

*“The vision of the International Society of Pharmacometrics (ISoP) is to promote and advance the discipline of pharmacometrics and **broaden its impact**”*

<http://www.go-isop.org/join-here/12-explore/43-isop-vision-and-mission>



# “Broadening the Impact”

## Identifying Some Novel Clinical Applications of Pharmacometrics Research

### *International Society of Pharmacometrics Lecture*

15<sup>th</sup> Annual PAGANZ Meeting - Brisbane, February 15<sup>th</sup>, 2013

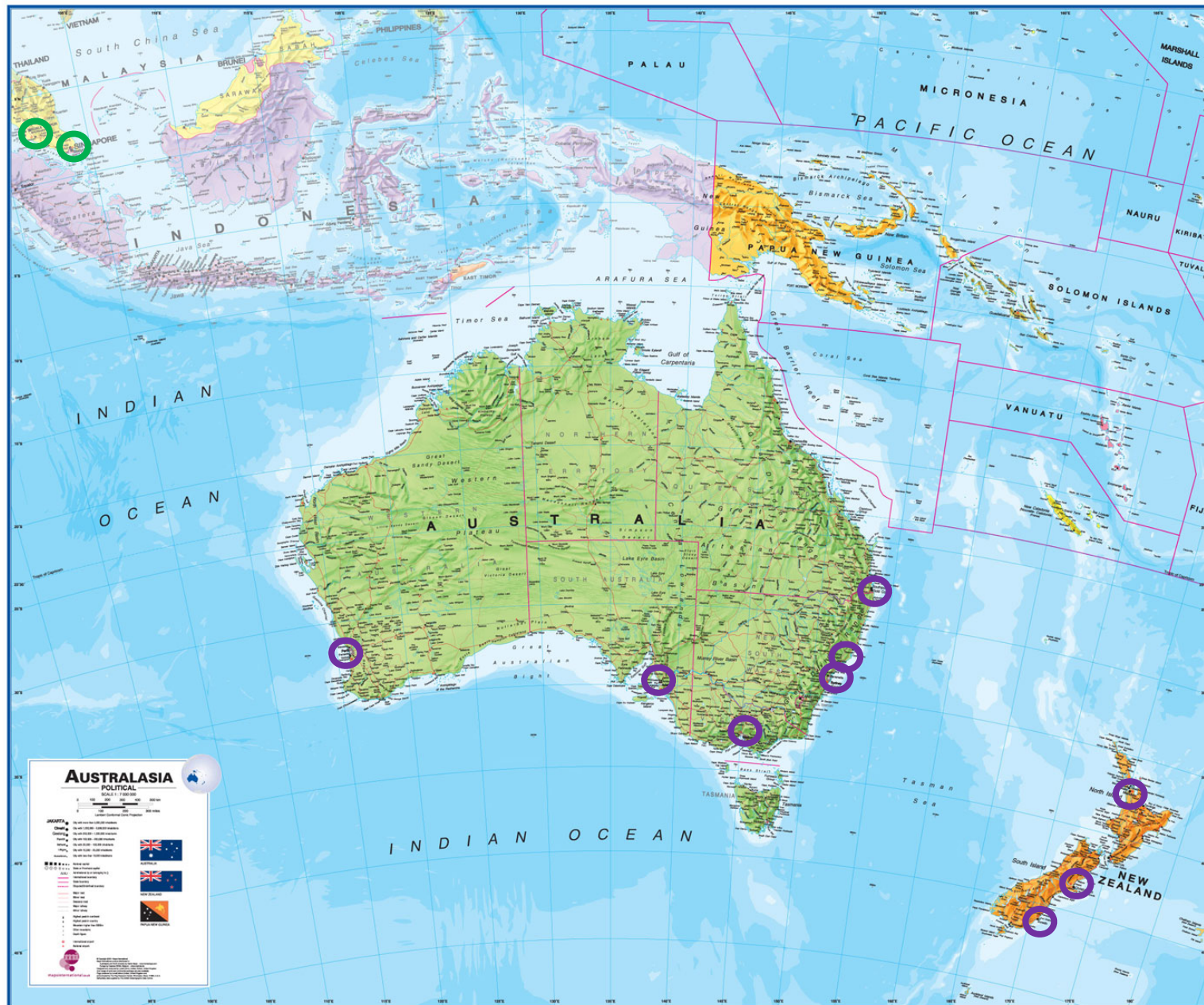
**Bruce Charles DSc, PhD**

School of Pharmacy  
Pharmacy Australia Centre of Excellence  
The University of Queensland  
Australia

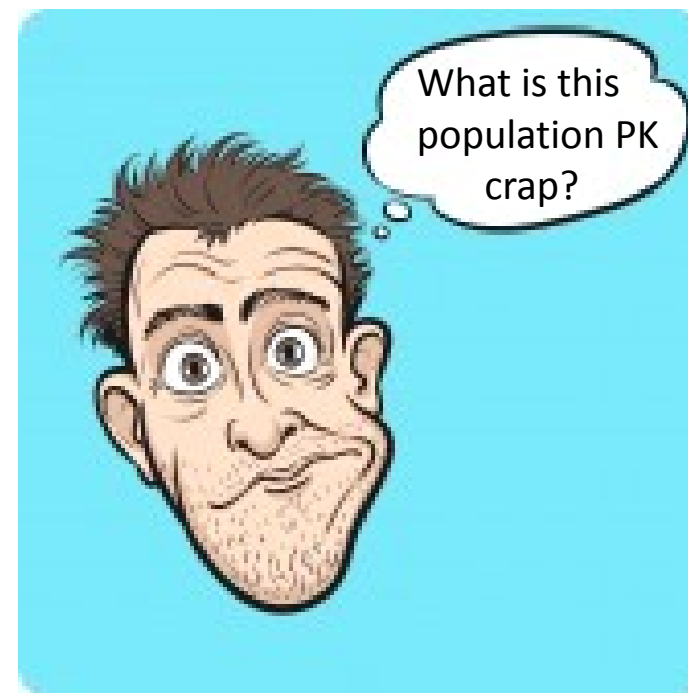
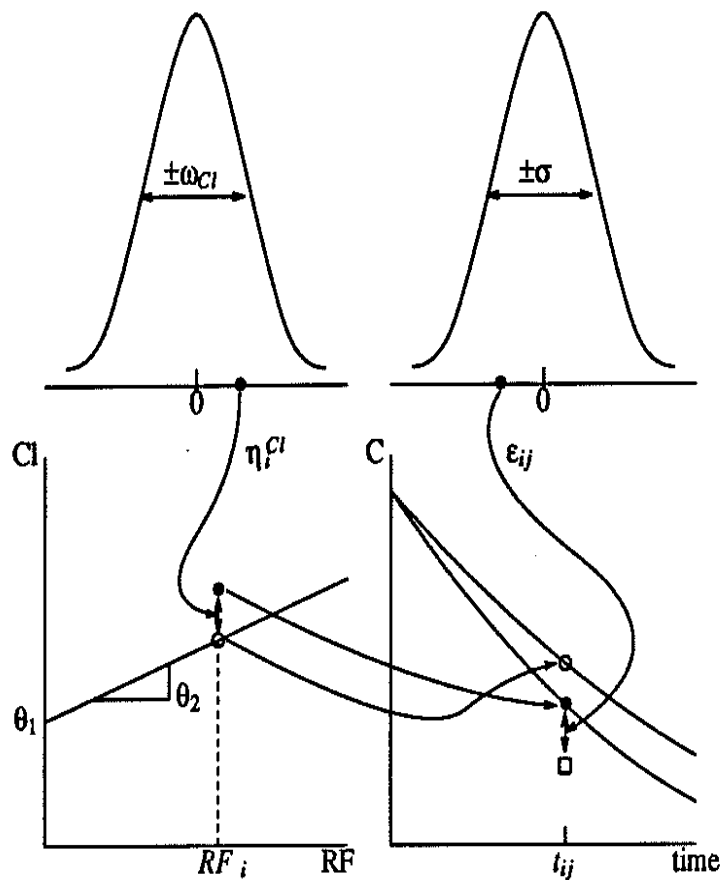
for those who came in late....

