Anesthesiology 2002; 96:769–70

Clinical and Experimental Research in Anesthesiology in Europe at the Change of the Millennium

To the Editor:—We have read with interest the letter of Hofbauer *et al.*[1] about research in anesthesiology in Europe. This group has made important clinical and experimental contributions. However, their letter has several flaws.

First, it is remarkable that Hofbauer *et al.* give no references, whereas several articles are published on this topic.[2–6]

Second, their claim to have searched 1965 to September 1999 is spurious. Address fields in MEDLINE are only available for publications added to the database after January 1988, equivalent to articles published after mid 1987 in most journals.[7]

Third, they rely on identifying anesthesia departments and countries in MEDLINE address fields rather than analyzing all articles in certain journals as done by most other groups.[2–5] This may be advantageous because (in Germany) only approximately 70% of the work of anesthesiologists is published in journals devoted to anesthesia or related fields, such as pain and critical care.[8,9] Also, only 90% of the articles in major anesthesia journals and one third in pain and critical care are by anesthesiologists (our own unpublished observations). In practice, this is difficult because (1) addresses are often incomplete; (2) addresses are often not in English, even for English-language articles; (3) many abbreviations and most e-mails are useless for searching; (4) information may be implicit (*e.g.*, region instead of country); (5) MEDLINE sometimes gives more than one department in the address; (6) for many journals in the Russian and Chinese languages (*e.g., Anesteziologiia i Reanimatologiia*), MEDLINE does not give address fields; and (7) misspellings occur. For publications by German anesthesia departments in the English language, one can use (ANESTH* OR ANAESTH* OR ANASTH*) AND (GERMAN OR GERMANY OR DEUTSCHE* OR DEUTSCHLAND OR FRG OR BRD OR DDR OR GDR) with about 95% sensitivity and 99% positive predictive value. This results in at least 1,379 English-language publications by German university anesthesiologists from 1988 to 1997.[8] There were at least 120 English-language publications by German nonuniversity anesthesiologists in 1988–1997 (own data). Extrapolation for mid 1987 through September 1999 yields approximately 1,800 publications by German anesthesia departments in the English language alone. There are (extrapolated) some 3,000 in these years in the German language.[9] The data by Hofbauer *et al.* of 1,605 publications from Germany in mid 1987 through September 1999 is thus only one third of the total 4,800 because of (1) a hidden language restriction because few German-language publications by Germans explicitly state the nation in the address and (2) omission of the search item ANASTH*, the MEDLINE transcription of the German umlaut in *Anästhesie*.

Table 1. MEDLINE-indexed Anesthesia Publications in 1998

Country	PpM	Total Publications	English Publications	Other Publications	Population (Millions)
Sweden	14.3	127	117	10	8.852
Finland	13.4	69	69	0	5.153
Austria	13.0	105	86	19	8.078
Denmark	8.9	47	47	0	5.301
Belgium	6.8	69	68	1	10.204
Germany	6.7	549	296	253	82.047
United Kingdom	6.5	386	386	0	59.055
Ireland	6.2	23	23	0	3.705
France	5.1	299	148	151	58.847
Netherlands	3.9	62	59	3	15.698
Italy	2.8	164	115	49	57.589
Spain	2.3	90	27	63	39.371
Greece	1.2	13	13	0	10.515
Portugal	0.2	2	2	0	9.968
Luxembourg	0.0	0	0	0	0.427
EU	5.3	2,005	1,456	549	374.810
Switzerland	12.8	91	72	19	7.106
Singapore	10.7	34	34	0	3.164
Norway	6.5	29	20	9	4.432
Israel	6.2	37	35	2	5.963
Canada	5.4	163	159	4	30.301
USA	5.3	1,439	1,434	5	270.299
Japan	5.0	629	418	211	126.410
Australia	5.0	93	93	0	18.751

1998 MEDLINE-indexed publication output per million inhabitants (PpM) for anesthesia providers in all European Union (EU) countries, for the EU as a whole, and for non-EU countries with a *per capita* output of 5 PpM or greater.

Data source for MEDLINE was Silverplatter on CD, edition 2000.[10]

1998 population figures are from Fischer-Weltalmanach.[14]

Search item was (journal-article IN PT) AND (PY=1998) AND (anesth* OR aneste* OR anaesth* OR anasth* OR d'anesth*) IN AD.

All hits were printed and manually analyzed for country.

Articles written by veterinary anesthetists or only coauthored by anesthetists were excluded. Articles published by nurse providers of anesthesia or perianesthesia care were not explicitly excluded. Analysis of the relevant journals (*e.g., Journal of the American Association of Nurse Anesthetists*) showed, however, that nurse anesthetists usually gave no departmental affiliation or departments of nursing rather than departments of anesthesia or nurse anesthesia in the address, so most of their articles were implicitly excluded.

Fourth, Hofbauer *et al.* list a country named England that does not exist. They probably mean the United Kingdom (UK). The UK is difficult to access by MEDLINE searching. Even the search (UK OR (UNITED KINGDOM) OR (GREAT BRITAIN) OR (ENGLAND NOT NEW) OR (WALES NOT (NEW OR PRINCE)) OR (NORTHERN IRELAND) OR SCOTLAND) is less than 50% sensitive for the years in question, necessitating additional city searching. The reason is omission of explicit country identification in domestic (British) journals. The situation has recently improved because most British journals now add UK to British addresses (*e.g.*, *Lancet* since 1990, *Anaesthesia* since 1997, *British Journal of Anaesthesia* since 1999), but others (*e.g.*, *BMJ*) still maintain that all addresses are British unless stated otherwise.

Fifth, similar problems exist for other countries. In some languages (*e.g.*, Italian, Spanish), the specialty search term is ANESTE* without an "h." In WinSPIRS[10] (but not PubMed[11]), French addresses must be sought as D'ANESTH*. Search routines for various nations—which, however, contain several obvious errors and which we have not tested— can be found in Jorgensen *et al.*[12]

Sixth, Hofbauer *et al.* use the same raw data for evaluating *per capita* and per medical school output. This is incorrect because there are publications by nonuniversity departments. For Germany, the amount is approximately 8% of the English- and 20% of the German-language articles. Also, the size of medical schools depends on the population served in education and treatment. For example, because Austria has three medical schools for 8.1 million inhabitants, each serves on average 2.7 million inhabitants. In Switzerland, which has five medical schools (not four, as stated by Hofbauer *et al.*) for 7.3 million inhabitants, each serves only 1.5 million people, with Germany in between. Consequently, the Austrian schools (or at least one of them) are likely to be large. This is true for the Vienna school (where Hofbauer *et al.* work), which in the mid 1990s had approximately 200 physicians and Ph.D.s in its anesthesia department, which to our knowledge was matched by only 1 of the 41 German and none of the 5 Swiss departments.[9,13]

Finally, in an article published in a North American journal, such as ANESTHESIOLOGY, it would have been interesting to give numbers for the United States and Canada for comparison.

