ADME Issues in Children: Pediatric Pharmacokinetics

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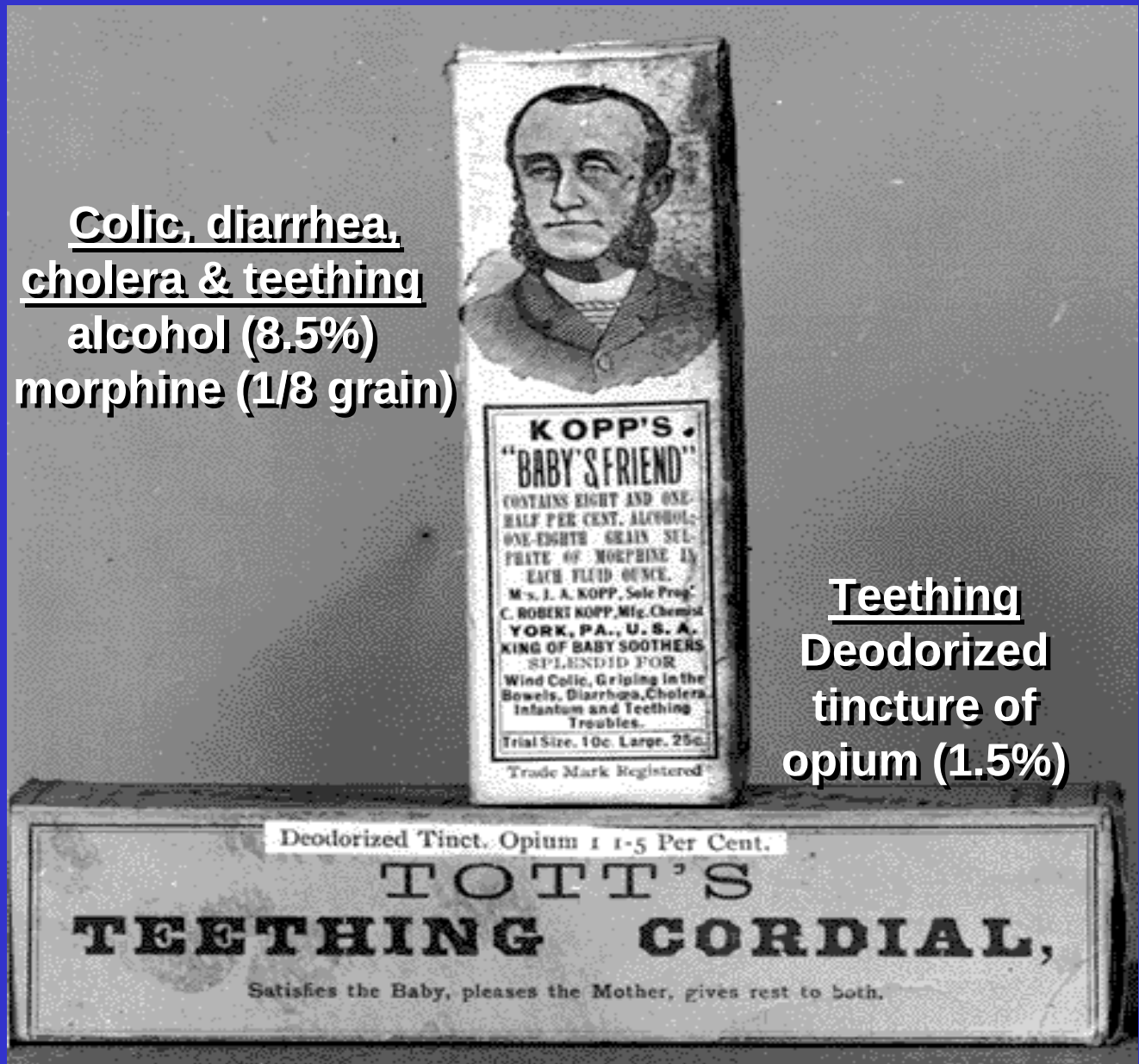
Children's

