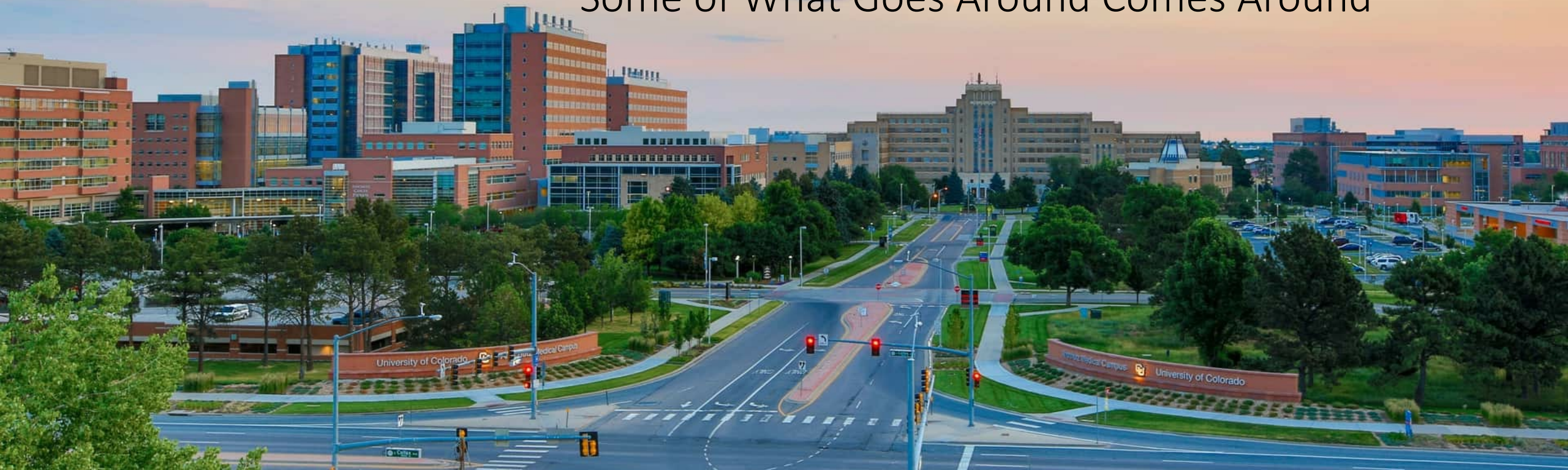
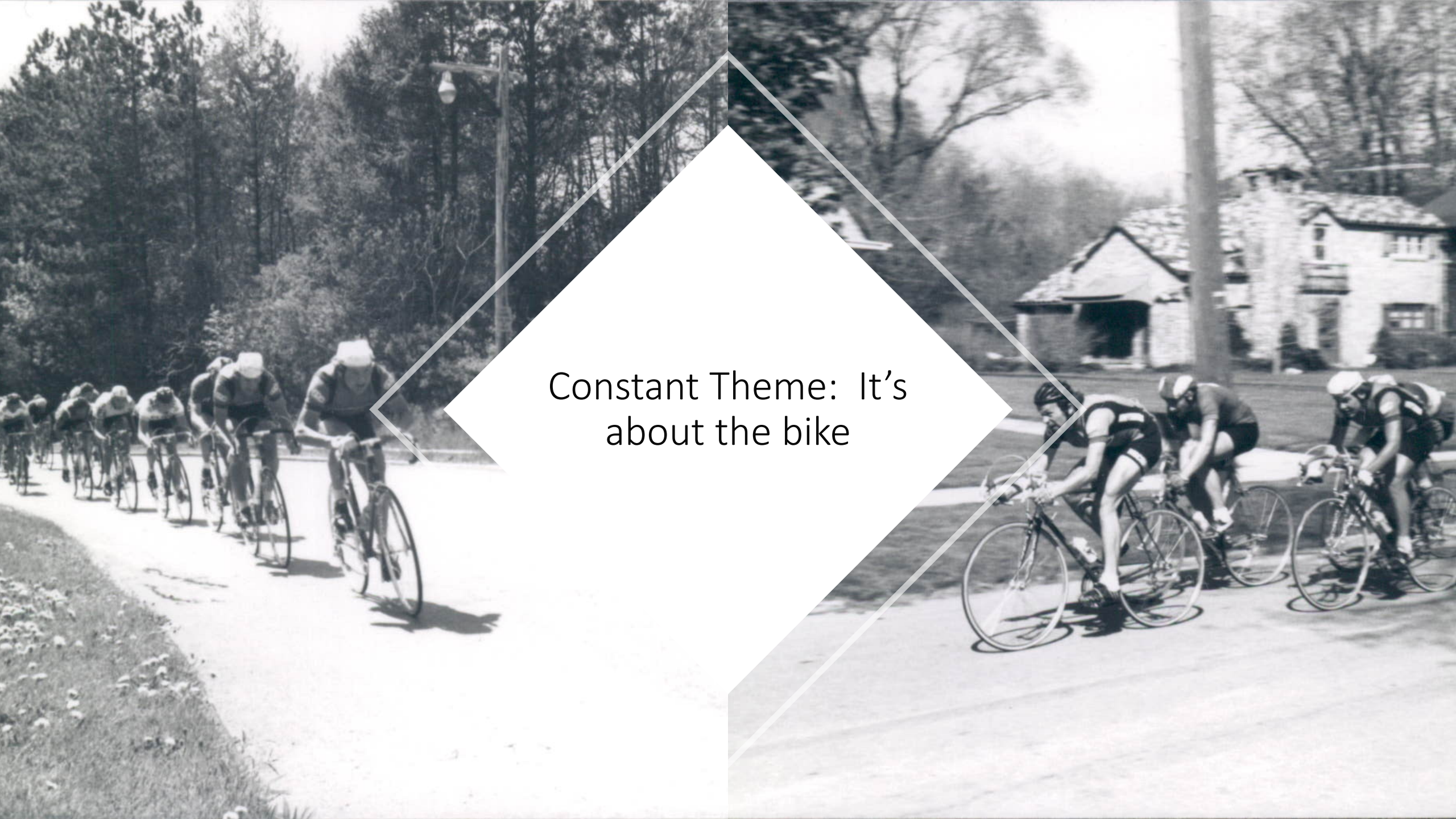
Anesthesiology
SCHOOL OF MEDICINE
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

A Life in Anesthetic Pharmacology

Some of What Goes Around Comes Around





Constant Theme: It's about the bike

Northwestern Medicine®

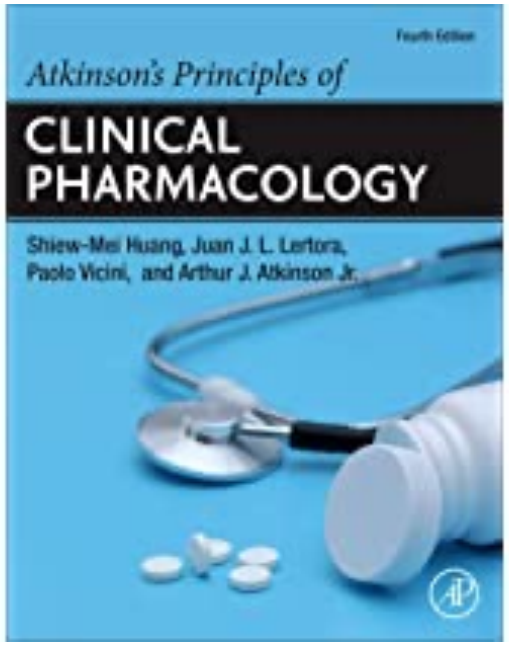
The Hook

The Hook *(the bait)*

- All Sr Medical Students at Northwestern, applying to Anesthesiology residencies, were strongly encouraged to enroll in the Clinical Pharmacokinetics seminar that was offered to Pharmacology graduate students
  - For my Med School class it was Rod Eckenhoff and me
  - Later, while I was the TA for the class, it included
    - Mark Derschwitz, MD, PhD
    - Evan Kharasch, MD, PhD
    - Chris Stock, MD

The class was assigned math-intensive homework for which our tools consisted of semi-log graph paper and a calculator

The Hook


Fourth Edition
Atkinson's Principles of
CLINICAL
PHARMACOLOGY
Shiew-Mei Huang, Juan J. L. Lertora,
Paolo Vicini, and Arthur J. Atkinson Jr.

Overview

About Us

Programs

Clinical Research Training

Funding Opportunities

Resources

Biomedical Translational Research Information System (BTRIS)

Scientific Review Process

Searching the NIH Website

Staff

NIH Associate Director for Clinical Research

Staff Directory

Principles of Clinical Pharmacology

Description | Course Information | Registration | Contact Us | Course Login

General Information

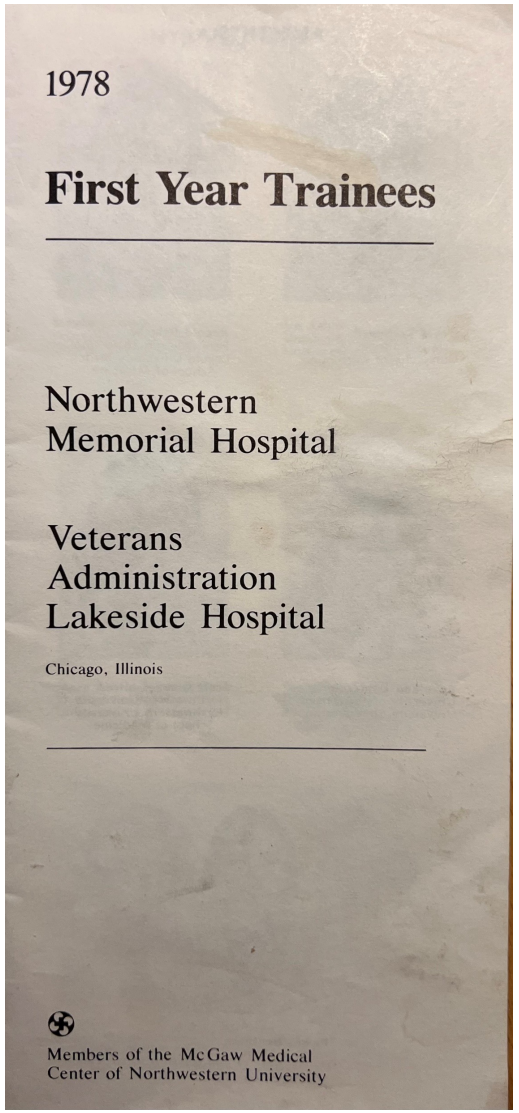
1. This course is offered at no cost.[1] The course is conducted via an online format through recorded lectures and activities. Progression through the course is self-paced and there is no live attendance requirement.

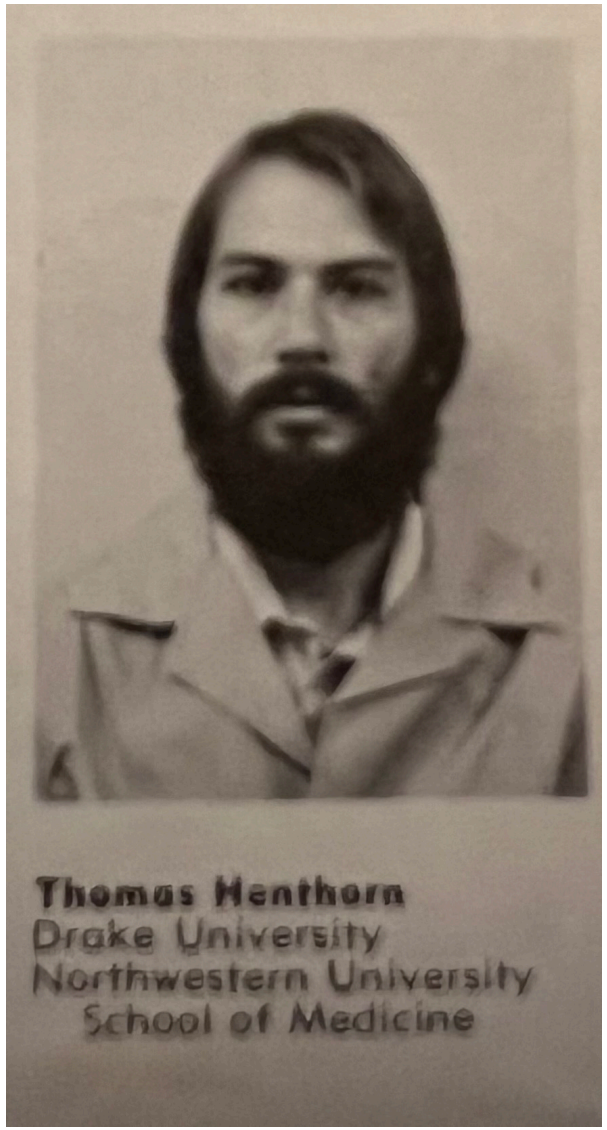
2. The course is divided into 7 modules, each with a brief introductory video. Divided amongst the modules are 48 core lectures which are each associated with a case study or post-lecture activity. The course syllabus, videos, handouts, case studies, and other material will be posted to the participant website.