To clarify this, we printed all MEDLINE-indexed publications by anesthetists in 1998 and analyzed them by hand (table 1). Although this is only an evaluation for 1 yr, it clarifies the following: (1) Non–English-language publications were still important in the European Union, being 27% overall and even higher for the large non–English-speaking nations (Spain, France, Germany, Italy). (2) Publication numbers by Hofbauer *et al.* for England–UK in 1987–1999 are impossibly low because the UK surpassed them in 1998 alone. (3) Our table confirms the good standing of the Scandinavian and Alpine nations, but the quotient between them and the large European Union nations was much less than what was suggested by Hofbauer *et al.* (4) Outside Europe, Singapore was the leader in anesthesia with respect to *per capita* output, although most of its anesthesia publications were published in local journals, such as *Singapore Medical Journal*. (5) The *per capita* output of both the USA and Canada matched that of the European Union as a whole closely.

Wolfgang H. Maleck, M.D.,* **Joachim Boldt, M.D.** *Klinikum, Ludwigshafen, Germany. wolfgang_maleck@hotmail.com

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(Accepted for publication September 8, 2001.)

Anesthesiology 2002; 96:770

Setting the Record Straight

To the Editor:—The letter by Hofbauer *et al.*[1] presented a table from which it is possible to determine the ranking order of the number of publications from anesthesiology departments of 16 European countries. It was a surprise to find that England (or the United Kingdom, as their number for population would indicate) should be almost the least productive country in Europe for all the indices they list. The mean productivity per million head of population for nine other European countries exceeded that of the United Kingdom by an order of magnitude.

My colleague Dr. R. S. Cormack was quick to note the improbability of the total number of publications for the United Kingdom, cited as 248 publications from 1965 to September 1999. This corresponds to a mean of approximately 7 publications per year. My belief that this number is erroneous is supported by other authors who have reported publications for the United Kingdom in a restricted number of journals, over shorter periods of time, and with varying criteria, as 428 per year[2] and 478 per year.[3] One is therefore tempted to wonder whether the numbers for the United Kingdom have been cited as mean annual publications rather than total publications for the 35-yr period, which seems unlikely for most other countries.

John Nunn, M.D., D.Sc., Ph.D., F.R.C.S., F.R.C.A., F.G.S., Northwood, Middlesex, United Kingdom

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(Accepted for publication September 8, 2001.)

Anesthesiology 2002; 96:771

In Reply:—The letters by Wolfgang H. Maleck, Joachim Boldt, and John F. Nunn critically review our recently published letter in ANESTHESIOLOGY about the European ranking in anesthesiology research.[1]

We agree with the statement of Drs. Maleck and Boldt that it is difficult to perform such research of the literature, especially in Germany. However, we have performed a meticulous database search.

We are aware of potential flaws which may be due to language difficulties, such as the German umlaut ä in the German version of the word anesthesiology. We strongly believe that scientists who want to compare internationally should be aware of these aspects of the English language. As we showed in several analyses, the German language has a minor role in international scientific contributions, *e.g.*, articles published in the German language are approximately 5% of all articles ranked in the best worldwide American biomedical database, MEDLINE. Even using the European databases PASCAL or EMBASE, the German language has a minor role.[5,6]

Possible differences in the analysis of Maleck and Boldt could be caused by using a different source. At our university hospital, we have the modern, permanent, updated version of MEDLINE on the university library server. We cannot judge the differences in using the older, CD-ROM version. We stopped using a CD-ROM version of MEDLINE approximately 9 yr ago at our university because of the more combination search strategies of the WinSPIRS version (WinSPIRS Software Version 4.0, SilverPlatter Information Inc., Norwood, MA).

We chose England instead of the United Kingdom because of the problems mentioned by Maleck and Boldt. We want to thank Drs. Maleck and Boldt for the stimulation about investigating America, where we would not have the multilingual limitations we have in Europe. Of course, there are other possibilities to compare scientific activities of countries rather than the number of medical schools. We decided to use the number of medical schools as a marker for the academic activities and believe this is better than only counting the inhabitants. The regular inhabitants of a country are not related to research. The power of a football team is better when related to the number of football teams in a high league rather than to the number of inhabitants. Comparing the states in the United States is of high interest. Currently, we are in the process of finalizing such a study, which will be presented as a full research article, allowing more space to explain our intention and to include a longer reference list.

The intention of our article was to make the reader in Europe aware of the secondary role of European research in international science and to stimulate European scientists in the future. We invite Drs. Maleck and Boldt and other interested readers to read our books about this subject for further information.

We apologize for not using German literature about this subject, but we think the language of science is English, although most members of our research group are native German speakers. We also did not cite Japanese or Chinese literature in this area, which might have interesting contributions, but we cannot presume that international researchers know the different international languages. Scientists should talk in one common language, and this is definitely English at this time. Maybe Spanish will be the dominating language in science in 50 yr, and then we will have to think about communicating in Spanish.

In response to Dr. Nunn, we are aware of the technical limits of some countries performing meta-analyses. Moreover, we are aware of the limitation on space in letters to the editor.

In our recently published book about this subject, *European Countries: Biomedical Research Ranking and the New MFBP-Index* by Hofbauer *et al.*,[5,6] we discussed the problems extensively. In this book, we state "The ranking of England in our quotation shows limitation, because England is not always indexed in the medical databases as England . . . Therefore we believe that England is more powerful than it might appear . . ."[5]

We can only repeat in this reply: England is better than it appears in any database analysis. The problem is the inconsequence of listing the affiliations by scientific authors from England. Ohio is clearly listed as Ohio, and Switzerland is clearly listed as Switzerland, even though they speak four different languages. We also can only repeat our recommendations to English authors as we did in our book: "We can warmly recommend to the English researchers to appear more unique in their locations . . ."

The rest of the analysis is clear because of the clear expression of authors from the other countries. We would like to test our other analysis, and we do not believe that we have drawn a hasty conclusion. Database analyses have limitations due to the clearness of the authors. England is the only country where these problems occur. Scottish people want to be Scottish. Bavarian researchers from Munich publish under the country Germany, without any doubt. We think that our analysis was a high-quality analysis and was unique to the biomedical literature; we were able to publish a book and a German translation of our book about these interesting subjects.