Historical Drug “Development” in Children

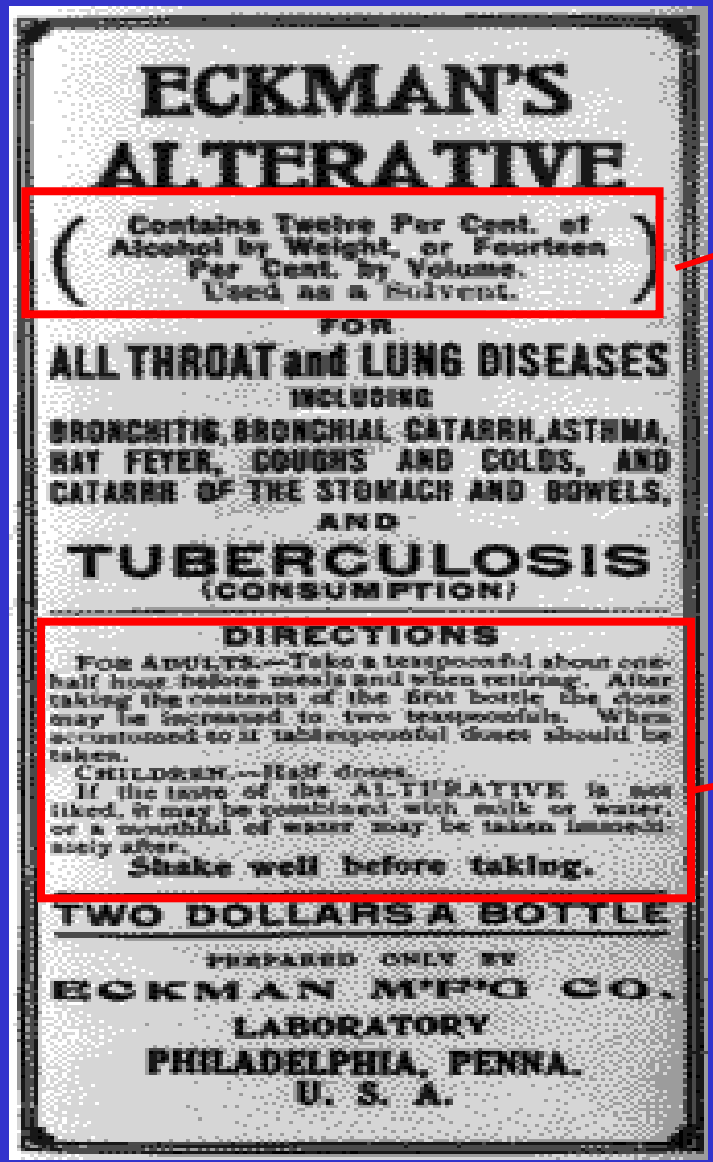


Colic, diarrhea, cholera & teething
alcohol (8.5%)
morphine (1/8 grain)

Teething
Deodorized tincture of opium (1.5%)

Historical Drug “Development” in Children

Historical Drug "Development" in Children



ECKMAN'S
ALTERATIVE

(Contains Twelve Per Cent. of Alcohol by Weight, or Fourteen Per Cent. by Volume. Used as a Solvent.)

FOR
ALL THROAT and LUNG DISEASES
INCLUDING
BRONCHITIS, BRONCHIAL CATARRH, ASTHMA, HAY FEVER, COUGHS AND COLDS, AND CATARRH OF THE STOMACH AND BOWELS,
AND
TUBERCULOSIS
(CONSUMPTION)

DIRECTIONS

FOR ADULTS.—Take a teaspoonful about one-half hour before meals and when retiring. After taking the contents of the first bottle the dose may be increased to two teaspoonfuls. When accustomed to it tablespoonful doses should be taken.

CHILDREN.—Half dose.

If the taste of the ALTERATIVE is not liked, it may be combined with milk or water, or a mouthful of water may be taken immediately after.

Shake well before taking.

