isoflurane, or in those receiving high doses of sufentanil.

The clinical anesthesiologist is thus faced with a dilemma: should isoflurane be avoided in patients with coronary artery disease out of concern that myocardial ischemia might result, or use an alternative approach with its own unique risks? I must admit that my strong bias was and still is that isoflurane is a safe and useful drug in most patients, including those with coronary artery disease.

Much like the hepatotoxicity question, however, the importance of the coronary steal syndrome story may deserve continued scrutiny. I base this comment on a 1988 report by Buffington *et al.* describing anatomic variations in patients with coronary artery disease.[21] Coronary artery steal is most likely to occur when a drug produces coronary arteriole dilation distal to a site of stenosis, thus reducing flow through high-resistance collateral vessels. As described by Buffington *et al.*, this pattern of coronary artery anatomy is present in about one fourth of affected patients (fig. 3).[21] Clearly, studies combining all patients with coronary artery disease but without considering the anatomy of the disease will bias results toward the conclusion of infrequent or even no drug-induced effect.

Perhaps Priebe said it best in the concluding paragraph of his detailed review of the coronary circulation.[22] "The question has been raised; is isoflurane dangerous for the patient with coronary artery disease? The answer should be: Yes, it is *potentially* dangerous in *some* patients, under *some* conditions–an answer that can be applied to all anesthetic agents, and for that matter to all efficacious drugs."

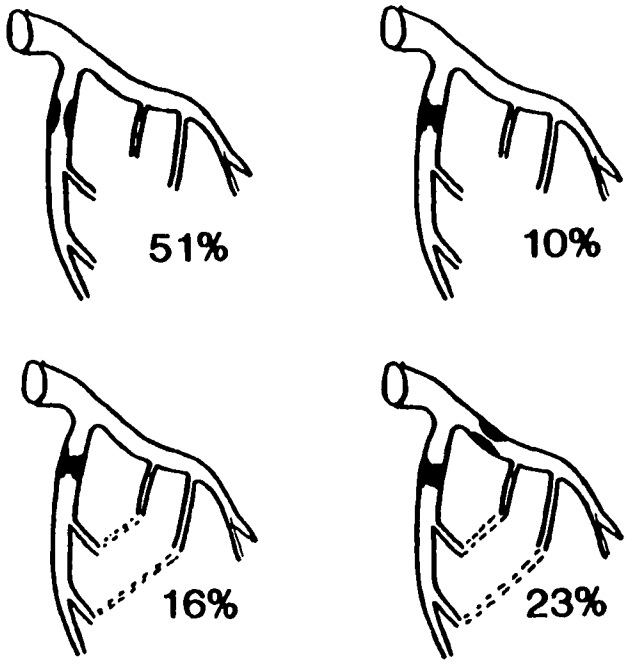

FIG. 3. Coronary artery steal is most likely to occur when a drug produces coronary arteriole dilation distal to a site of stenosis, thereby reducing flow through high resistance collateral vessels. This type of vulnerable coronary artery disease anatomy was present in 23% of the patients studied. (Reproduced with permission.[21])

NPO After Midnight

A traditional but unproven practice that is undergoing renewed interpretation is the concept of NPO after midnight and the resulting risk factors for pulmonary aspiration. This issue reflects the principles of periodic reevaluation of traditional but unproven concepts and receptivity to new information. Recently, two important and clinically pertinent questions have been posed.[23] First, how common is life-threatening pulmonary aspiration in the elective surgical patient with no recognized risk factors, and, second, is it necessary for these healthy patients to abstain from ingesting both liquids and solids for as long as current recommendations suggest? Based on both retrospective and prospective studies in over 225,000 adult and pediatric patients, it is concluded that the rate of clinically significant aspiration in healthy patients scheduled for elective surgery is exceedingly low and that morbidity is modest even when the rare aspiration event occurs.[23–25]

For example, in a 1986 report Olsson and colleagues described a retrospective examination of over 185,000 anesthesia records of pediatric and adult patients.[24] Aspiration was rare but was most often associated with difficulty in airway management. Most importantly, symptoms from aspiration in these patients were minimal, and

mortality was zero. In 1988, Tiret *et al.* reported a prospective study of more than 40,000 pediatric patients.[25] Aspiration occurred in four children, and there was one death unrelated to aspiration. Clearly, if one accepts these data, routine pharmacologic prophylaxis designed to alter the volume and/or *p*H of gastric fluid is not warranted.