Roland Hofbauer, M.D.,* **Alan D. Kaye, M.D., Ph.D., Bernhard Gmeiner, M.D., Ph.D., Michael Frass, M.D.** *University of Vienna, Vienna, Austria. roland.hofbauer@akh-wien.ac.at

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(Accepted for publication September 8, 2001.)

Anesthesiology 2002; 96:771–2

Propofol, Metabisulfite, and Bronchoconstriction

To the Editor:—Brown *et al.*[1] found that infusion of propofol with or without metabisulfite into the bronchial artery does not alter airway resistance. However, they also found that propofol without metabisulfite can attenuate bronchoconstriction produced by vagal nerve stimulation and that the addition of metabisulfite can reverse this effect. Commenting on these results, "This Month in Anesthesiology" suggested that "[The] preservative used in propofol can have an effect on the ability of propofol to attenuate bronchoconstriction."[2]

Three observations may be made regarding these results. First, the effect was small. In the presence of vagal nerve stimulation, a 0.06-ml/min propofol infusion without metabisulfite decreased airway resistance by 16 ± 15% (mean ± SD). The same infusion with metabisulfite decreased airway resistance by 5 ± 8% (difference not significant by an unpaired *t* test). At an infusion rate of 0.2 ml/min, the decreases were

Dr. Eger is a paid consultant to Baxter Healthcare Corporation, Deerfield, Illinois (distributor of propofol with metabisulfite).

29 ± 10 and 2 ± 16%, respectively ($P < 0.01$), and at an infusion rate of 0.6 ml/min, they were 42 ± 10 and 13 ± 23% ($P < 0.05$). Methacholine infusion produced trends similar to those seen with vagal nerve stimulation, but no individual pair of results differed significantly.

Second, the metabisulfite concentration in the bronchial artery resulting from direct continuous (10 min) infusion into the artery may considerably exceed the concentration that would result in well-perfused tissues (*e.g.*, bronchi and brain) from an intravenous injection for induction of anesthesia. Blood flow through the bronchial artery in sheep has been measured at 25.3 ± 5.2 ml/min.[3] Infusion of 0.06, 0.2, and 0.6 ml/min of 5 mg/ml propofol (plus 0.125 mg/ml metabisulfite) gives concentrations of 11.9, 39.5, and 118.6 μg/ml propofol, respectively (or 6.7×10^{-5}, 2.2×10^{-4}, and 6.7×10^{-4} M). These concentrations are modestly less than (80% of) those calculated by Brown *et al.*[1] (8.4×10^{-5}, 2.8×10^{-4}, and 8.4×10^{-4} M), possibly because the sheep in the article defining bronchial artery blood flow were larger (35–50 kg) than those used by Brown *et al.*[1] (30 kg). In 50-kg sheep given 100 mg propofol intravenously, the peak brain and sagittal sinus concentrations of propofol equal approximately 5 μg/ml,[4] and the steady-state concentration at which 95% of 20- to 55-yr-old patients do not respond to command is 5.4 μg/ml propofol.[5] Thus, the lowest concentration applied by Brown *et al.*,[1] one that did not result in a statistically significant difference between propofol with and without metabisulfite, is twice the concentration required for loss of consciousness in humans. The concentrations that did produce statistically significant differences are approximately 7 and 22 times the concentrations required for loss of consciousness.

Third, "Propofol without metabisulfite. . . , propofol with metabisulfite . . . , and lidocaine . . . were administered in concentrations of 5 mg/ml."[1] Such a concentration of propofol is half that used for induction of anesthesia. Did the lesser propofol concentration affect the balance of the effect of the metabisulfite and the propofol on bronchoconstriction?

In summary, it seems that metabisulfite can modestly reverse propofol's dilation of constricted bronchial muscles, but such reversal requires metabisulfite doses much greater than those used clinically. The metabisulfite effect also may have been overestimated because the ratio of the propofol dose to the metabisulfite dose was half that use in clinical practice. If these observations are correct, do the findings apply to our patients?

Edmond I Eger II, M.D., University of California, San Francisco, California. egere@anesthesia.ucsf.edu

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(Accepted for publication September 8, 2001.)

Anesthesiology 2002; 96:772–3

In Reply:—We wish to thank Dr. Eger for his interest in our work and we appreciate the chance to respond to his comments. However, we disagree with his observations about our work.[1] Dr. Eger raised three issues. We would like to respond in reverse order to his comments. First, the concentrations of propofol with and without metabisulfite were diluted with normal saline to 5 mg/ml to facilitate the infusions. However, Dr. Eger seems to misunderstand that the metabisulfite that was in the commercially available propofol was also diluted. Therefore, the same ratio of propofol to metabisulfite in the infusion was maintained. Thus, there was no "lesser propofol concentration [to] affect the balance of the effect of the metabisulfite and the propofol on bronchoconstriction." Also, the fact that the same concentration of metabisulfite alone as that delivered in the propofol with metabisulfite solution enhanced both the vagal nerve stimulation and the direct smooth muscle–induced bronchoconstriction supports our findings that the metabisulfite attenuated the response of propofol to prevent bronchoconstriction.

We also disagree with Dr. Eger's calculations of clinically relevant dose. The infusion rates were 0.06, 0.2, and 0.6 ml/min for propofol with and without metabisulfite. For propofol, we calculated the molar concentrations from our continuous infusion into the bronchial circulation to be 8.4×10^{-5}, 2.8×10^{-4}, and 8.4×10^{-4} M, respectively. As pointed out in our Discussion section, these doses are within the range of clinical relevance as demonstrated by other investigators studying the effects of propofol in a sheep model for induction of anesthesia.[2] Using a continuous infusion, Ludbrook *et al.*[2] observed concentrations of propofol in the brain of the sheep as measured by the area under the curve of 73.7 ± 15.2, 54 ± 4.4, and 67.7 ± 11.9 $\mu g \cdot min^{-1} \cdot ml^{-1}$, concentrations comparable to those calculated by Dr. Eger of our concentrations. Furthermore, there are clearly species and even strain differences in anesthetic potency as demonstrated by Dr. Eger himself[3,4] and others.[5] Thus, the anesthetic dose in sheep does not necessarily equate to the same anesthetic dose in humans.

Dr. Eger does raise an extremely important point that requires clarification. He compares the doses we used to blunt airway responsiveness to those that cause loss of consciousness or failure to respond to commands. The dose required for loss of consciousness or failure to respond to commands should not be assumed to be adequate anesthesia for procedures, especially for bronchoprotection. The minimum dose to cause loss of consciousness would most likely be inadequate anesthesia for tracheal intubation in a healthy individual and particularly in an asthmatic patient. Clearly, instrumentation of the airway of an inadequately anesthetized asthmatic patient can have catastrophic consequences.