3. Although not required [2], **each registered participant to expected to take the online final exam**, which consists of 25-50 multiple choice questions. Participants are permitted to use course materials during the final exam.

4. An electronic Certificate of Completion is awarded to each registered participant who achieves a score of 70% or higher on the final exam.

The Hook

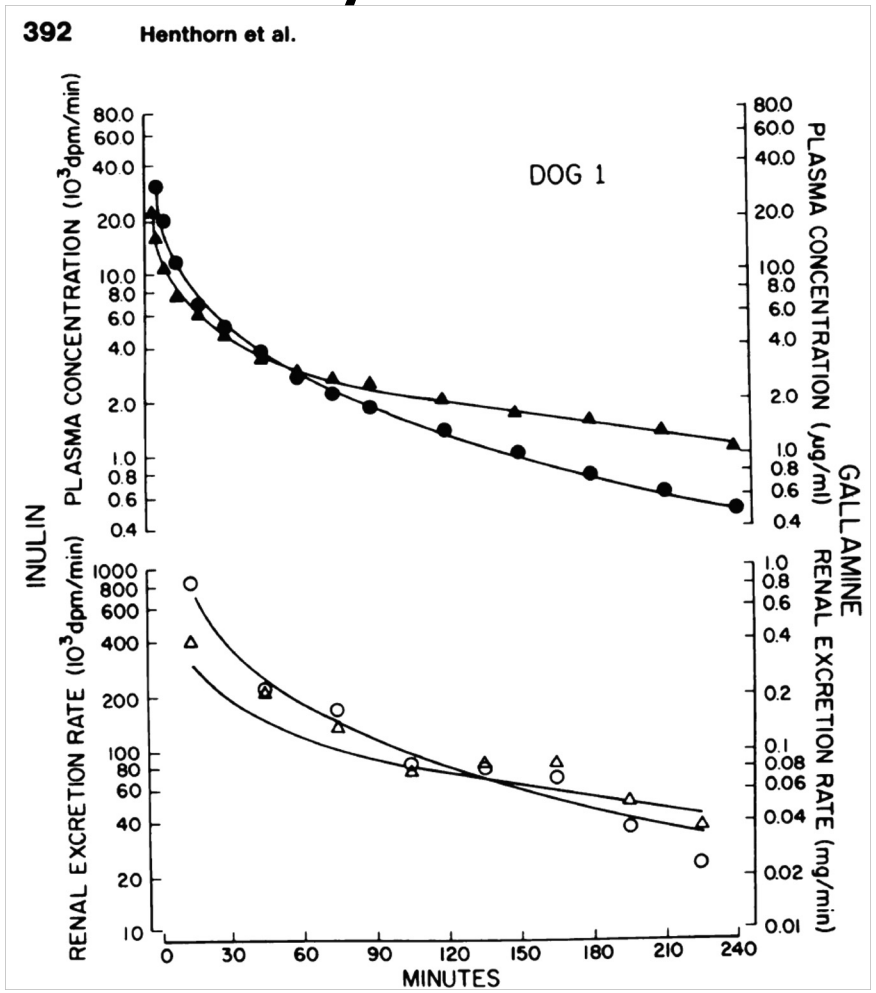

1978
First Year Trainees
Northwestern
Memorial Hospital
Veterans
Administration
Lakeside Hospital
Chicago, Illinois
Members of the McGaw Medical
Center of Northwestern University

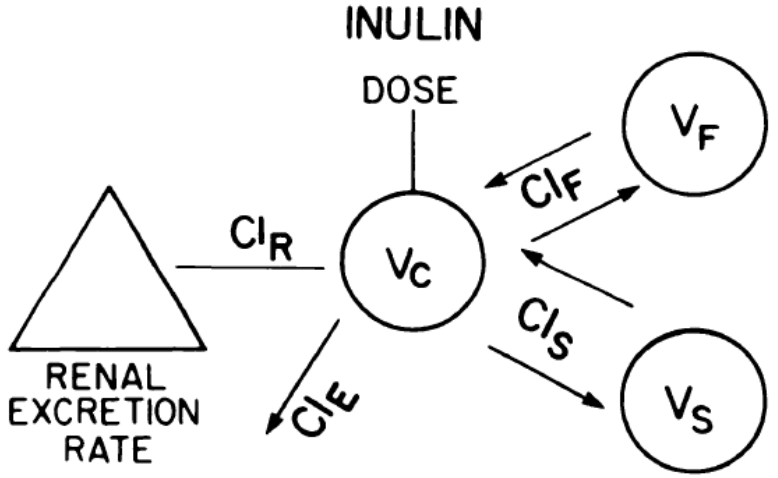

Thomas Henthorn
Drake University
Northwestern University
School of Medicine

The Hook

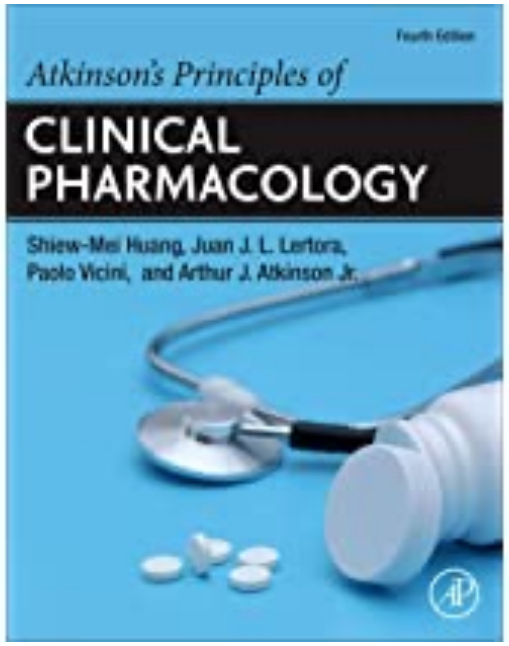
- Clinical Base year elective rotation in Clinical Pharmacology
  - Every day was a ‘study day’ with one of the projects of the labs’ three PIs
    - Samples were spun and analyzed, usually by HPLC, the day they were collected
    - Art’s motto: “***Science is the triumph of rigor over reason***”
  - Mid-month, an immunology fellow who had just given birth showed up ready to do the planned-for-the-future Theophylline Breast Milk study that week
    - Perception that asthmatics had ‘jittery’ babies
  - Everyone in the lab was too busy to study her, so the clin pharm fellow, G Paul Stec, told Art, “Let Henthorn do it.”
    - Even though no protocol had been developed

Kidneys on the chest





The Hook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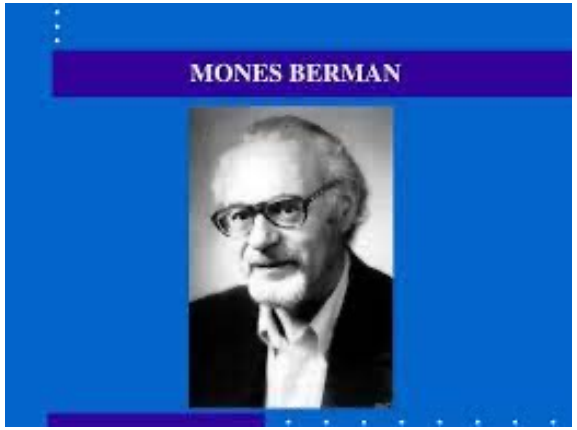
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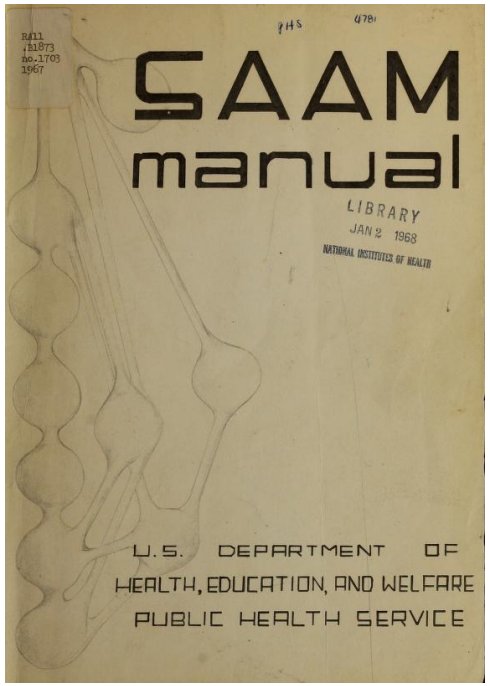
SAAM
manual
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NATIONAL INSTITUTES OF HEALTH
U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

FOREWORD

SAAM is a digital computer program developed for the analysis of data in terms of models. It permits simulation and data fitting, and contains various techniques encountered in model building.

Although developed primarily for biological systems and more specifically for kinetic models, the program is of general utility. It differs from other simulation and analysis systems in that the "language" is geared towards the bio-medical "system" investigator and its elements are direct counterparts of techniques and conceptualizations used by the experimenter.

Model building is complicated and requires--in addition to intuition and speculation--knowledge of mathematical and statistical procedures and their limitations. This manual is only a brief description of the procedures used in SAAM and some of their limitations. For additional background material the reader is referred to the reference section.

SAAM is a large, complex program and is continuously being extended and revised. Like any large program, SAAM is difficult to completely debug, and it probably contains some undetected errors, even through it has been in use since 1959. It is recommended, therefore, that the user run some test problems of his own, the answers to which he knows. We also invite users to call to our attention any questionable results which may be attributed to the program and not to errors in the data.

This manual is for the SAAM 23 version of the program. Revisions and updates will appear occasionally, and will be sent to those who request that their names be placed on our mailing list. A new version of SAAM is

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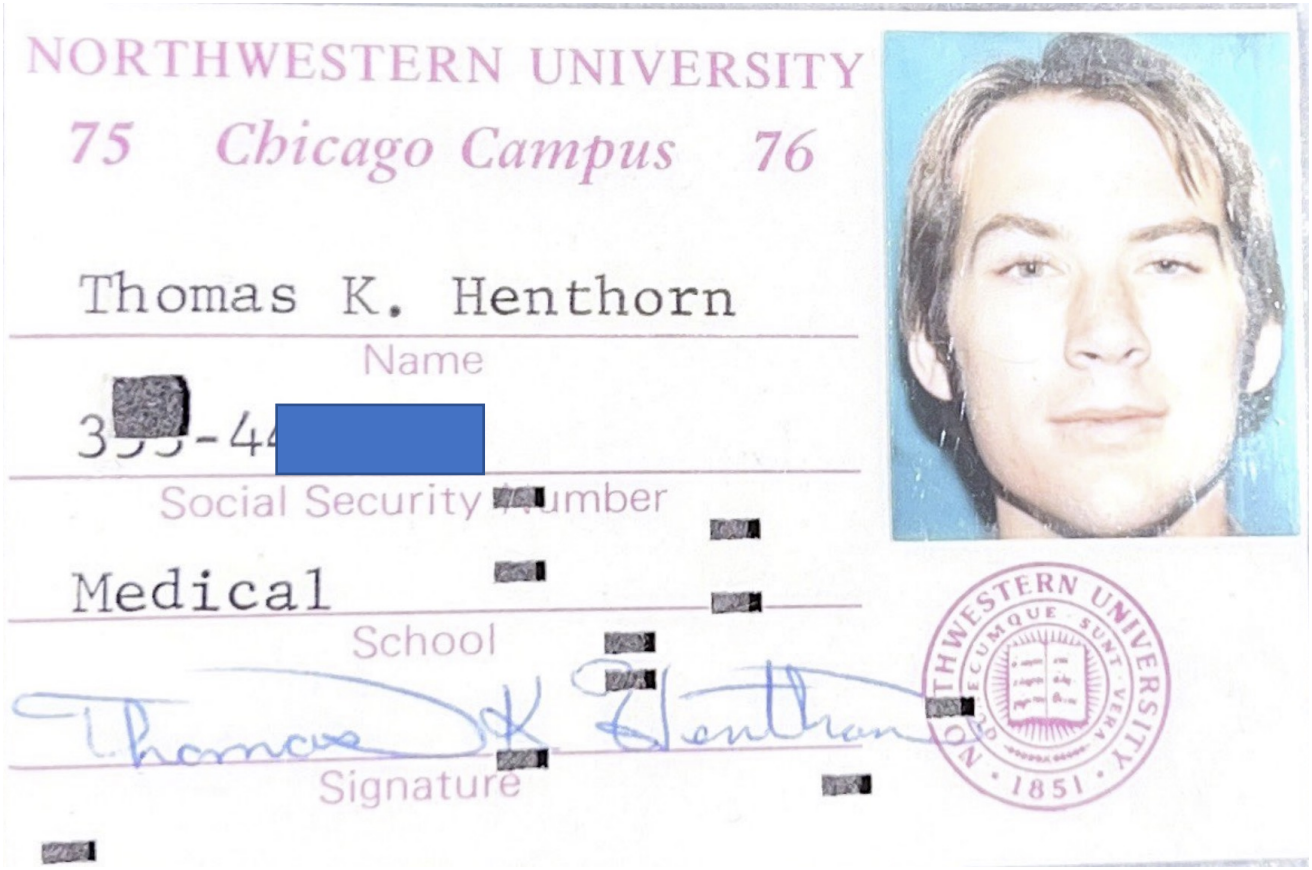
The Era