As correctly emphasized by several authors, the critical combination of gastric fluid of volume 0.4 $ml \cdot kg^{-1}$ and *p*H < 2.5 has not and will never be verified in humans. The 0.4 $ml \cdot kg^{-1}$ figure perpetuated by myself and other investigators has its origin in the following statement from the discussion section of a paper by Roberts and Shirley in 1974.[26] "Our preliminary work in the Rhesus monkey suggests that 0.4 $ml \cdot kg^{-1}$ is the maximum aspirate that does not produce significant changes in the lung. As this translates to approximately 25 ml in the adult human female, we have arbitrarily defined the patient at risk as the patient with at least 25 ml of gastric juice of *p*H below 2.5 in the stomach at delivery."

Obviously, the scientific validity of this figure in patients was not proven by these comments. In fact, there are recent data suggesting that the critical volume in animals may be as much as 0.8 $ml \cdot kg^{-1}$.[27] If these results were to be extrapolated to humans, and I am not necessarily suggesting they should be, the critical volume for severe aspiration could be increased from 25 to 50 ml, considerably reducing the number of patients considered to be at risk.

What is a reasonable period of time to refrain from ingestion of liquids prior to elective induction of anesthesia? Several recent articles as depicted by a report from Maltby *et al.* have challenged the concept of prolonged fasting before elective surgery.[28] Other reports have consistently demonstrated that clear liquids administered up to 2 h before the induction of anesthesia do not increase gastric fluid volume and may actually facilitate gastric emptying. For example, in 1988 McGrady and MacDonald reported that patients given 100 ml of water 2 h before induction of anesthesia had lower gastric fluid volumes than did patients who were fasted in the usual manner.[29] A consistent finding is that gastric fluid *p*H and volume are independent of the duration of the fluid fast beyond 2 h provided that only clear fluids are ingested. Clear fluids that have been studied include water, carbonated beverages, clear fruit juice, tea, and coffee. It is of interest that a small amount of cream or sugar added to coffee or tea does not appear to cause a delay in gastric emptying.

I agree with Coté, who, in his recent editorial, stated, "I believe that we have had enough publications directed at preventing a problem that may not be clinically important, and suggest instead that we focus our attention upon fasting guidelines, and the type, timing, and volume of fluid that is 'safe' for elective surgical patients to consume with and without premedication."[23]

Future studies may result in significant modification of current fasting guidelines and make anesthesia safer and more pleasant for children and adults. Clearly, this enthusiasm for reevaluation of the traditional NPO-after-midnight concept does not apply to patients at known risk for aspiration. Furthermore, solid food is not the same as clear liquids. Finally, I cannot leave this issue without a reminder that the best protection against pulmonary aspiration is maintenance of an unobstructed upper airway and, when indicated, placement and subsequent removal of a cuffed tracheal tube by a skilled anesthesiologist.

Side Effects of Muscle Relaxants

I wish to use muscle relaxants as my example of the importance of establishing realistic priorities in dealing with available information. Specifically, I am alluding to the importance that is attached to the circulatory side effects produced by these drugs. There is no question that the safe use of any drug requires an understanding of that drug's side effects. At the same time, the relative importance of these side effects must be considered in the more global perception of the beneficial effects of these drugs at the neuromuscular junction.