Finally, a "small effect" is a relative term. We believe that our observed difference of 30% in prevention of bronchoconstriction between propofol without and with metabisulfite is not an inconsequential effect. It is clearly statistically significant and would likely be clinically relevant. Although this is an animal model of airway responsiveness, an equivalent prevention of a 30% decrease in airway resistance in an anesthetized asthmatic patient may be the difference between being able to ventilate the patient or not. We continue to believe that propofol is an excellent drug for the prevention of bronchoconstriction and that the preservative used for propofol can have a significant effect on its ability to attenuate bronchoconstriction.

Robert H. Brown, M.D., M.P.H.,* Robert S. Greenberg, M.D., Elizabeth M. Wagner, Ph.D. *The Johns Hopkins Medical Institutions, Baltimore, Maryland. rbrown@welch.jhu.edu

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(Accepted for publication September 8, 2001.)

Anesthesiology 2002; 96:773–4

Electrocautery-induced Pacemaker Tachycardia: Why Does This Error Continue?

To the Editor:—The recent case report, "Electrocautery-induced Tachycardia in a Rate-responsive Pacemaker," by Drs. Wong and Middleton[1] indicates that widespread understanding of certain aspects of pacemaker function and management is not optimum. In their report, Wong and Middleton state that during the use of monopolar electrosurgery, they noted the "gradual" onset of pacemaker-driven tachycardia. Their patient possessed a Telectronics Meta VVIR device (Englewood, CO), which is one of the earliest devices to incorporate a bioimpedance, minute ventilation activity sensor. Our concerns go beyond the specific experience cited by the authors, and it is appropriate to discuss again a number of issues relevant to this topic.

Issue 1: Pacing at the upper activity rate (UAR) in response to electromagnetic interference by devices that incorporate minute ventilation sensors should be well-known. Van Hemel *et al.*[2] first described such behavior in 1989. Smith *et al.*[3] reported two cases of inappropriate UAR pacing to diathermy (the British term for electrosurgical unit) in 1993. Vangelder *et al.*[4] reported UAR pacing during a radiofrequency ablation in 1994. In 1997, Chew *et al.*[5] reported inappropriate UAR pacing owing to connection to a Marquette 7010 monitor (Marquette Medical Systems, Milwaukee, WI), Spacelabs Alpha PC-1 monitor (Spacelabs Medical, Redmond, WA), or a Hewlett Packard Sonos 2500 Cardiac Doppler Ultrasound echocardiograph machine (Phillips Medical, Andover, MA). Subsequently, Troughear[6] reported UAR in a patient connected to an IVY Biomedical Systems Model 101 ECG monitor (Ivy Biomedical Systems, Branford, CT). He showed that any device applying a small amount of electrical current to a patient's chest (for respiratory rate monitoring, electrocardiographic lead-off detection, or from allowable leakage) could cause a pacemaker using a bioimpedance sensor to believe that a patient has begun to exercise. In addition, this inappropriate response is not gradual. The device changes to UAR pacing abruptly after the electromagnetic interference begins.

In July 1998, after Wallden *et al.*[7] published their report of inappropriate UAR pacing owing to connection to a Datex monitor (Datex-Ohmeda, Madison, WI), Rozner and Nishman petitioned the Center for Devices and Radiologic Health at the US Food and Drug Administration to issue an alert about this problem. The Food and Drug Administration quickly reviewed the data, and they placed an alert in October 1998 on the Food and Drug Administration Web site.* The alert was sent to numerous medical groups; the American Society of Anesthesiology included the alert in their January 1999 newsletter.[8]

These alerts, along with other primers about the perioperative care of the patient with an implantable generator,[9–11] make clear that failure to disable rate-responsive minute ventilation sensors can lead to inappropriate tachycardia with misinterpretation and possible poor patient outcome. In fact, nearly any kind of activity sensor can be fooled during an anesthetic procedure, and pacemaker manufacturers routinely suggest suspending such behavior.[12]

Issue 2: The strips shown in the report have poorly visible electrocardiographic pacemaker artifacts (*i.e.*, "spikes"). Thus, one could easily misinterpret the second tracing as a sinus tachycardia with aberrant conduction or, even worse, as ventricular tachycardia resulting in the administration of intravenous antiarrhythmic medications or initiation of external cardioversion. These tracings likely were obtained from a Datex or Marquette intraoperative monitor. Both of these devices collect digitized electrocardiographic information and, when appropriately programmed, will "paint" pacemaker artifacts onto the record. The default mode for these devices, however, is to treat the sensed pacemaker artifacts as noise with subsequent filtering. When caring for a patient with an implantable pulse generator, it is imperative to remove this filtering.[10] On the Datex machine, the setting should be "Show pacing artifacts"; on the Marquette, either "Pace 1" or "Pace 2" under the "Detect Pace" selection should be made. Perhaps the filtering of pacemaker artifacts made the immediate detection of the paced tachycardia more difficult to detect.

Issue 3: The recommendations by the authors are incomplete. More complete recommendations include: checking the device before the procedure to ensure adequate safety margins for pacing and sensing; obtaining current programming information to ensure appropriate behavior for the case; reprogramming to "OFF" features that can mimic pacer dysfunction (such as rate responsiveness, rate hysteresis, sleep mode, circadian rate, AV search hysteresis, and automatic detection of threshold levels); taking appropriate steps in the operating room (or elsewhere) to limit exposure to monopolar electrosurgery; and checking the device after the procedure is complete to ensure appropriate function and correct programming.[13]

Issue 4: In the absence of specific knowledge of a device, a call to the manufacturer will provide general guidelines for pacemaker evaluation and reprogramming for any case. Most manufacturers provide toll-free support throughout North America, and toll-free numbers are found on the patient's pacemaker card, on the Internet,[14] and in a variety of publications.[10,11,15]

The apparent simplicity of the original report belies the multitude of potential problems faced when caring for a patient with an implantable generator. This report, in conjunction with the literature, provides evidence that any physician who must care for a patient with an implantable pulse generator needs to stay abreast of the field, which is constantly changing.

Marc A. Rozner, Ph.D., M.D.,† Richard J. Nishman, M.D. †MD Anderson Cancer Center, Houston, Texas. mrozner@mdanderson.org

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(Accepted for publication September 12, 2001.)

Anesthesiology 2002; 96:774

In Reply:—We thank Drs. Rozner and Nishman for taking the time to increase the amount of issues about our case report that we were unable to address because of word limitations.