**Pharmacometrics is the science of  
interpreting and describing  
pharmacology in a quantitative  
fashion**

# Pharmacometrics in Australasia



## My “Road to Damascus” moment (ASCEPT 1992)

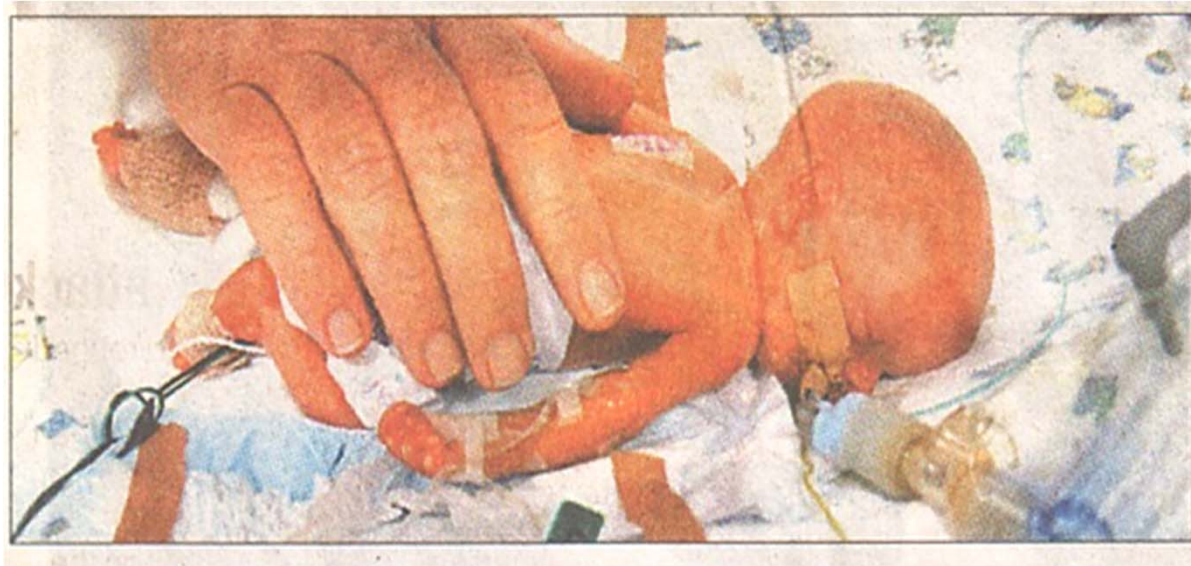


## “Broadening the Impact” – 4 examples

- Therapeutic Hypothermia and Anticonvulsant Pharmacokinetics in Newborn Infants with Hypoxic Ischemic Encephalopathy (HIE)
- Melatonin Pharmacokinetics in Tetraplegia
- Modeling Fetal Drug Exposure
- A Thymine-Based PK Screening Test for 5-Fluorouracil (5FU) toxicity?



# *Therapeutic Hypothermia and Anticonvulsant Pharmacokinetics in Newborn Infants with HIE*



# **The Pharmacokinetics of Remifentanil in Patients Undergoing Coronary Artery Bypass Grafting with Cardiopulmonary Bypass**

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\*Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia; †Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand; and ‡Department of Clinical Pharmacology, Glaxo, Inc., Research Triangle Park, North Carolina

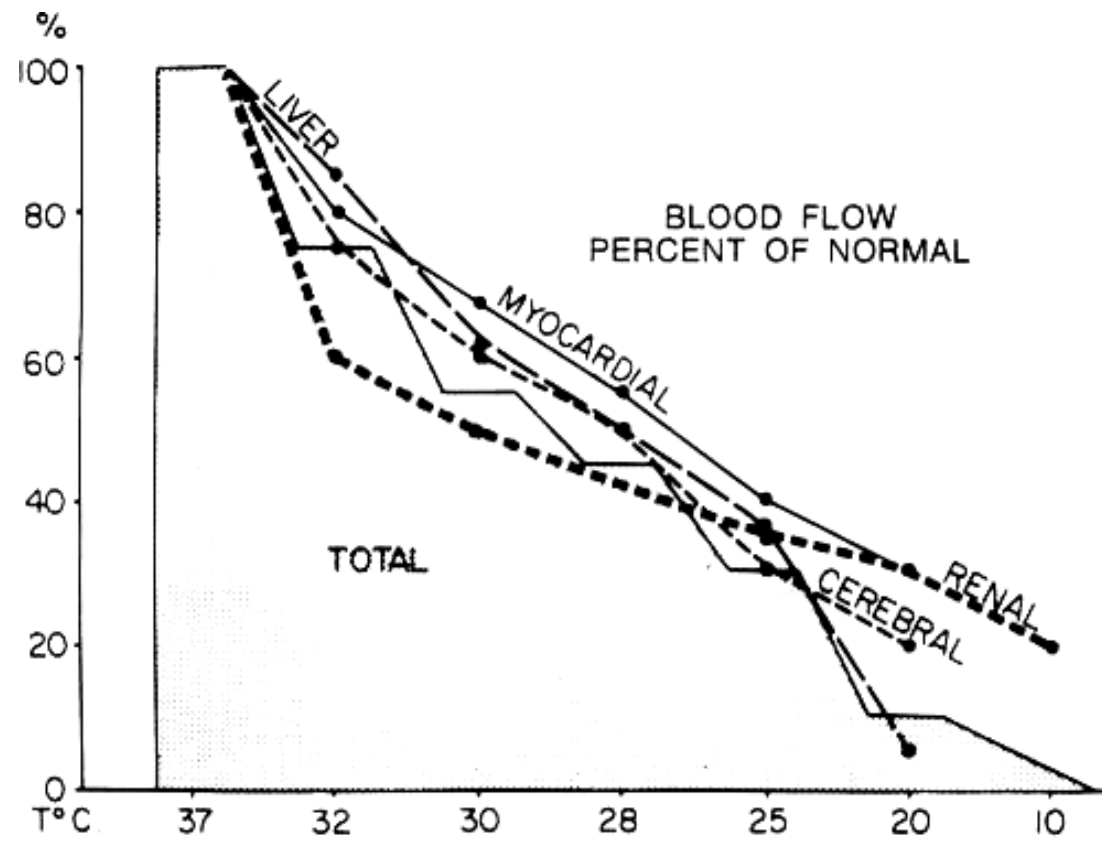
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Remifentanil is a potent opioid with a short duration of action. It has the potential for large-dose opioid anesthesia without an obligatory prolonged period of mechanical ventilation. However, because of high clearance and rapid tissue distribution, cardiopulmonary bypass (CPB) may influence its pharmacokinetics and alter drug requirements. We administered remifentanil by continuous infusion to 68 patients having coronary artery bypass graft surgery during

CPB with hypothermia to describe the effects of these interventions on its pharmacokinetics. Remifentanil concentrations were measured before, during, and after CPB. Disposition was best described by a two-compartment model. The volume of distribution increased by 86% with institution of CPB and remained increased after CPB. Elimination clearance decreased by 6.37% for each degree Celsius decrease from 37°C. (Anesth Analg 2001;93:1100–5)

