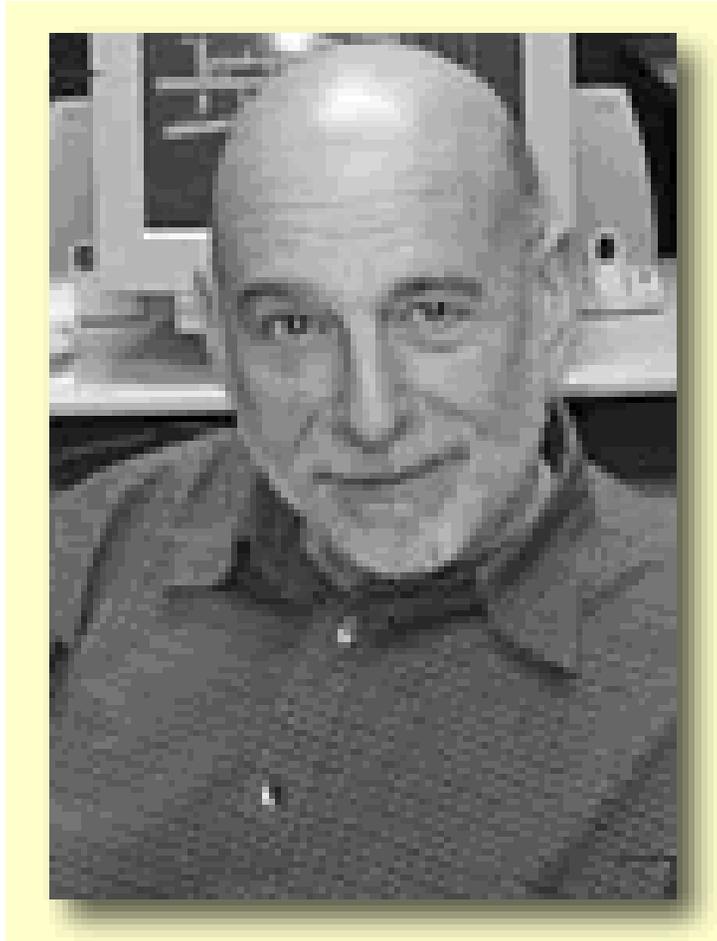


# Lewis B Sheiner



# 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
    - <http://www.lewissheiner.com/>

# How did Michael see him?

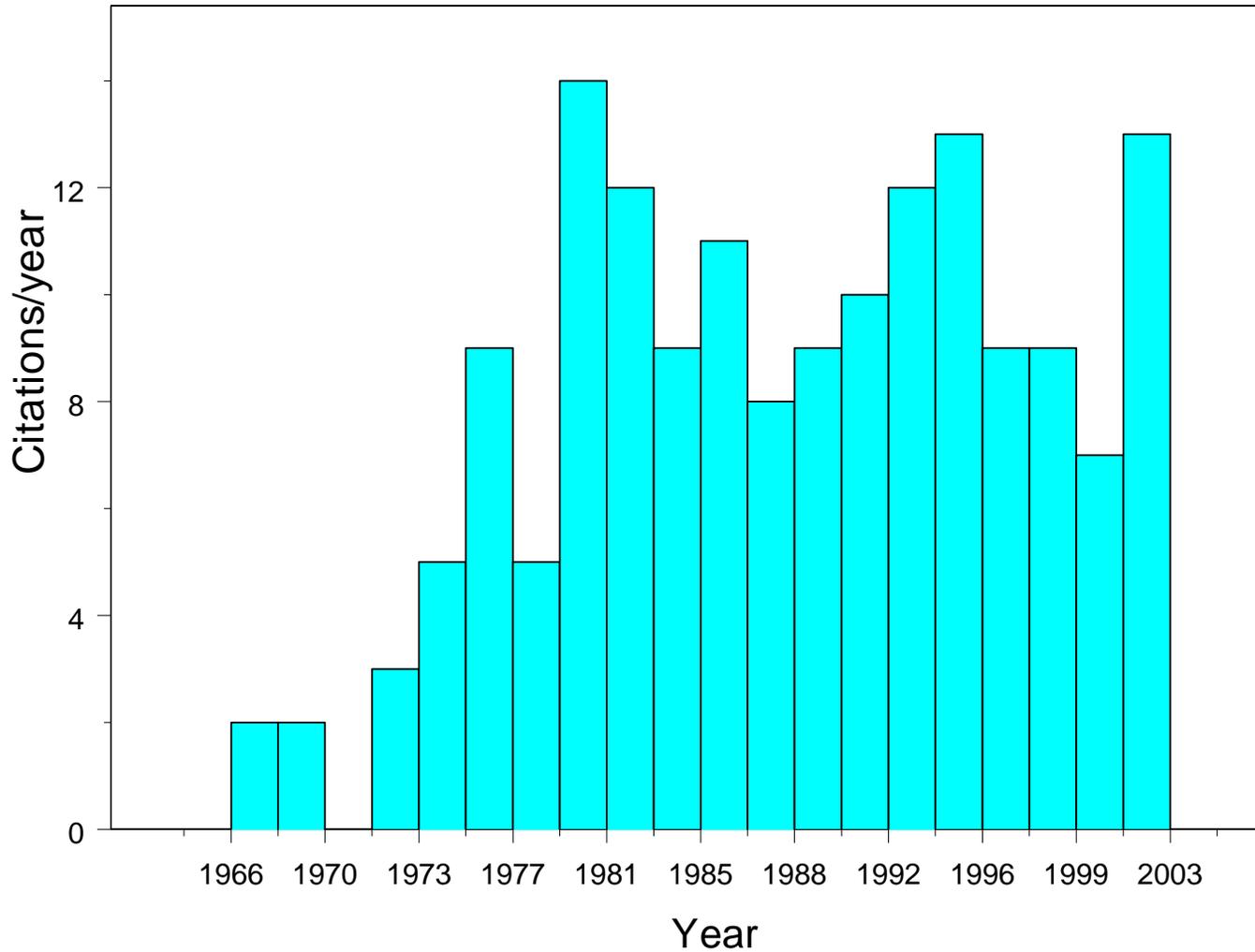
- “He loved to think about models”
- “At home he spent a lot of time with his computer”
- “We only recently understood he was doing something in drug development”