In response to issue 1, we believe that anesthesiologists in general do not have in-depth knowledge of pacemakers, especially newer pacemakers with features such as rate responsiveness. Drs. Rozner and Nishman cited a number of references reporting upper activity rate pacing in response to electromagnetic interference. However, the majority of these were case reports in nonanesthesia journals, such as *Pacing and Clinical Electrophysiology*. One needs only to refer to major anesthesia textbooks to see the lack of details regarding these devices. We practice in an academic center with a large cardiovascular program. Although most anesthesiologists are aware of potential problems with pacemakers, many are not familiar with the details for this type of pacemaker. The patient in our case report was referred to a cardiologist at a pacemaker clinic in another academic center who did not reprogram the pacemaker out of the rate-responsive mode preoperatively. Therefore, we believe that it is worthwhile to draw wider attention to electromagnetic interference in rate-responsive pacemakers with our case report.

Drs. Rozner and Nishman implied that a gradual onset of pacemaker-driven tachycardia is not possible. A company representative from St. Jude Medical in California stated that a gradual onset of pacemaker driven tachycardia is the usual response to cautery interference in the Telectronics META II pacemaker (Englewood, CO). This pacemaker has two programmable response times: medium (36 s) or fast (18 s). The response time determines the time required to reach 50% of the metabolically indicated rate in response to an instantaneous change in the measured minute ventilation. Therefore, it would typically take four response times to reach greater than 90% of maximum programmed rate with real or perceived step changes in minute ventilation. This abnormal response to electromagnetic interference usually results from erroneous interpretation of the mixture of bioimpedance signals rather than a direct effect on the pulse generator itself; thus, a gradual rather than a sudden response is expected.

In response to issue 2, the pacemaker spikes were clearly visible on the monitor screen and to a lesser extent on the printout tracing. Therefore, recognition of pacemaker tachycardia is not the central issue—prevention and management are.

In response to issue 3, we intentionally kept our recommendations brief because of word limitations and at the request of the editor. Detailed recommendations could be obtained from the Web page* cited in the case report reference.

In response to issue 4, we agree with the recommendations of Drs. Nishman and Rosner.

We believe that practicing anesthesiologists need to maintain knowledge of and be familiar with the potential complications of rate-responsive pacemakers, and we hope the case report and its correspondence will heighten awareness of this subject.

David T. Wong, M.D.,† William Middleton, M.D. †Toronto Western Hospital, Toronto, Ontario, Canada. david.wong@uhn.on.ca

(Accepted for publication September 12, 2001.)

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Anesthesiology 2002; 96:774–5

The Effect of Edrophonium on Autonomic Outflow

To the Editor:—We read with great interest the elegant *in vitro* study by Tanito *et al.*[1] that demonstrates that edrophonium binds to muscarinic M_2 and M_3 receptors and acts as a competitive muscarinic antagonist. The authors speculate that this antimuscarinic effect may explain the modest bradycardia produced by edrophonium, compared with other anticholinesterase drugs, such as neostigmine. In this regard, the bradycardia resulting from enhancement of cholinergic transmission in parasympathetic autonomic ganglia and at the sinoatrial node, as a consequence of cholinesterase inhibition, would be reduced by the direct antimuscarinic action of edrophonium at the sinoatrial node.

Another mechanism to account for edrophonium's modest parasympathomimetic effect may be that it inhibits autonomic ganglionic cholinergic transmission. In studies in anesthetized cats, with tonic cardiac parasympathetic drive provided by continuous electrical stimulation of the vagus nerve, edrophonium produced a biphasic effect on the evoked bradycardia.[2] At lower doses, the bradycardia was augmented, presumably as a consequence of the anticholinesterase effect, whereas at higher (but clinically relevant) doses, it was blocked. Even when the *evoked* bradycardia was completely abolished by edrophonium, a small reduction in heart rate persisted, which was thought to be the consequence of the acetylcholine *spontaneously released* from the intrinsic cardiac postganglionic cells.[2,3] The failure of edrophonium to block this persistent bradycardia suggested that in this preparation, edrophonium does not block the M_2 receptors. Rather, it was

hypothesized that block of the evoked bradycardia occurred in the autonomic ganglion. Indeed, using the rat sympathetic superior cervical ganglion as a model for autonomic ganglionic transmission, clinically relevant doses of edrophonium (10–500 μM, ED_{50} 163 μM) were shown to decrease the compound action potential amplitude recorded from the postganglionic axons in response to electrical stimulation of preganglionic axons.[4] Block of the synaptic transmission was shown to occur postsynaptically (presumably *via* block of nicotinic receptors), as edrophonium inhibited postganglionic cell firing in response to exogenously administered acetylcholine. In other models of cholinergic transmission, mouse tumor cells[5] and *Xenopus laevis* oocytes[6] with expressed nicotinic receptors, clinically relevant doses of edrophonium (ED_{50} 3.8 and 82 μM, respectively) decrease acetylcholine-activated channel open time[5] and DMPP (a selective nicotinic agonist)-activated currents,[6] indicating a postsynaptic nicotinic blocking effect. Edrophonium may also block ganglionic transmission by decreasing release of acetylcholine from preganglionic terminals, although this effect, if present, is likely to be small.[4]

From these facts, it is predicted that edrophonium may have the potential to reduce cardiovascular autonomic drive in both sympathetic (block of ganglionic nicotinic transmission) and parasympathetic (block of ganglionic nicotinic transmission and of muscarinic transmission at the sinoatrial node) pathways. This was recently demonstrated in a study of the effects of clinically relevant doses of edrophonium on the spectral analysis of blood pressure and heart rate variability in patients.[7] Regardless of whether edrophonium blocks cholinergic transmission in autonomic ganglia, at the sinoatrial node, or both, both effects would reduce cardiovascular autonomic drive and could account for the modest parasympathomimetic effects produced by cholinesterase inhibition.

Steven B. Backman, M.D.C.M., Ph.D., F.R.C.P.C.,* Alain Deschamps, M.D., Ph.D., F.R.C.P.C. *Royal Victoria Hospital, Montreal, Quebec, Canada. steven.backman@muhc.mcgill.ca

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(Accepted for publication September 16, 2001.)