TWO DOLLARS A BOTTLE

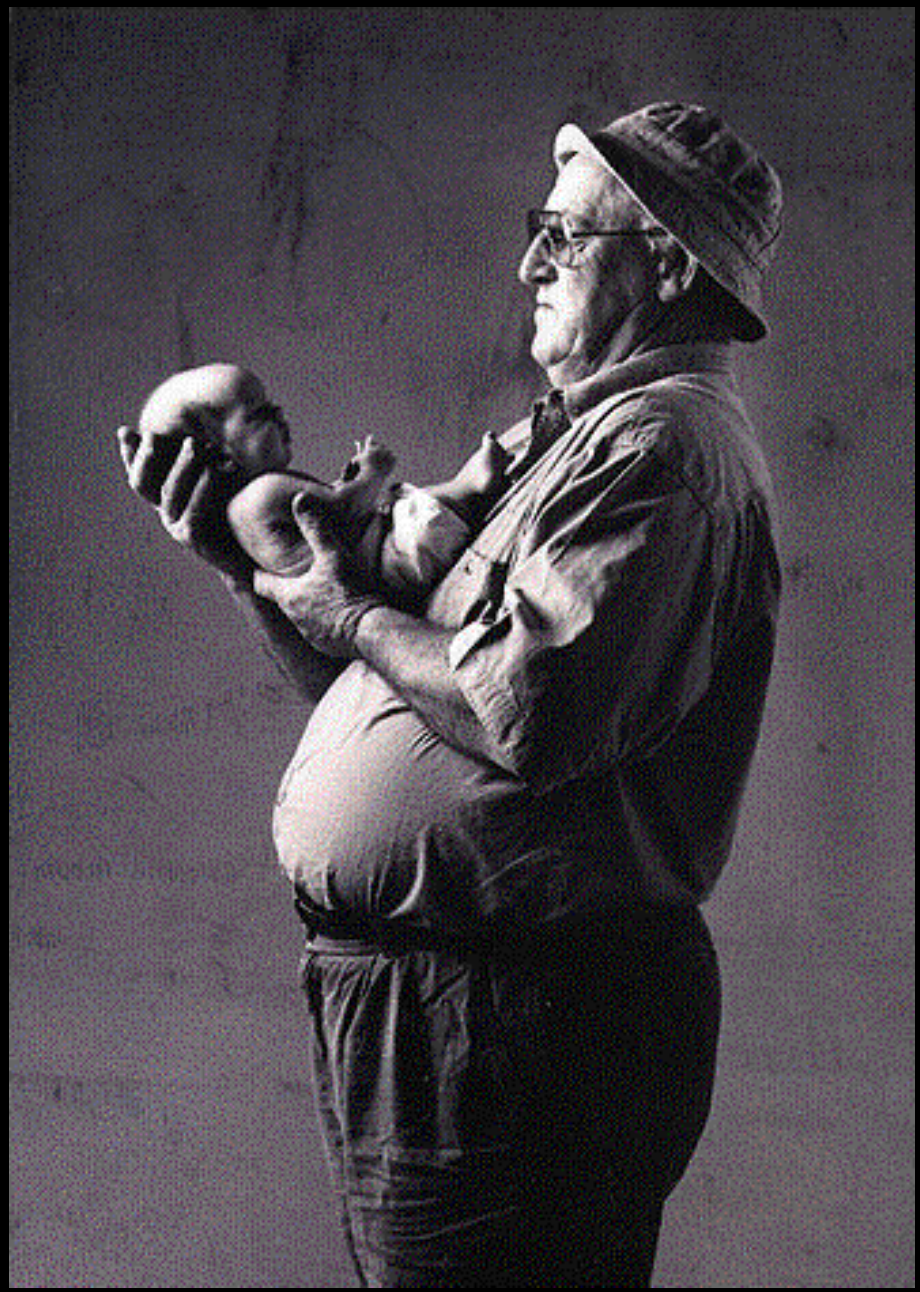
PREPARED ONLY BY
ECKMAN M'F'G CO.
LABORATORY
PHILADELPHIA, PENNA.
U. S. A.

Contains 12% of alcohol by weight or 14% per volume.
Used as a solvent.

DIRECTIONS

For adults: Take a teaspoonful about one-half hour before meals and when retiring.

For children: Half dose.
If the taste is not liked, it may be combined with milk or water or a mouthful of water may be taken immediately after.



Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but….it has its own independent range and horizon…"

Dr. Abraham Jacobi, 1889

Inadequacy of traditional dosing schema

Comparison of total daily gabapentin (Neurontin®) maintenance doses calculated via “traditional” and current dosing guidelines for a 4-year-old, 17 kg child

	Young	Cowling	Clark	BSA	2003 Peds Dosing Handbook
Fraction of adult dose	25%	21%	25%	N/A	N/A
Total daily dose (mg)	225 – 450			391-783	680
Total daily dose (mg/kg)	13 - 26			23 - 46	40

The Developmental Continuum

Fetus

Newborn

Infant

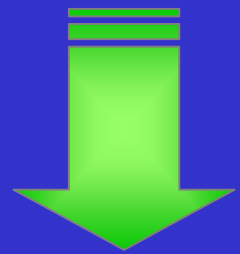
Preschooler

School-age

Adolescent

Adult

- Weight doubles by 5 months; triples by 1 year
- Body surface area doubles by 1 year
- Caloric expenditures increase 3- to 4-fold by 1 year

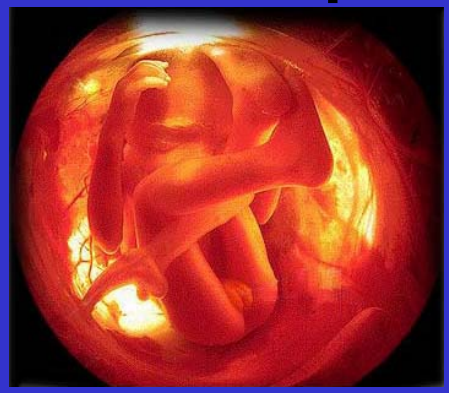


?

