Developmental and Pediatric Pharmacology

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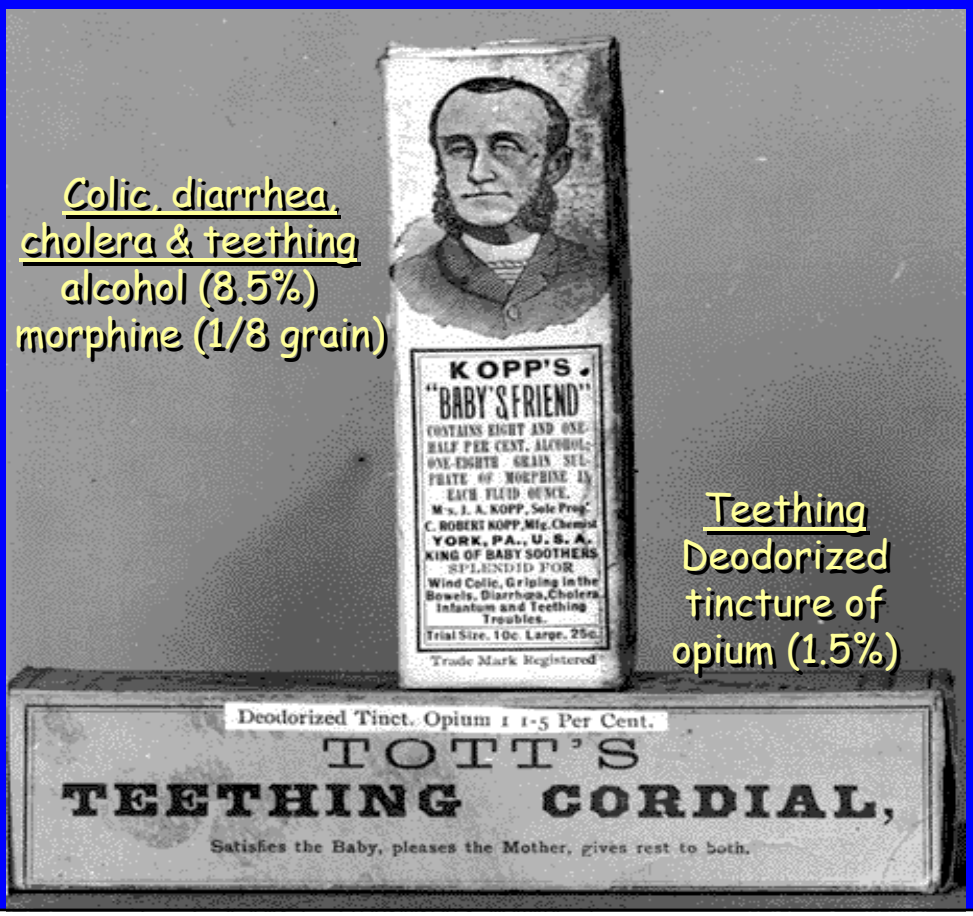
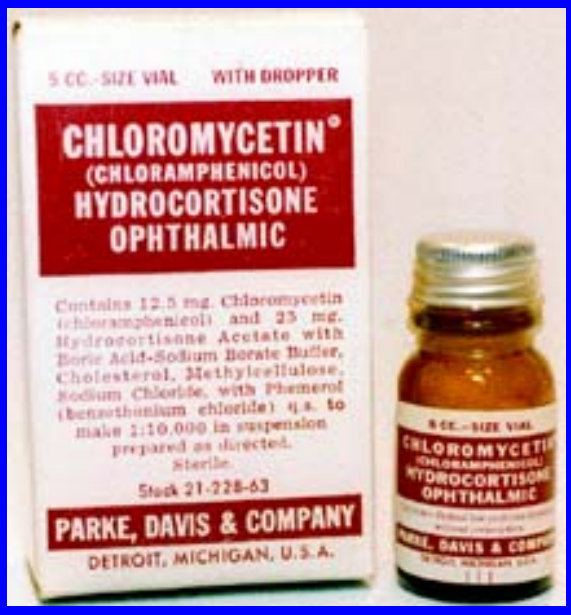


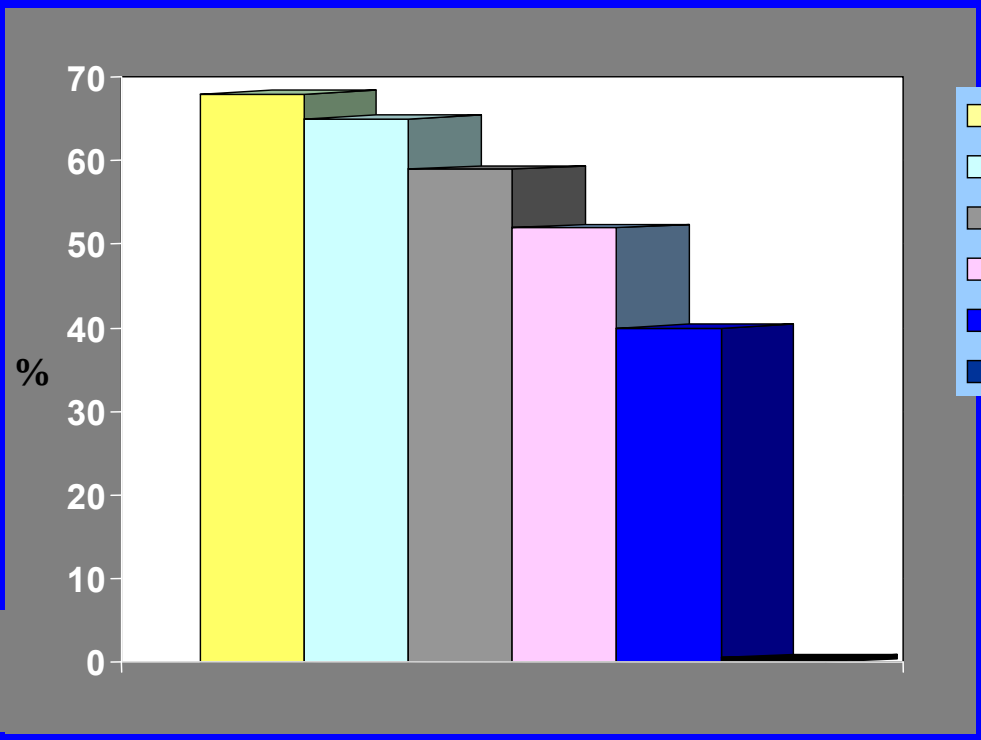
Colic, diarrhea, cholera & teething
alcohol (8.5%)
morphine (1/8 grain)

Teething
Deodorized tincture of opium (1.5%)

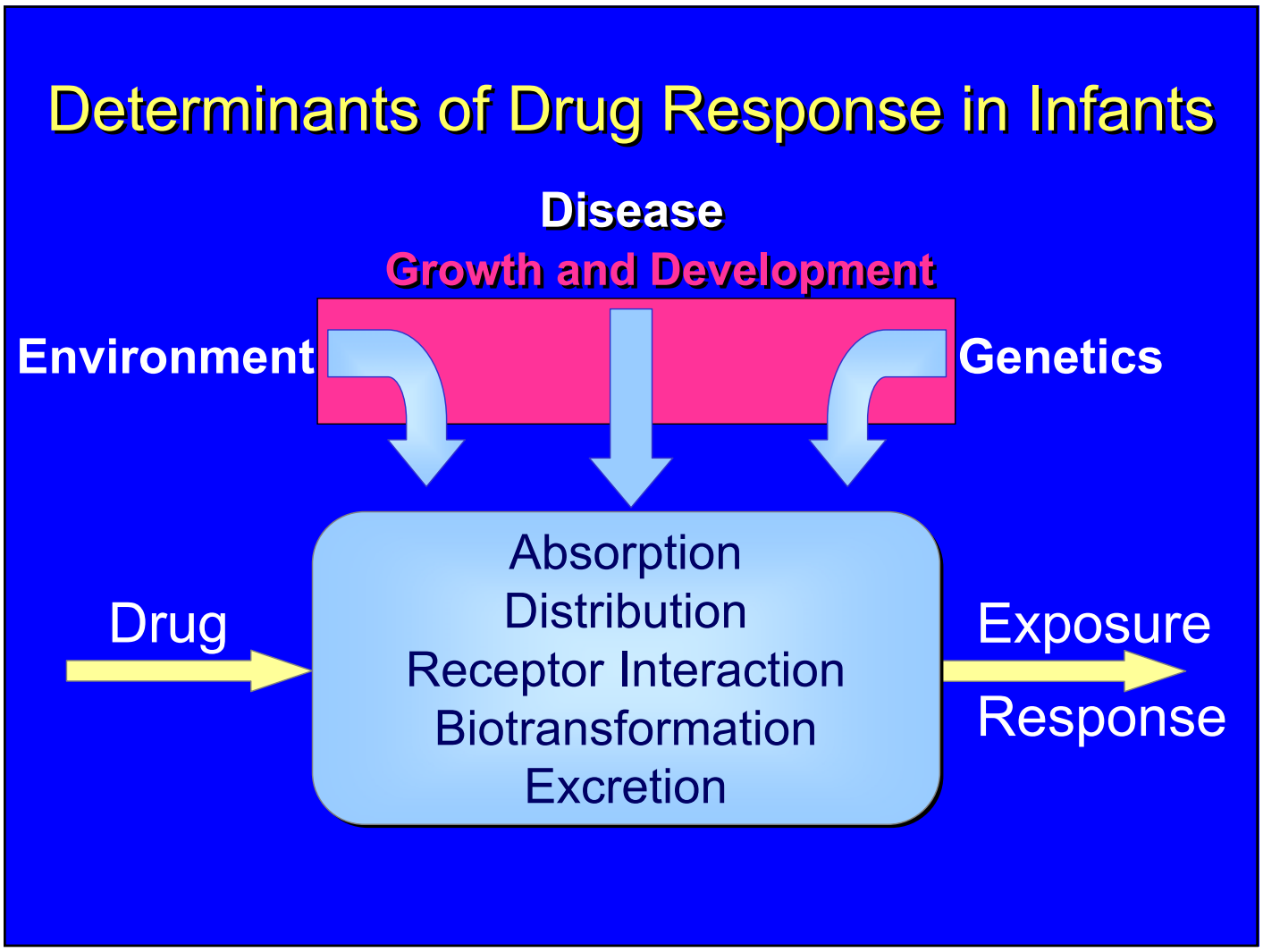

ELIXIR
SULFANILAMIDE
Each fluidounce represents:
Sulfanilamide, 40 gr.
Dose, begin with 2 to 3 teaspoonfuls in water every four hours. Decrease in twenty-four to forty-eight hours to 1 or 2 teaspoonfuls and continue at this dose until recovery.
THE S. E. MASSENGILL COMPANY
Manufacturing Pharmacists
BRISTOL, TENN.-VA.


5 CC.-SIZE VIAL WITH DROPPER
CHLOROMYCETIN®
(CHLORAMPHENICOL)
HYDROCORTISONE
OPHTHALMIC
Contains 12.5 mg. Chloromycetin (chloramphenicol) and 25 mg. Hydrocortisone Acetate with Boric Acid-Sodium Borate Buffer, Cholesterol, Methylcellulose, Sodium Chloride, with Phemerol (benzethonium chloride) q.s. to make 1:10,000 in suspension prepared as directed.
Sterile.
Stock 21-228-63
PARKE, DAVIS & COMPANY
DETROIT, MICHIGAN, U.S.A.

Unlicensed and « off-label drugs » in paediatric and neonatal intensive care units



Treluyer et al 1999


Determinants of Drug Response in Infants
Disease
Growth and Development
Environment
Genetics
Drug
Absorption
Distribution
Receptor Interaction
Biotransformation
Excretion
Exposure
Response

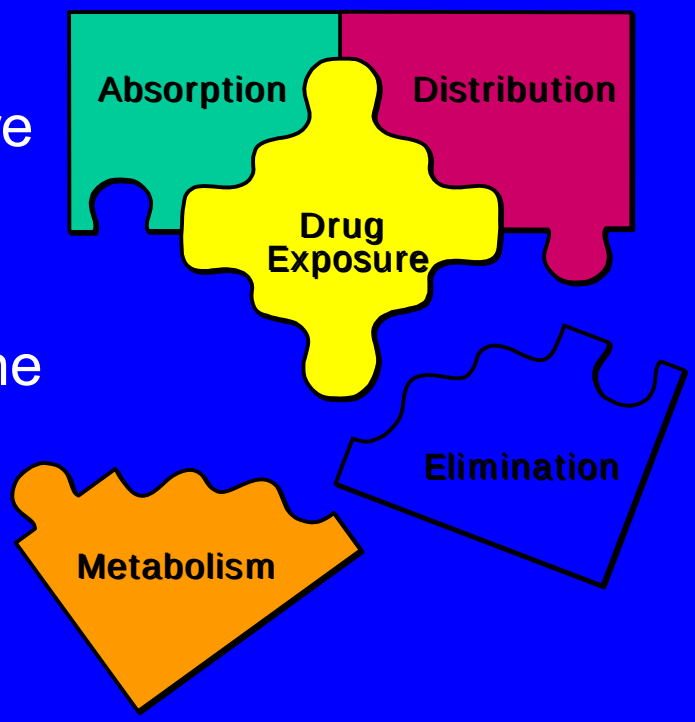
The Challenge of Pediatric Clinical Pharmacology: Determining the Source(s) of Variability…...

Ontogeny ***Pharmacogenetics***

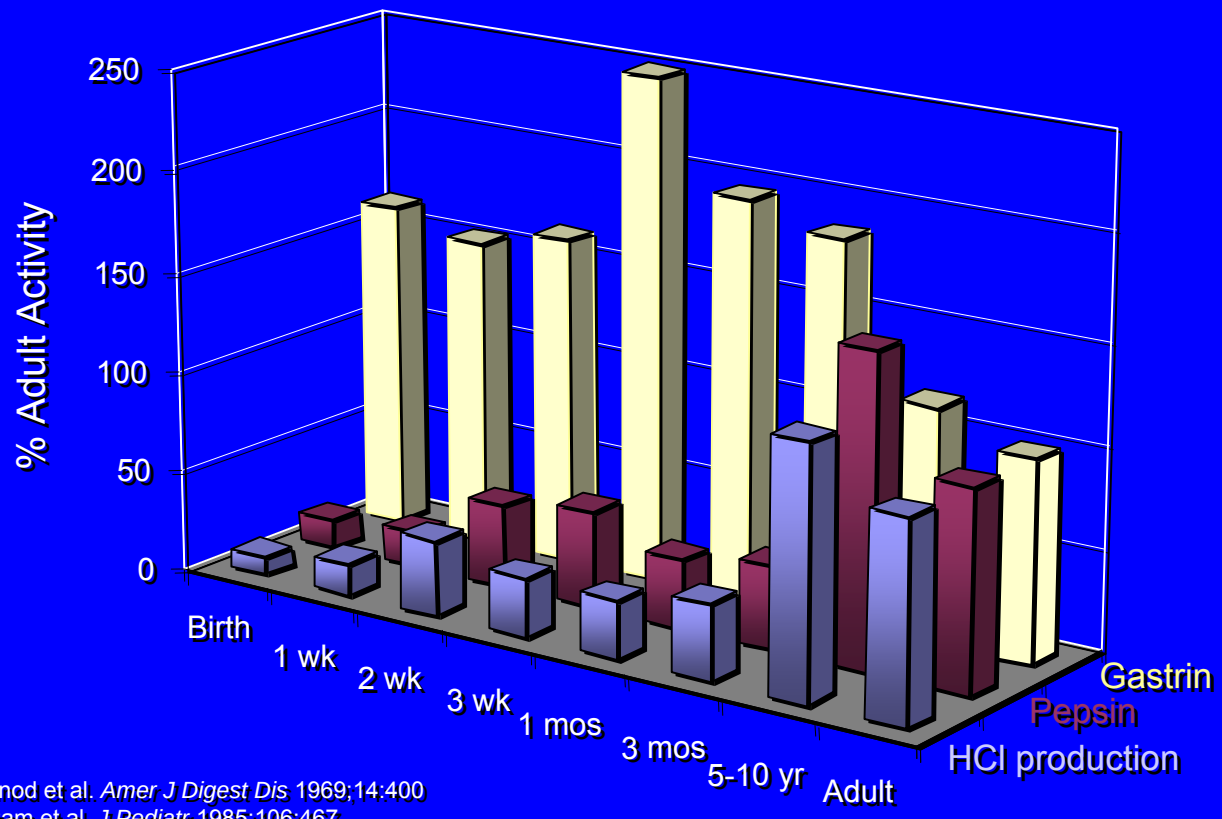
Variability

Critical Role of Pharmacokinetics in Pharmacotherapy……

- The combination of ADME dictate exposure which dictates dose.
- Exposure along with the interaction with therapeutic targets (e.g., receptors) dictates response.

