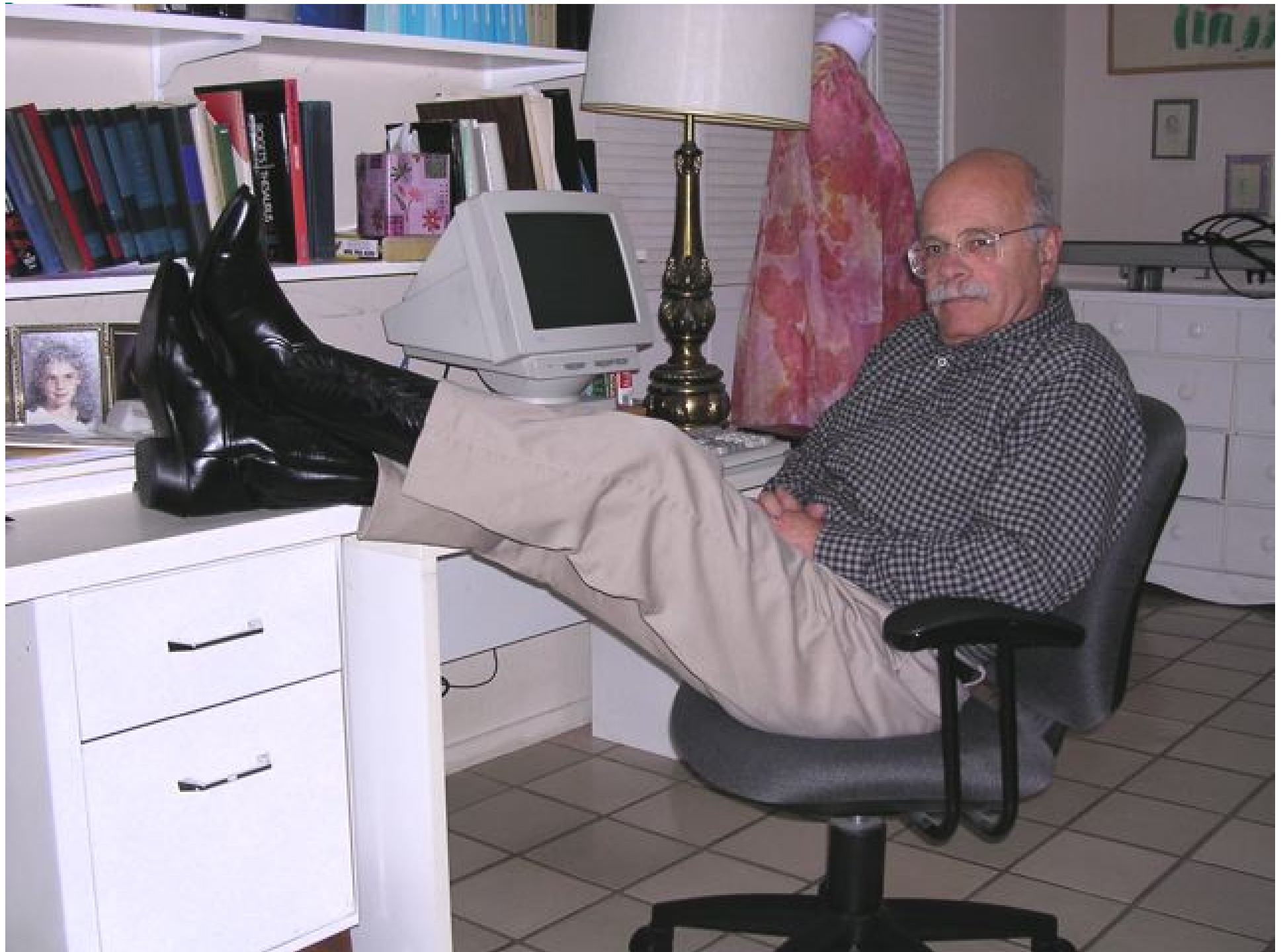


**In Fond Memory of
Professor Stuart L. Beal
June, 1941 – January, 2006**

**2006 ECPAG Meeting
Rockville, MD**



Education – Univ. of California, Los Angeles

- **B.A. Mathematics with Minors in Logic and Fine Arts**
- **Graduate Studies in Mathematics**
- **M.S. Biostatistics – Thesis: A Stochastic Model (and Its Computer Implementation) for the Population Sizes of Maturing Cell Types in a Clone**
- **Ph.D. Biostatistics – Dissertation: Adaptive M Estimation with Independent Nonidentically Distributed Data**

University of California – San Francisco

- **Senior Statistician, Step V, Office of Information Systems (1973-1976)**
- **Assistant, Associate, Full Professor, Department of Laboratory Medicine (1976 – 2006)**

Early Publications - UCSF

- L.B. Sheiner, B. Rosenberg, V.V. Marathe. “Estimation of Population Characteristics of Pharmacokinetic Parameters from Routine Clinical Data”, J. Pharmacokin. Biopharm. 1977; 5:445-479. Acknowledged Stuart Beal for helpful discussions.
- L.B. Sheiner, S.L. Beal, B. Rosenberg, V.V. Marathe. “Forecasting Individual Pharmacokinetics”, Clin. Pharmacol. Ther. 1979; 26: 294-305.
- S. Beal, L.B. Sheiner. “The NONMEM System”, The American Statistician, 1980; 34: 118-119.