Anesthesiology 2002; 96:775

In Reply:—We read the letter by Drs. Backman and Deschamps regarding our article. We have demonstrated the antimuscarinic effect of edrophonium by using functional, electrophysiologic, and radioligand binding experiments. Based on the results, we have speculated that the antimuscarinic effect of edrophonium could contribute to less parasympathomimetic effects of the agent compared with those of neostigmine observed in the clinical setting. Against our speculation, Backman and Deschamps stated that edrophonium could reduce cholinergic transmission in autonomic ganglia, and this effect could account for the modest parasympathomimetic effects of edrophonium. The basis of their claim seems to be derived from the article entitled "Heart rate changes in cardiac transplant patients and in the denervated cat heart after edrophonium" by Backman *et al.*[1] As described in their letter, edrophonium failed to block the persistent bradycardia produced by high doses of edrophonium itself in vagus nerve–stimulated cats. Therefore, they concluded that edrophonium did not block the M_2 receptors in their experimental model. However, we think that there is a serious defect in their statement. If atropine could block the edrophonium-produced persistent bradycardia, the bradycardia would be mediated through the muscarinic receptors, and the antimuscarinic effects of edrophonium, which we have shown, would not work in their model, as they claimed. However, the authors did not examine whether atropine could block the persistent bradycardia produced by edrophonium. If atropine does not block the persistent bradycardia, the underlying mechanism of the persistent bradycardia produced by edrophonium is independent of the muscarinic receptors. As shown in figures 2 and 3 of their article, edrophonium could reduce the heart rate in anesthetized cats with vagotomy and sympathectomy. Again, they did not examine whether atropine could block this edrophonium-produced bradycardia. Rather, it is rational that one thinks that the bradycardic effect of edrophonium in cats with vagotomy and sympathectomy is independent of both parasympathetic and sympathetic nervous systems. Consequently, the results shown in figures 2 and 3 in their article seem to support our speculation. That is, high doses of edrophonium could completely abolish not only the bradycardia produced by the electrical stimulation of vagus nerve but also the bradycardia produced by the anticholinesterase activity of edrophonium by means of its antimuscarinic effect. Backman and Deschamps also cited the report that edrophonium decreased the action potential amplitude recorded from postganglionic axons in the rat sympathetic superior cervical ganglion.[2] However, this result indicates that edrophonium could produce bradycardia by inhibiting sympathetic nervous activity, resulting in an augmentation of its bradycardic effect. We understand that they intended to speculate that edrophonium could inhibit the transmission in the parasympathetic ganglion as in the sympathetic ganglion. However, what happens when edrophonium inhibits the parasympathetic ganglion and sympathetic ganglion simultaneously? In conclusion, there is no obvious evidence that edrophonium inhibits the autonomic transmission in the parasympathetic ganglia and that this effect weakens its parasympathomimetic effects produced by cholinesterase inhibition.

Yasuto Tanito, M.D., Ph.D., Takaaki Miwa, M.D., Ph.D., Masayuki Endou, M.D., Ph.D.,* Yoshihumi Hirose, M.D., Ph.D., Masahiro Gamoh, M.D., Haruaki Nakaya, M.D., Ph.D., Fukuichiro Okumura, M.D., Ph.D. *Fujisawa Shonandai Hospital, Fujisawa, Japan. endo@ac7.mopera.ne.jp

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(Accepted for publication September 16, 2001.)

Anesthesiology 2002; 96:776

World War II and Physician Specialization

To the Editor:—The history of anesthesiology as a physician specialty in the USA is fragmented at best. A handful of books, numerous articles, and piles of primary source documents must be read to fashion a coherent picture of historical events and social forces responsible for transforming anesthesia from a merciful craft to the medical specialty. Dr. David Waisel's article about physicians' roles in education and organization of anesthesia during World War II contributes in this regard.[1] It joins Courington and Calverley's article about anesthesia during World War I to fill a gap in our specialty's history about professionalization.[2]

However, like many anesthesiologist–authors before him, Dr. Waisel overstates the role technical skills in drug administration play in explaining why nurse anesthetists arose in America alongside physicians. In his article he states[1]:

> In contrast to the development of anesthesia in the United States, anesthesia developed as a physician specialty in Great Britain because of the complexity of administering chloroform and the precedent of the physicians administering anesthesia in Great Britain.

This explanation is suspect in an otherwise scholarly article. It is small comfort that as an explanation for an extremely complex historical process, others still invoke it as dogma. Indeed, the myth that British chloroform required more skill in administration than American ether cannot serve to explain, in total, the American origins of the anesthesia care team. Nonetheless, a version of this explanation is also found in a recent edition of a popular basic anesthesia textbook.[3]

The notion that a simple but deterministic dichotomy existed between American and British anesthetic preferences is referred to as the Great Trans-Atlantic Debate. About it, Greene, the same author Waisel references, said[4]:

> Purposeless, tedious, and often irrational on both sides, the Debate accomplished little except ultimately detract from the stature of those involved. The acrimony generated by the Debate and the unscientific hyperboles indulged in by those involved, did little to augment the stature of anesthesia as a scientific field in the eyes of objective observers.

That chloroform was used more than occasionally in the United States between 1846 and 1900 is an established fact. During the War Between the States, chloroform found favor in America (mostly in the Confederacy) because of its availability, lower flammability, and smoother emergence properties compared with ether.[5] However, this does not mean that some greater bias toward ether did not also exist at the same time, especially where it was available.

That the Debate should resurface in contemporary form speaks to the persistent need for anesthesiologists to better understand the specialty's history differently.[6] If acknowledged as such, the Great Trans-Atlantic Debate might be better understood as "The Fallacy of Pharmacologic Determinism." As the phrase implies, a damaging falseness lies at the heart of any claim that skill in drug use is the most important determinant justifying the existence of any medical specialty, including anesthesiology. Consideration of multiple historical, social, and ethical factors best explains how physicians came to dominate anesthesia care early on in Great Britain but not the United States. To simply imply physician dominance was rooted in more skillful use of the preferred drug obscures the role other more important factors played in our specialty's professional history.[7–10]

Vincent J. Kopp, M.D., University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. vkopp@aims.unc.edu

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(Accepted for publication September 24, 2001.)

Anesthesiology 2002; 96:776–7

Calling All Anesthetists to Service in World War II

To the Editor:—I read with appreciation and interest the recent special article by Dr. David B. Waisel, "The Role of World War II [WWII] and the European Theater of Operations [ETO] in the Development of Anesthesiology as a Physician Specialty in the USA."[1] I would like to comment on three assertions made in the article based on my father's personal experiences as a staff officer with the 24th General US Army Hospital in the ETO during WWII, 1943–1945. These three assertions included the following: (1) predominately physicians and some nurses were trained as wartime anesthetists in the US and England in 1943 and 1944; (2) military physician–anesthetists were deployed in the ETO primarily after late 1943; and (3) and Dr. Henry K. Beecher was primarily active in behind-the-lines training of US physician–anesthetists in the US and England in 1943 and 1944.[1]

In fact, designated dentists, nurses, generalist physicians, and, physician–specialists with limited wartime skills, particularly obstetricians and pediatricians, received anesthesia training at US institutions both before and after the outbreak of WWII. My father, Major Abram H. Diaz, D.D.S., USA, joined the US Army in 1937 as a dentist and oral surgeon and was further trained as a maxillofacial surgeon and dentist–anesthetist at the Walter Reed Army Hospital in 1942 and 1943. In addition, my uncle, an obstetrician, received further training in abdominal and thoracic surgery and anesthesia at the Mayo Clinic. In July 1942, they and others were mobilized in New Orleans, Louisiana, as the 24th General US Army Hospital, under the command of Colonel I. Mims Gage, a general and thoracic surgeon trained by Dr. Alton Ochsner. The chief physician–anesthetist of the 24th General was

Major George B. Grant, a professional anesthesiologist and early member of the American Society of Anesthesiologists and a respected colleague of Drs. Gage and Ochsner. Dr. Grant directed two professional nurse–anesthetists and all of the multiskilled physician– and dentist–anesthetists in the 24th General's anesthesia department and trained many more "nurse"–anesthetists in the ETO throughout WWII (E. D. Matthews, personal interview, June 17, 2001).