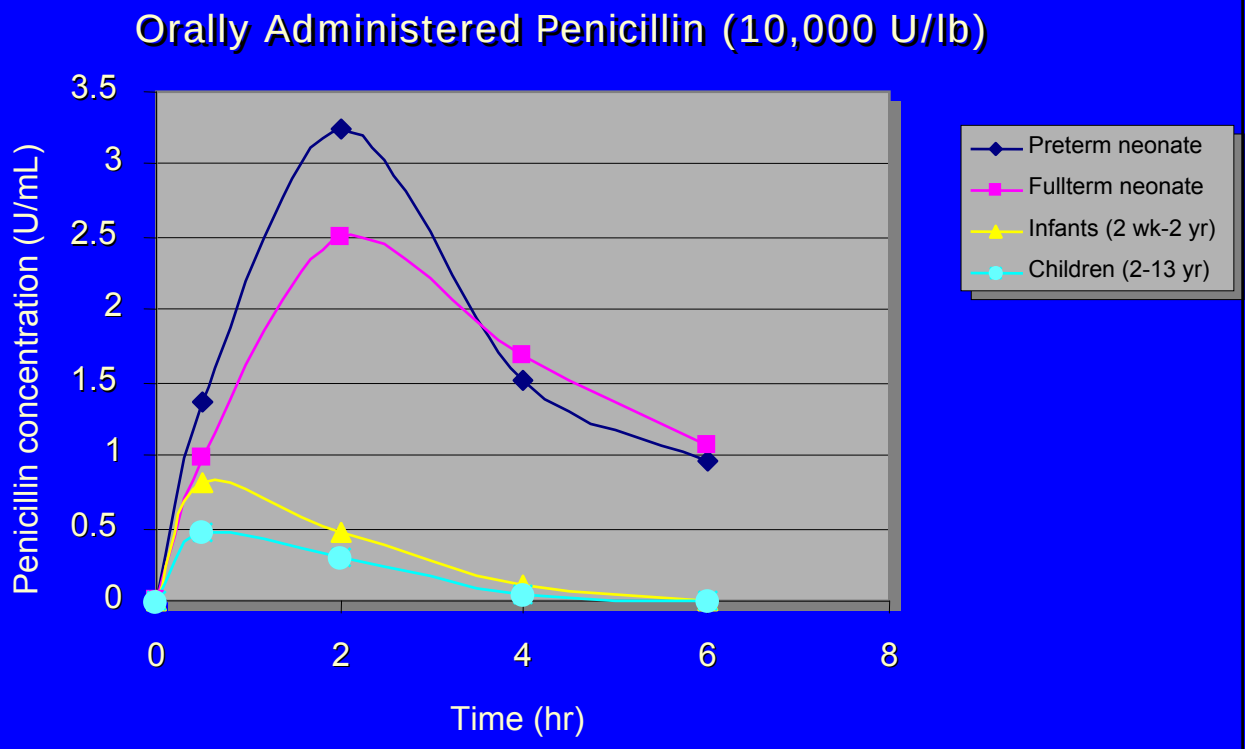


Drug Absorption
Developmental Changes in Gastric pH



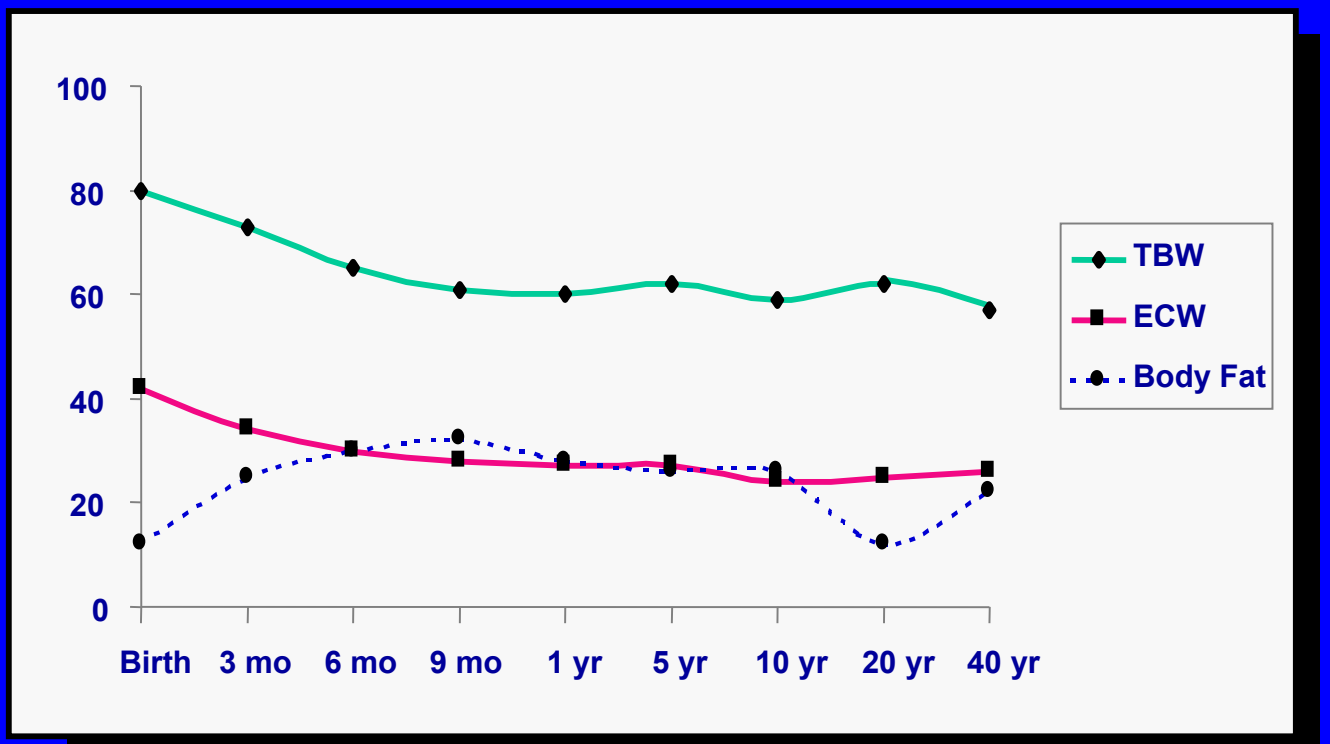
Agunod et al. *Amer J Digest Dis* 1969;14:400
Mozam et al. *J Pediatr* 1985;106:467
Rodgers et al. *J. Pediatr Surg* 1978;13:13

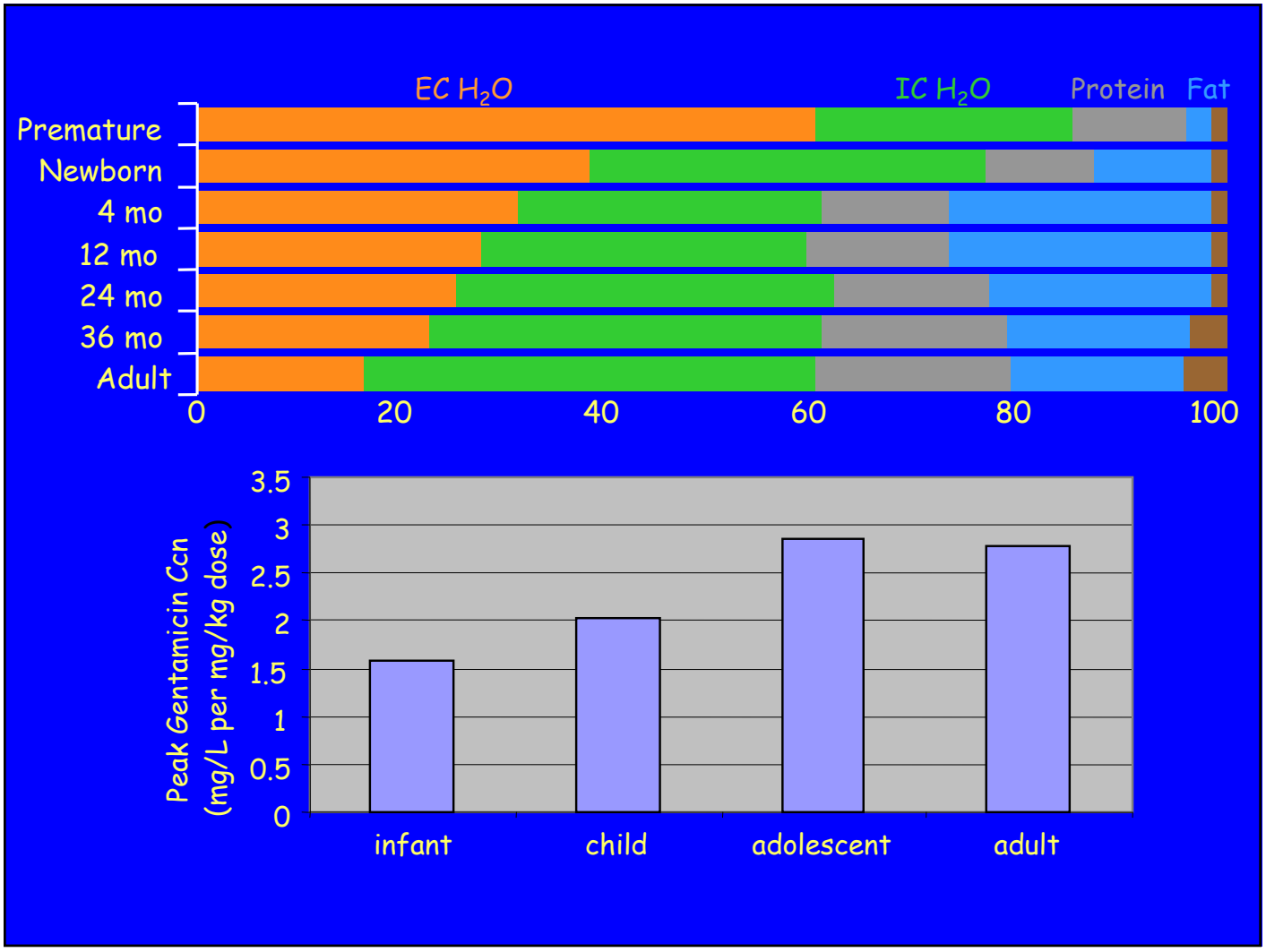
Developmental Alterations in Intestinal Drug Absorption
Influence of Higher Gastric pH



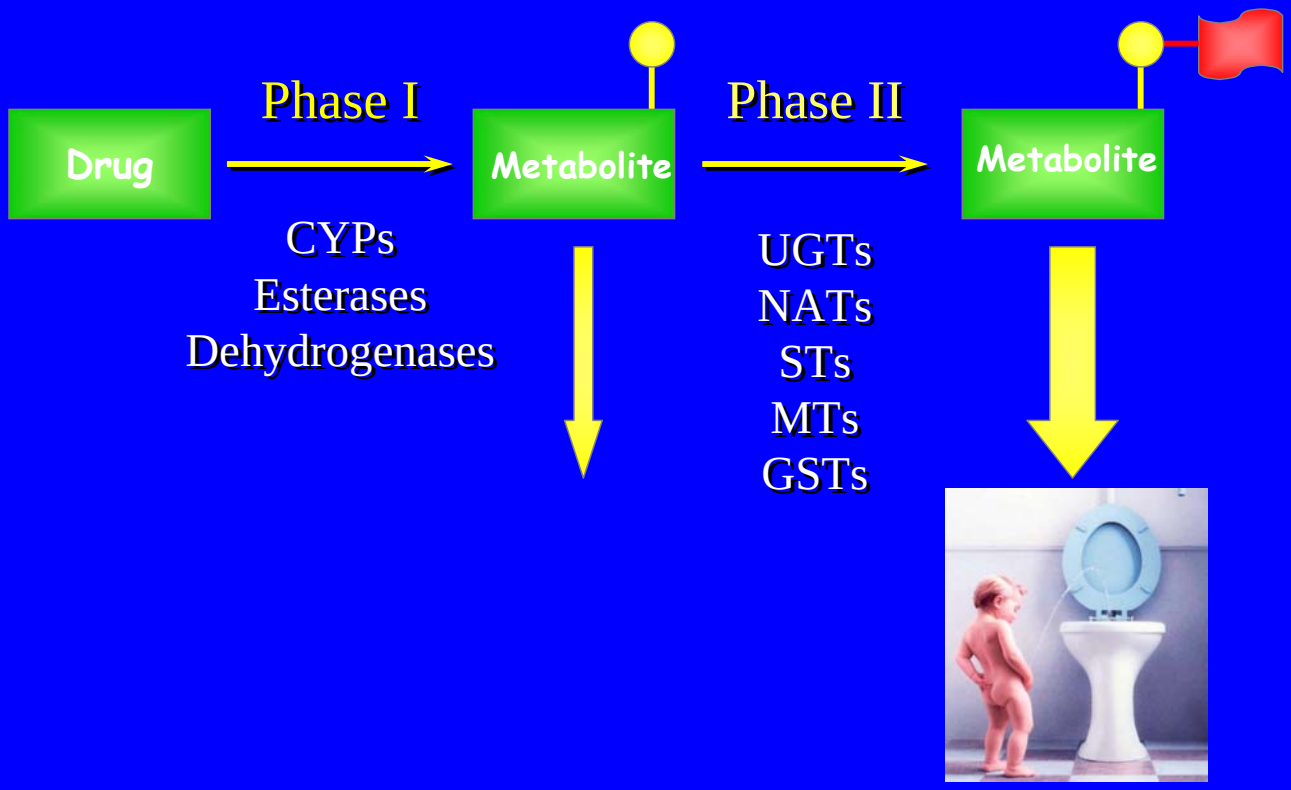
Huang et al. *J Pediatr* 1953;42:657

Drug distribution
Age-dependent changes in body composition



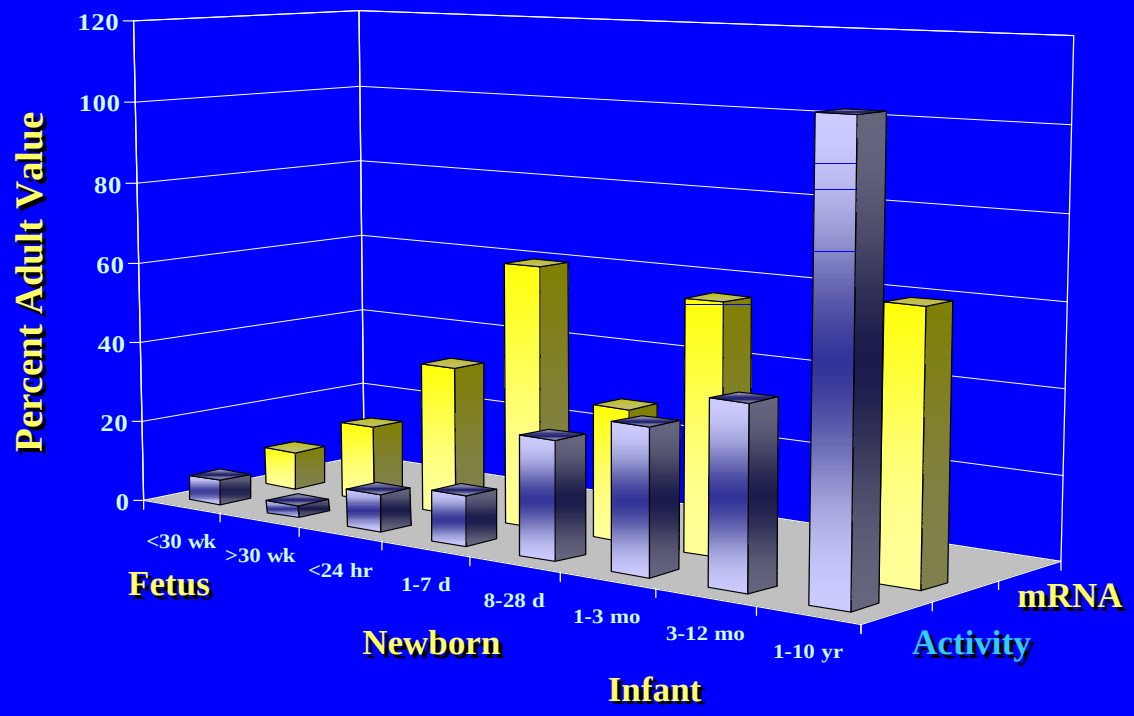

EC H_2O
IC H_2O
Protein
Fat
Premature
Newborn
4 mo
12 mo
24 mo
36 mo
Adult
0
20
40
60
80
100
Peak Gentamicin Ccn (mg/L per mg/kg dose)
3.5
3
2.5
2
1.5
1
0.5
0
infant
child
adolescent
adult

