

Science Marches Forward

A New Tool to Study the Progress of Labor

FOR decades, carpenters used a mechanical level—a liquid-filled tube whose position is adjusted until a bubble is centered—to ensure the angles in their projects. In recent decades, mechanical levels have been supplanted by laser-driven devices. Now, an "app" permits an iPhone® (Apple, Inc., Cupertino, CA) to accomplish the same thing. So it is in science; new tools enable us to replace old tools and thereby enable us to ask new questions or old questions in a more precise manner. This issue of ANESTHESIOLOGY contains an article by Debiec *et al.*[1] describing this type of change.

The underlying causes of onset and progress of labor in humans remain a mystery and represent important public health concerns, given the high cost of premature birth. The wide interindividual variability of the progress of labor has always been of interest to obstetricians and anesthesiologists. Anesthesiologists have been primarily concerned over the past two decades with whether their interventions, such as epidural analgesia, slow the progress of labor. The tool used most often to examine the progress of labor is based on work done by an obstetrician, Friedman,[2] initially in the 1950s. Friedman tracked the course of labor (quantified by cervical dilatation) in 500 primigravid parturients and then quantified the time course of labor (cervical dilatation *vs.* time). His model consisted of two portions: a shallow linear phase ("latent" labor) and a steeper curvilinear portion ("active" labor). The active portion was further divided into four portions: an acceleration phase (the transition between latent and active labor), a linear portion ("phase of maximal slope"), a curvilinear portion ("deceleration phase"), then a plateau at full dilatation ("second stage").

Friedman's approach offered limited opportunity for mathematical analysis. Thus, the richness of data collected over the course of labor underwent minimal scrutiny. Perhaps important issues could not be addressed because the analysis tools were lacking. Debiec *et al.*[1] applied methods commonly associated with pharmacokinetic analysis to labor data. To accomplish this, they first needed to define a "model," *i.e.*, to assess the "shape" of the time course of labor. Whereas Friedman had described the course of labor with intersecting lines, Debiec *et al.*[1] concluded that a continuous function based on exponentials worked better in their hands. They then needed to determine if a single exponential or the sum of two exponentials was justified by the data. This is similar to the process in pharmacokinetic analyses, where one decides between one- and two-compartment models. Having found a model that fit the data, the authors could then evaluate the effects of covariates (*e.g.*, did the course of labor differ as a function of self-proclaimed race?). Although the results of this manuscript focus on the latter, the major contribution of Debiec *et al.*[1] is actually development of the model.

The method used by Debiec *et al.*[1] is called "mixed-effects modeling" in which the relative contribution of fixed-effects (things that one can measure; in this case, things like ethnicity) and random effects (random variability among subjects that cannot be attributed to measurable characteristics) are considered. In medicine, the first major use of mixed-effects modeling was for pharmacokinetic analysis. In particular, the computer program NONMEM (*non*-linear *m*ixed *e*ffects *m*odeling) was developed at the University of California, San Francisco, by the late Lewis Sheiner, M.D., Ph.D. (Professor, Departments of Laboratory Medicine and Biopharmaceutical Sciences, University of California San Francisco, California, 1940–2004) and Stuart Beal, Ph.D. (Professor of Laboratory Medicine, University of California, San Francisco, 1941–2006) to facilitate modeling of drug behavior. Much seminal work in anesthesia has been performed by using NONMEM, and it is rare for an issue of a major anesthesia journal to appear without one or more articles that depend on its use. However, the article by Debiec *et al.*[1] probably represents the first application of mixed-effects modeling to the time course of labor.

By using NONMEM, the authors identified the effects of several maternal characteristics that influence the time course of labor with high degrees of statistical significance. Debiec *et al.*[1] also showed that the magnitude of these effects was trivial, despite their statistical significance. From their analysis, we learn that the factors measured in their study do not explain why some women have fast labor and others have slow labor. However, the authors have provided a sharp

This Editorial View accompanies the following article: Debiec J, Conell-Price J, Evansmith J, Shafer SL, Flood P: Mathematical modeling of the pain and progress of the first stage of nulliparous labor. ANESTHESIOLOGY 2009; 111:1093–110.

Accepted for publication July 22, 2009. The software (PLT Tools) used by Debiec *et al.* was developed and is owned jointly by Dr. Fisher and Steven Shafer, M.D. (senior author of the Debiec *et al.* article).

Timothy J. Brennan, Ph.D., M.D., served as Handling Editor for this article; James C. Eisenach, M.D., was not involved in the decision-making process.

tool to quantitatively assess the effect of any patient or environmental covariate (*e.g.*, genetic influences, barometric pressure) on the time course of labor. Understanding the causes of interindividual variability in physiologic responses, disease progression, and response to therapy is a central theme to 21st century biomedical research. Debiec *et al.*[1] have provided an important tool to perinatal and pain medicine to probe root causes of such variability in progress of labor and the pain it causes.

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References

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2. Friedman EA: Primigravid labor. Obstet Gyn 1955; 6:567–89

ANESTHESIOLOGY REFLECTIONS

The Horton Intercoupler

Surgeon-manufacturer Karl Connell (1878–1941) was alarmed by the fatal explosion in Boston resulting from static ignition of cyclopropane vapor delivered by one of his Connell DeLuxe anesthesia machines. He collaborated in 1939 with a Massachusetts Institute of Technology professor of engineering, J. Warren Horton, and a Lahey Clinic anesthesiologist, Phillip D. Woodbridge, to produce the "Horton Intercoupler" (*see above*). This device used its metal casing, woven metallic bracelets, spring clamps, and often a drag chain to provide high-resistance electric coupling of the patient, the anesthesiologist, the operating room table, and the anesthesia machine to the conductive flooring. Once nonexplosive gases were introduced as general anesthetics, use of the cumbersome Horton Intercoupler waned. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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