The NONMEM System

- **Software for nonlinear mixed effect modeling implemented through the use of a first-order approximation. Provided a means to analyze (sparse per individual) data collected during routine clinical care. Fortran programming knowledge was needed. Required derivatives of the model response w.r.t. the random terms. Ugh!**
- **PREDPP – Simpler derivatives were needed. Library of standard pharmacokinetic models as well as general routines for linear and nonlinear models. A data structure that particularly suited the analysis of observational, pharmacokinetic and pharmacodynamic data. (with Alison Boeckmann)**

The NONMEM System Evolves

- **NM-TRAN – developed by Alison Boeckmann**
No derivatives required. Increased flexibility in data set format. Many details of Fortran programming could be ignored. Relative user-friendliness expanded access to the program.
- **First-order Conditional Estimation – Empirical Bayes estimation of interindividual random terms.**
- **Eta-Epsilon Interaction**
- **Laplacian Method**

The NONMEM System – An Essential Option

NOABORT

If you sent Stuart a control stream with this option, you were almost certain to get a lecture about using this only if absolutely necessary, (which it almost always was).

Stuart Beal's Genius and Attention to Detail are Evident Throughout the NONMEM Program

Essentially all of the estimation methods in NONMEM are derivative based methods. Careful attention was paid to specifying the appropriate objective function for each method implemented.

Impressive flexibility for modeling, simulation, estimation and statistical assessment.

Only a genius could construct and maintain code like that used to determine the execution path required by the chosen estimation method.

```

IF (OPETA1.EQ.1) THEN
  IF (OPGR.EQ.0) THEN
    IF (IST.EQ.1) THEN
      IF (OPTWO.EQ.1) THEN
        IF (OPLAPN.EQ.0) THEN
          IF (NROB.NE.0.AND.(MODE.LE.2.OR.IST.EQ.2)) THEN
            IF (ISHORT.EQ.1.AND.IFRIND.EQ.1.AND.MCALL.EQ.1)
              1      CALL OBETA (6,JJ,IE)
              CALL OBETA (2,JJ,IE)
            ELSE
              IF (ISHORT.EQ.1.AND.IFRIND.EQ.1.AND.MCALL.EQ.1)
                1      CALL OBETA2 (6,JJ,IE)
                CALL OBETA2 (2,JJ,IE)
              ENDIF
            ELSE
              IF (IFRIND.EQ.1.AND.IND.EQ.0.AND.MCALL.EQ.1)
                1      CALL OBETA (6,JJ,IE)
                CALL OBETA (2,JJ,IE)
              ENDIF
            ELSE
              IF (IET.EQ.1) THEN
                IF (IFRIND.EQ.1.AND.IST1.EQ.1.AND.IND.EQ.0.
                  AND.MCALL.EQ.1) CALL OBETA (7,JJ,IE)
                1
                IF (OPTWO.EQ.2) THEN
                  IF (IND.EQ.0.OR.MODE.GT.1) THEN
                    CALL OBETA (8,JJ,IE)
                  ELSE
                    CALL OBETA (11,JJ,IE)
                  ENDIF
                ELSE
                    CALL OBETA (4,JJ,IE)
                ENDIF
              ELSE
                IF (OPLAPN.EQ.0) THEN
                  CALL OBETA (10,JJ,IE)
                ELSE
                  CALL OBETA2 (10,JJ,IE)
                ENDIF
              ENDIF
            ENDIF
          ELSE
            IF (IST.EQ.1) THEN
              IF (OPTWO.EQ.1) THEN
                CALL OBETA2 (2,JJ,IE)
              ELSE
                IF (IFRIND.EQ.1.AND.MCALL.EQ.1)
                  1      CALL OBETA (6,JJ,IE)
                  CALL OBETA (2,JJ,IE)
                ENDIF
              ELSE
                IF (IET.EQ.1) THEN
                  IF (IFRIND.EQ.1.AND.MCALL.EQ.1)
                    1      CALL OBETA2 (7,JJ,IE)
                    CALL OBETA2 (8,JJ,IE)
                  ELSE
                    IF (OPLIN.EQ.0) CALL OBETA2 (10,JJ,IE)
                  ENDIF
                ENDIF
              ENDIF
            ENDIF
          ENDIF
        ENDIF
      ENDIF
    ENDIF
  ENDIF

```

Recent Publications

- **“Ways to Fit a Pharmacokinetic Model with Some Data Below the Quantification Limit”, J. Pharmacokin. Pharmacodyn. 2001; 28:481-504.**
- **“Commentary on Significance Levels for Covariate Effects in NONMEM”, J. Pharmacokin. Pharmacodyn. 2002; 29:403-410.**
- **“Conditioning on Certain Random Events Associated with Statistical Variability in PK/PD”, J. Pharmacokin. Pharmacodyn. 2005; 213-243.**

Stuart Beal and Lewis Sheiner

An incredibly creative and productive collaboration.

The NONMEM Software

Pharmacometrics as a new discipline

**A new, more rational approach to drug
development**

**1996-2006 National Institutes of Health Merit
Award**



Most Impressive Characteristic

The love and devotion he had for his wife and family, e.g. an e-mail exchange.

How was your visit to Italy?

Stuart: Trip was a trip of a lifetime! Saw astounding things - things I hadn't at all anticipated. Got to spend 24 hours a day with Lauren for 5 weeks, which was lovely.



The NONMEM System – Stuart Beal's Scientific Legacy

The NONMEM System is used every day by hundreds of pharmaceutical scientists in government, industry and universities world wide.

The NONMEM System – NONMEM 6.1.0

- **Increased flexibility in modeling**
 - Event times
 - Repeat option
 - Simultaneous analysis of continuous and odd-type data
 - Compartment initialization
 - User-written Functions
- **Additional estimation methods**
 - Use of a Frequency Prior
 - Hybrid with Interaction
 - Laplacian with Interaction
 - Nonparametric step
- **Customization of Output**
 - \$INFN record
 - DO WHILE(DATA) to facilitate the use of the PASS utility.