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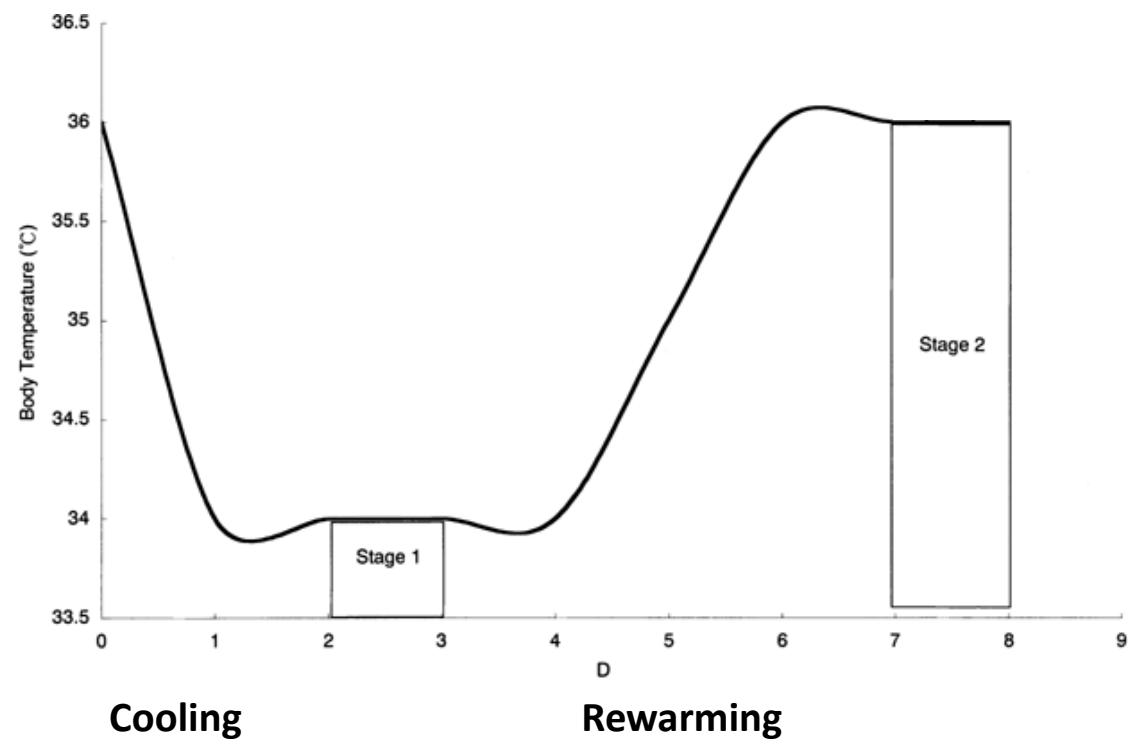


KC Wong, *West Med J* 1983;138:227-232

## BACKGROUND

- Approx. 1 in 1000 infants suffer from hypoxic ischemic encephalopathy → cerebral palsy/neurological deficits → development problems (death if severe)
- Treated with anticonvulsants and mild TH (33-34 °C for several days)
- TH → decreased basal metabolic rate, cardiac output, blood pH, GI motility
- Adult data;  $-\Delta 3\text{ }^{\circ}\text{C} \rightarrow -\Delta 67\% \text{ CL}_{\text{PHB}}$  (*Ther Drug Monit* 2001;23:192-197)
- Cooling blanket (*Techotherm Neo*); Monitor rectal and skin °C)





## APPROACH

- Blood sampling at 33-34 °C, then during and after rewarming
- Serum phenobarbitone assayed by HPLC
- Data can be “continuous” or “discontinuous” (last °C reading)

Candidate structural model during rewarming phase....

$$CL_T = \Theta_1 \cdot [1 - \exp \{-\Theta_2 \cdot (T_0 - T)\}]$$

$$k = A \cdot \exp [-E_a \div (R \cdot T)]$$

Arrhenius equation

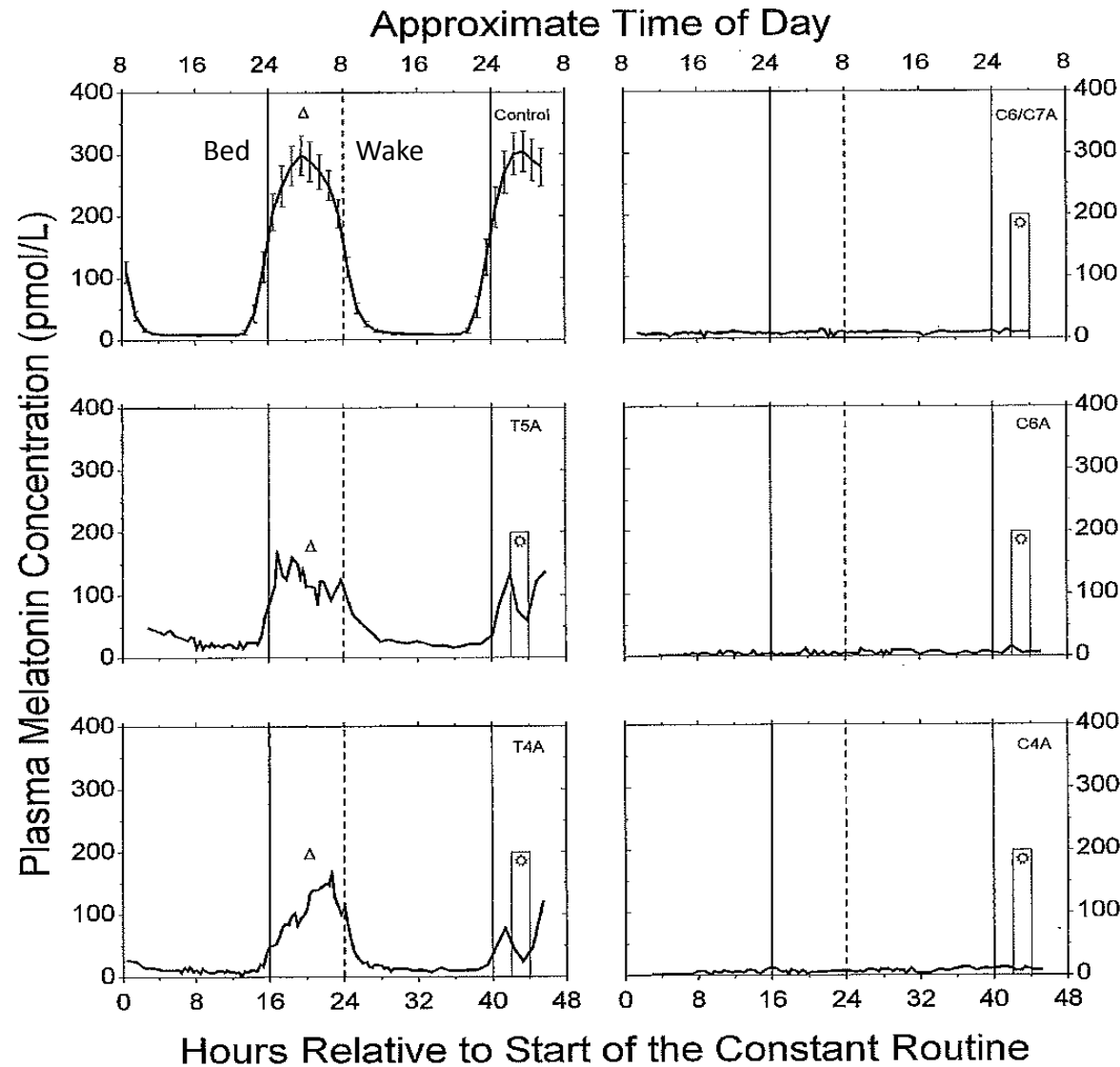
- $k$  Collisions per second resulting in a reaction (i.e. reaction rate)
- $A$  Total collisions per second (reaction or no reaction)
- $E_a$  Energy of activation
- $R$  Gas constant
- $T$  Temperature

- Pilot cooling study presently underway; also pop PK study of phenobarb on >100 non-cooled infants (Angela Williams' presentation on Thursday)