Drug Biotransformation



Ontogeny of CYP3A4

From Lacroix D et al. *Eur. J. Biochem.* 247: 625-634, 1997

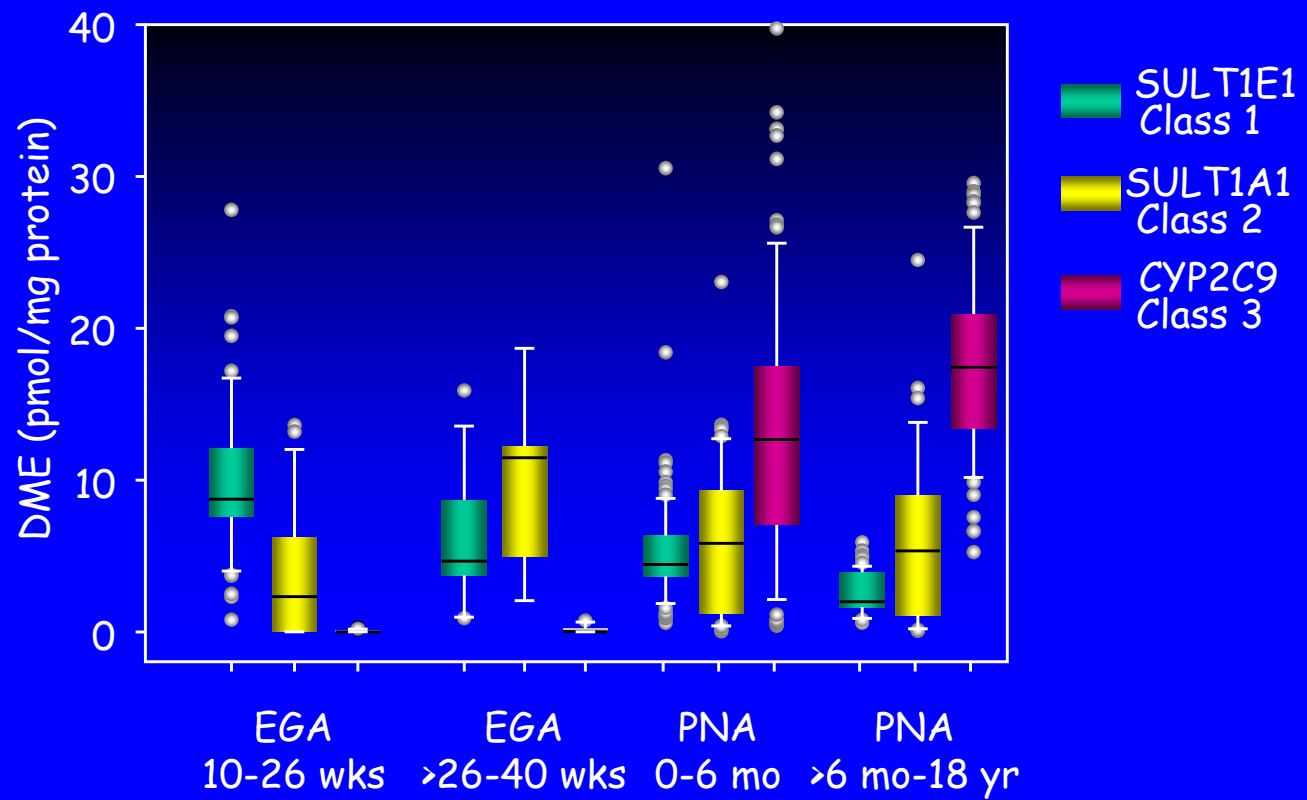


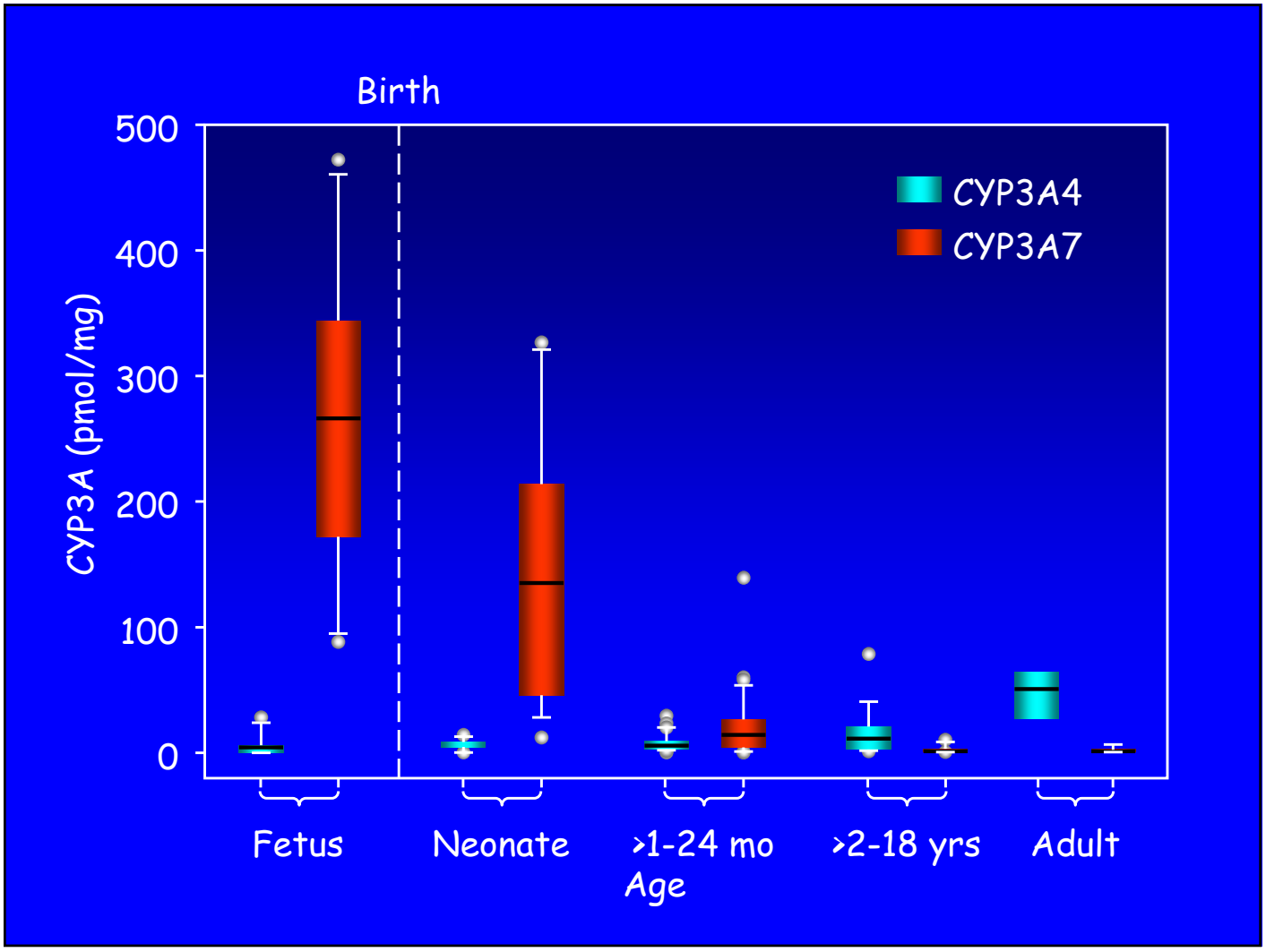
Human Hepatic DME Ontogeny

Class 1	Class 2	Class 3	
ADH1A	CYP2C19	ADH1B	EPHX2
CYP3A7	CYP3A5	ADH1C	FMO3
FMO1	GSTA1	AOX	GSTM
GSTP	GSTA2	CYP1A2	SULT2A1
SULT1E1	SULT1A1	CYP2C9	UGT1A1
SULT1A3		CYP2D6	UGT1A6
		CYP2E1	UGT2B7
		CYP3A4	PON1
		EPHX1	

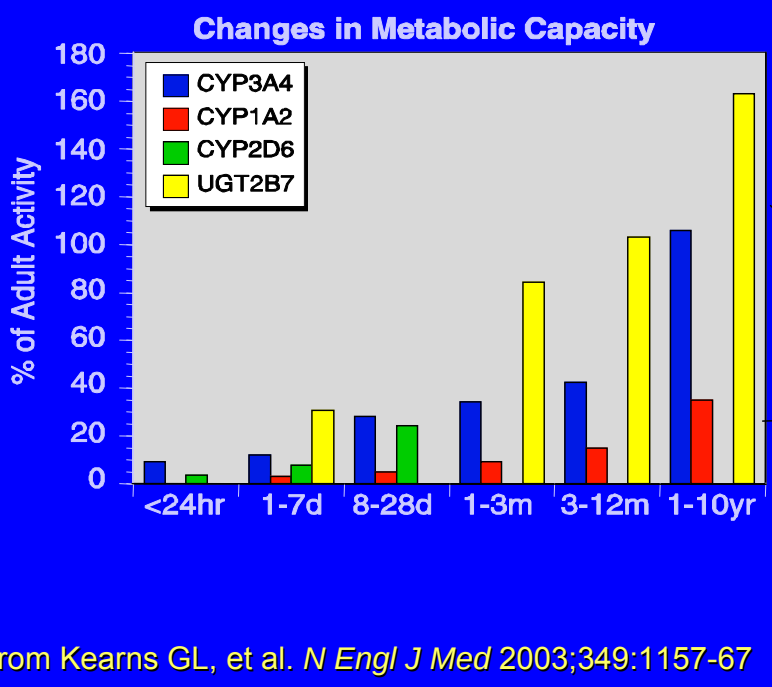
Hines, Pharmacol & Therap. 118:250-267, 2008

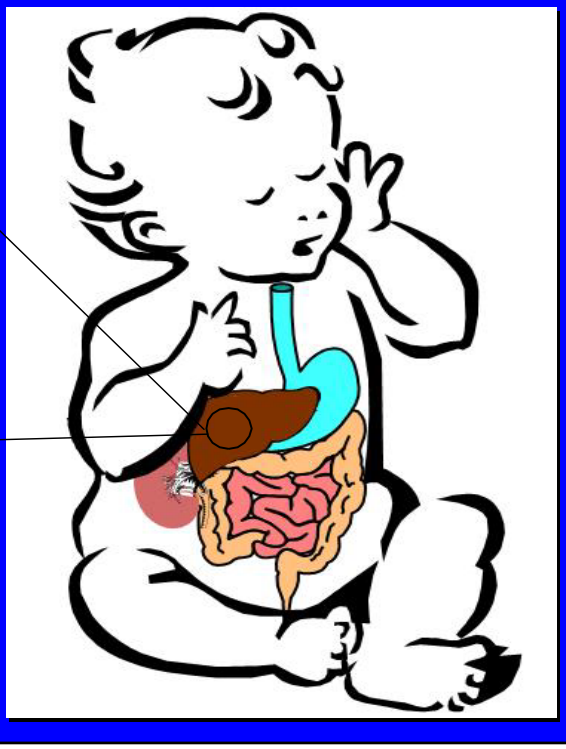
Human DME Ontogeny



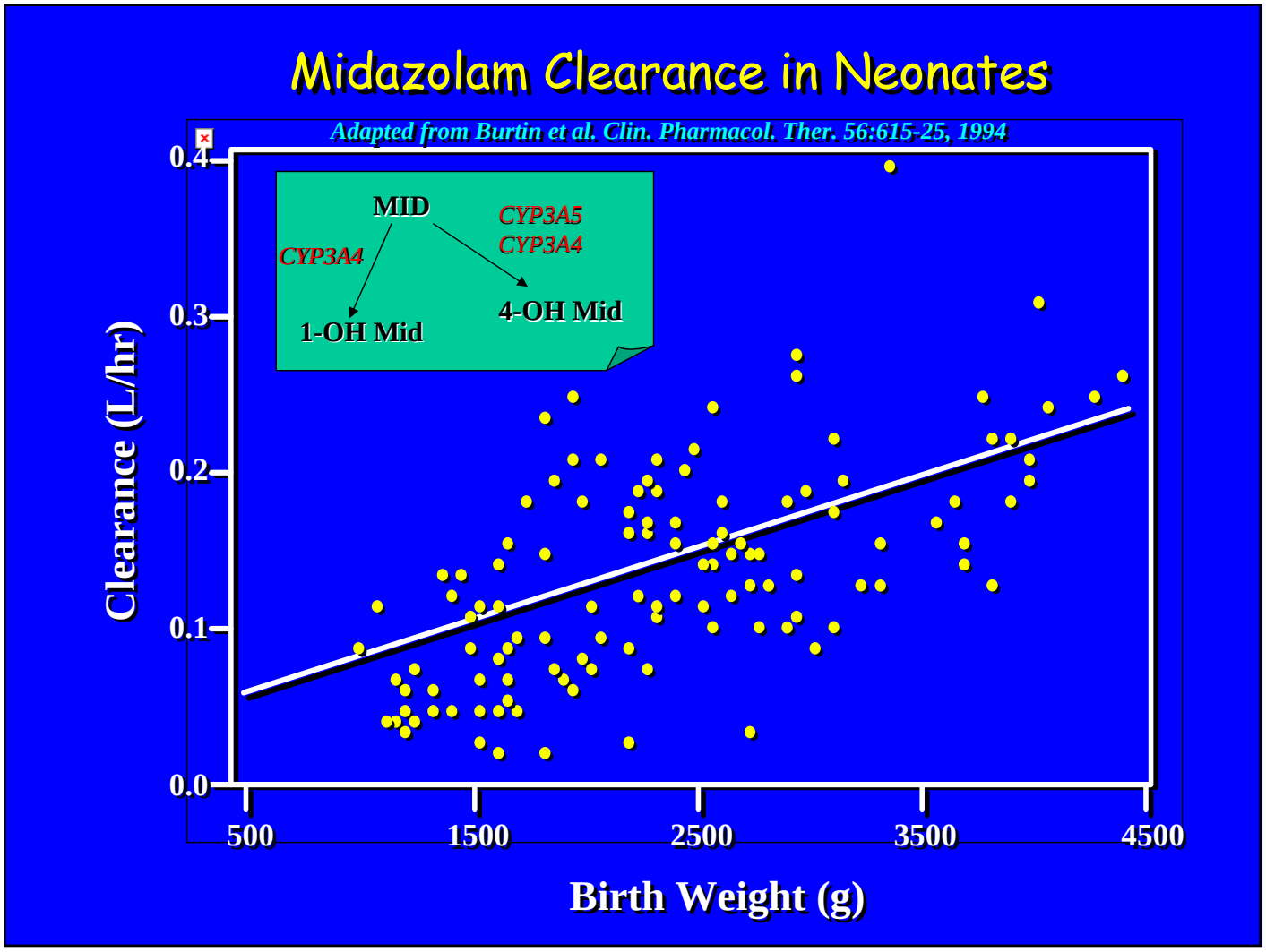

Birth
500
400
300
200
100
0
CYP3A (pmol/mg)
CYP3A4
CYP3A7
Fetus
Neonate
>1-24 mo
>2-18 yrs
Adult
Age