NORTHWESTERN UNIVERSITY

75 Chicago Campus 76

Thomas K. Henthorn

Name

[redacted]-44[redacted]

Social Security Number

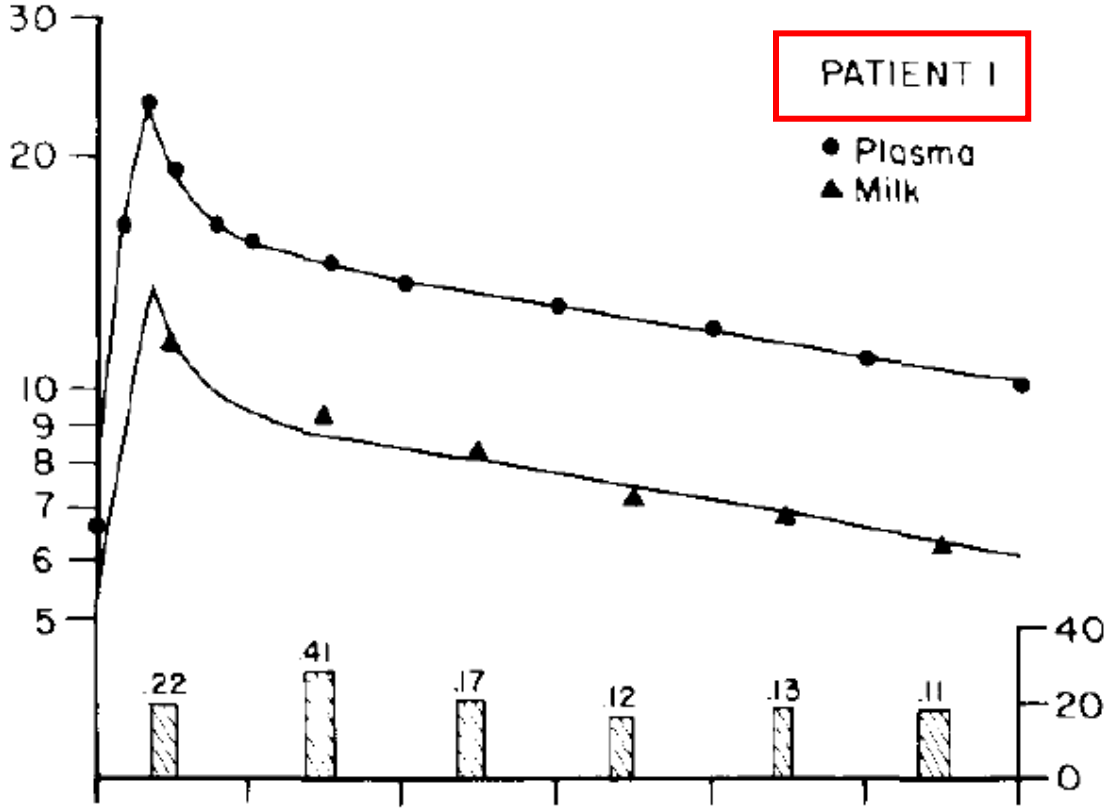
Medical

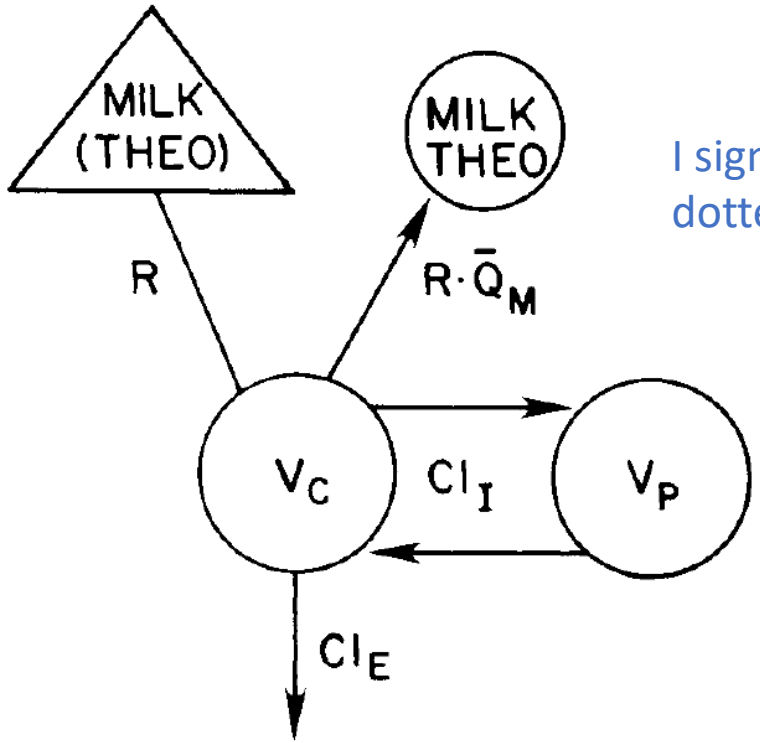
School

[redacted]

Signature

Not Kidneys, but Dialysis Chambers





I signed on the dotted line!

Clin. Pharmacol. Ther.
September 1980

Physiologic Basis of Pharmacokinetic Models

THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 222, No. 2

Printed in U.S.A.

Heterogeneity of Interstitial Fluid Space Demonstrated by Simultaneous Kinetic Analysis of the Distribution and Elimination of Inulin and Gallamine[1]

THOMAS K. HENTHORN, MICHAEL J. AVRAM, MARILYNN C. FREDERIKSEN and ARTHUR J. ATKINSON, JR.

Clinical Pharmacology Center and Departments of Anesthesia, Pharmacology and Medicine, Northwestern University Medical School, Chicago, Illinois

Accepted for publication May 10, 1982

Plasma gallamine concentrations were measured by the spectrofluorometric method of Ramzan and colleagues (1980). Their modification of this method was used to measure gallamine concentrations in by spectrophotometric detection with the absorbance set at 560 nm.

On Wednesday, Octobe
presented with the You
Year Award at the 201
Dinner held at The Art
Modern Wing.

Ane
SCHO
UNIVE
ANSC

Dr. Jaimie Henthorn (She/Her) · 1st

Director of Academic Innovation Programs at University of Colorado System

Denver, Colorado, United States · Contact info

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Anesthesiology
SCHOOL OF MEDICINE
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Physiologic Basis of Pharmacokinetic Models

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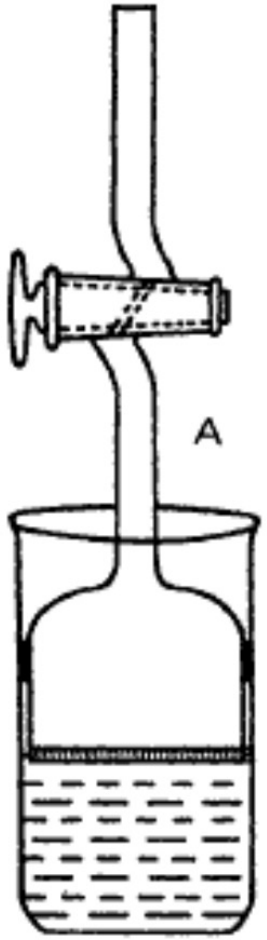
Physiologic Basis of Pharmacokinetic Models



Diffusion coefficient (volume/time)

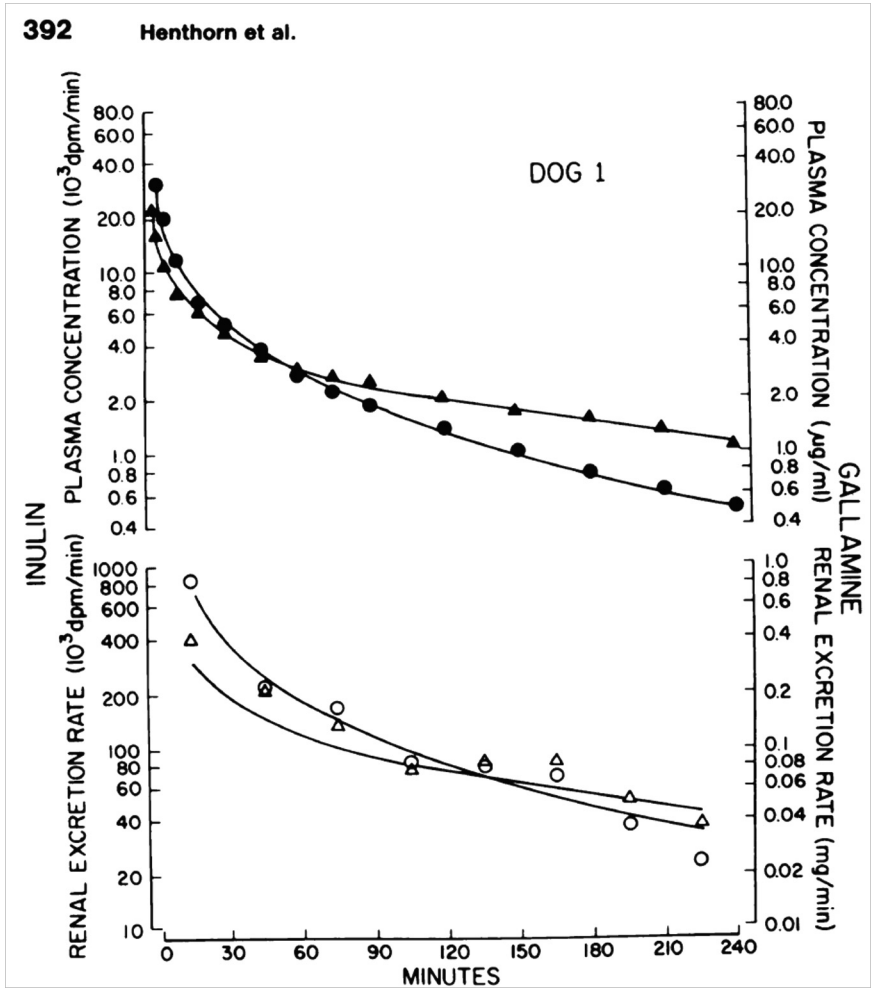
Renkin Equation

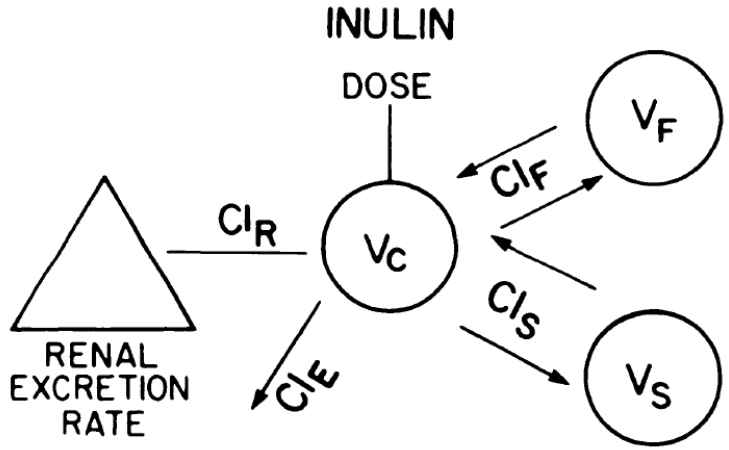
$$Cl = Q(1 - e^{-P/Q})$$

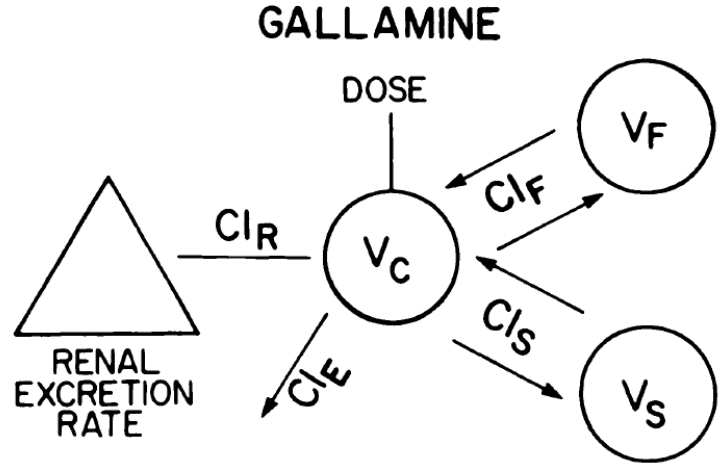
$$Cl_B = Cl_P/[(1\text{-}Hct) + Hct(RBC/Plasma)]$$