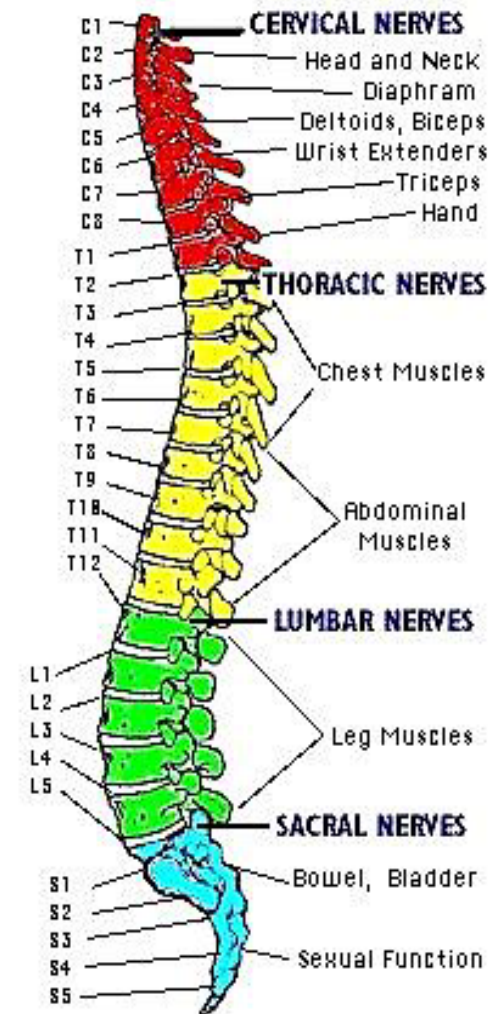
# *Melatonin Pharmacokinetics in Tetraplegia*







JM Zeitzer et al. *J Clin Endocrinol Metab* 2000; 85:2189-2196



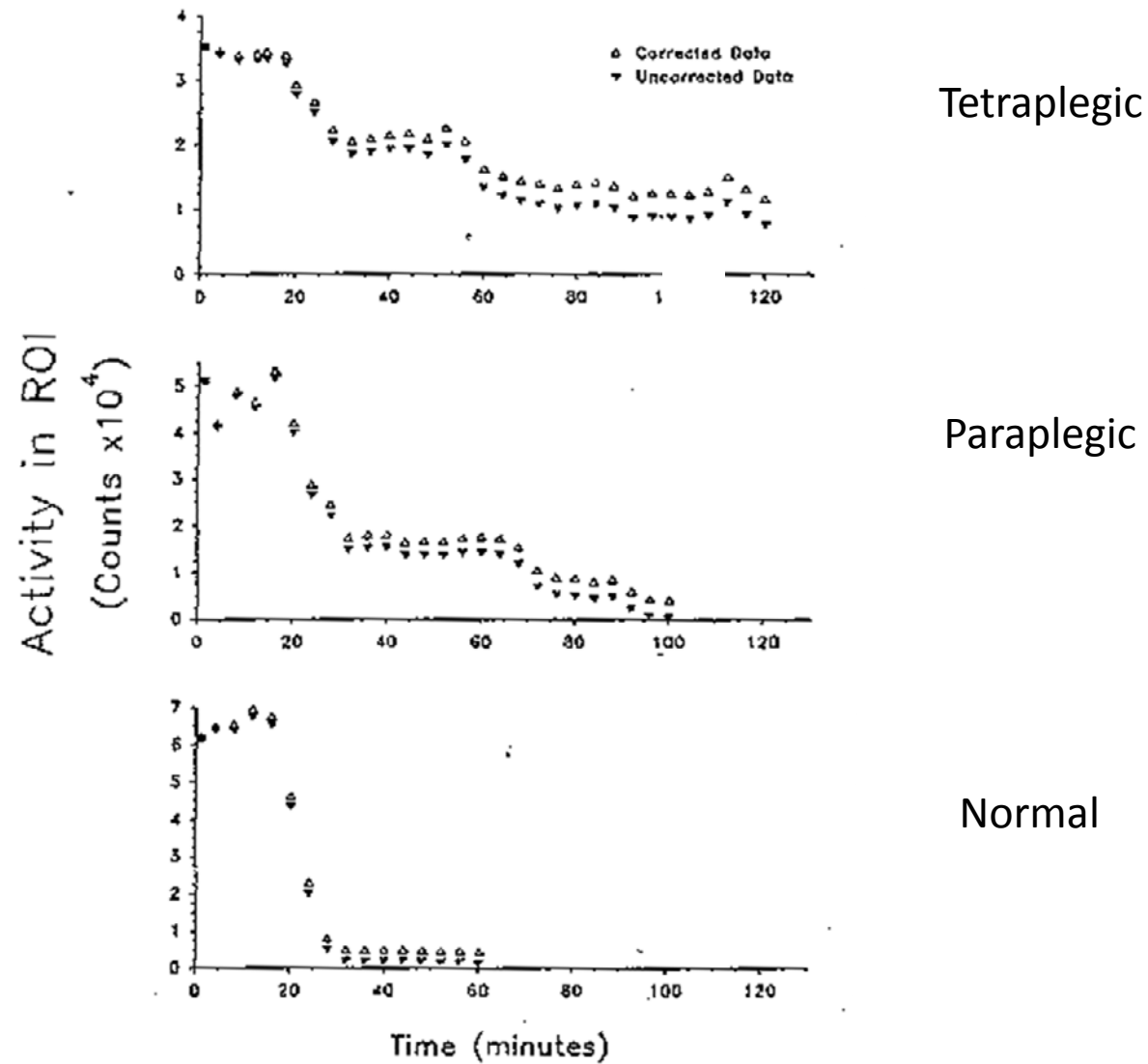
Google Images



## BACKGROUND

- Nocturnal melatonin secretion is disturbed in spinal cord injury (SCI); Less in thoracic (T) or lower (L,S) SCI; Abolished in cervical (C) SCI
- Thus, sleep disturbances can be profound in tetraplegic patients
- Recent pilot study: Melatonin supplementation (3 mg p.o.) → improved sleep quality in SCI (Institute for Breathing & Sleep, Austin Hospital)
- SCI → GIT motility, hemodynamic effects, fluid redistribution
- Loss of GIT motility (lesions T7-T12) potentially affects drug absorption
- Nothing is known of the pharmacokinetics of exogenous oral melatonin in tetraplegic patients