Impact of Ontogeny on Drug Metabolism





From Kearns GL, et al. *N Engl J Med* 2003;349:1157-67

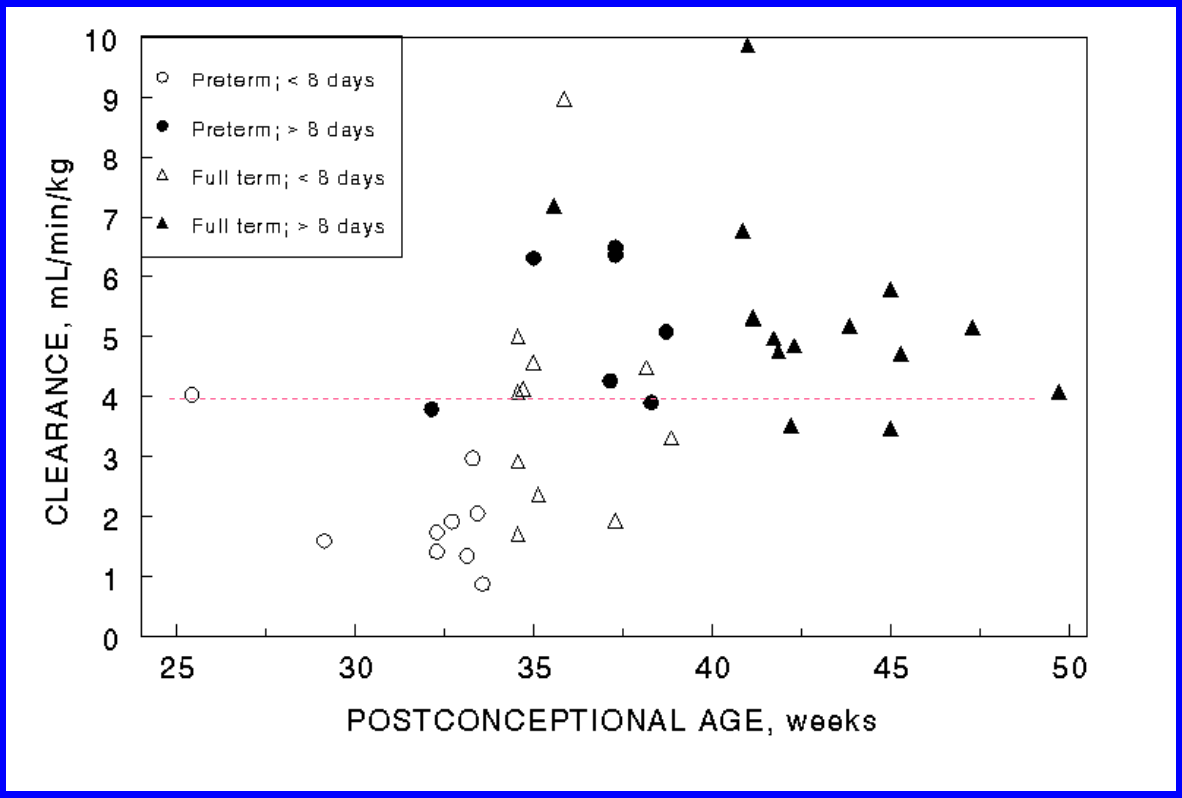

Midazolam Clearance in Neonates
Adapted from Burtin et al. Clin. Pharmacol. Ther. 56:615-25, 1994
MID
CYP3A4
CYP3A5
CYP3A4
1-OH Mid
4-OH Mid
Clearance (L/hr)
0.4
0.3
0.2
0.1
0.0
500
1500
2500
3500
4500
Birth Weight (g)

Impact of Age on Linezolid Pharmacokinetics

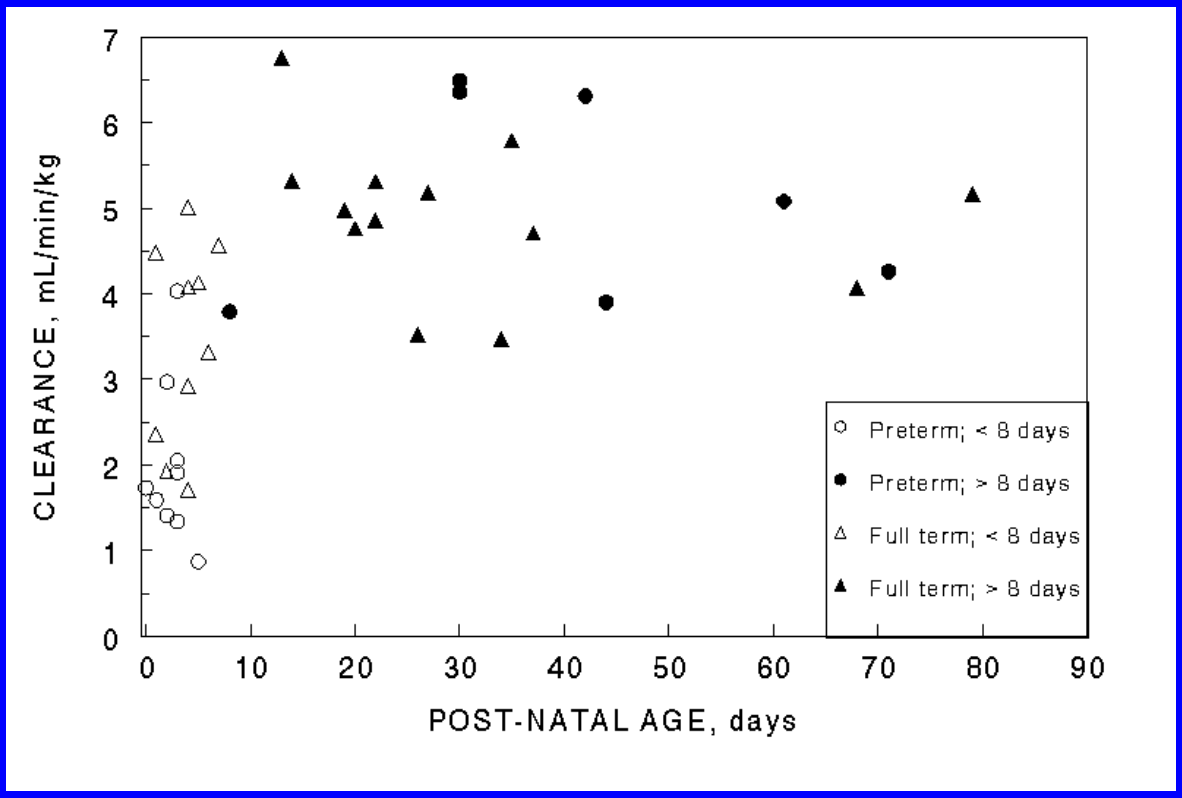
Kearns GL, Jungbluth GL, Abdel-Rahman SM, Hopkins NK, Welshman IR, Grzebyk RP, Bruss JB, van den Anker JN. Impact of ontogeny on linezolid disposition in neonates and infants. *Clin Pharmacol Ther* 2003:74(5):413-422.

Parameter	Adult (n=57)	Child (n=44)	Infant (n=10)
Vdss (L/kg)	0.63 ± 0.13	0.71 ± 0.18	0.83 ± 0.18
Cl (L/hr/kg)	0.10 ± 0.03	0.30 ± 0.12	0.52 ± 0.15
$t_{1/2}$ (hr)	4.6 ± 1.7	3.3 ± 0.9	2.0 ± 0.9
$Cmax_{norm}$ (mg/L)	19.7 ± 4.9	17.0 ± 5.2	12.5 ± 3.5
$C_{12\ pred}$ (mg/L)	3.3 ± 2.1	0.41 ± 0.72	0.03 ± 0.05
$T>MIC_{90}$ (%)	70-100%	35-70%	20-35%

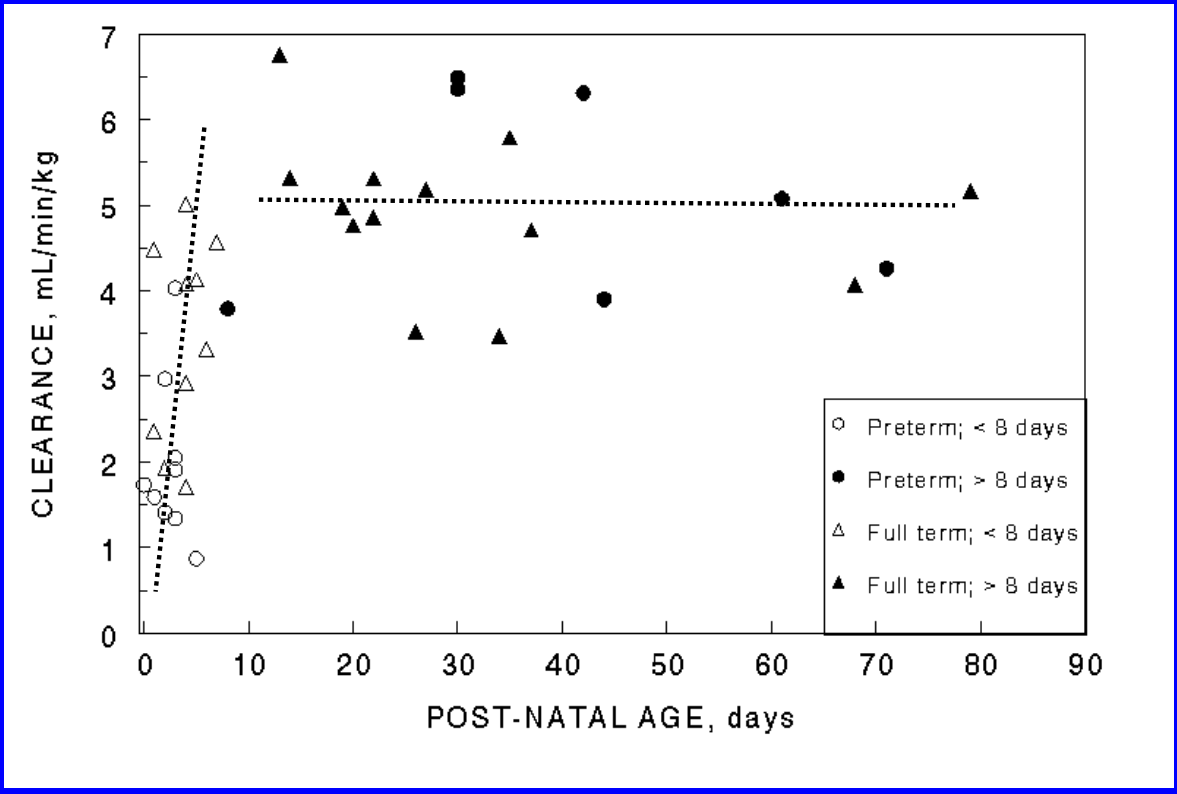
Linezolid Plasma Clearance Association with PCA



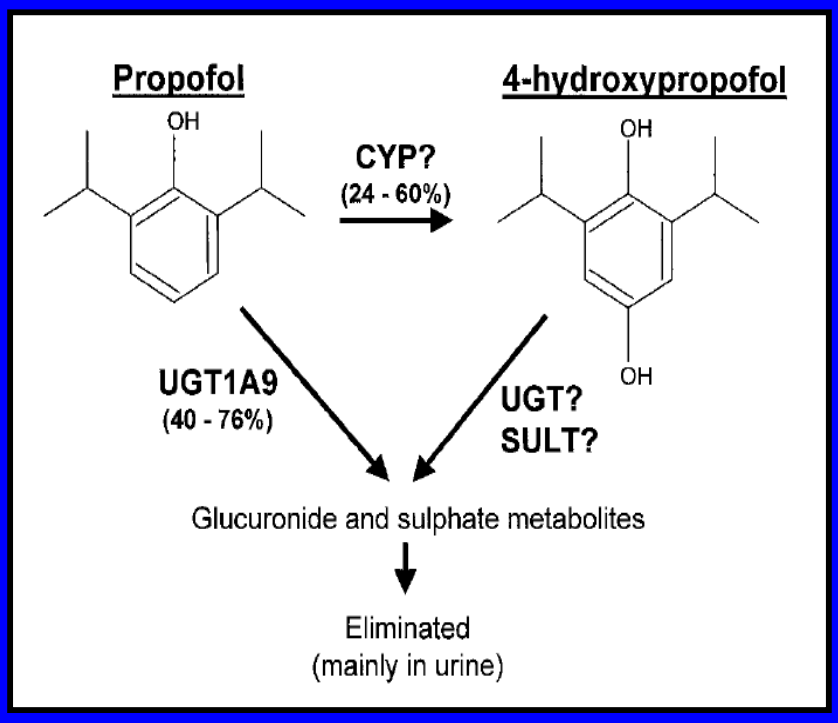
Linezolid Plasma Clearance Association with PNA