$$P_F = Q_F \ln[Q_F/(Q_F - Cl_F)]$$
$$P_S = Q_S \ln[Q_S/(Q_S - Cl_S)]$$

Physiologic Basis of Pharmacokinetic Models







Physiologic Basis of Pharmacokinetic Models

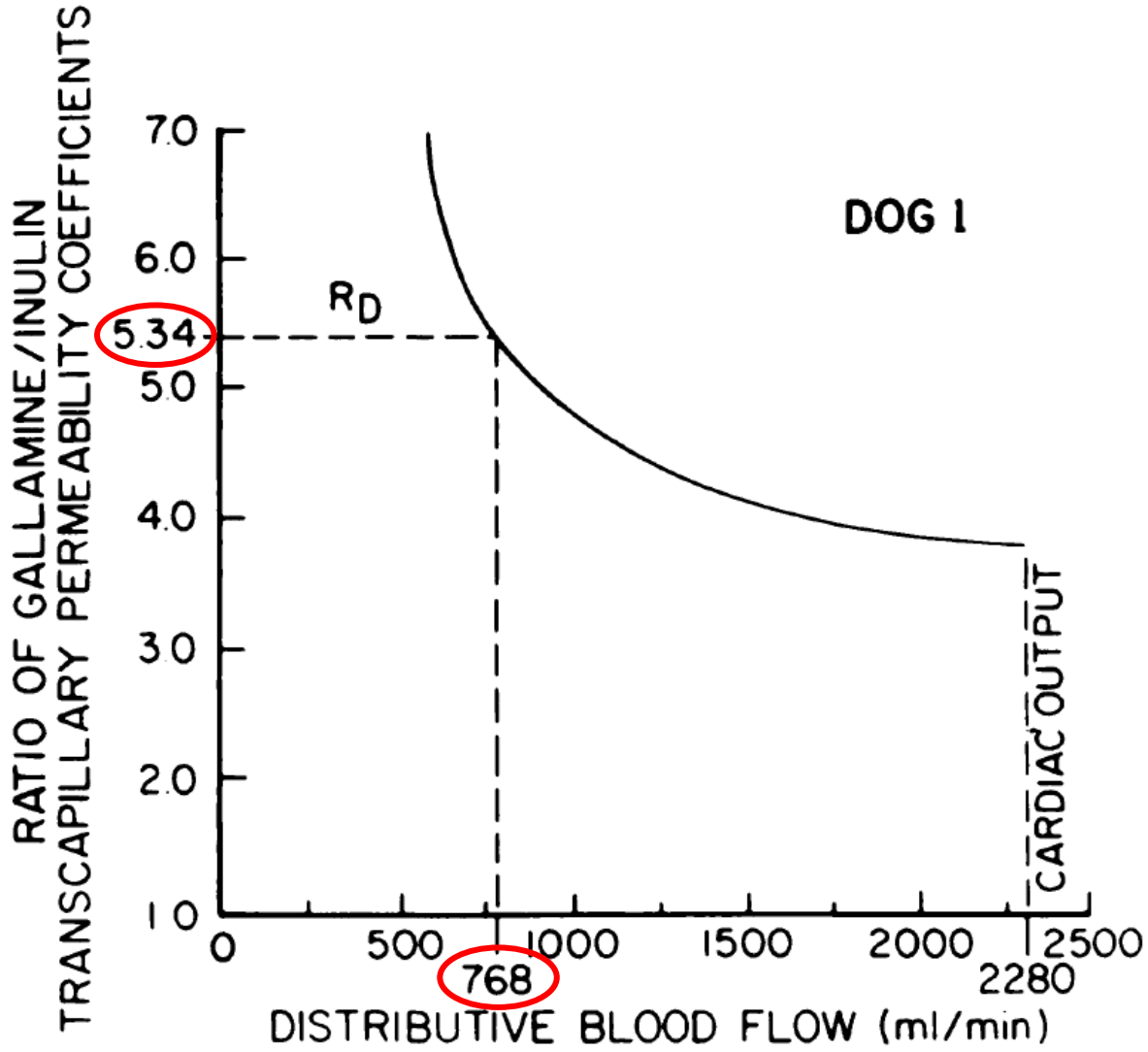
TABLE 1

Gallamine and inulin pharmacokinetic parameters

Dog No.	V_C	V_F		V_S		V_T		Cl_E		Cl_F (Blood)[a]		Cl_S (Blood)[a]	
		Gallamine	Inulin	Gallamine	Inulin	Gallamine	Inulin	Gallamine	Inulin	Gallamine	Inulin	Gallamine	Inulin
	l	*l*		*l*		*l/kg*		*ml/min*		*ml/min*		*ml/min*	
1	1.01	1.22	1.00	3.60	2.55	0.30	0.23	36.8	62.6	464.2	133.5	101.4	54.2
2	1.09	1.34	1.46	1.90	1.60	0.27	0.26	49.2	65.3	958.1	236.6	110.3	43.4
3	0.81	0.89	0.74	1.28	1.26	0.19	0.21	32.8	43.6	607.9	158.1	98.0	43.4
4	0.77	0.93	0.71	1.24	1.54	0.19	0.20	32.8	44.0	430.6	125.8	66.5	44.7
5	0.86	0.63	0.45	1.32	1.21	0.21	0.19	23.0	36.8	415.4	105.7	89.7	50.4
6	0.80	0.89	0.82	1.21	1.57	0.19	0.21	37.3	50.5	429.2	150.5	69.8	38.8
Mean	0.89	0.98	0.86	1.76	1.60	0.23	0.22	35.3	50.3	550.9	151.7	89.3	45.8
±S.D.	0.13	0.26	0.34	0.94	0.49	0.05	0.03	8.5	11.3	211.3	45.5	17.7	5.5

[a] Intercompartmental clearances are referenced to whole blood as described under "Methods."

Physiologic Basis of Pharmacokinetic Models



Physiologic Basis of Pharmacokinetic Models

TABLE 2

Kinetically determined blood volumes compared with expected values

Dog No.	Hct	Weight	Blood Volume	
			Observed[a]	Expected[b]
	%	kg	l	l
1	29.0	19.5	1.42	1.72
2	35.0	15.9	1.67	1.40
3	42.5	14.5	1.41	1.28
4	37.0	15.0	1.12	1.32
5	31.0	13.6	1.25	1.20
6	41.0	15.0	1.36	1.32
Mean	35.9	15.6	1.37	1.37
±S.D.	5.4	2.1	0.19	0.18

[a] Calculated from central compartment volume and Hct.
[b] Estimated from body weight (Reeve *et al.*, 1953).

Karolinska Institutet: Huddinge Hospital

Lars Gustafsson

Julbocken

Physiologic Basis of Pharmacokinetic Models

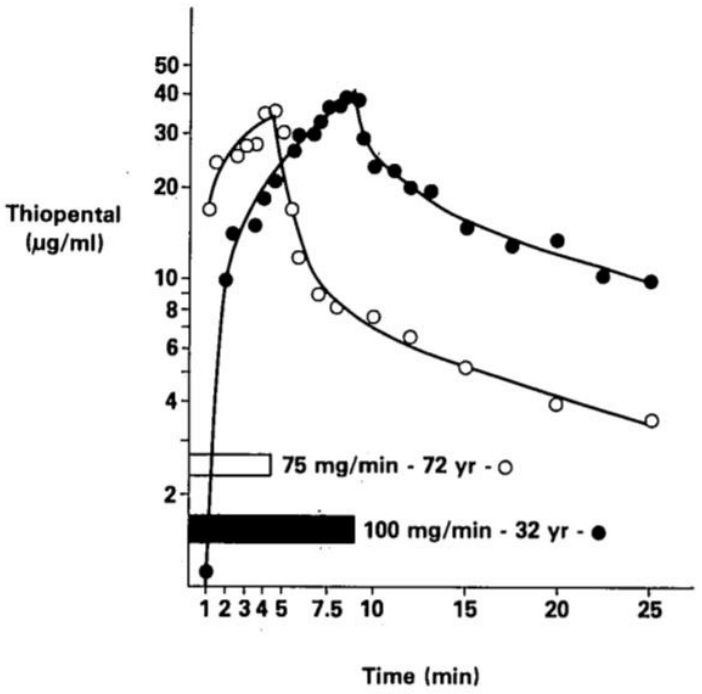


FIG. 5. Serum thiopental concentration (log scale) *versus* time for the young (filled circles and bars) and the elderly (unfilled circles and bars) patients shown in figure 3. All of the measured thiopental

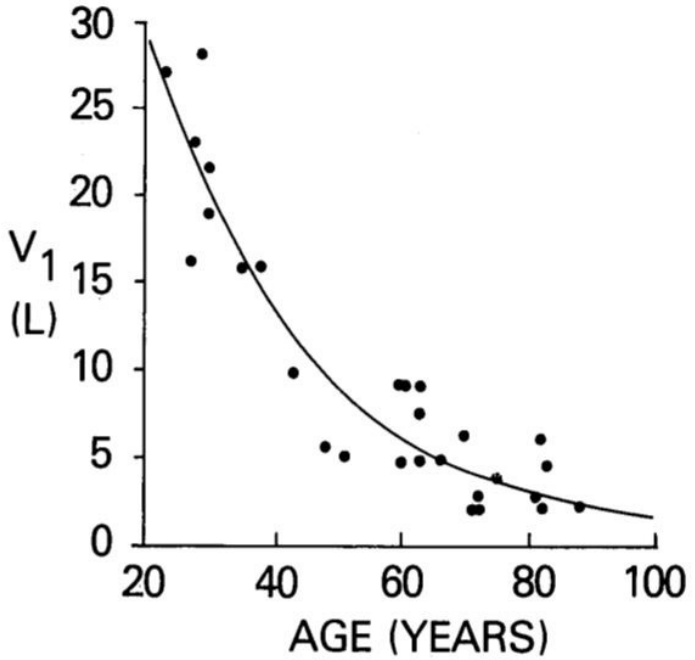


FIG. 6. Volume of the central compartment (V_1) *versus* age. The dots represent the V_1, derived from the pharmacokinetic analysis for each patient. The solid curve was derived using nonlinear regression of V_1 *versus* age to an exponential equation (see table 2).

Homer TD, Stanski DR. Anesthesiology, 1985

Physiologic Basis of Pharmacokinetic Models

Did somebody say physiology??

Experimental Design and Conduct
Keeper of ‘Real’

Laboratory Manager
Language Cop

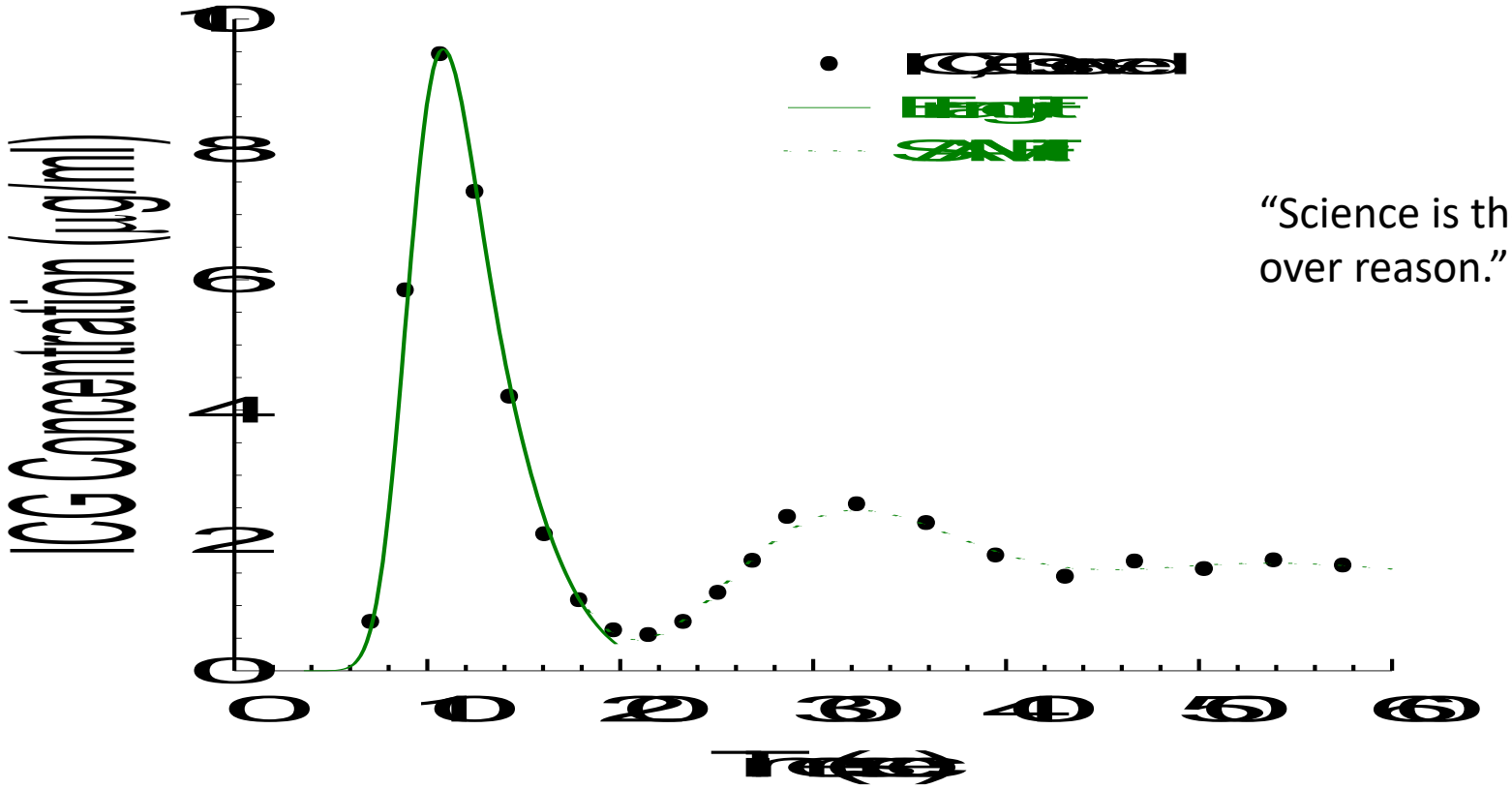
Protector

Anesthesia Pharmacokinetic Swat Team

Physiologic Basis of Pharmacokinetic Models Recirculatory *in vivo* pk experimental paradigm:

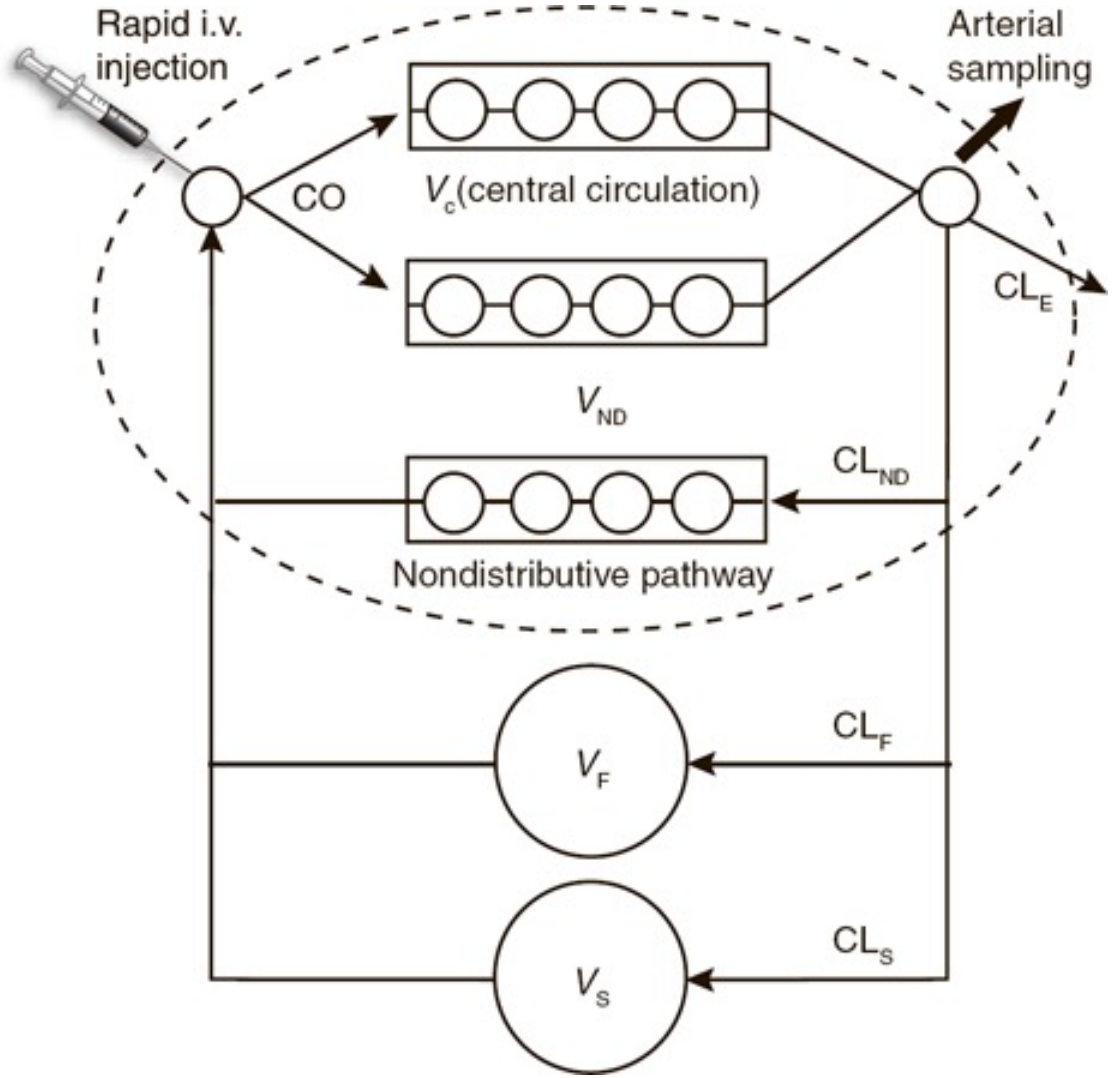
- Drug and physiologic markers
    - indocyanine green - intravascular space, mixing
    - antipyrine - total body water, flow-limited diffusion
    - e.g.,lidocaine – partitions to lung and other tissue
- Rapid central venous injection
- Nearly continuous arterial sampling
- Cross fingers that a model of the data could be constructed

Physiologic Basis of Pharmacokinetic Models



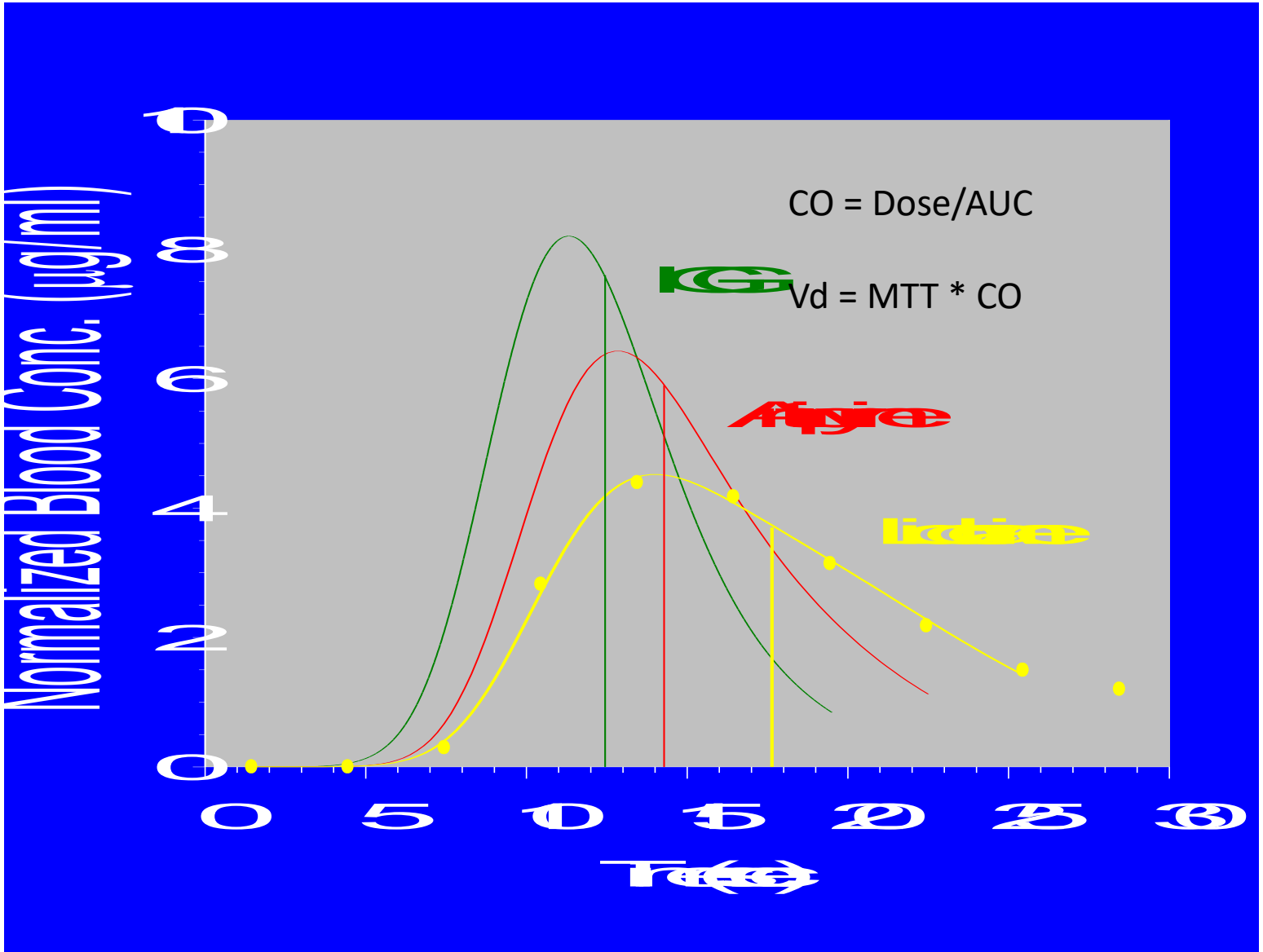
"Science is the triumph of rigor over reason."

Physiologic Basis of Pharmacokinetic Models



mtt = n/k

Physiologic Basis of Pharmacokinetic Models

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Tom Hertzhorn
Has completed the
Leadville Trail 100
Place Overall 100
Age Group MMC 5
Time 09.45.28
Race Director
Date August 15, 1998
Awarded in Leadville, Colorado

Physiologic Basis of Pharmacokinetic Models

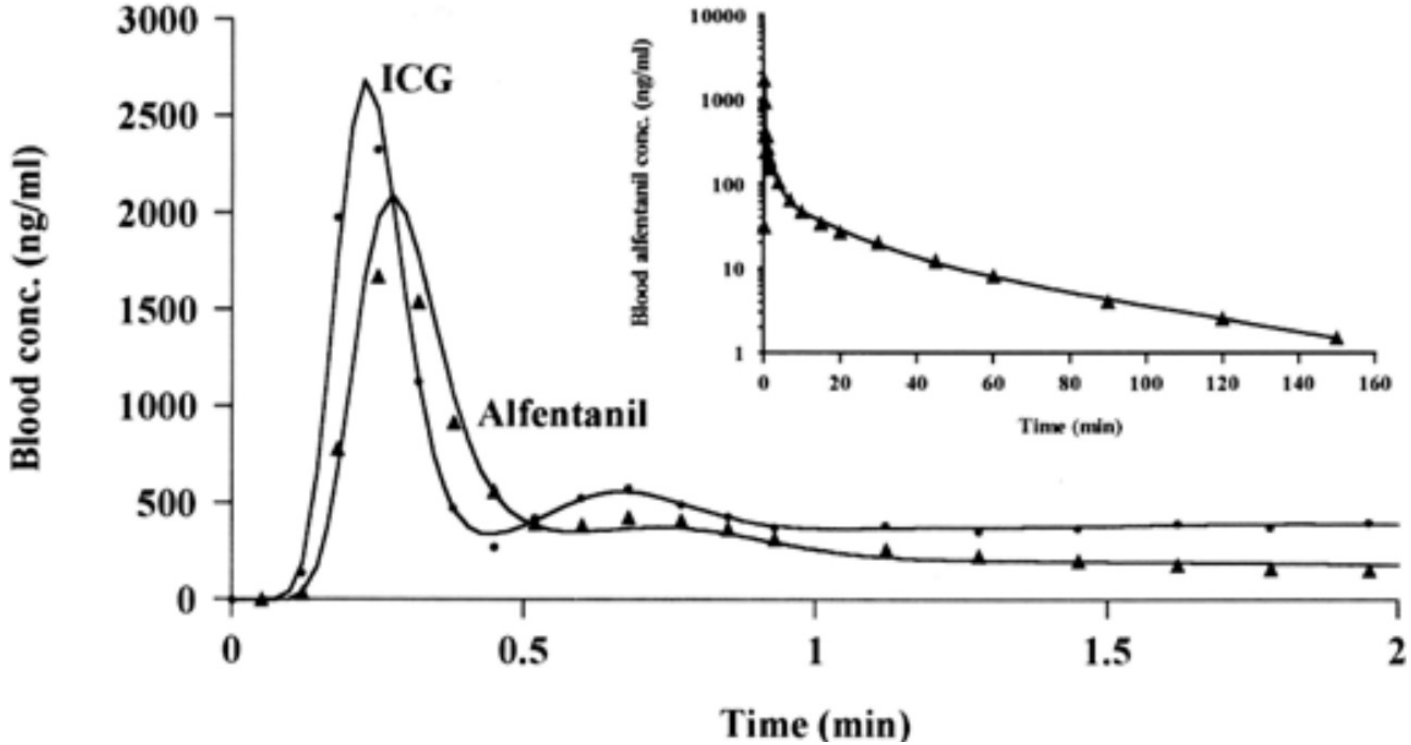
Laboratory Investigations | April 1999

Recirculatory and Compartmental Pharmacokinetic Modeling of Alfentanil in Pigs : The Influence of Cardiac Output FREE

Jette A. Kuipers, BSc; Fred Boer, MD, PhD; Erik Olofsen, MSc; Wim Olieman; Arie A. Vletter, BSc; Anton G. L. Burm, PhD; James G. Bovill, MD, PhD, FFARCSI

+ Author and Article Information

Anesthesiology April 1999, Vol. 90, 1146–1157.