Besides Dr. Grant, no other formally trained anesthesiologists served in the 24th General (E. D. Matthews, personal interview, June 17, 2001). My father, a dentist, administered head and facial blocks and neuroleptanesthetics that combined craniofacial blocks with pentothal and morphine, both as a surgeon and as a dentist–anesthetist. Nitrous oxide, which was favored by dentists for neuroleptanesthetics but supported combustion, was not uniformly available in the ETO, especially in forward-area hospitals, like the 24th General. Explosive volatile anesthetics were also not available.[1] My uncle, an obstetrician, also performed regional anesthetics in the ETO, both as a surgeon and as a physician–anesthetist. The 24th General Hospital had a distinguished wartime record in the Mediterranean and participated in two massive amphibious assaults, the North African invasion and the Italian invasion. Thus, many nurses, dentists, and even physician–specialists, particularly obstetricians and pediatricians, served as anesthetists and assisted professional physician–anesthetists, like Dr. Grant, in the ETO in WWII. As an anesthesiologist, I have had the privilege of administering subsequent anesthetics to WWII veterans treated by both my father and uncle in the ETO, 1943–1945.

The first 24th General Hospital was established in Bizerté, Tunisia, in the spring and summer of 1943. This hospital was composed of tents for staff housing and recovery wards and temporary buildings for laboratories, specialty units, and prisoner-of-war quarters. The staff of the 24th General treated the heavy casualties experienced by the US Army during the early part of the North African campaign. The Tunisian 24th General Hospital was dismantled in early 1944 in anticipation of the Italian invasion. The second 24th General Hospital was established in an abandoned cigarette factory in Grosseto, Italy, north of Rome on the Mediterranean Sea, and on the parallel with the fiercely defended German defensive lines anchored at Montecassino on the Adriatic side of Italy. The Italian 24th General Hospital provided expert specialty care for all allied soldiers serving in the Italian campaign until the end of WWII. Some of the most experienced medical officers in the 24th General were then sent to the Pacific Theater of Operations for additional military service after the end of the war in the ETO in the spring of 1945. Thus, there were indeed many highly experienced physician and nonphysician anesthetists, not previously trained in British or US northeastern noncombatant hospitals serving in forward-area hospitals in the ETO before late 1943.

In an interview with one of the few surviving veterans of wartime service with the 24th General in the ETO, Edward D. Matthews, M.D., a retired internist, recalled a personal visit with medical and postsurgical rounds made by Dr. Henry K. Beecher to the Tunisian Hospital in 1943 (E. D. Matthews, personal interview, June 17, 2001, and letter to the author, June 20, 2001). Both Dr. Matthews and Dr. Grant provided postoperative critical care to surgical patients. After WWII, Dr. Grant was credited with establishing the first postoperative recovery room in the USA at the original Ochsner Foundation Hospital, located in the former US Army Camp Plauché in New Orleans, Louisiana.[2] This first recovery room also functioned as an intensive care unit for patients undergoing endotracheal anesthesia and was modeled on similar units established for postoperative patients at the 24th General Hospitals in Tunisia and Italy (E. D. Matthews, letter to the author, June 20, 2001).[2] Thus, Dr. Beecher not only trained physician–anesthetists in the US and England, but also personally visited with staff and patients at forward-area hospitals in the ETO, many of which came under enemy air and artillery attack (E. D. Matthews, letter to the author, June 20, 2001).[1] In addition, Dr. Beecher encouraged physician and nonphysician US Army anesthetists to use endotracheal anesthetics for thoracoabdominal surgery, to explore new combinations of regional and intravenous anesthetics for wound management, and to design unique areas for intensive postoperative care, such as early postsurgical recovery rooms, now contemporary intensive care units (E. D. Matthews, personal interview, June 17, 2001, and letter to the author, June 20, 2001).

James H. Diaz, M.D., M.H.A., M.P.H. & T.M., Dr.P.H., Louisiana State University School of Medicine, New Orleans, Louisiana. jdiaz@lsuhsc.edu

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(Accepted for publication September 24, 2001.)

In Reply:—I thank Dr. Diaz for taking the time to add to our knowledge of anesthesia during World War II, and particularly for bringing to light some of the experiences of the 24th General Hospital. Because I was focusing on the European Theater of Operations, I did not fully comment on operations in North Africa, Italy, and southern France, which the military considered to be in the Mediterranean Theater of Operations. Diaz is particularly correct to honor the extensive contributions of Beecher, who was Consultant in Anesthesia and Resuscitation, Mediterranean Theater of Operations. From those experiences, Beecher authored such seminal works as "Pain in Men Wounded in Battle," which was originally published in the *Medical Bulletin of the Mediterranean Theater of Operations* and subsequently published in the *Annals of Surgery*.[1]

Dr. Kopp focuses on an interesting and valid question worthy of its own series of articles: to what extent did anesthetic agents used influence the progression of the profession of anesthesiology? He is right, of course, in that different factors affected the growth of medical and nonmedical practice of anesthesia. However, I think to characterize the ether–chloroform element of this discussion as "pharmacologic determinism" unfairly overstates the purported argument to the point of creating a straw man. Although it was far from the sole factor, the pharmacologic agents used were a considerable cause in the substantial rejection of careers in anesthesia by physicians in the United States. The ease of administering ether anesthesia coupled with a more dramatic response in the United States to the reports of chloroform deaths in the late 1800s led to a predominantly ether-based inhalation practice, which was wholly amenable to having the least-skilled individual provide it. This practice, in concert with other factors, encouraged physicians to scorn careers in anesthesia and permitted other professions, such as nursing and dentistry, to fill the void. I thank Dr. Kopp for his insightful letter and I look forward to continuing this most important discussion with him and other interested parties.

David B. Waisel, M.D., Children's Hospital, Boston, Massachusetts. david.waisel@tch.harvard.edu

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(Accepted for publication September 24, 2001.)