# 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

# The Scholarly Record

10 a Year at Steady State



# Where did he start?

## Computer-Aided Long-Term Anticoagulation Therapy

LEWIS B. SHEINER\*

*Division of Computer Research and Technology, National Institutes of Health,  
Public Health Service, Department of Health, Education, and Welfare,  
Bethesda, Maryland 20014*

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)

# Pharmacometrics

1. Sheiner LB, Rosenberg B, Melmon KL. Modelling of individual pharmacokinetics for computer-aided drug dosage. *Comput Biomed Res* 1972;5(5):441-59.
2. Sheiner LB, Beal SL. *NONMEM Users Guide*. San Francisco: Division of Pharmacology: University of California; 1979.
3. Sheiner LB, Beal SL. Evaluation of methods for estimating population pharmacokinetics parameters. I. Michaelis-Menten model: routine clinical pharmacokinetic data. *Journal of Pharmacokinetics & Biopharmaceutics* 1980; 8(6):553-71.
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# The Birth of Population PK

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

## **Modelling of Individual Pharmacokinetics for Computer-Aided Drug Dosage\***

LEWIS B. SHEINER, BARR ROSENBERG, AND KENNETH L. MELMON

*Departments of Medicine and Pharmacology, Division of Clinical Pharmacology,  
University of California San Francisco Medical Center, San Francisco, California 94122*

Received August 12, 1971

# “The rest, as they say, is history...”

Date: Thu, 09 Oct 2003 20:38:35 -0700  
From: "Lewis B. Sheiner" <lewis@c255.ucsf.edu>  
To: Nick Holford <n.holford@auckland.ac.nz>

*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 Interoccasion Variability in Population Pharmacokinetic Analyses**

M. O. Karlsson<sup>1,3</sup> and L. B. Sheiner<sup>1,2,4</sup>

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

# Clinical Pharmacology

1. Sheiner LB. Computer-aided long-term anticoagulation therapy. *Comput Biomed Res* 1969;2(6):507-18.
2. Sheiner LB, Tozer T. Clinical pharmacokinetics: The use of plasma concentrations of drugs. In: Melmon K, Morelli H, editors. *Clinical Pharmacology: Basic Principles of Therapeutics*. New York: Macmillan; 1978. p. 71-109.
3. Sheiner LB, Beal SL, Rosenberg B, Marathe VV. Forecasting individual pharmacokinetics. *Clinical Pharmacology and Therapeutics* 1979;25(9):294-305.
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5. Sheiner LB, Beal SL. Bayesian Individualization of pharmacokinetics: Simple implementation and comparison with Non-Bayesian Methods. *J Pharm Sci* 1982;71(1344-48)
6. Sheiner LB. Clinical pharmacology and the choice between theory and empiricism. *Clinical Pharmacology & Therapeutics* 1989;46(6):605-15.
7. Sheiner LB, Holford NHG. Determination of maximum effect. *Clinical Pharmacology & Therapeutics* 2002;71(4):304.