2000-2016: Years as Department Chair, University of Colorado

Journal Club

Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits

Vesna Jevtovic-Todorovic, Richard E. Hartman, Yukitoshi Izumi, Nicholas D. Benshoff, Krikor Dikranian, Charles F. Zorumski, John W. Olney, and David F. Wozniak

Journal of Neuroscience 1 February 2003, 23 (3) 876-882; DOI: https://doi.org/10.1523/JNEUROSCI.23-03-00876.2003

INTERNATIONAL SOCIETY FOR ANAESTHETIC PHARMACOLOGY
ISAP

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UNIVERSITY OF COLORADO
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2000-2016: Years as Department Chair, University of Colorado

SESSION #2 (10:50 – 12:15)

Theme: *Alzheimer's Disease*

Moderators: **Vesna Jevtovic-Todorovic, MD, PhD, MBA**
Professor of Anesthesiology and Neuroscience
University of Virginia
Charlottesville, NC

Mohamed Naguib, MD
Professor
Department of General Anesthesiology
Cleveland Clinic, Institute of Anesthesiology
Cleveland, OH

10:50 – 11:20 ***Anesthetic Modulation of Neuroinflammation in Alzheimer's Disease***
Rod Eckenhoff MD
Professor of Anesthesiology and Critical Care
University of Pennsylvania
Philadelphia, PA

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Stanford University School of Medicine
Stanford, CA USA

2017 President
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2016 President
Vesna Jevtovic -Todorovic, MD, PhD, MBA
University of Colorado
Englewood, CO USA

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James M. Sonner, MD
University of California, San Francisco
Palo Alto, CA USA

2014 President
Yuguang Huang, MD
Peking Union Medical College Hospital
Beijing, CHINA

2016 - : Anesthesiology Department Chair

Airways October Newsletter

Department of Anesthesiology
UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

AIRWAYS

NEWSLETTER

Welcome to Fall, a very busy time of year for all of us. Yet, even with tight schedules, I hope you take some time to read through this issue to capture all the amazing activities taking place across teams and our department.

First, I'd like to share the incredible news that an endowment has been made in honor of Dr. Robert H. Friesen, MD, Professor Emeritus, University of Colorado Department of Anesthesiology. The Chair will be called the Robert Friesen, MD Endowed Chair in Anesthesiology. Please click on the article below to learn more about this

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Piet Hein van der Graaf, PhD – LU, Pharmacology

Albert Dahan, MD, PhD and Erik Olofsen, PhD – LUMC, Anesthesiology

MARNIX J. SIGTERMANS

Ketamine's second life
Treatment of acute and chronic pain

Chronic pain is a widespread condition in the general population. For this reason, chronic pain management has received increased attention in recent years, both in clinical practice and in scientific research.
This thesis describes a series of experiments which studied the efficacy and safety of ketamine in subanesthetic doses. Both healthy volunteers and chronic pain patients were recruited for these studies.
The specific chronic pain condition studied in these experiments was *Complex Regional Pain Syndrome type 1*, which is characterized by chronic pain affecting one or more extremities. It is very difficult to treat this condition with current pharmacotherapeutic interventions. However, one of the studies in this thesis showed that a continuous ketamine infusion, lasting for several days, can have a prolonged effect in reducing pain scores for up to several weeks (despite rapidly decreasing ketamine plasma concentrations after termination of the infusion).
In addition, experiments in both healthy volunteers and patients were performed to study the pharmacokinetics and pharmacodynamics of ketamine in subanesthetic doses.

9 789090 254838

European Journal of Pain 15 (2011) 258–267

Contents lists available at ScienceDirect

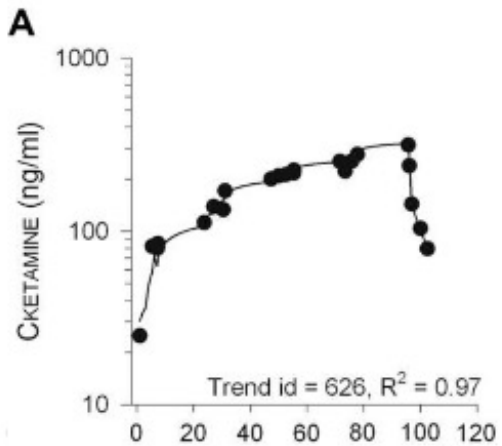
European Journal of Pain

journal homepage: www.EuropeanJournalPain.com

Population pharmacokinetic–pharmacodynamic modeling of ketamine-induced pain relief of chronic pain

Albert Dahan [*,1], Erik Olofsen [1], Marnix Sigtermans, Ingeborg Noppers, Marieke Niesters, Leon Aarts, Martin Bauer, Elise Sarton

Department of Anesthesiology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands

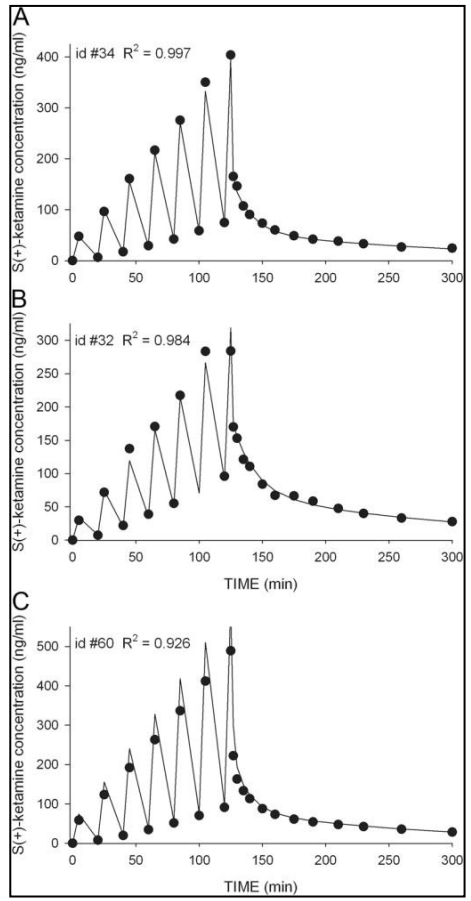


International Society for Anaesthetic Pharmacology

Anesthetic Pharmacology and Preclinical Pharmacology Section Editor: **Marcel E. Durieux**
Clinical Pharmacology Section Editor: **Tony Gin**

The Dose-Dependent Effect of S(+)-Ketamine on Cardiac Output in Healthy Volunteers and Complex Regional Pain Syndrome Type 1 Chronic Pain Patients

Erik Olofsen, MSc, Marnix Sigtermans, MD, PhD, Ingeborg Noppers, MD, PhD, Marieke Niesters, MD, Msc, Rene Mooren, MSc, Martin Bauer, MD, Leon Aarts, MD, PhD, Elise Sarton, MD, PhD, and Albert Dahan, MD, PhD

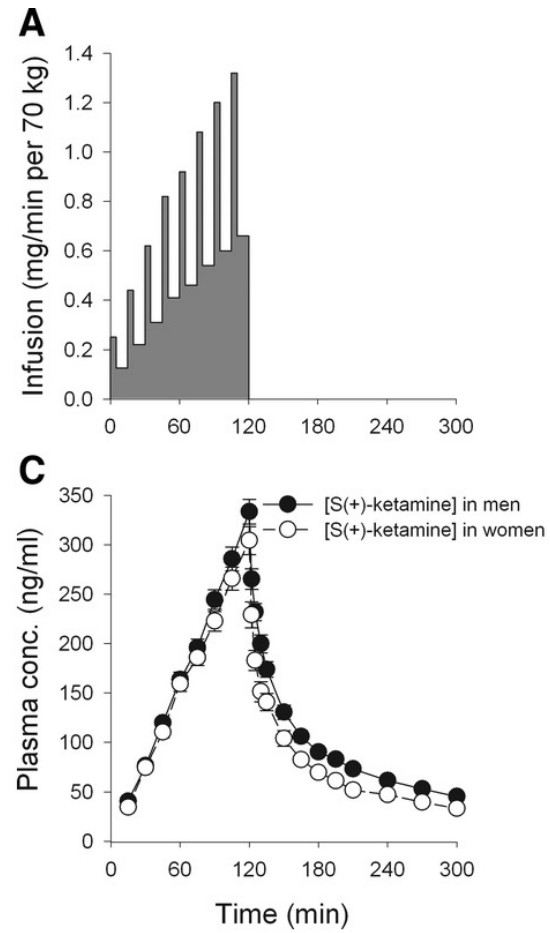


Anesthesiology 2009; 111:892–903

S(+)-ketamine Effect on Experimental Pain and Cardiac Output

A Population Pharmacokinetic-Pharmacodynamic Modeling Study in Healthy Volunteers

Marnix Sigtermans, M.D., Albert Dahan, M.D., Ph.D.,† René Mooren, B.Sc.,‡ Martin Bauer, M.D.,§ Benjamin Kest, Ph.D.,‖ Elise Sarton, M.D., Ph.D.,§ Erik Olofsen, M.Sc.#*



NONMEM Users Guide - Part V

Introductory Guide

November 2013

by

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Chapter 2 - NONMEM Examples

1. What This Chapter is About

In this chapter, two examples of the use of NONMEM will be given. The first estimates pharmacokinetic parameters of an individual from his data; the second estimates so-called population parameters from data from a group of individuals. The examples serve to introduce NONMEM notation, input and output, and to provide an idea of what is possible using the system. The second example will be discussed again in Chapter 11.

2. An Individual's Theophylline Kinetics

Figure 2.1 shows the input used to fit a model to observations of theophylline plasma concentration *vs* time in a single individual after a single dose of 320 mg.

```
$PROB  SIMPLE NONLINEAR REGRESSION - THEOPHYLLINE
$INPUT ID AMT TIME DV
$DATA  P2DATA
$SUBROUTINE ADVAN2
$PK
 KA=THETA(1)
 K=THETA(2)
 V=THETA(3)
 S2=V
$ERROR
 Y=F+ERR(1)
$THETA  (0, 1.7)  (0, .102)  (0, 29.)
$OMEGA  1.2
$ESTIMATION PRINT=5
$COVARIANCE
$TABLE ID AMT TIME
$SCATTER PRED VS DV  UNIT
```

Figure 2.1. The input (i.e., NM-TRAN control records) for analysis of some individual theophylline data.

The first line (record) gives a name to the problem. The rest of the lines (records) discuss the data, the model, and the desired output. Before going into these in some greater detail, you may want to look right now at figures 2.1 and 2.2, and then 2.4 and 2.5. Figure 2.2 shows the data for this problem, and figures 2.4 and 2.5 show some of NONMEM's output. All you need to know to get a good idea of what this analysis shows is that the one-compartment model with first-order absorption has been used; the observed concentrations and the times of observation after the bolus dose are in columns 4 and 3, respectively, of figure 2.2; and that the symbol DV stands for dependent variable (the observed concentrations, in this case). You should, for example, even at this point, be able to tell that the estimate of Volume of Distribution (V in figure 2.1, and THETA(3) in figure 2.4) is 32 liters (L), with a standard error of ±1.26 L. Now consider the figures in greater detail.

2.1. The NM-TRAN Control Records

The second record of figure 2.1 names the data items that appear on each data record, and the third record gives the name of the file containing the data records, P2DATA in this example. Figure 2.2 shows the contents of P2DATA.

Eur J Clin Pharmac
DOI 10.1007/s00228

PHARMACO

J. Persson · J. H
J.-O. Svensson ·
L. L. Gustafsson

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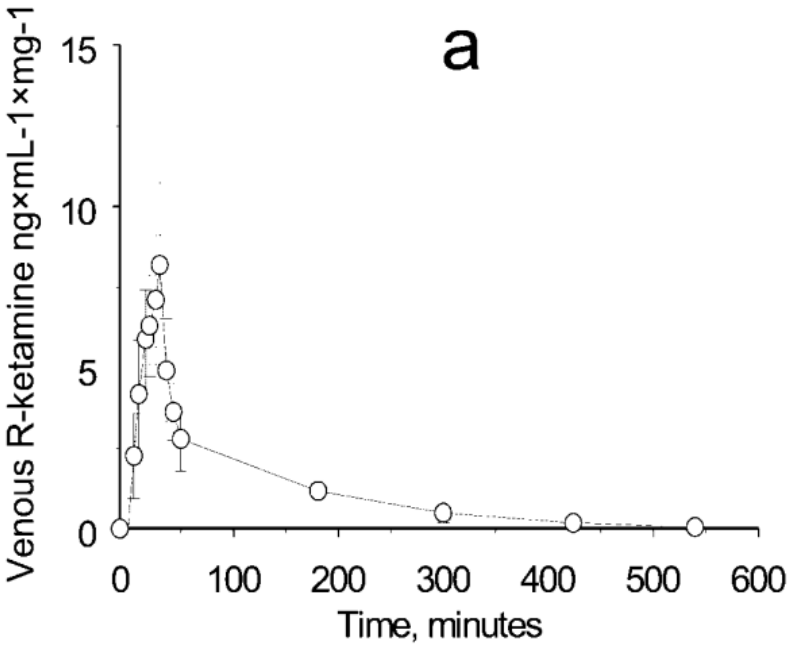