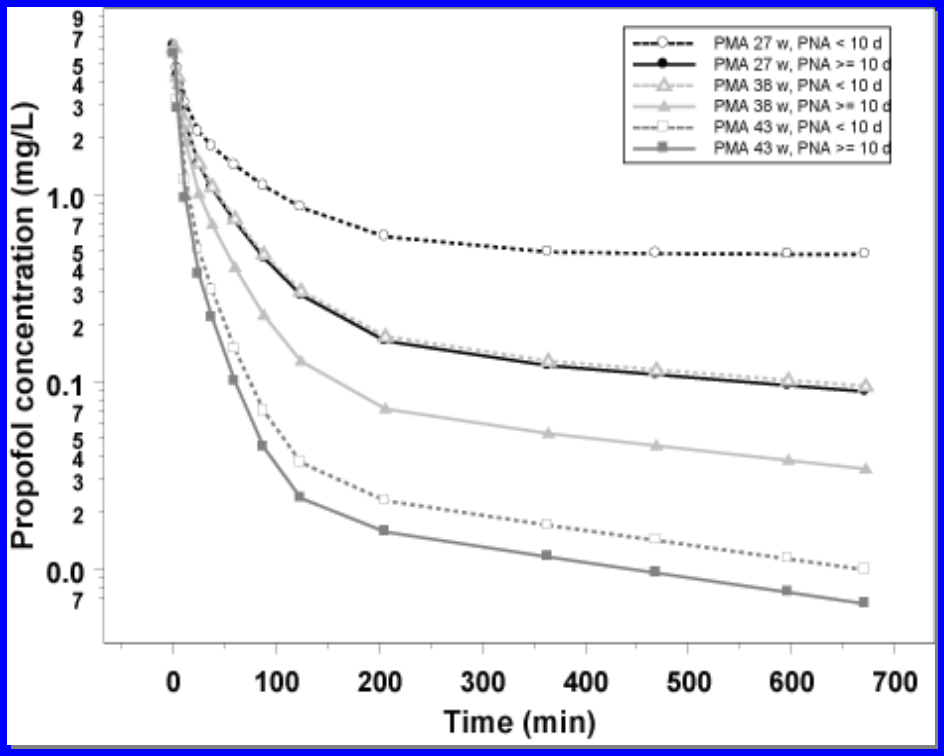


Linezolid plasma clearance in neonates

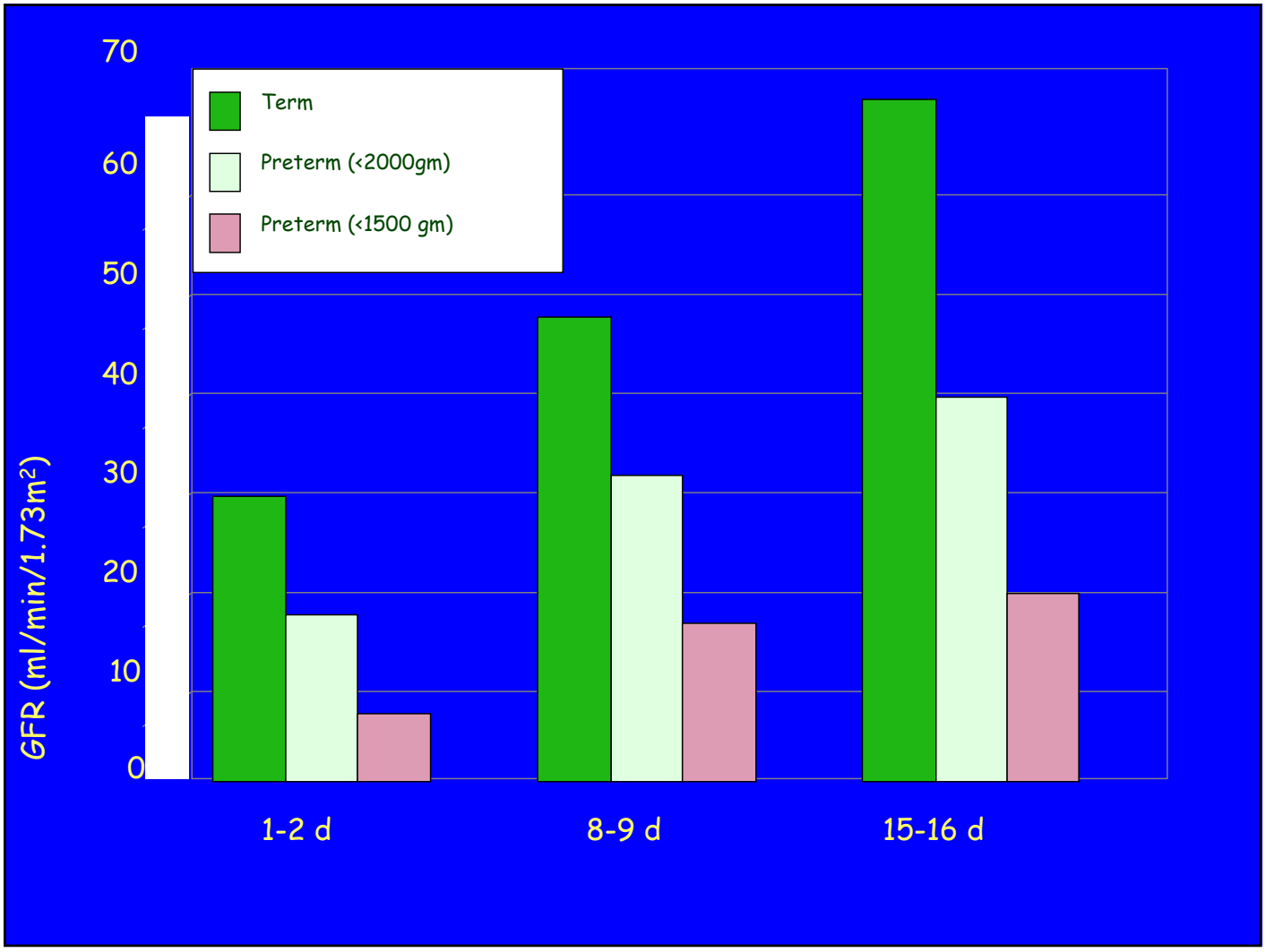


Propofol clearance almost exclusively depends on metabolic clearance





Allegaert K, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term infants. Br J Anesth 2007 dec 99(6):864-70.


70
60
50
40
30
20
10
0
GFR (ml/min/1.73m²)
Term
Preterm (<2000gm)
Preterm (<1500 gm)
1-2 d
8-9 d
15-16 d

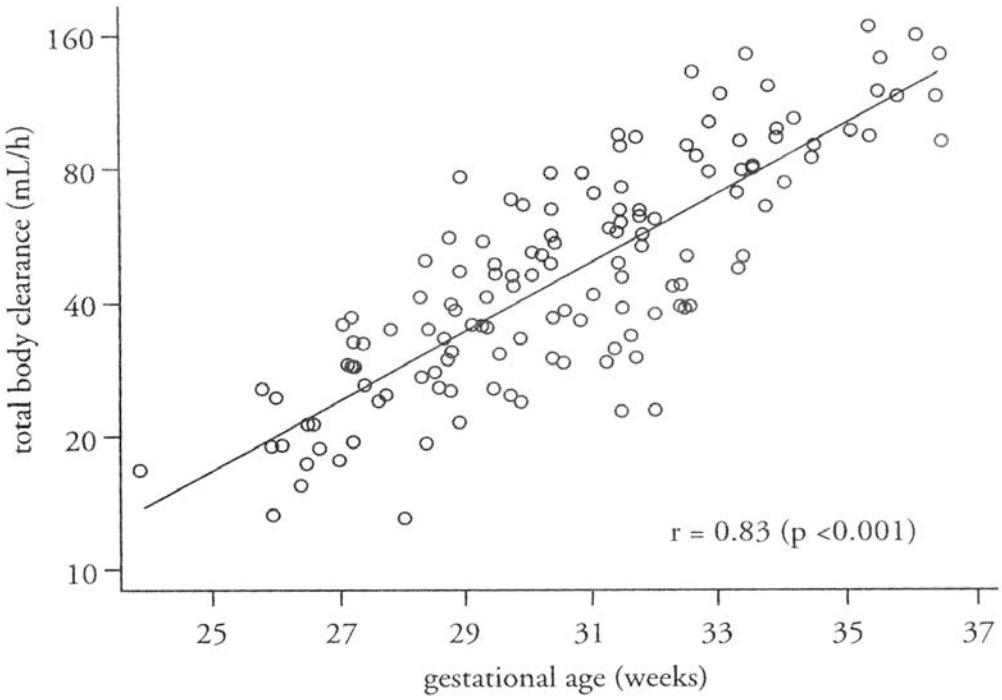
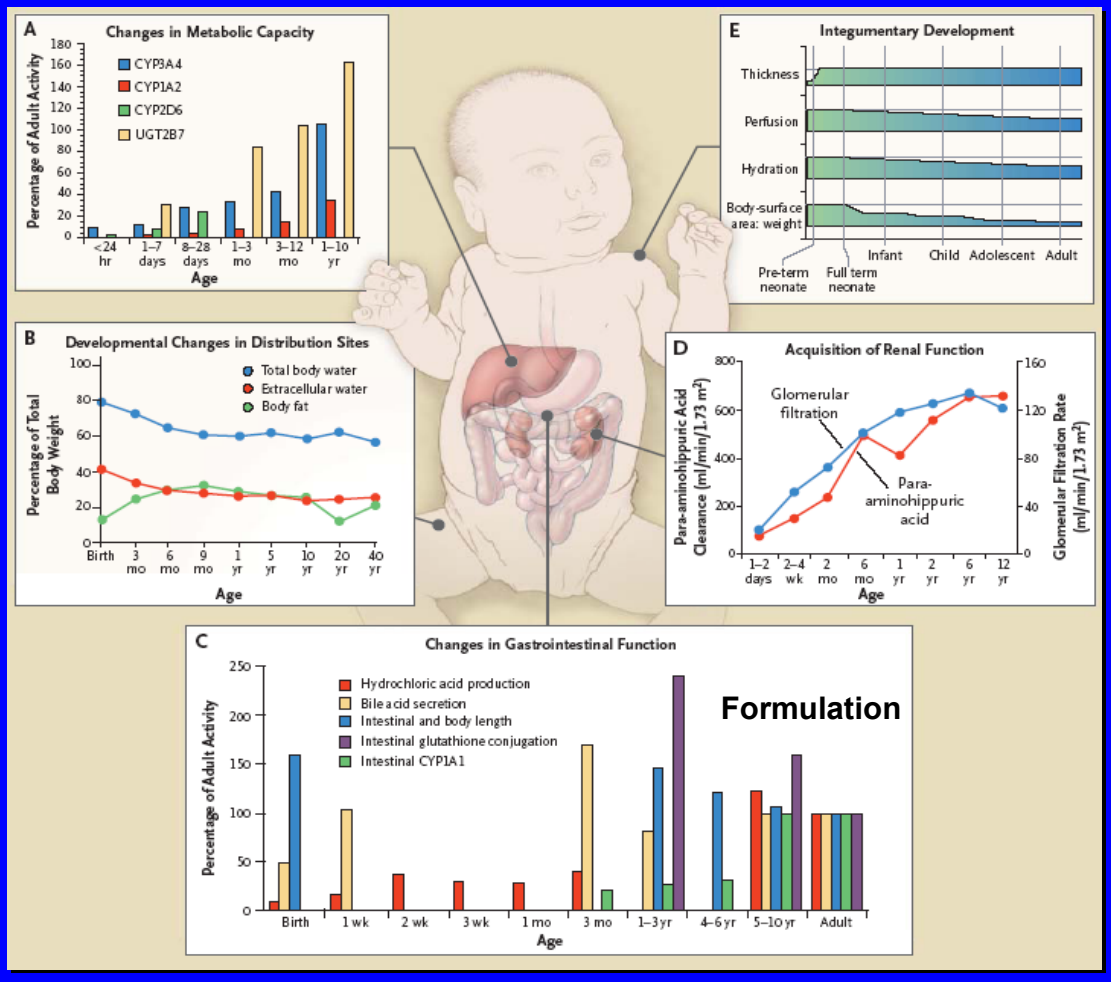


Figure 1. **Linear regression analysis of total body clearance of ceftazidime (mL/h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth. Note the logarithmically transformed vertical axis**



Ref: Kearns et al, NEJM 2003

All neonates are not created equal

- post-conceptional age
- gestational age
- postnatal age
- asphyxia at birth
- PDA
- prenatal drug exposure

These will increase variability in outcome measures

Factors influencing drug disposition in infants, children and adolescents……

- Genetics
- Environment
- Disease
- Treatment
- Growth and development

Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus

Objective: Our objective was to study the pharmacokinetics of ibuprofen in premature infants with patent ductus arteriosus on day 3 and day 5 after birth.
Methods: Ibuprofen was administered on days 3, 4, and 5 by a 15-minute intravenous infusion of 10, 5, and 5 mg/kg, respectively, with the aim of closing the ductus arteriosus. Blood samples were drawn at time zero and at 0.5, 1, 2, 4, 12, and 24 hours after the first and third doses. Ibuprofen plasma concentrations were assayed by HPLC.
Results: A total of 27 premature infants were included (gestational age, 28.6 ± 1.9 weeks; birth weight, 1250 ± 460 g; values are mean ± standard deviation). Ibuprofen pharmacokinetics followed a 2-compartment open model. Between the first and third doses (day 3 and day 5) there was a significant decrease of the volume of distribution of the central compartment (Vd_c) (0.244 versus 0.171 L/kg; $P = .03$) and area under the plasma concentration-time curve (524 versus 447 mg · h/L; $P = .01$). The decrease in Vd_c was most pronounced in patients with a closing ductus. Total body clearance and plasma half-life did not change significantly. No significant differences were observed in ibuprofen peak plasma concentrations after the first and third doses in relation to ductal status after treatment.
Conclusion: Ibuprofen pharmacokinetics showed a large interindividual variation in premature infants during treatment for patent ductus arteriosus, and significant changes may occur between day 3 and day 5 after birth in those infants with a closing ductus. These findings may have implications for the treatment schedule with ibuprofen in patients with patent ductus arteriosus. (Clin Pharmacol Ther 2001;70:336-43.)

Bart Van Overmeire, MD, PhD, Daan Touw, PharmD, PhD, Paul J. C. Schepens, PhD, Gregory L. Kearns, PharmD, and John N. van den Anker, MD, PhD
Edegem and Wilrijk, Belgium, Amsterdam and Rotterdam, The Netherlands, Kansas City, Mo, and Columbus, Ohio

Elevated Morphine Concentrations in Neonates Treated With Morphine and Prolonged Hypothermia for Hypoxic Ischemic Encephalopathy

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[a]First Department of Paediatrics, Semmelweis University, Budapest, Hungary; [b]Research Group of Paediatrics and Nephrology, Hungarian Academy of Sciences, Budapest, Hungary; [c]Division of Clinical Sciences, Hammersmith Campus, Imperial College London, United Kingdom

The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Data obtained in adults indicate that even short-term hypothermia may have an effect on the metabolism of major analgesics and other drugs. No data are available for neonates concerning the impact of hypothermia on the pharmacokinetics of morphine.

What This Study Adds

The aim of our observational study, therefore, was to investigate whether morphine pharmacokinetics are altered during prolonged moderate systemic hypothermia in asphyxiated neonates, resulting in excessively high morphine concentrations compared with infants kept at normothermia; this would be important information for clinicians wishing to provide hypothermia.

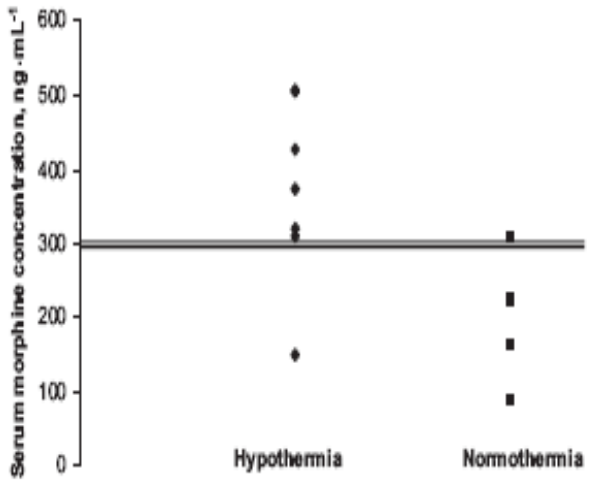


FIGURE 1
Serum morphine concentrations at 72 hours after birth in asphyxiated neonates treated with hypothermia or on normothermia. At this time point, 6 of 7 infants in the hypothermia group and 1 of 6 in the normothermia group had potentially toxic morphine serum levels >300 ng/mL ($P = .007$).

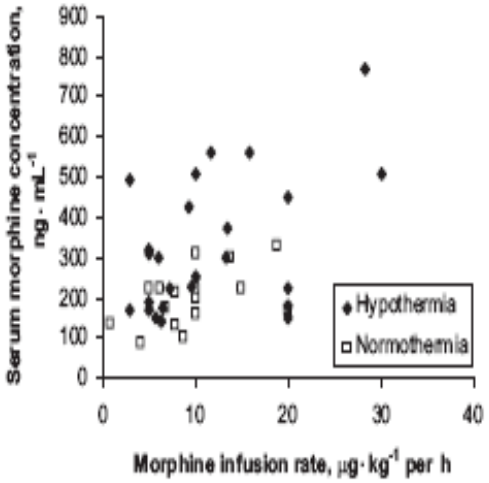


FIGURE 2
Relation between serum morphine concentrations and infusion rates in asphyxiated neonates treated with hypothermia or on normothermia. Morphine concentrations at 24, 48, and 72 hours after birth were related to infusion rate (averaged over previous 24 hours) and hypothermia (adjusted $r^2 = 0.527$; $P \leq .0001$).