# 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*

Wheeler LA, Sheiner LB. Clinical estimation of creatinine clearance. Am J Clin Pathol 1979;72(1):27-32.

# Best Seller

Clinical Pharmacokinetics 6: 429-453 (1981)

0312-5963/81/0011-0429/\$06.25/0

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## **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

1. Sheiner LB, Benet LZ. Premarketing observational studies of population pharmacokinetics of new drugs. *Clinical Pharmacology & Therapeutics* 1985;38(5):481-487.
2. Sheiner LB, Beal SL, Sambol NC. Study designs for dose-ranging. *Clinical Pharmacology & Therapeutics* 1989;46(1):63-77.
3. Sheiner LB, Hashimoto Y, Beal SL. A simulation study comparing designs for dose ranging. *Statistics in Medicine* 1991;10:303-321.
4. Sheiner LB. The intellectual health of clinical drug evaluation. *Clinical Pharmacology & Therapeutics* 1991;50(1):4-9.
5. Sheiner LB. A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data. *Clinical Pharmacology & Therapeutics* 1994;56(3):309-22
6. Sheiner LB. Learning versus confirming in clinical drug development. *Clinical Pharmacology & Therapeutics* 1997;61(3):275-91.
7. Sheiner LB. Is intent-to-treat analysis always (ever) enough? *Br J Clin Pharmacol* 2002;54(2):203-11.

# The QT Interval

## Scientists but no Regulators

*Br. J. clin. Pharmac.* (1981), **11**, 187–195

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

**NICHOLAS H.G. HOLFORD, PETER E. COATES, THEODORE W. GUENTERT, 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

# Drug Development Science

## CLINICAL PHARMACOLOGY & THERAPEUTICS

VOLUME 72 NUMBER 6

DECEMBER 2002

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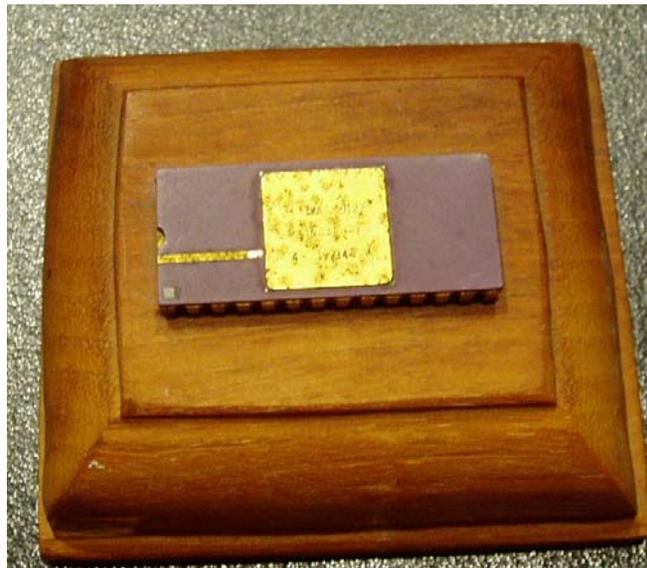
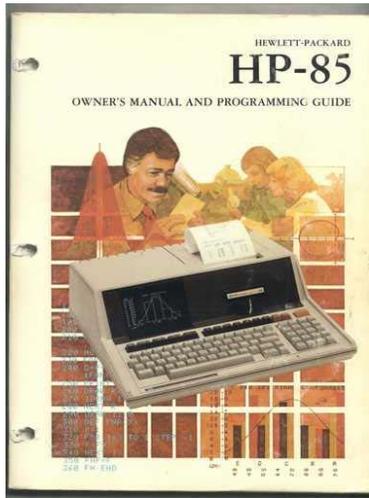
### COMMENTARY

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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



Sheiner LB. *ELSFIT Users Manual*. San Francisco, Calif: Division of Clinical Pharmacology of the University of California; 1983. Technical report.

Goodbye  
-- We enjoyed the ride