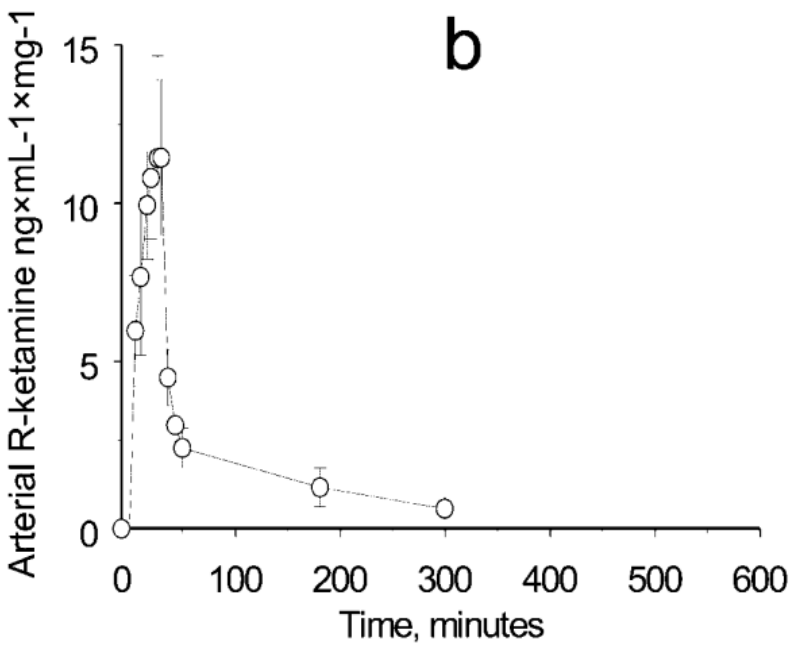

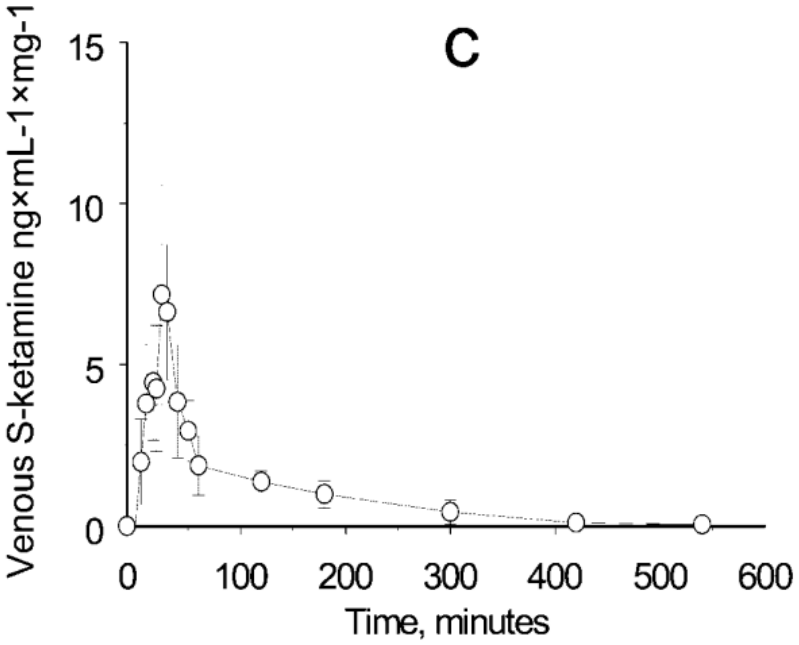

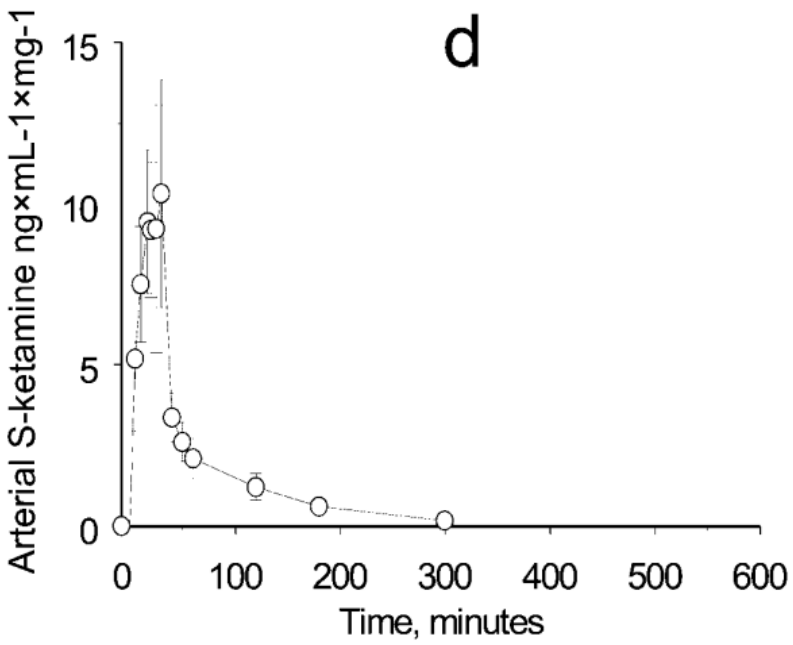

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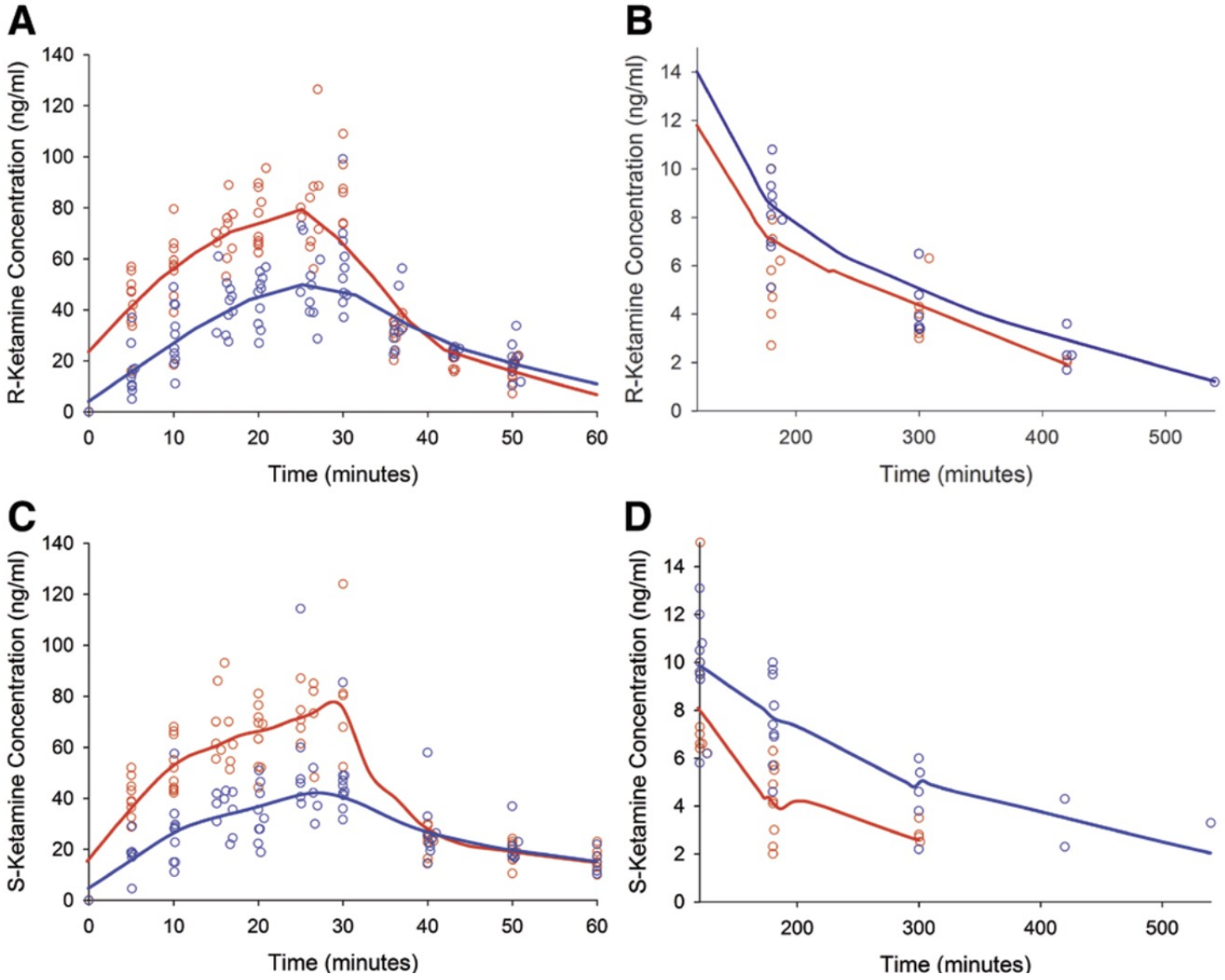
Physiologic Basis of Pharmacokinetic Models

Combined Recirculatory-compartmental Population Pharmacokinetic Modeling of Arterial and Venous Plasma S(+) and R(–) Ketamine Concentrations

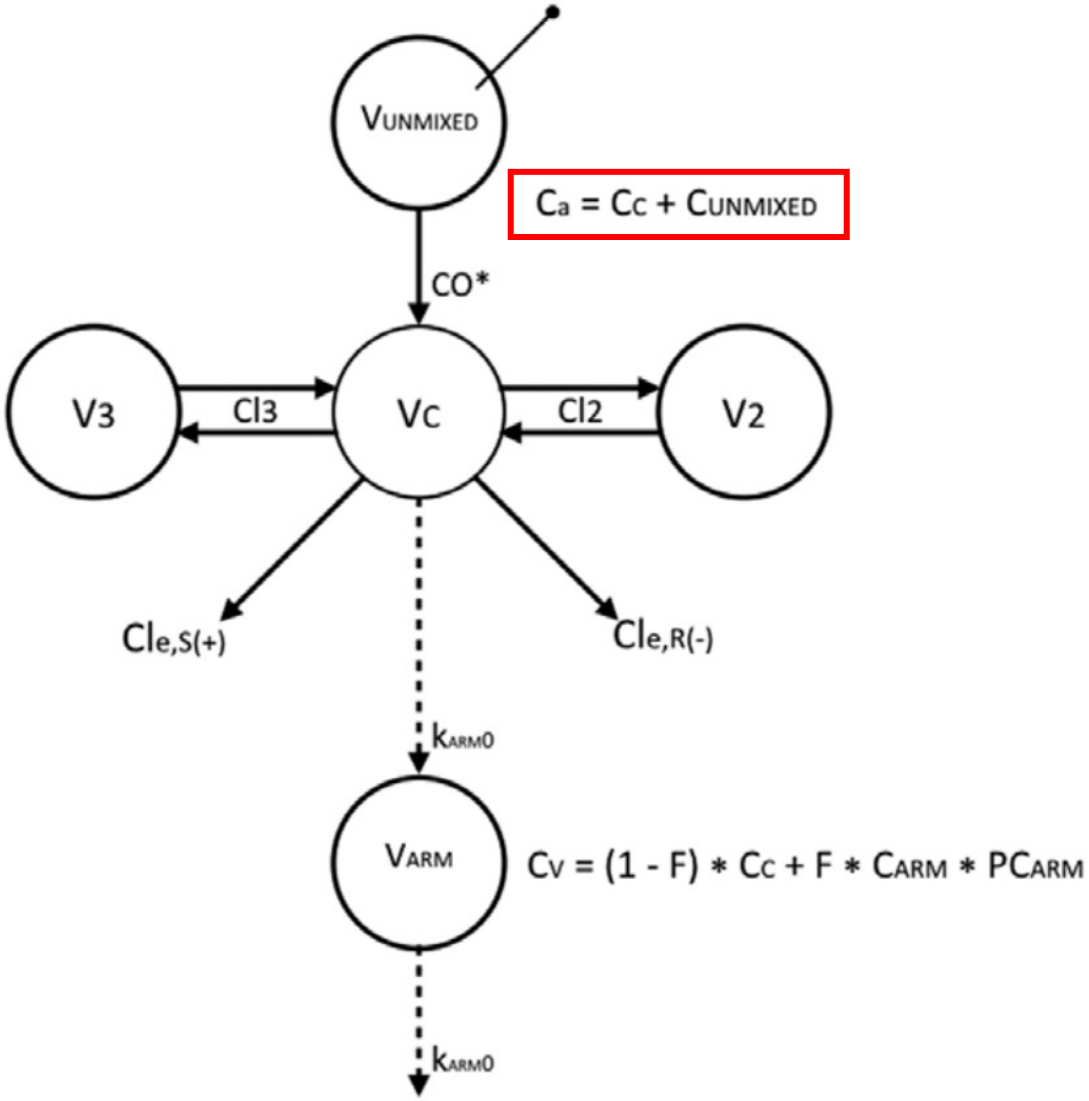
Thomas K. Henthorn, M.D., Michael J. Avram, Ph.D., Albert Dahan, M.D., Ph.D.,
Lars L. Gustafsson, M.D., Ph.D., Jan Persson, M.D., Ph.D., Tom C. Krejcie, M.D., Erik Olofsen, Ph.D.