PHARMACOGENETICS

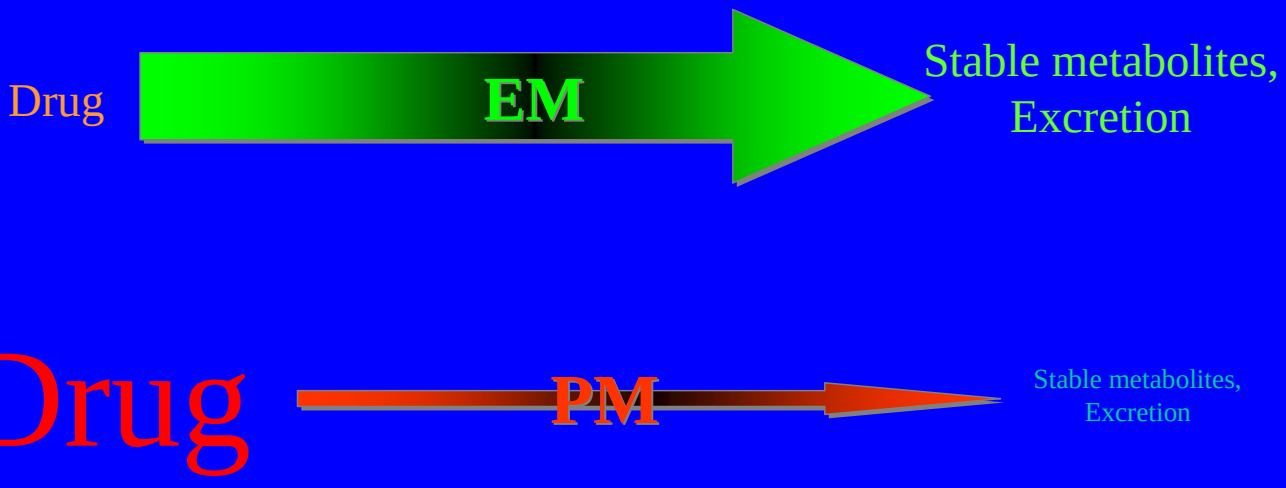
The study of the role of genetic factors in drug disposition, response and toxicity - relating variation in human genes to variation in drug responses at the level of the individual patient (the right drug for the right patient)

Some important milestones in the history of pharmacogenomics

1866 Mendel Lays down the principles of heredity
1909 Garrod Publication of 'Inborn Errors of Metabolism'
1932 Snyder Characterization of the *phenylthiourea-non-taster* as an autosomal recessive trait
1954 Hughes *et al.* Relates isoniazid neuropathy to metabolism –n-acetyltransferase
1956 Carson *et al.* Discovery of glucose G-6 PD deficiency
1957 Kalow Characterizes acetylcholinesterase deficiency
1957 Motulsky Inherited differences in drug metabolism
1957 Vogel Coins the term 'pharmakogenetik'
1960 Price Evans Characterization of acetylators polymorphisms
1962 Kalow The first textbook on pharmacogenetics
1979 Eichelbaum*et al.* Describes sparteine metabolism polymorphism
1982 Eichelbaum *et al.* Recognition of link between sparteine and debrisoquine metabolism
1984 Wedlund *et al.* Description of the cytochrome CYP2C19 polymorphism
1988 Gonzalez Explanation for the debrisoquine phenotype
1997 Yates *et al.* Polymerase chain reaction (PCR) based methods used to detect thiopurine


slow
CYP2D6
intermediate
rapid
ultrarapid
anti-depressants,
anti-psychotics,
anti-arrhythmics,
beta-blockers,
pain medications,
anti-emetics,
anti-cancer drugs
CYP2C19
Poor
metabolizer
normal
anti-convulsants,
proton pump inhibitors,
benzodiazepines,
anti-malarials

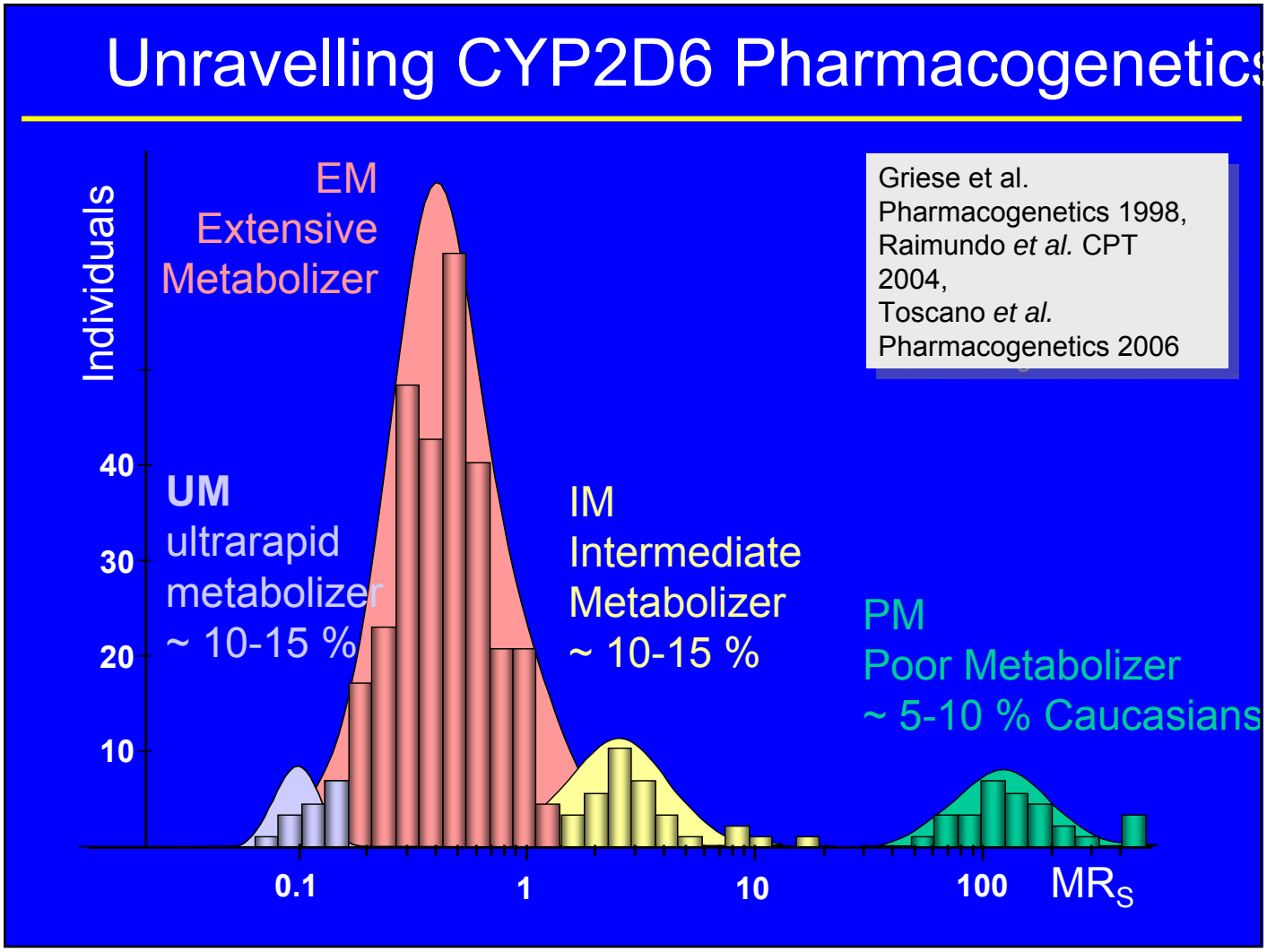
CYP2D6 Pharmacogenetics



"Functional" overdose

CYP2D6 Pharmacogenetics

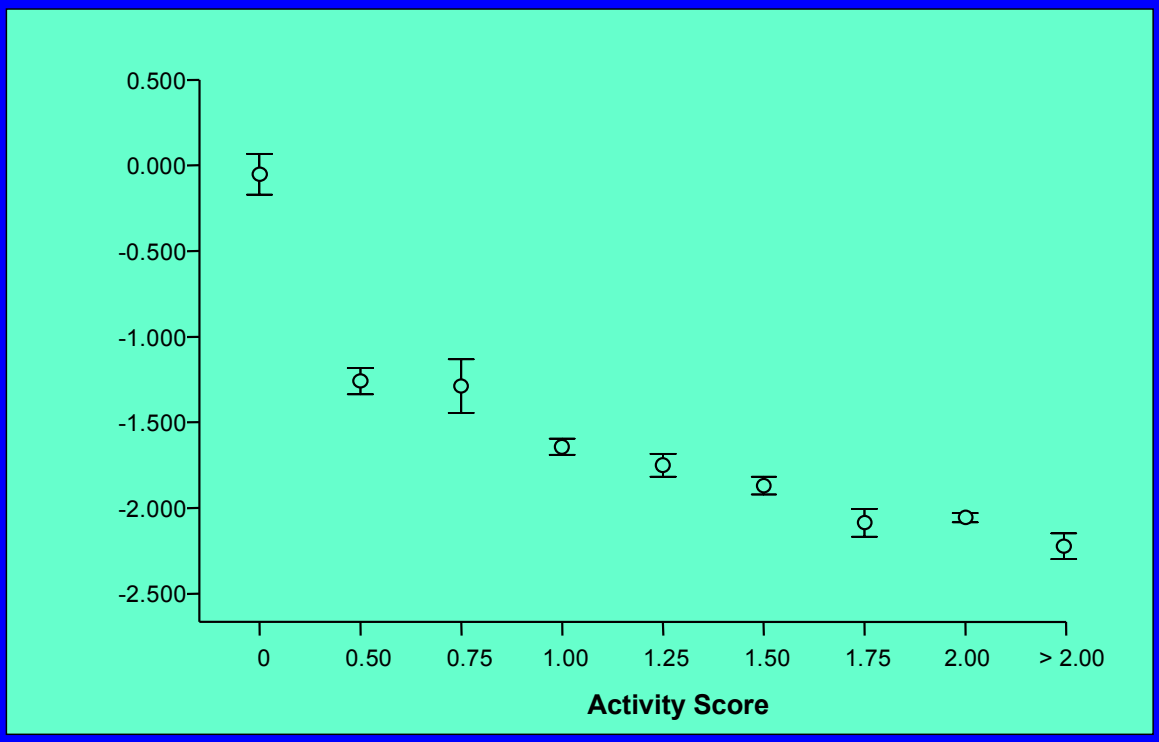
- CYP2D6 activity displays bimodal distribution in Caucasian subjects
- 5-10% of Caucasian population deficient in CYP2D6 activity
- “Poor metabolizers” or “PMs” have two “inactive” forms (alleles) of the CYP2D6 gene
- PMs at increased risk for concentration-dependent side effects with “normal” drug doses
- Some drugs may not work (codeine; tramadol)


Unravelling CYP2D6 Pharmacogenetics
Individuals
40
30
20
10
EM
Extensive
Metabolizer
UM
ultrarapid
metabolizer
~ 10-15 %
IM
Intermediate
Metabolizer
~ 10-15 %
PM
Poor Metabolizer
~ 5-10 % Caucasians
Griese et al.
Pharmacogenetics 1998,
Raimundo et al. CPT
2004,
Toscano et al.
Pharmacogenetics 2006
0.1
1
10
100
MRS

Inferring CYP2D6 Phenotype from Genotype: "Activity Score"

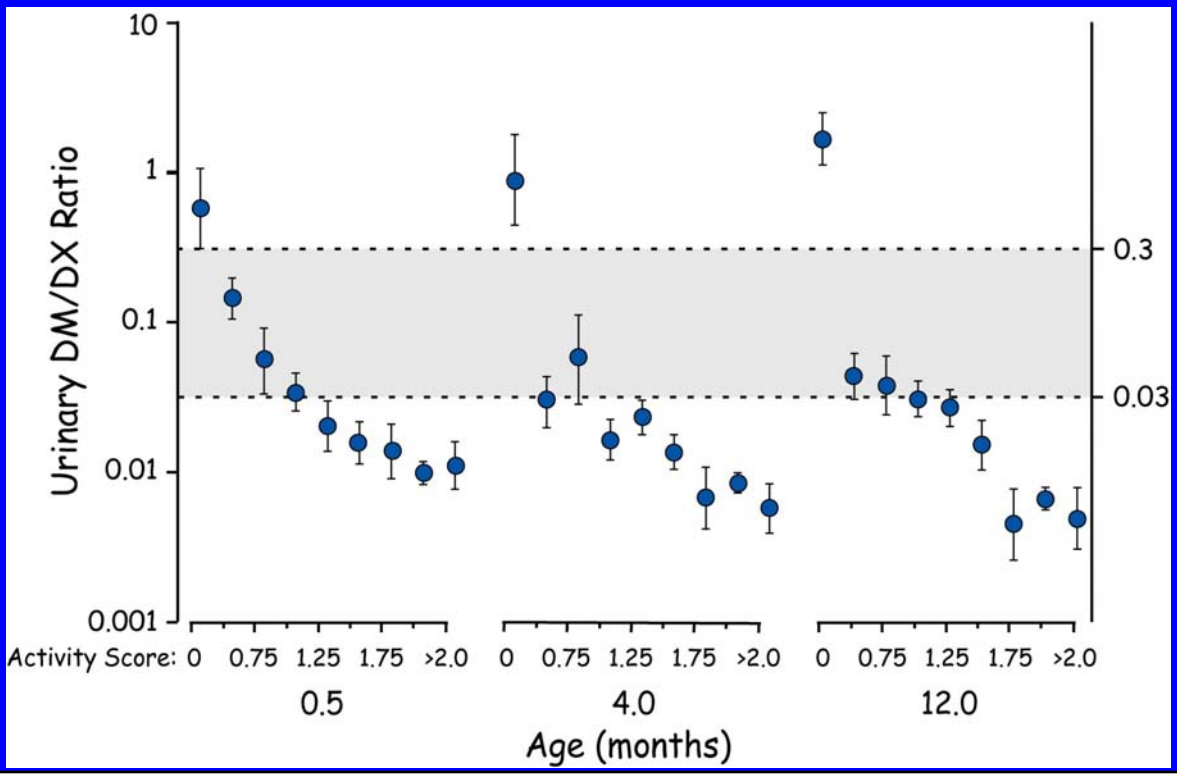
2	*1x2, *2x2
1	*1, *2, *10x2, *35, *41[2988G]
0.75	*9, *29, *45, *46
0.5	*10, *17, *41[2988A]
0	*3, *4, *5, *6, *7, *8, *11, *12, *15, *36, *40, *42