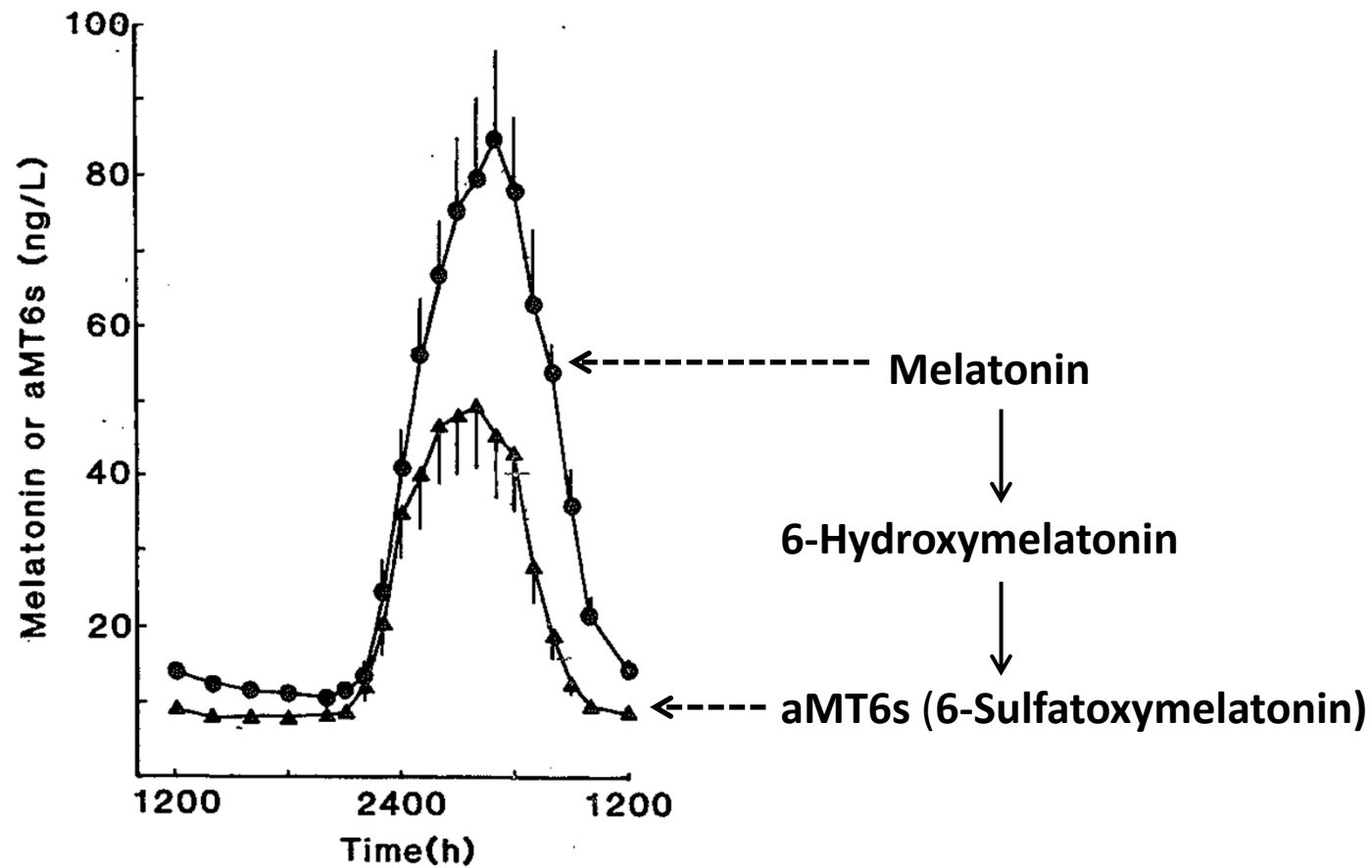
# Gastric Emptying



JL Segal, N Milne, SR Brunnemann. Gastric Emptying is Impaired in Patients with Spinal Cord Injury. American Journal of Gastroenterology - Volume 90, Issue 3 (March 1995)

# APPROACH

- Cannot use blood or saliva sampling in tetraplegics (increased risk of aggravating existing sleep disturbances)
- But all tetraplegic patients have chronic urinary catheterization due to permanent incontinence (lesions are above S1, S2)
- Since little melatonin is excreted unchanged in urine (high 1<sup>st</sup> pass metabolism), the rate and extent of excretion of the major metabolite, 6-sulfatoxymelatonin, is used in studies of circadian rhythmicity
- Urine 6-sulfatoxymelatonin measured by RIA or LC-MS/MS
- “Rich” data; urine sampling can be conducted for any specified duration/interval (including overnight) in tetraplegic patients

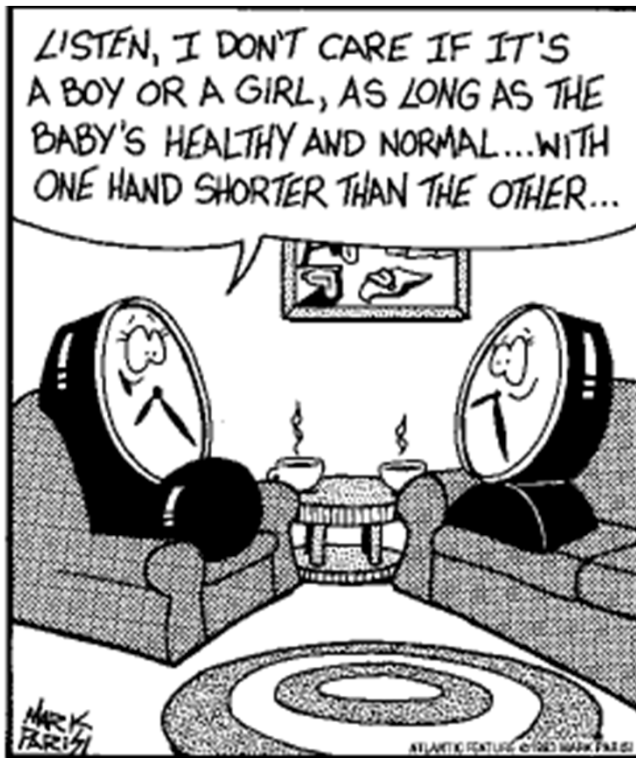


CJ Bojkowski et al. Melatonin Secretion in Humans Assessed by Measuring Its Metabolite, 6-Sulfatoxymelatonin. *Clin Chem* 33(8), 1343-1348 (1987)