Anesthesiology 2018; 129:260-70

Physiologic Basis of Pharmacokinetic Models



Physiologic Basis of Pharmacokinetic Models



$C_{UNMIXED}$ = Infusion Rate / CO

Physiologic Basis of Pharmacokinetic Models

British Journal of Anaesthesia **92 (4)**: 475–84 (2004)
DOI: 10.1093/bja/aeh089 Advance Access publication February 6, 2004

BJA

The two-compartment recirculatory pharmacokinetic model—an introduction to recirculatory pharmacokinetic concepts

R. N. Upton

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E-mail: richard.upton@adelaide.edu.au

Physiologic Basis of Pharmacokinetic Models

Upton RN. British Journal of Anaesthesia 92 (4): 475-84 (2004)

$$V_{lung} * dC_a / dt = R_0 - CO * (C_a - C_C) \quad (1)$$

$$C_a = R_0 / \Sigma Cl + C_C \quad (2)$$

$C_{UNMIXED}$ = Infusion Rate / CO

Presented by:
John Schoenknecht
Author and Educator

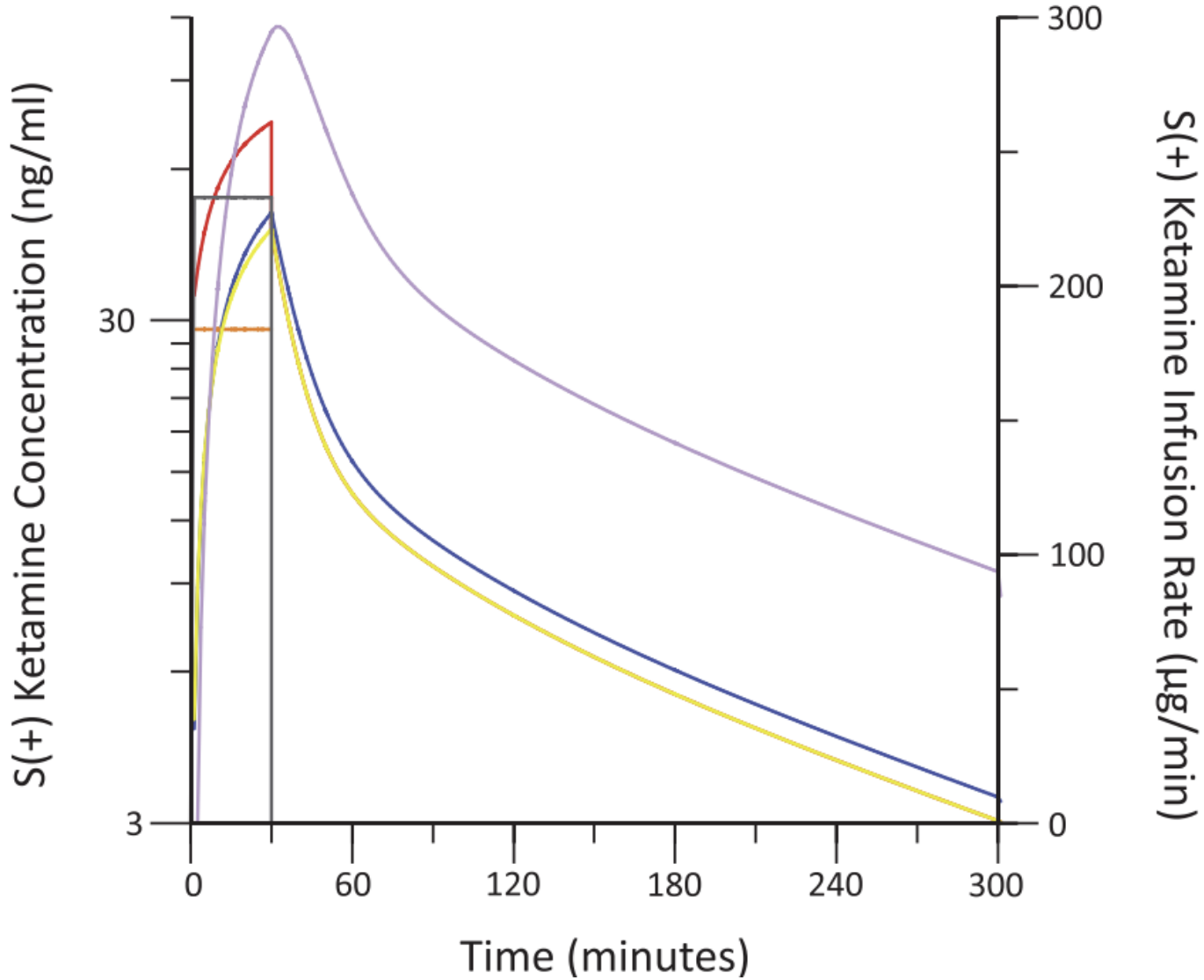
The Great Waukesha Water War

Pleasant Lake, Wisconsin

Anesthesiology
SCHOOL OF MEDICINE
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Spring = Drug Infusion Cold Jet = Unmixed Arterial Blood Pleasant Water = V_C

Physiologic Basis of Pharmacokinetic Models



Physiologic Basis of Pharmacokinetic Models

Question: If $C_{UNMIXED}$ = Infusion/CO, what happens to C_a in low cardiac ouput states?

Corollary Question: What happens to context-sensitive C_a in low cardiac output states?

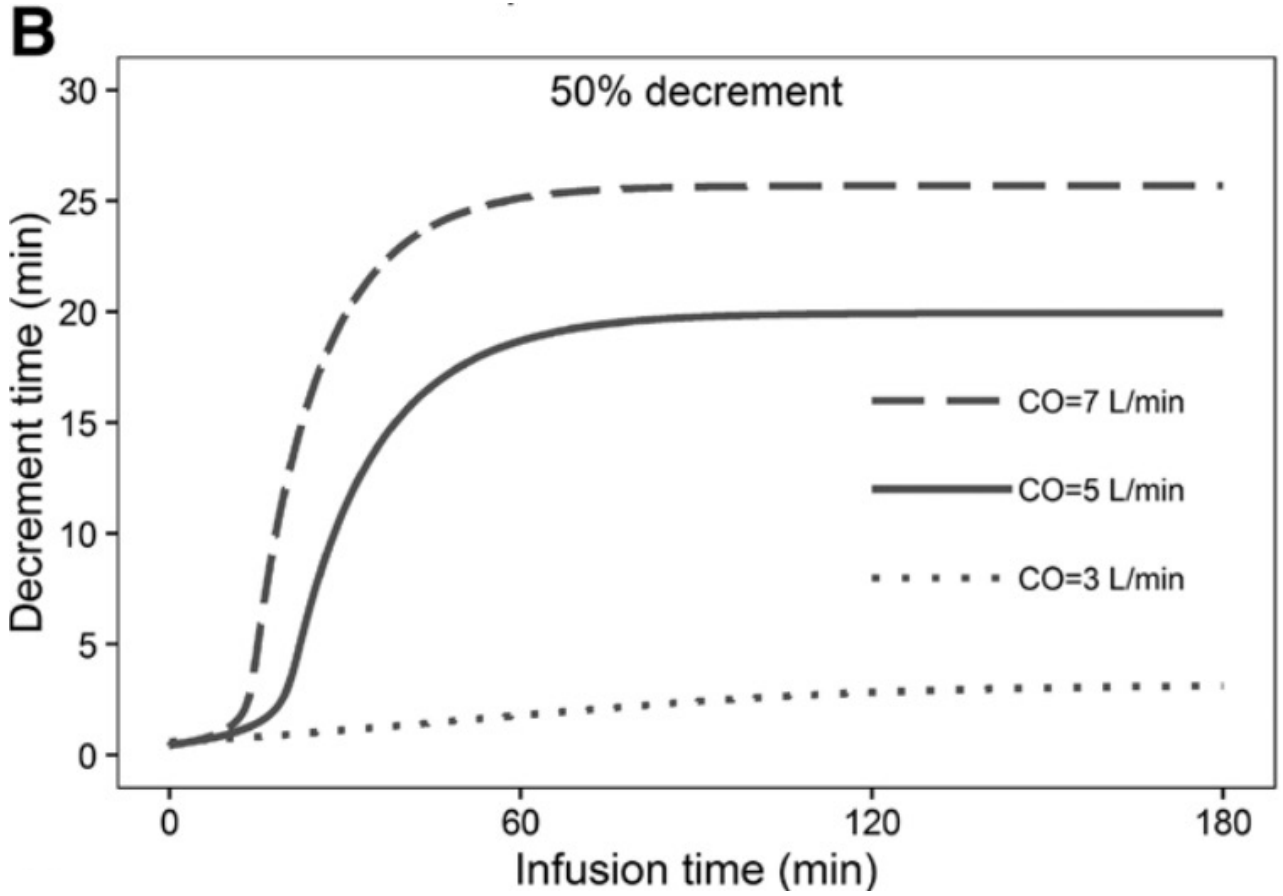
Physiologic Basis of Pharmacokinetic Models

Anesthesiology 2018; 128:912-20

Influence of Cardiac Output on the Pharmacokinetics of Sufentanil in Anesthetized Pigs

Torsten Birkholz, M.D., Christian Leuthold, M.D., Joachim Schmidt, M.D., Harald Ihmsen, Ph.D., Jürgen Schüttler, M.D., Christian Jeleazcov, M.D., M.Sc.

Physiologic Basis of Pharmacokinetic Models



After 3h of infusion, the simulated context-sensitive half time for a CO of 7 l/ min was approximately eight times longer than for a CO of 3 l/min. This is surprising, because one may expect a more rapid decrease in plasma concentrations with increased drug clearance due to increased CO.

Anesthesiology 2018; 128:912-20

Physiologic Basis of Pharmacokinetic Models

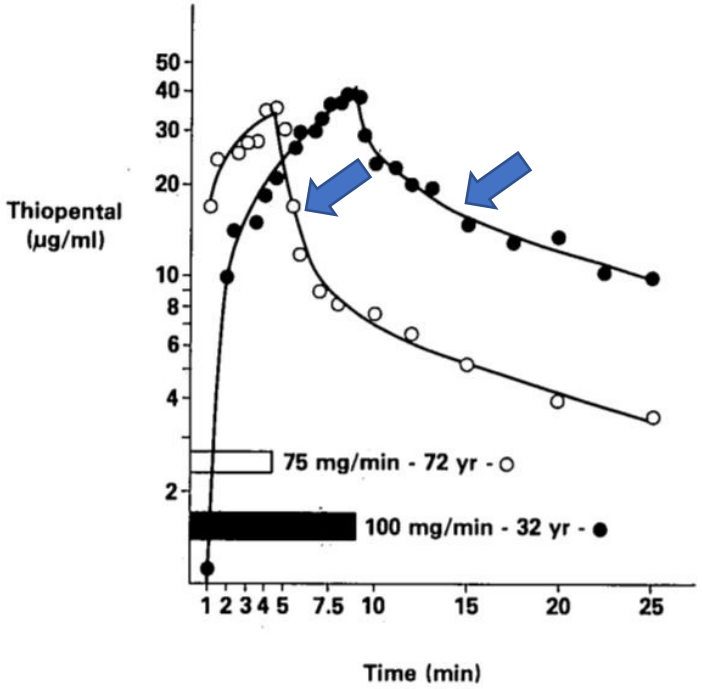


FIG. 5. Serum thiopental concentration (log scale) *versus* time for the young (filled circles and bars) and the elderly (unfilled circles and bars) patients shown in figure 3. All of the measured thiopental

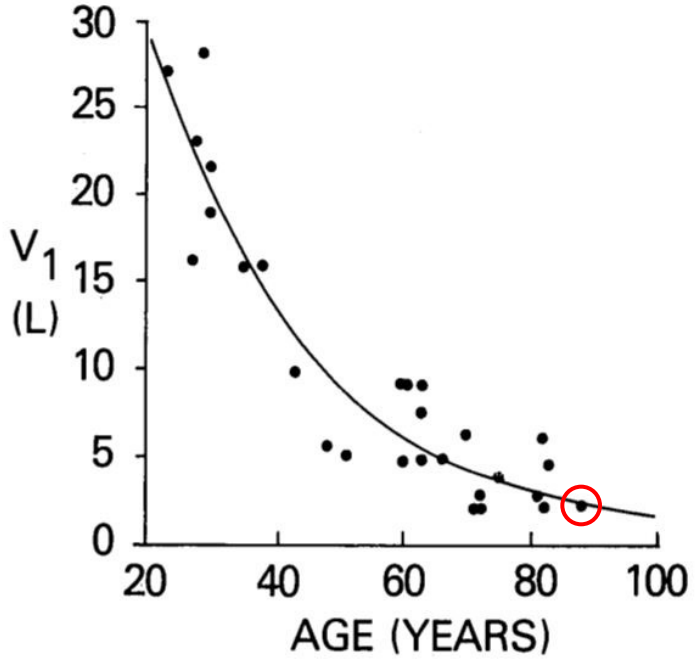


FIG. 6. Volume of the central compartment (V_1) *versus* age. The dots represent the V_1, derived from the pharmacokinetic analysis for each patient. The solid curve was derived using nonlinear regression of V_1 *versus* age to an exponential equation (see table 2).

Homer TD, Stanski DR. Anesthesiology, 1985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