The so-called modern muscle relaxants represented by pancuronium, atracurium, and vecuronium have, in my opinion, modest and predictable effects or lack of effects on blood pressure and heart rate. My quarrel is not with consideration of these effects but rather with the importance that is placed on them. For example, blood pressure and heart rate changes attributed to muscle relaxants are usually modest and nearly always transient and often occur only with rapid administration of large doses.[30] Nevertheless, these changes may be considered grounds for avoiding a specific muscle relaxant, whereas similar changes produced by thiopental are rarely discussed.

Perhaps the cost of the drug rather than modest circulatory responses deserves the greatest consideration. It also seems ironic that the lack of heart rate effects possessed by atracurium and vecuronium is now perceived by some as a disadvantage when opioid-induced heart rate slowing is likely.

Premature Drug Obituaries

Succinylcholine is a classic example, perhaps along with nitrous oxide, of a drug that has served us well but for which the obituary has already been written. We recite long and impressive lists of side effects unique to succinylcholine, often without giving proper credit to the desirable attributes of this drug. I have often wondered how the history of anesthesia would have been changed had

succinylcholine's neuromuscular blocking properties been recognized in 1906, when this drug was studied for its vagomimetic effects in a curarized frog preparation.[31] I have not experienced the same curiosity in speculating about the likeliness of approval of succinylcholine if it were submitted to the Food and Drug Administration in 1990.

There is no doubt that the first nondepolarizing muscle relaxant that mimics succinylcholine in onset and to a lesser extent duration of action will replace this valuable drug. Until that time, however, I emphasize the important role this drug plays in our daily practice, with the following question. If you could have all the monitors, equipment, and inhaled drugs you wish for an anesthetic but only one injected drug, which drug would you select? The correct answer, in my opinion, is two bottles of succinylcholine. To those who said thiopental or a similar drug, I will grant you runner-up status but point out that only succinylcholine allows one rapidly and reliably to ventilate the lungs in a patient with a previously closed glottic opening. To those who favor atropine or a vasopressor such as ephedrine, I remind you of the value of the mechanical stimulus provided by the laryngoscope blade.

Much like succinylcholine, nitrous oxide is an example of a drug with known desirable effects that are often relegated to lesser importance when considering adverse side effects. The long clinical history of safe nitrous oxide use suggests that much of its recently documented toxicity and concern about trace concentrations are of modest clinical importance. It is nevertheless likely that nitrous oxide, like succinylcholine, will experience disuse as soon as a suitable alternative becomes available—specifically, a potent drug with solubility characteristics similar to those of nitrous oxide. Desflurane and perhaps sevoflurane may be the drugs that indeed challenge the future role of nitrous oxide.

Standards of Monitoring

An example of the need to be receptive to new information and technology is the rapid acceptance of pulse oximetry as a standard of patient monitoring in the perioperative period. As a personal bias, I believe that the acceptance of capnography is not far behind. There is an old adage that there is nothing more compelling than an idea whose time has come.

There are some who fear that increased reliance on monitors will distract the anesthesiologist and thus reduce the level of personal or hands-on vigilance. Examples have been cited of time wasted checking instruments that were presumed to be malfunctioning when in fact attention should have been directed to the patient.[32] I believe, however, that these are infrequent and correctable errors that can be eliminated with proper education and experience. Certainly, early warning of adverse trends is the most likely result of using pulse oximetry and capnography.

Anyone who believes that clinical observation is a substitute for recognition of arterial hemoglobin desaturation as measured by pulse oximetry should consider the findings of Comroe and Botelho in an article published in 1947.[33] In this report, the majority of 127 observers ranging from medical students to professors were unable to detect the presence of cyanosis until the arterial hemoglobin oxygen saturation was about 80%, and one fourth of the observers could not detect cyanosis even at saturations of 75% or less. Clearly, visual impressions of the presence or absence of cyanosis are unreliable, and clinical experience makes little difference in the accuracy of assessment.