Anesthesiology 2002; 96:778

The LTA® Cannula and Difficult Intubations

To the Editor:—I read with interest Dr. Feingold's technique for using the LTA® cannula (Abbott Laboratories, North Chicago, IL) to facilitate a difficult intubation.[1] What I do not understand is, after the cannula is through the vocal cords and in the trachea, why not use it as a stylet guide over which the endotracheal tube is advanced into the trachea? We originally described this technique in 1977.[2] Cahen independently described the same technique in 1991.[3] Others[4] have reported using our technique many times to "save the day."

Denis L. Bourke, M.D., University of Maryland at Baltimore, Baltimore, Maryland. Squashwiz@aol.com

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(Accepted for publication October 31, 2001.)

Anesthesiology 2002; 96:778

Another Technique of Facilitating a Difficult Intubation

To the Editor:—We would like to comment on Dr. Feingold's technique of facilitating a difficult intubation with an LTA® cannula (Abbott Laboratories, North Chicago, IL), described in the June 2001 issue of ANESTHESIOLOGY.[1] We described an instrument to help solve the same problem in the January–February 1967 issue of ANESTHESIOLOGY.[2] Our instrument is called an "epiglottic elevator" and was made for us by Foregger and Company (Long Island, NY). This instrument might have some advantages over the flexible LTA® cannula. The probe was rigid and was more controllable. The handle was offset and weighted. It could be released outside the mouth and became a self-retaining epiglottic elevator, maintaining the elevation of the epiglottis and a view of the glottic chink. The right hand was free to insert the endotracheal tube alongside the epiglottic elevator extended into the trachea.

Martin Livingston, M.D.,* Robert Durell, M.D. New York Ear and Eye Infirmary, New York, New York

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1. Feingold A: LTA cannula can facilitate a difficult tracheal intubation (letter). ANESTHESIOLOGY 2001; 94:1153
2. Livingston M, Durell R: Epiglottic elevator. ANESTHESIOLOGY 1967; 28:214–5

(Accepted for publication October 31, 2001.)

Anesthesiology 2002; 96:778

In Reply:—I am grateful to Dr. Livingston, Dr. Durell, and Dr. Bourke for their relevant comments and references. Dr. Livingston and Dr. Durell are correct in suggesting that their previously described[1] "epiglottic elevator" for difficult intubations has features similar to my technique using the LTA® cannula (LTA® 360 Kit, Abbott Laboratories, North Chicago, IL). However, the LTA® cannula dispenses topical anesthesia, which is useful in its own right. Also, I believe that by naming their device an "epiglottic elevator," they underestimate the benefit of the anatomic distortion of the glottis that may occur when their device is positioned in the trachea.

Dr. Bourke's remarks are also cogent. His reference[2] refers to the technique of passing the LTA® cannula through the Murphy eye of the endotracheal tube, placing the LTA® cannula into the trachea, and then sliding the tube over the LTA® cannula into the trachea. This technique requires loading the endotracheal tube on the LTA® cannula before insertion of the cannula into the trachea. Perhaps Dr. Bourke is also suggesting that the LTA® cannula can be passed into the trachea without first loading the endotracheal tube. The LTA® syringe could be removed from the cannula, and the cannula could be threaded through the Murphy eye "as a stylet guide over which the endotracheal tube is advanced into the trachea." This modification sounds possible; however, I have neither tried it myself nor seen it reported. In any case, I believe that these previous techniques, although relevant and useful, will result in no greater success than the placement of the endotracheal tube beside the LTA® cannula as described in my letter to the editor.

Alfred Feingold, M.D., Cedars Medical Center, Miami, Florida. afein@sprintmail.com

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(Accepted for publication October 31, 2001.)

Anesthesiology 2002; 96:779

Subtle Hyperkalemia Detected through Monitor "Artifact"

To the Editor:—We report a case of hyperkalemia identified after changes in the heart rate count by the electrocardiographic monitor. A 14-yr-old girl was undergoing transplant nephrectomy from the right iliac fossa with use of a balanced anesthetic. She had been dialyzed the day before, and the serum potassium concentration after induction was 5.3 mEq/l. Lead II was monitored using an Agilent Component Monitoring System (ACMS M 1176 A; Agilent Technologies, Andover/Burlington, MA) with the QRS detection level in auto mode. After approximately 1 h, the electrocardiographic rate determined by the monitor doubled over the period of 1 min, while the pulse rate counted from the pulse oximeter remained unchanged (fig. 1). The electrocardiographic monitor was counting both R waves and the now elevated T waves of the seemingly unchanged sinus rhythm displayed on the screen. The serum potassium concentration was now 5.9 mEq/l. Glucose and insulin were administered. For approximately 45 min, the monitor continued to display the heart rate by electrocardiography as double the pulse rate by oximetry. Then, the electrocardiographic rate returned to the level of the pulse rate within 2 min (fig. 1). The serum potassium concentration was now 5.4 mEq/l.

We were impressed by the acuteness of onset and offset of the observed changes and the correlation with potassium concentrations. Modern electrocardiographic monitors rarely count the tall T wave of hyperkalemia as another R wave. Other than just amplitude, their algorithm for automatic QRS detection analyzes timing and configuration of the wave, heart rate alarm limits, or patient age setting (adult *vs.* neonatal). We want to remind every practitioner to consider possible pathophysiologic reasons for monitor phenomena before discounting them as artifacts.

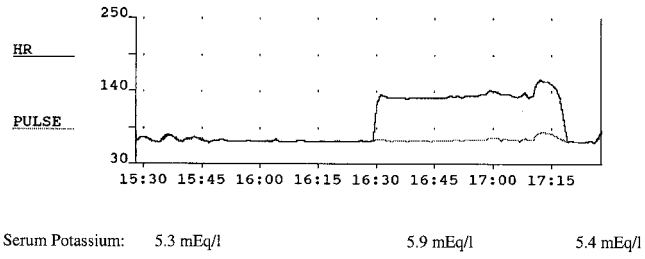

Fig. 1. Trend traces of heart rate (HR, as measured from the electrocardiograph) and pulse rate (PULSE, as counted from the pulse oximeter). Subtle changes of the T wave led to doubling of the heart rate count correlating with hyperkalemia. After glucose-insulin treatment, the HR curve returns to match the PULSE curve as the potassium concentration decreases.

Christian Seefelder, M.D.,* Marcy S. Tucker, Ph.D., M.D., Craig W. Lillehei, M.D. *Children's Hospital, Boston, Massachusetts. christian.seefelder@tch.harvard.edu

(Accepted for publication October 2, 2001.)

Support was provided solely from institutional and departmental sources.