with $Ce_{i\ real}$ and $Ce_{i\ estimated}$ as the population means of the patients in study i for the real and estimated value of *Ce*, respectively.

Four case combinations are shown that use different settings for the simulation. For each case, a plot is shown with the distribution of the $bias_i$ as shown in equation A.1 (fig. 8). Each of these cases has different underlying assumptions, ranging from hypothetical to closely corresponding to our study setting.

Case 1 assumes a very small (unrealistic) variance for *Ce1*, $\beta = 1$, with very small variance (basically *Ce1* = *Ce2*), sampling only at one drug concentration of 3.5 (equal to *Ce1*); with this hypothetical setting, a huge bias of on average more than 20% has to be expected (fig. 8A).

Case 2 assumes a population distribution with a variance of 0.5 for *Ce1* (fig. 9), a β as in case 1, and a sampling at drug concentrations [2, 3, 4, 6, 8] drug units; bias is much smaller and can be expected to be around average 4% (fig. 8B).

Case 3 closely corresponds to our clinical study situation; it assumes a population distribution with a variance of 0.5 for *Ce1*, a β of 1.1 corresponding to the smallest difference of approximately 10% as found in the study (typical Ce_{50} values of TLAR compared to TLMA, table 2), and the same sampling as in case 2. On average, the bias disappears and is constrained between $\pm$ 4% (fig. 8C).

Case 4 assumes wrong order sampling, expressed with a $\beta = 0.8$ (assuming that *Ce2* is 20% smaller than *Ce1*), and same distribution and sampling as in case 3. Not surprisingly, there is a huge bias of on average 25%, and *Ce2* is estimated to be the same as *Ce1* (fig. 8D).

Even with identical *Ce*s, bias is relatively small if there is some population distribution of the *Ce*s and when a reasonable sampling is done. Bias is significant when the order of the stimulations is reversed. This could be the case, if the stimulation strength is not known *a priori*, but it could potentially be detected if *Ce*s of different stimulations are found to be equal. If the order is correct and the difference in *Ce*s is 10% and more, no bias was found in our simulations. This is indirectly confirmed by our study with the good estimates for the Ce_{50}s, and the good correlation with other studies that specifically looked at only one stimulation at a time.

ANESTHESIOLOGY REFLECTIONS

Cordus' Synthesis of Ether

In 1540 Valerius Cordus (1515–1544; German botanist, pharmacist, and physician) synthesized ether ("sweet oil of vitriol") in his alchemist's still from ethanol ("triply-distilled" wine) and sulfuric acid ("sour oil of vitriol"). His "sweet" mixture floated on water (the volatile diethyl ether portion, which would be vaporized three centuries later as an anesthetic) yet felt greasy to touch (the aromatic diethyl sulfate portion). Hailed later as the Father of Descriptive Botany and of the Legally Sanctioned Pharmacopoeia, Cordus died, possibly from malaria, soon after the 29-year-old's leg was kicked savagely by a horse. The world's first record of the synthesis of ether, *De Artificiosis Extractionibus*, was published 17 years later in a posthumous compilation. In July of 2009, the Wood Library-Museum acquired this "new" tome from 1561 (see above—note its pigskin-quarterbound, antiphonal-vellum-over-pasteboard covers).

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.