Relationship between CYP2D6 activity (DM/DX) and Activity Score

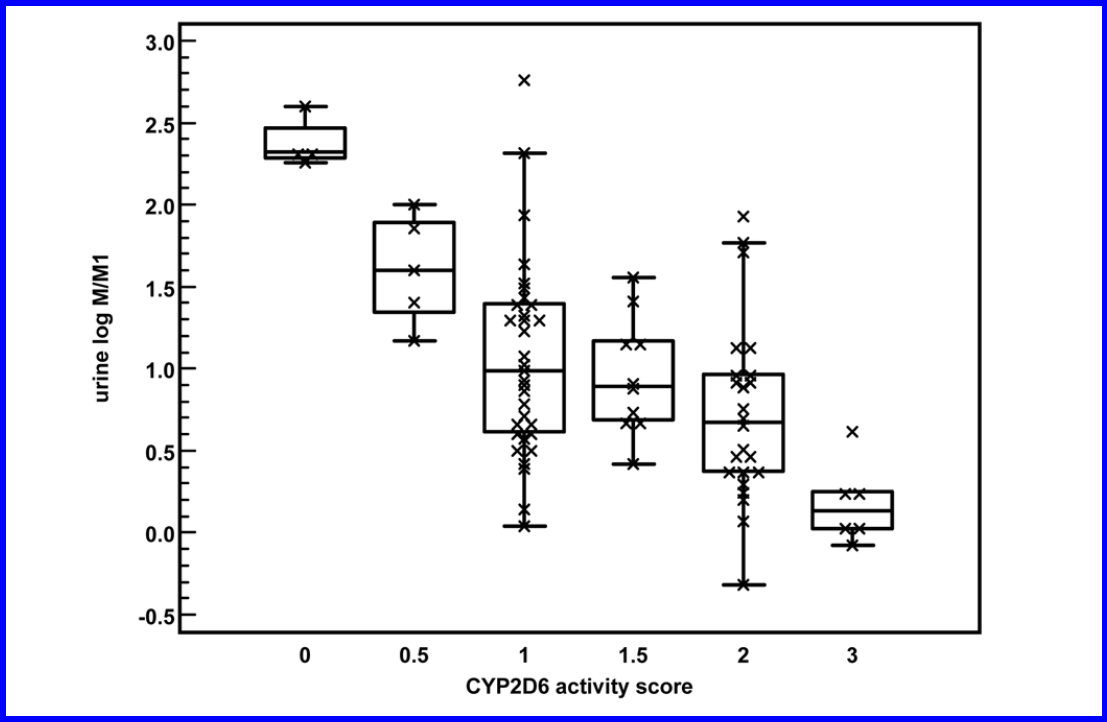


Blake M, et al. 2007

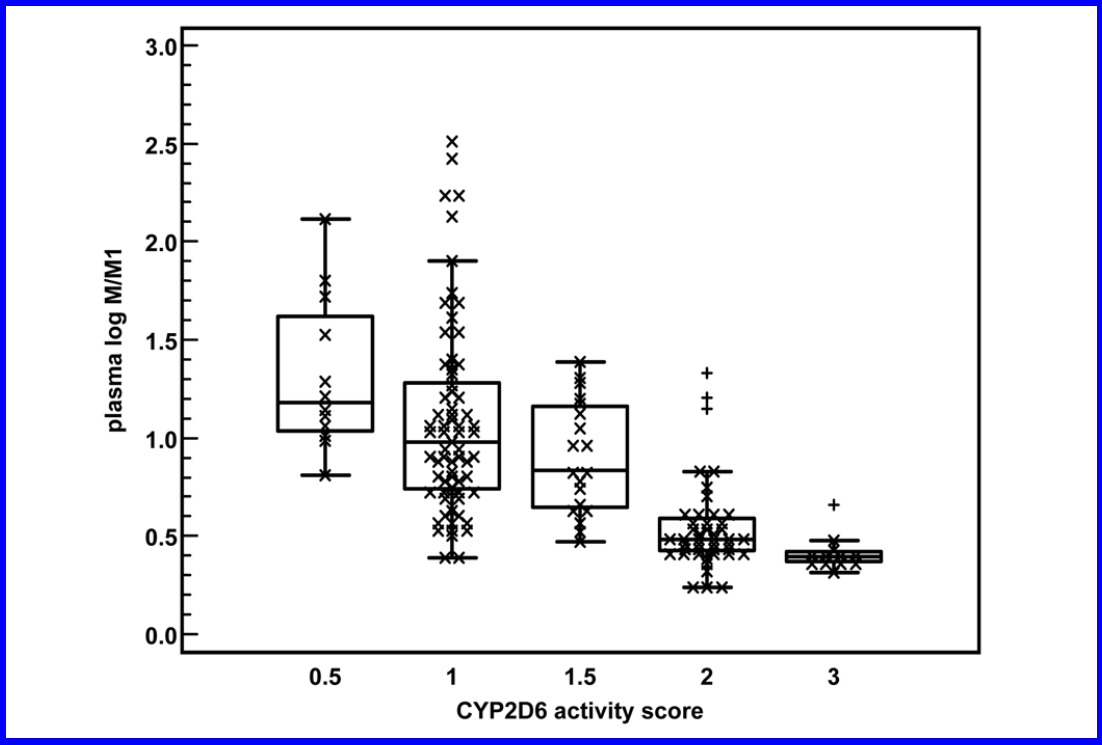
CYP2D6 Genotype-Phenotype Correlation in First Year of Life



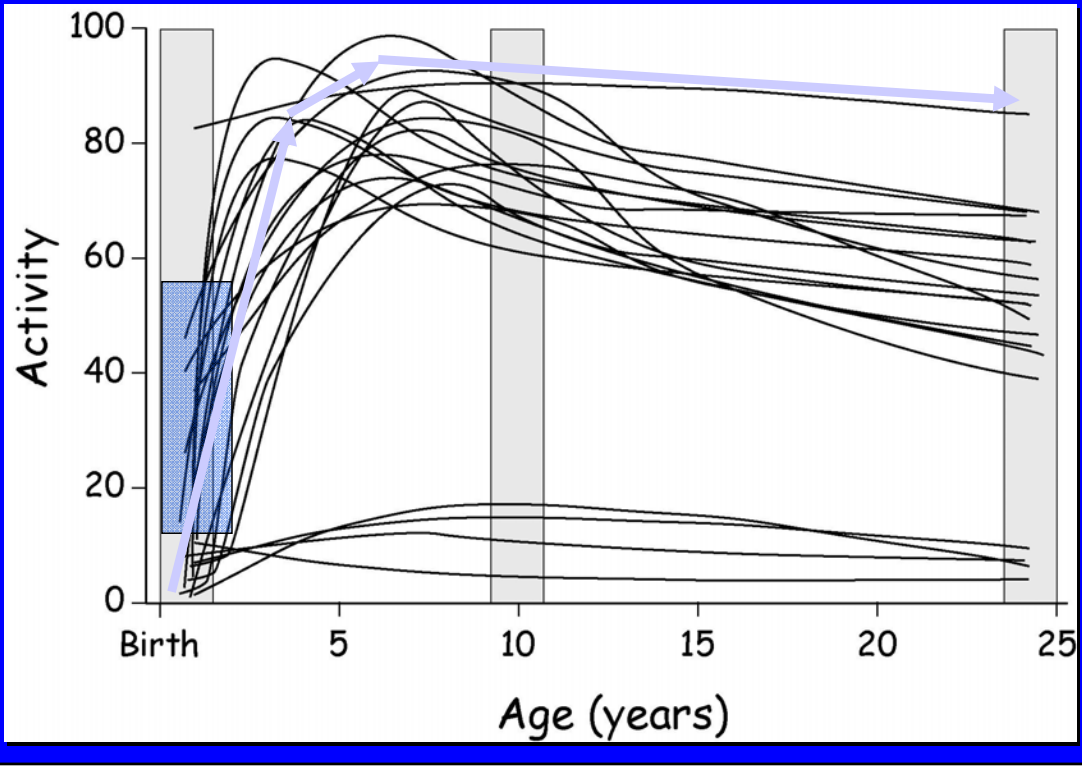
Postmenstrual Age and CYP2D6 Polymorphisms Determine Tramadol O-Demethylation in Critically ill Neonates and Infants (Allegaert K, van den Anker JN, et al. Pediatr Res, 2008)

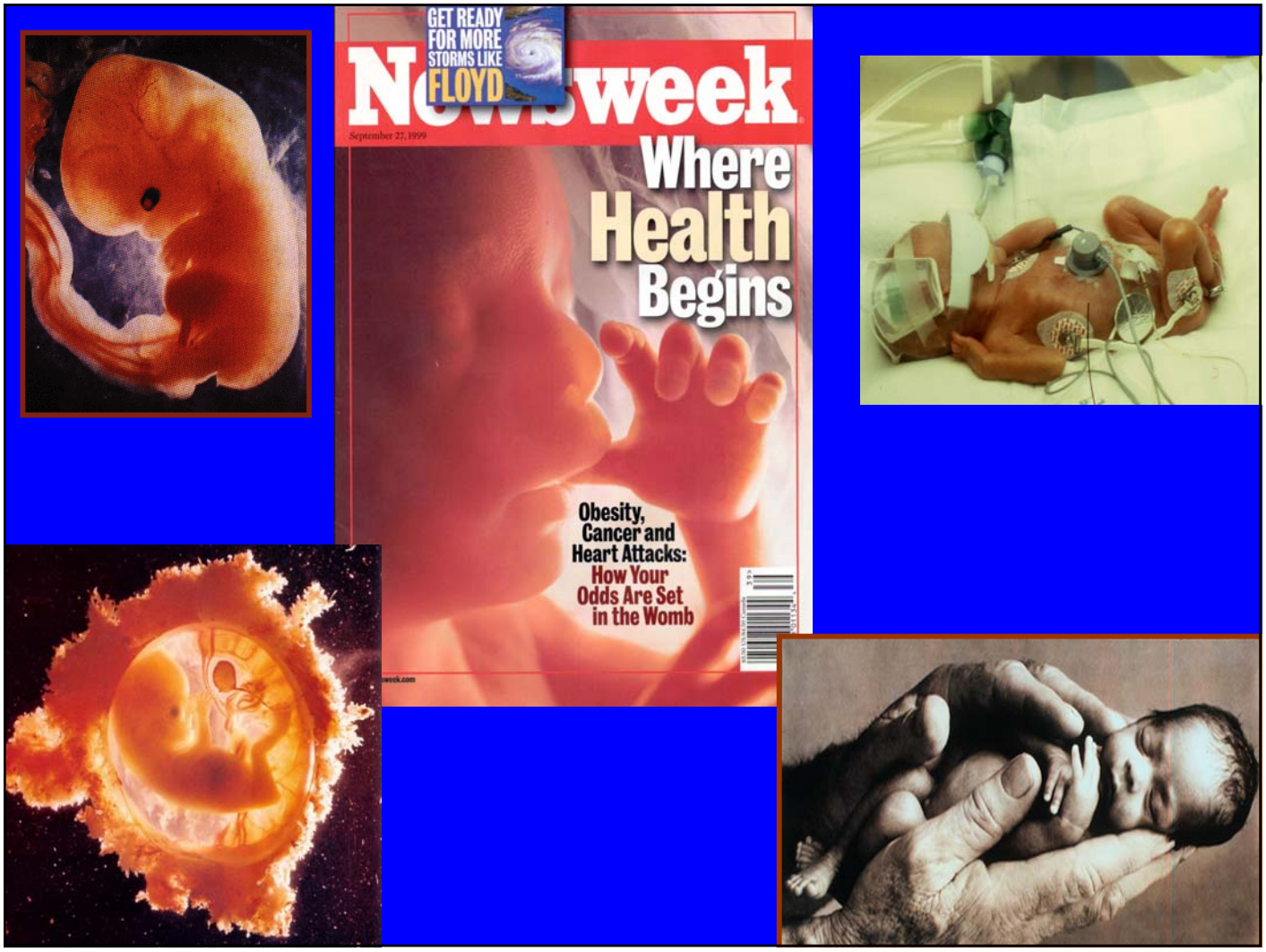


Postmenstrual Age and CYP2D6 Polymorphisms Determine Tramadol O-Demethylation in Critically ill Neonates and Infants (Allegaert K, van den Anker JN, et al. Pediatr Res, 2008)



Developmental Trajectories: Pediatric Pharmacogenetics




GET READY FOR MORE STORMS LIKE FLOYD
Newsweek
September 27, 1999
Where Health Begins
Obesity, Cancer and Heart Attacks: How Your Odds Are Set in the Womb

Case Report

Lancet 2006; 368: 704

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

- full-term healthy male infant
- day 7 pp: intermittent periods of difficulty in breastfeeding
- day 11: the baby had regained his birthweight
- day 12: grey skin, milk intake had fallen
- day 13: the baby was found dead

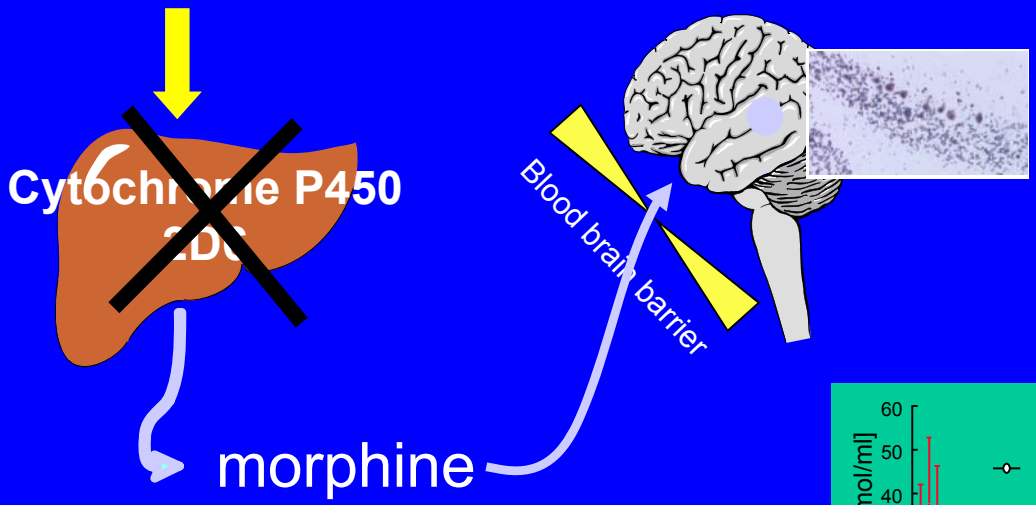
- autopsy: no abnormality
- blood concentration of morphine (metabolite of codeine):

70 ng/mL versus 0-2.2 ng/mL (typical)

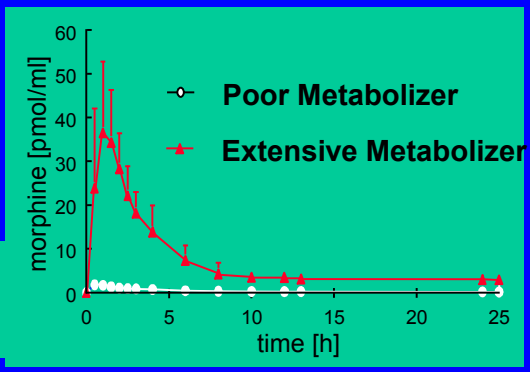
Pharmacogenetics of Codeine

codeine

site of action



plasma morphine levels
after 170 mg codeine p.o.



Eckhardt *et al.*, Pain 199

Case Report

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Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

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Explanation:

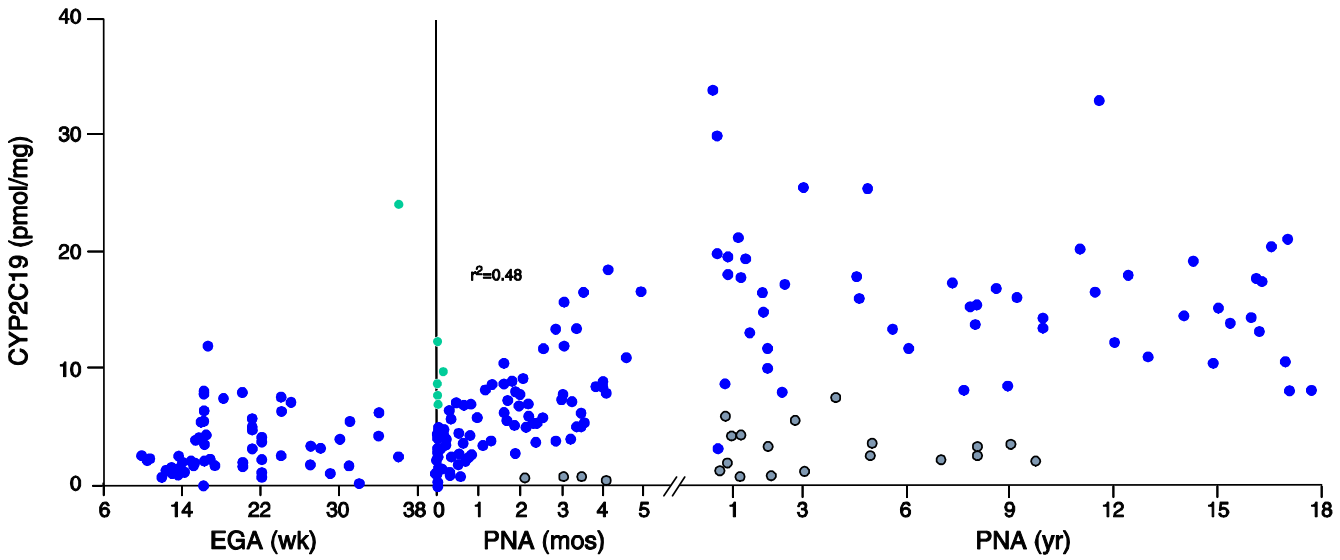
- medication mother due to episiotomy pain:
  codeine 60 mg plus paracetamol 1000 mg every 12 hrs for 2 weeks
- Morphine concentration in stored milk: 87 ng/mL
- mother: CYP2D6 genotype: *CYP2D6*2x2* gene duplication

= Ultra rapid metabolizer phenotype

CYP2C19 Pharmacogenetics

- 1984: Unusual sedation in a subject receiving anticonvulsant mephenytion
- Impaired 4-hydroxylation of *S*-mephenytoin
- Affects 2-5% of Caucasians; 20-25% of Asians
- Affected drugs include omeprazole, lansoprazole, pantoprazole, diazepam
- Major clinical consequence at present related to omeprazole pharmacodynamics and efficacy