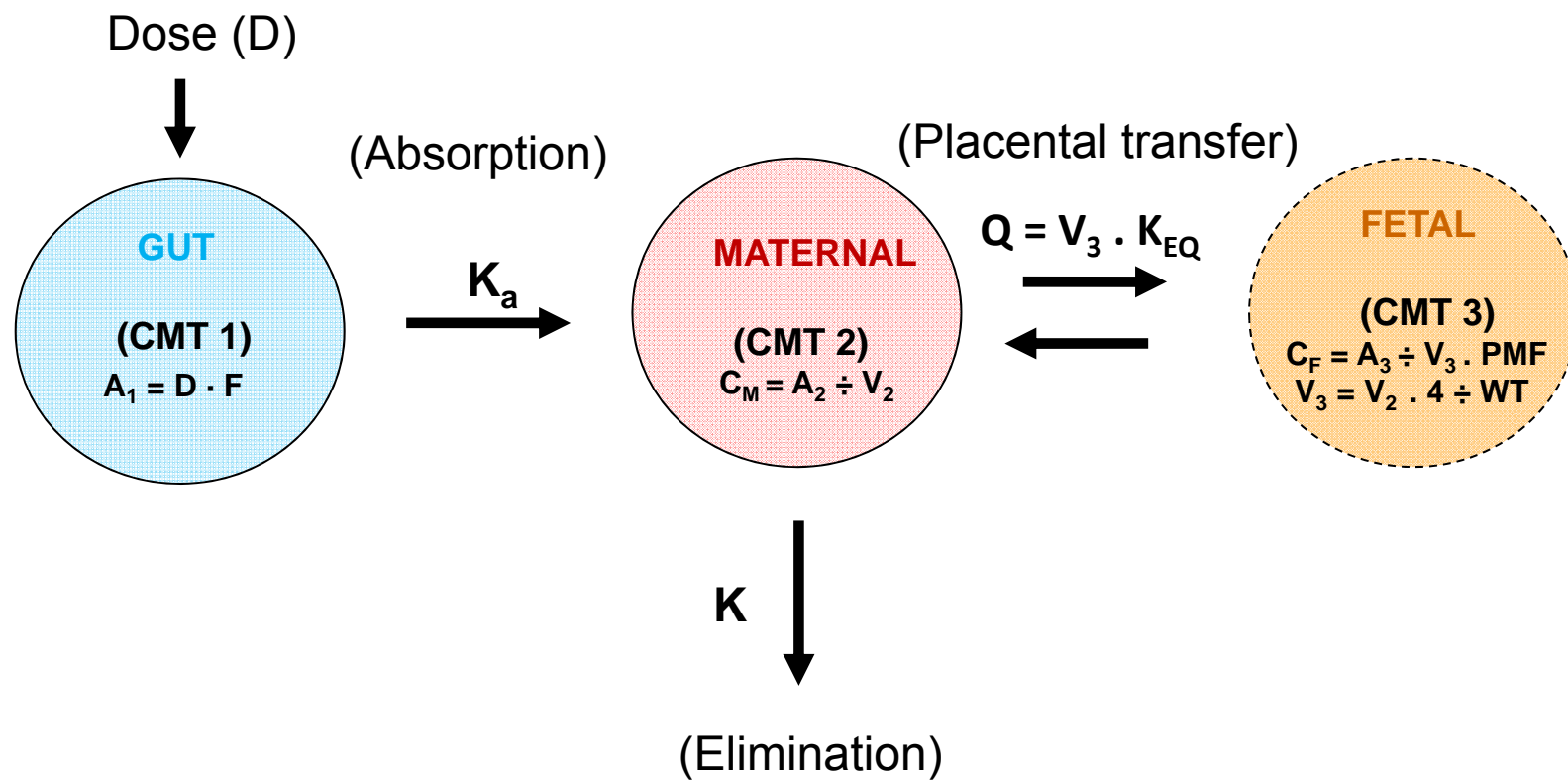
## CHALLENGES

- Very large variability in degree of “completeness” of SCI (rarely is the spinal cord completely severed)
- Does melatonin metabolic profile change? ( $F_{PO} = 0.1$  to  $0.2$ )
- Hemodynamic abnormalities and cardiac dysrhythmias are common in SCI
- Gross body composition and fluid changes in tetraplegia
- Is glomerular filtration and renal clearance of 6-sulfatoxymelatonin constant in tetraplegia?
- Link PK with PD outcomes? (sleep quality, accelerometry data)

# *Modeling Fetal Drug Exposure*



Antidepressants  
Antihypertensives  
Antidiabetics  
Antiepileptics  
Alcohol  
OTCs  
(many others)

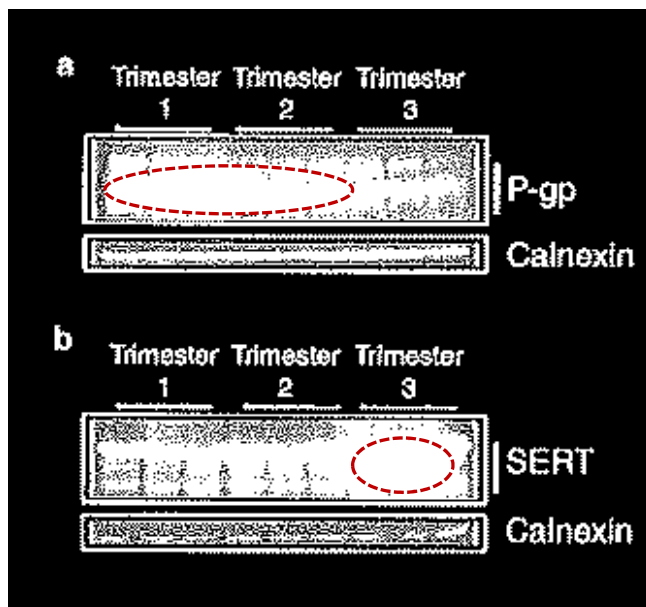


BG Charles et al, Population pharmacokinetic of metformin in late pregnancy. *Ther Drug Monit* 2006;28:67-72



# CHALLENGES

- Large inter-subject variability in maternal-fetal plasma drug levels
- Physiological and biochemical changes during pregnancy
- Must assume value for fetal weight
- Drug may be passively and/or actively transported
- Cord blood only gives single “snapshot” after a 9 month exposure, but drug transporters may change level of expression during pregnancy:
  - Cord blood data may over-estimate overall exposure from P-gp drugs
  - Cord blood data may under-estimate overall exposure from drugs transported by SERT



Western immunoblot showing expression by trimester of 2 drug transporters in placental samples from 9 women.

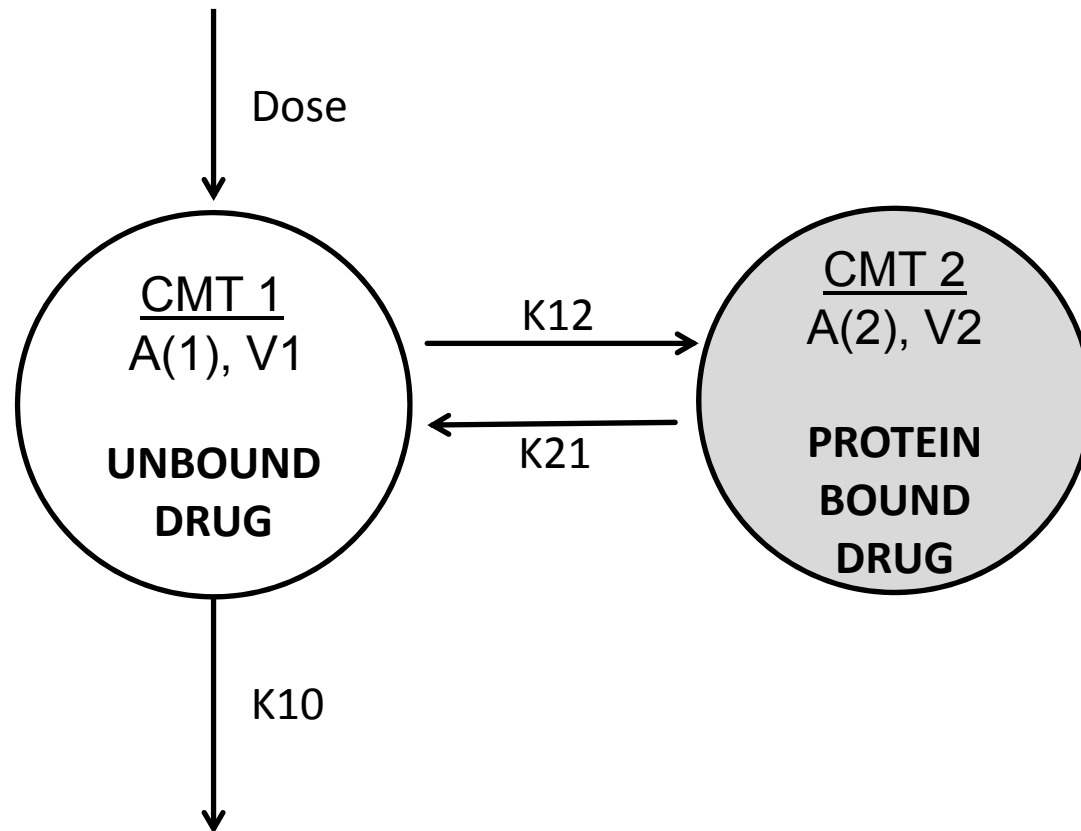
**a.** P-glycoprotein transporter (P-gp)

**b.** Serotonin transporter (SERT)

[Calnexin = standard control]

