Lewis B Sheiner
Who was he?

- **Clinical Pharmacologist**
  - MD Albert Einstein College of Medicine 1964
  - President ASCPT 1991

- **Scholar**
  - Professor of Laboratory Medicine, Biopharmaceutical Sciences, and Medicine UCSF 1972-2004

- **Human Being**
  - Wife Michael, Children Tim and Amanda
  - Relatives and Friends
How did Michael see him?

- “He loved to think about models”
- “At home he spent a lot of time with his computer”
- “We only recently understood he was doing something in drug development”
What did he give to us?

• The creator of the population approach
  – Without him PAGE would not have been born and we would not be here

• The co-developer of NONMEM
  – Without the tool we would not be able to do anything

• A scholarly record
  – Without these papers we would not know what we know
Where did he start?

Computer-Aided Long-Term Anticoagulation Therapy

LEWIS B. SHEINER*

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Received June 2, 1969

- Parameters estimated with turnover (indirect effect) model
  - DEQ model in PL/1 on IBM 360/50
- Individualized dose prediction
  - Program did better than 2 out of 3 cardiologists
- Pharmacoeconomic analysis
  - Cost per consultation $0.65 ($12/CPU minute)


The Birth of Population PK

COMPUTERS AND BIOMEDICAL RESEARCH 5, 441-459 (1972)

Modelling of Individual Pharmacokinetics for Computer-Aided Drug Dosage*

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Received August 12, 1971
At the risk of being a garrulous old codger...

...I was looking around for a fellowship and Henry [Bourne] invited me to present my NIH work at one of [Ken] Melmon's weekly Clin Pharm seminars. Meantime, around '67 Rosenberg had observed that his mother with CHF (I think she had mitral insufficiency) seemed to get worse every time her docs raised her dose of digoxin. Barr [Rosenberg], who was working on forecasting investment risk using hierarchical mixed effect models of stock prices vs time, somehow found Melmon, and went to see him to ask how come MDs didn't seem to know anything about forecasting, when he (Barr) could forecast his Mother's exacerbations with ease.

Melmon, with his genius for recognizing talent and somehow incorporating it into his world, got Barr to agree to work with I can't remember who at UC, a collaboration that was going nowhere by '69. So, when I came to give my seminar, Ken had invited Barr. He listened politely to the whole story, and -- I shall never forget -- at the end, in his very gentlemanly way, when asked to comment, said "That was very nice, but here is how you should have done it..." and proceeded right there to outline the appropriate hierarchical model / empirical Bayes framework I should indeed have used. It was all new to me! So naturally, I decided then & there to do a fellowship with Ken and work with Barr... The rest, as they say, is history...
Within Subject Variability

PHARMACOMETRICS

The Importance of Modeling Interooccasion Variability in Population Pharmacokinetic Analyses

M. O. Karlsson\textsuperscript{1,3} and L. B. Sheiner\textsuperscript{1,2,4}

Karlsson MO, Sheiner LB. The importance of modeling interoccasion variability in population pharmacokinetic analyses. J Pharmacokinet Biopharm 1993;21(6):735-50
Clinical Pharmacology


Blood beats Urine

Clinical Estimation of Creatinine Clearance

LAWRENCE A. WHEELER, M.D., PH.D., AND LEWIS B. SHEINER, M.D.

Department of Laboratory Medicine and Division of Clinical Pharmacology, Department of Medicine, University of California, San Francisco, California

Understanding the Dose-Effect Relationship: Clinical Application of Pharmacokinetic-Pharmacodynamic Models

Nicholas H.G. Holford and Lewis B. Sheiner

Division of Clinical Pharmacology, Departments of Medicine and Pharmacy, Schools of Medicine and Pharmacy; and Department of Laboratory Medicine, School of Medicine, University of California, San Francisco, California
Drug Development


The QT Interval
Scientists but no Regulators


THE EFFECT OF QUINIDINE AND ITS METABOLITES ON THE
ELECTROCARDIOGRAM AND SYSTOLIC TIME INTERVALS:
CONCENTRATION—EFFECT RELATIONSHIPS

NICHOLAS H.G. HOLFFORD, PETER E. COATES, THEODORE W. GUEBERT,
SIDNEY RIEGELMAN & LEWIS B. SHEINER
Department of Medicine, Division of Clinical Pharmacology, Department of Pharmacy, and Department of Laboratory Medicine, University of California Medical Centre, San Francisco, California 94143
More efficient clinical trials through use of scientific model-based statistical tests

E. Niclas Jonsson, PhD, and Lewis B. Sheiner, MD  Uppsala, Sweden, and San Francisco, Calif
A Personal Memory

Goodbye
-- We enjoyed the ride