More recently, a study conducted in children reaffirmed the value of pulse oximetry.[34] In this report, 10 of 24 episodes of arterial hemoglobin oxygen saturations of less than 73% were undetected without pulse oximetry and, as in Comroe and Botelho's report, there was no relation between the accuracy of reporting and the experience of the observer. Decreased arterial hemoglobin oxygen saturations preceded changes in skin color or hemodynamic variables; in fact, changes in heart rate and the electrocardiogram occurred in only a minority of patients experiencing arterial hypoxemia.

Vigilance alone is not a guarantee of patient safety, and monitoring is designed to enhance vigilance and detect adverse trends before they become irreversible. As stated in an article in the Journal of Clinical Monitoring, it is clear that pulse oximetry and capnography greatly contribute to the ability of clinical anesthesiologists to recognize undesirable trends or mishaps (fig. 4).[35] At the same time, the much-revered value of the oxygen analyzer and electrocardiogram is not supported by that article's data.

I strongly endorse the primary value of the vigilant anesthesiologist, but I conclude it is equally important, as recently emphasized by Tinker *et al.*, to embrace proven and practical monitors that enhance this vigilance.[36] I believe that pulse oximetry and capnography are examples of such monitoring which, when properly used, improve anesthesia care, as suggested by a reduction in the occurrence of preventable anesthetic mishaps.

Summary

In conclusion, I hope that my comments have reaffirmed your biases or, even more importantly, stimulated you to think in a different way about the information explosion in our specialty and medicine in general. I be-

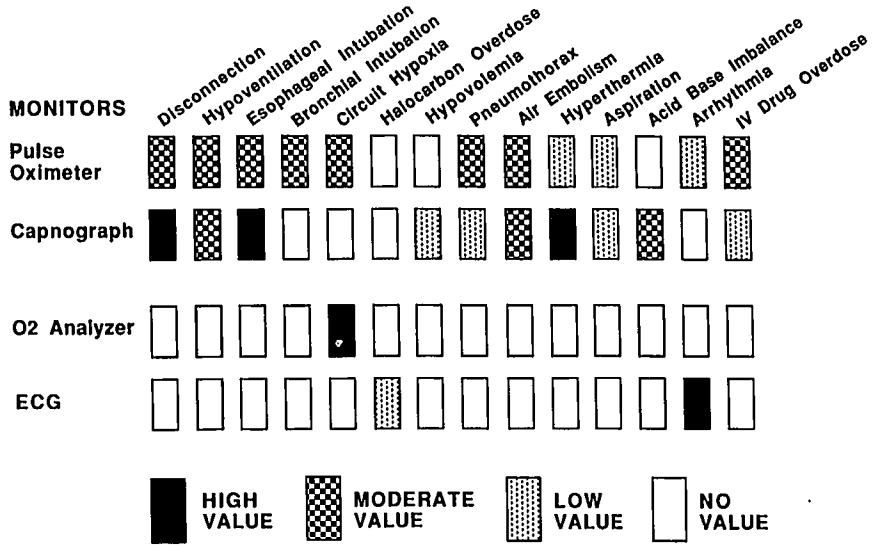

FIG. 4. Pulse oximetry and capnography are frequently of some value in detecting mishaps that may occur in the anesthetized patient. The value of the oxygen analyzer and electrocardiogram (ECG) in detecting these mishaps is limited. (Adapted with permission.[35]).

lieve our specialty is in a golden era that will benefit from the past and be nourished by new discoveries and understanding. We as clinicians must accept the challenge of recognizing what new information deserves incorporation into our practice, what old information deserves to be sustained, and what merits new scrutiny and perhaps should be discarded.

If I had one wish, it would be that anesthesiologists would never lose their zeal to be students—their thirst for new information—as the continuum of anesthesia education is indeed a life-long process. That wish, ladies and gentlemen, is my challenge to all anesthesiologists.

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