L. DeVane et al, *CPT* 2011;89:786-788.

## Spinoff application: Protein binding

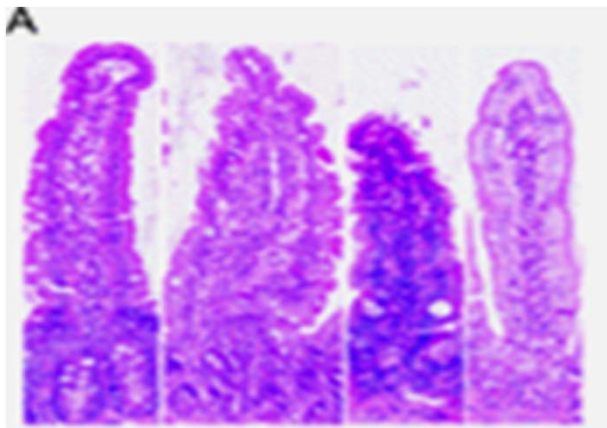
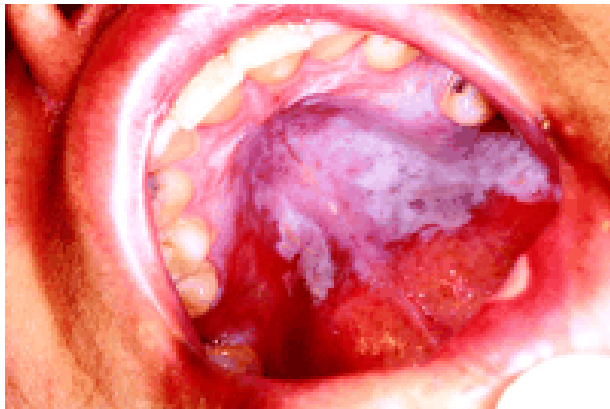


```

$PROB
$INPUT
$DATA
$SUBR ADVAN3 TRANS4
$PK
;-----PK -----
CL = THETA(1)*EXP(ETA(1))
V1 = THETA(2)*EXP(ETA(2))
S1 = V1
K10 = CL/V1
;-----Protein binding -----
PFB = THETA(3)*EXP(ETA(3))
TEQ = 0.0001 ; short equil. time
KEQ = LOG(2)/TEQ
V2 = THETA(5) ; albumin volume
Q = V2*KEQ ; inter-cmt CL
K21 = Q/V2
K12 = Q/V1

$ERROR
Cu = A(1)/S1
Cb = A(2)/V2*PFB
Ct = Cb + Cu
IF (CMT.EQ.2) THEN
  IPRED = Cb
ELSE
  IPRED = Cu
ENDIF
    
```

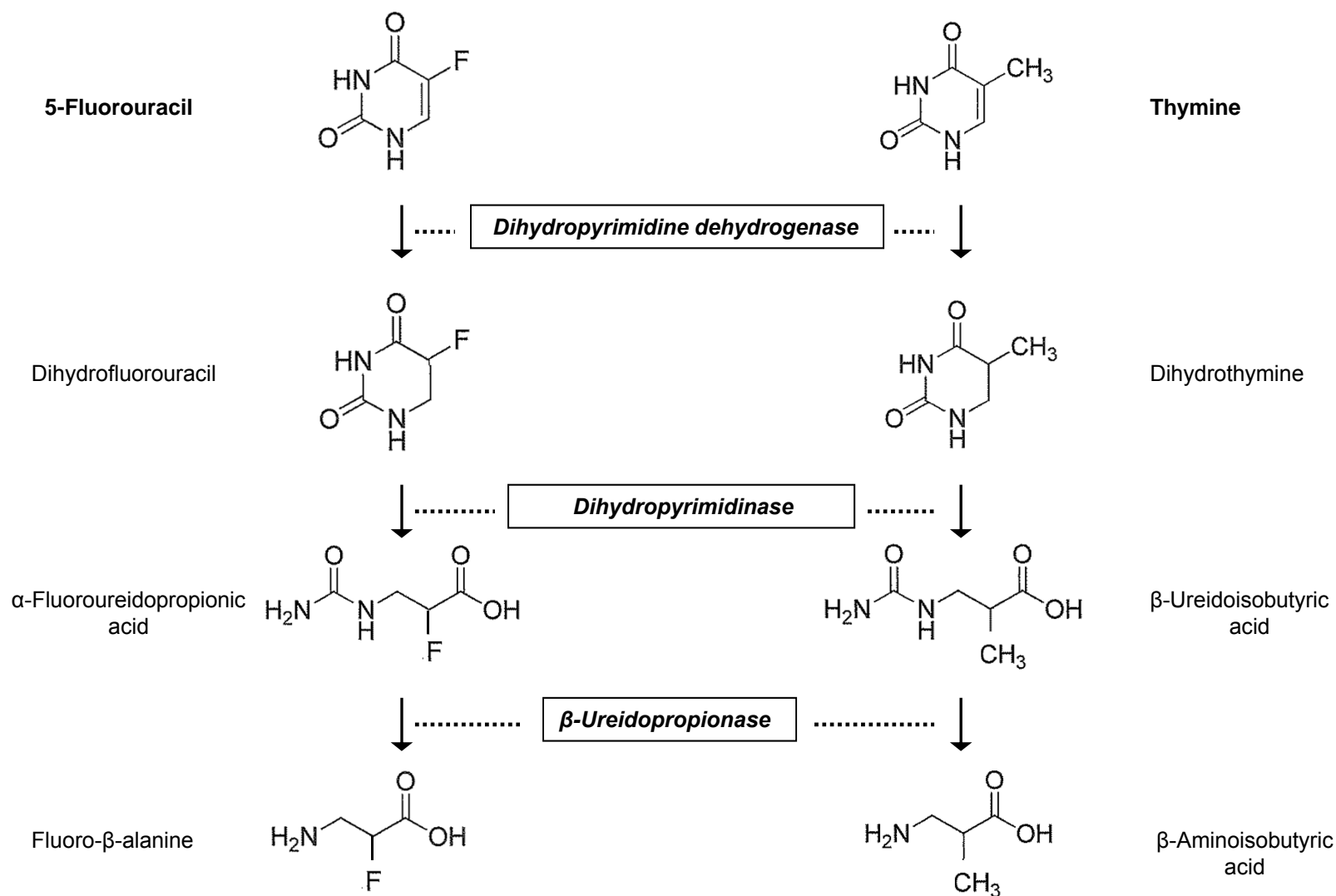
# *A Thymine-Based PK Screening Test for 5FU Toxicity?*



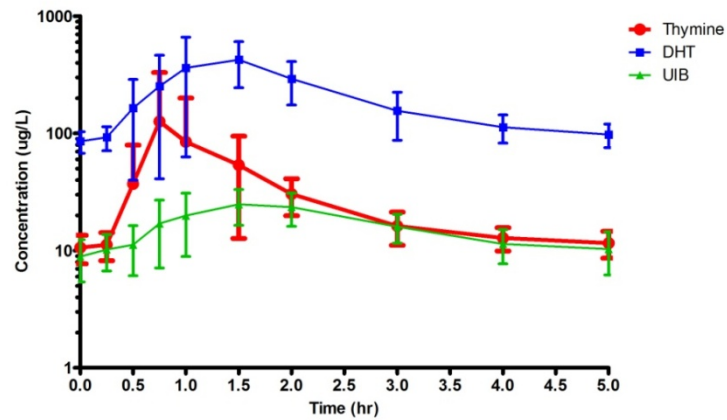
## 5-Fluorouracil in Cancer Chemotherapy

- 5FU and capecitabine (5FU oral prodrug) is widely used in colon, breast, head/neck cancers
- Toxicity is a major, ongoing concern; serious Grade 3-4 toxicity occurs with 1 in 6 patients
- Toxicity presumably due to increased systemic 5FU exposure, i.e. reduced 5FU clearance
- Dosage reductions may be too late (even 1 high dose can be lethal); a small 5FU test dose may be catastrophic in DPD homozygous recessive patients!
- Therefore, would a screening test using a natural pyrimidine (e.g. thymine 250 mg p.o.) be useful for minimising 5FU toxicity?