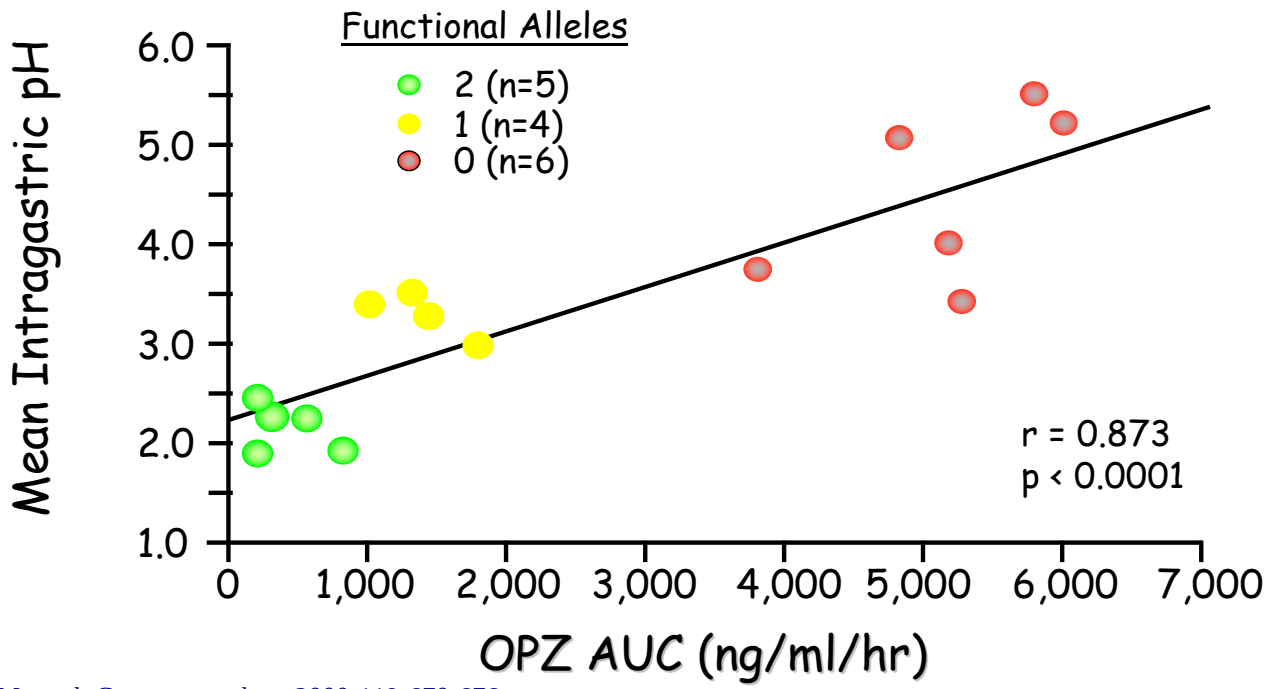
Developmental Alterations in CYP2C19 Expression



Koukouritaki et al. *J Pharmacol Exp Ther* 2004;308:965

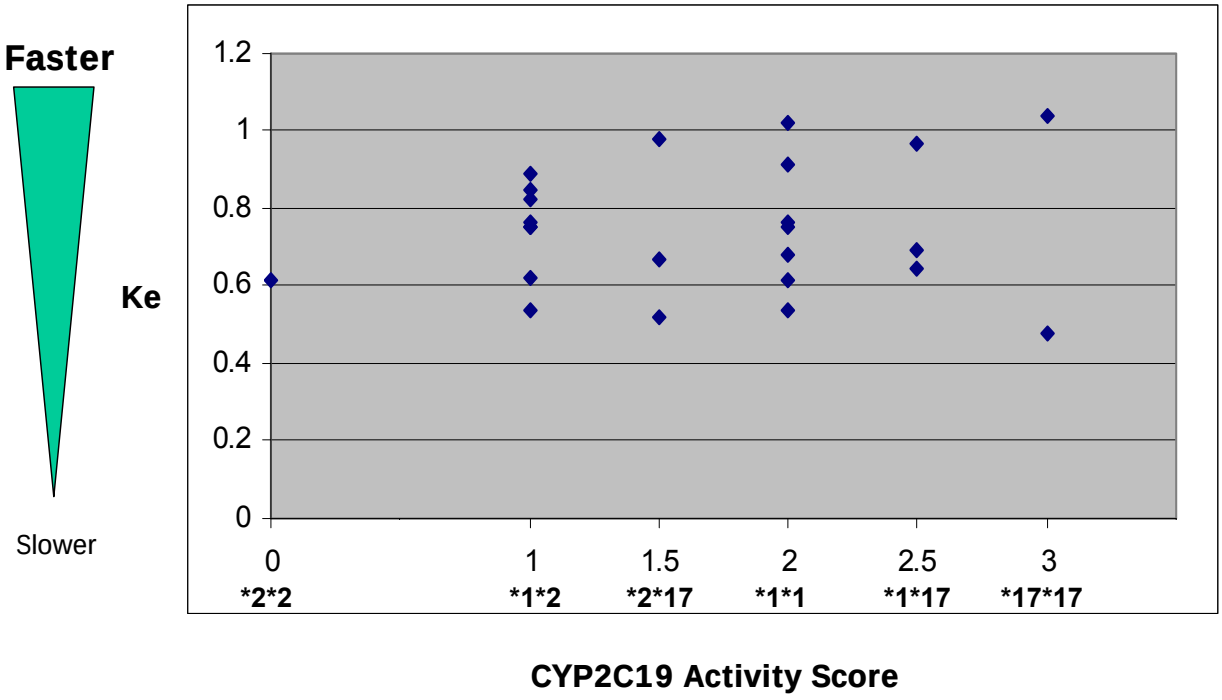
CYP2C19 Pharmacogenetics

Omeprazole PK After a Single 20 mg Oral Dose

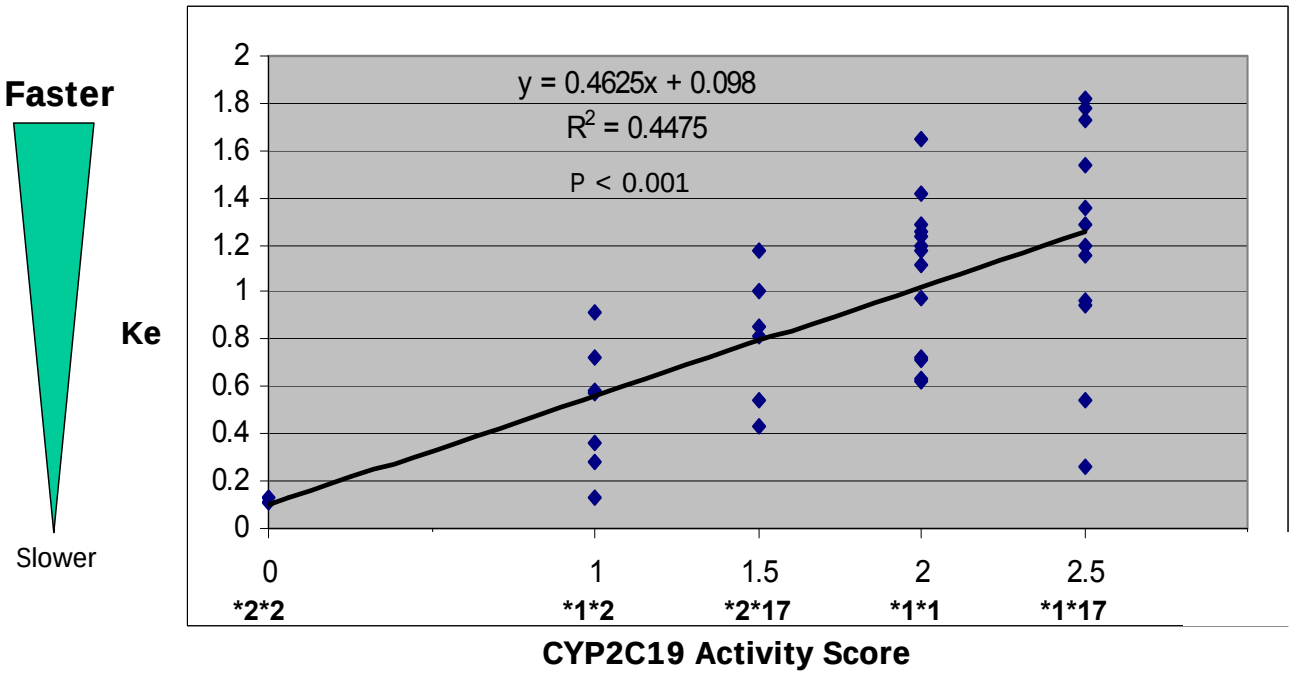


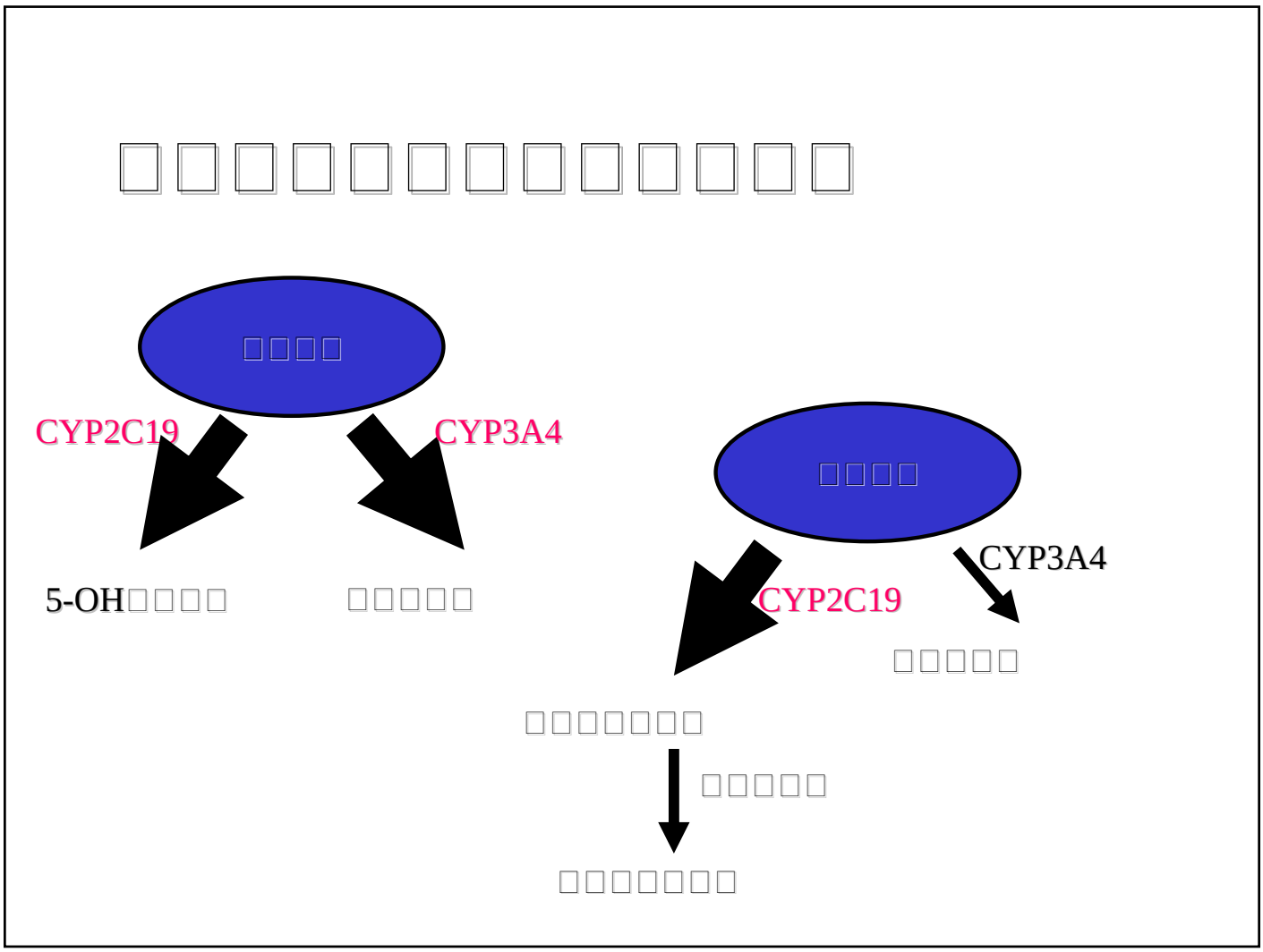
Sagar M, et al. Gastroenterology 2000;119:670-676

Drug X: no relationship between CYP2C19 activity score and Clearance



Drug Y: a clear relationship between CYP2C19 activity score and Clearance

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□□□□
CYP2C19
CYP3A4
5-OH□□□□
□□□□□
□□□□
CYP3A4
CYP2C19
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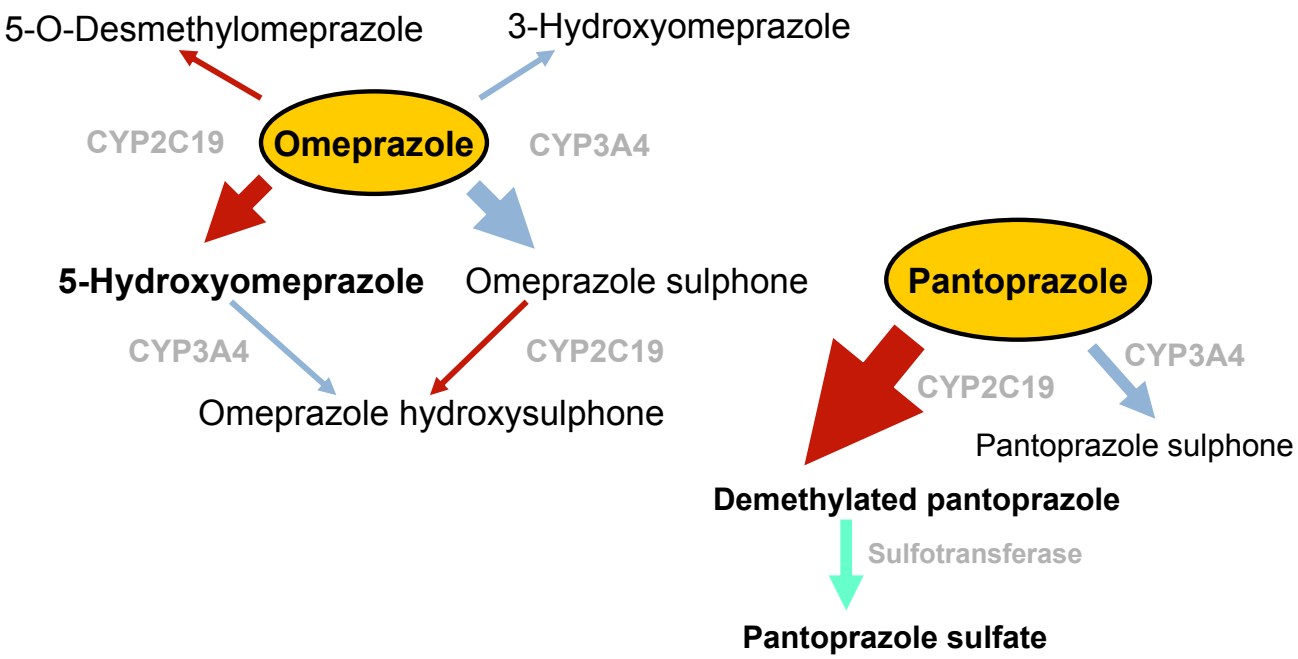
Metabolic Pathways for Selected Proton Pump Inhibitors



The need for drug studies in critically ill preterm infants

- Drug studies in adults or animal models may not adequately predict pharmacokinetic or pharmacodynamic properties in neonatal patients
- Unable to reliably extrapolate adult data to the neonatal population
- Drugs must be studied in neonates to determine their pharmacokinetics, pharmacodynamics, appropriate dose, safety and efficacy


Target therapy
M. Hoskins '99

There are two ways to live your life.
One is as though nothing is a miracle.
The other is as though everything is a miracle.

Albert Einstein (1879–1955)