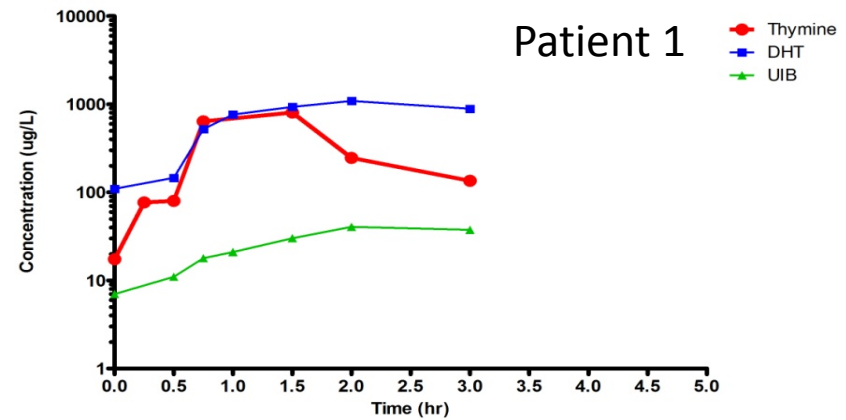
# Pyrimidine Catabolic Pathway



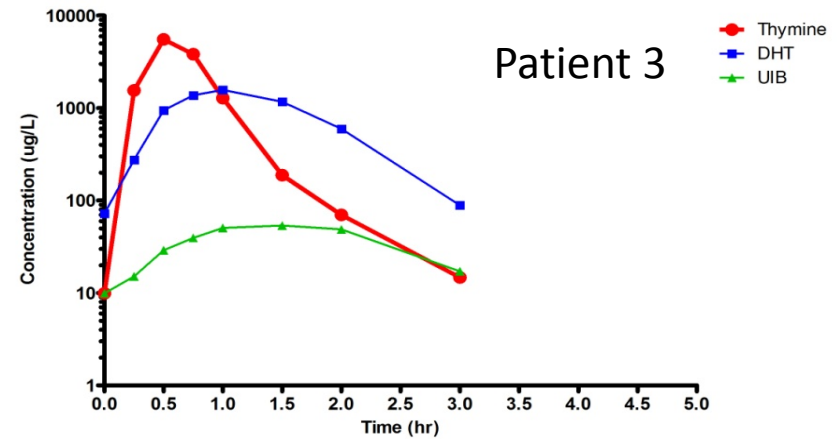
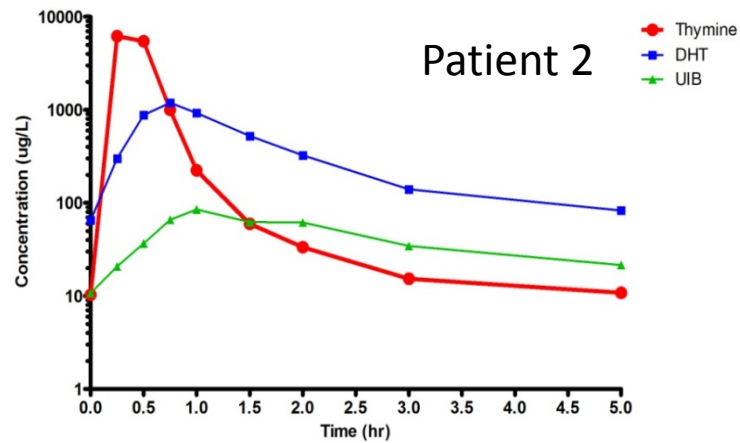
## Normals (n=12)



## DPD deficiency (THY → DHT)



## Is there an overexpressed pyrimidine transporter?



## Towards a Thymine PK Screening Test

- Assay enzyme activity directly: Complex, inaccurate
- Gene analysis: Large DPD gene, many mutations, cost
- PK of 5FU test dose: Risk of serious toxicity/death

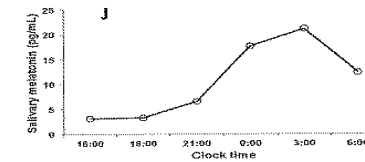
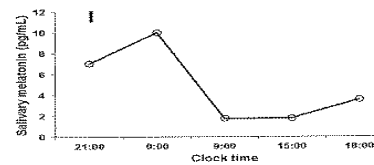
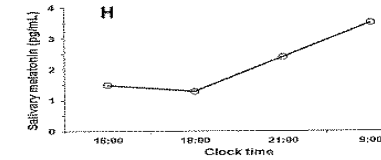
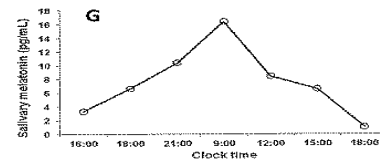
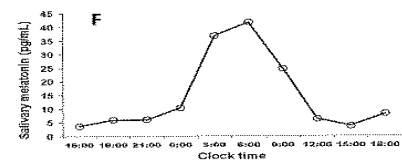
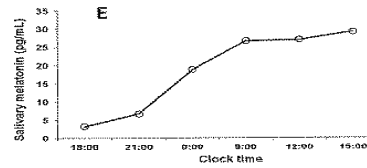
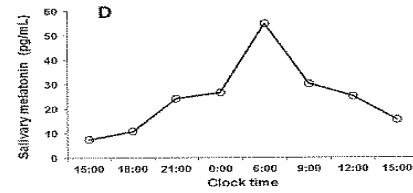
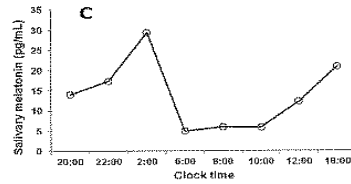
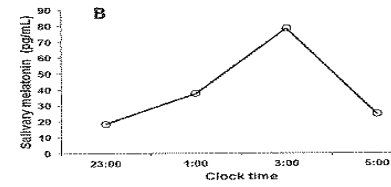
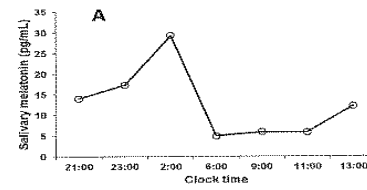
## CHALLENGES

- ❑ Ethical and logistical restrictions permit only limited sampling ( $N \leq 4$ ) over a restrictive period ( $\leq 3$  h post-dose)
- ❑ Are there 2 (or more) mechanisms for 5FU toxicity, e.g. low clearance and/or expression of a “super transporter” gene?
- ❑ Optimal sampling design(s) for a thymine screening test, and population PK of thymine and metabolites in patients?
- ❑ Influence of PG covariates on clearance? But only ~40% match between DPD mutation and enzyme activity



and the list goes on....

- Modeling and prediction of renal function in the first week(s) of life in very premature infants
- Modeling pharmacogenomic influences in the developmental pharmacology of newborn infants
- Application of microbiomic-derived response data in PK-PD of antimicrobial action
- Pop PK modeling of rhythm of circadian markers (melatonin) in children with major sleep disorders....



Khan SA, George R, Charles BG, Taylor PJ, Heussler HS, Cooper DM, McGuire TM, Pache D, Norris RLG. Monitoring salivary melatonin concentrations in children with sleep disorders using liquid chromatography-tandem mass spectrometry. *Ther Drug Monit* (2013, in press)

# “Broadening the Impact”....Making it happen!

- Get involved with a tertiary care teaching hospital
- Join special interest group(s); Identify “niche” areas
- Become the visible PM expert (e.g. Grand Rounds)
- Present at high-impact PM meetings (e.g. PAGE, ISoP)
- Value-add to “non-PM” studies (e.g. high-dose caffeine in premature infants with apnea)
- Translation; New dosage guidelines from PM analyses
- Supervise specialist practitioners (e.g. PhD/Fellowship)
- Learn some pharmacogenomics
- Continuously nurture the curiosity

Lots to be done....but remember to have FUN!



*Back  
By Popular  
Demand*

**DOOMBEN 10,000  
RACE DAY PARTY**

**Whybrew-Williams Member's Stand (Our House)**  
**Saturday Afternoon 26<sup>th</sup> May 2012**  
BYO Drinks and Nibbles  
**Dress for the races!**

# Acknowledgments

- To ISoP for sponsorship and for the opportunity to present this lecture
- To you, for your attention