- Adolescence: transition to adulthood
- Changes incomprehensible to most adults

The Developmental Continuum

Fetus



Newborn

Infant

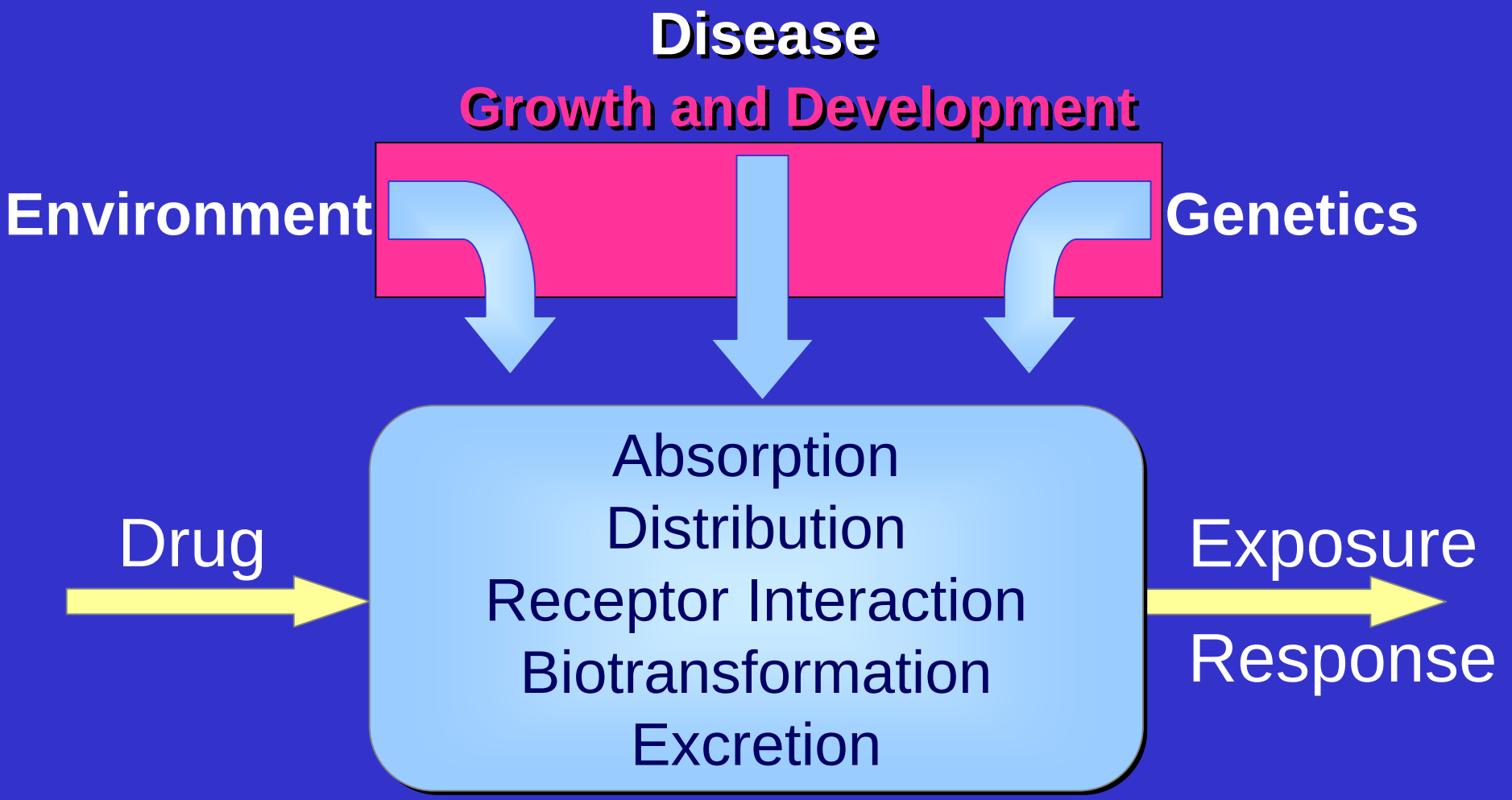
Preschooler

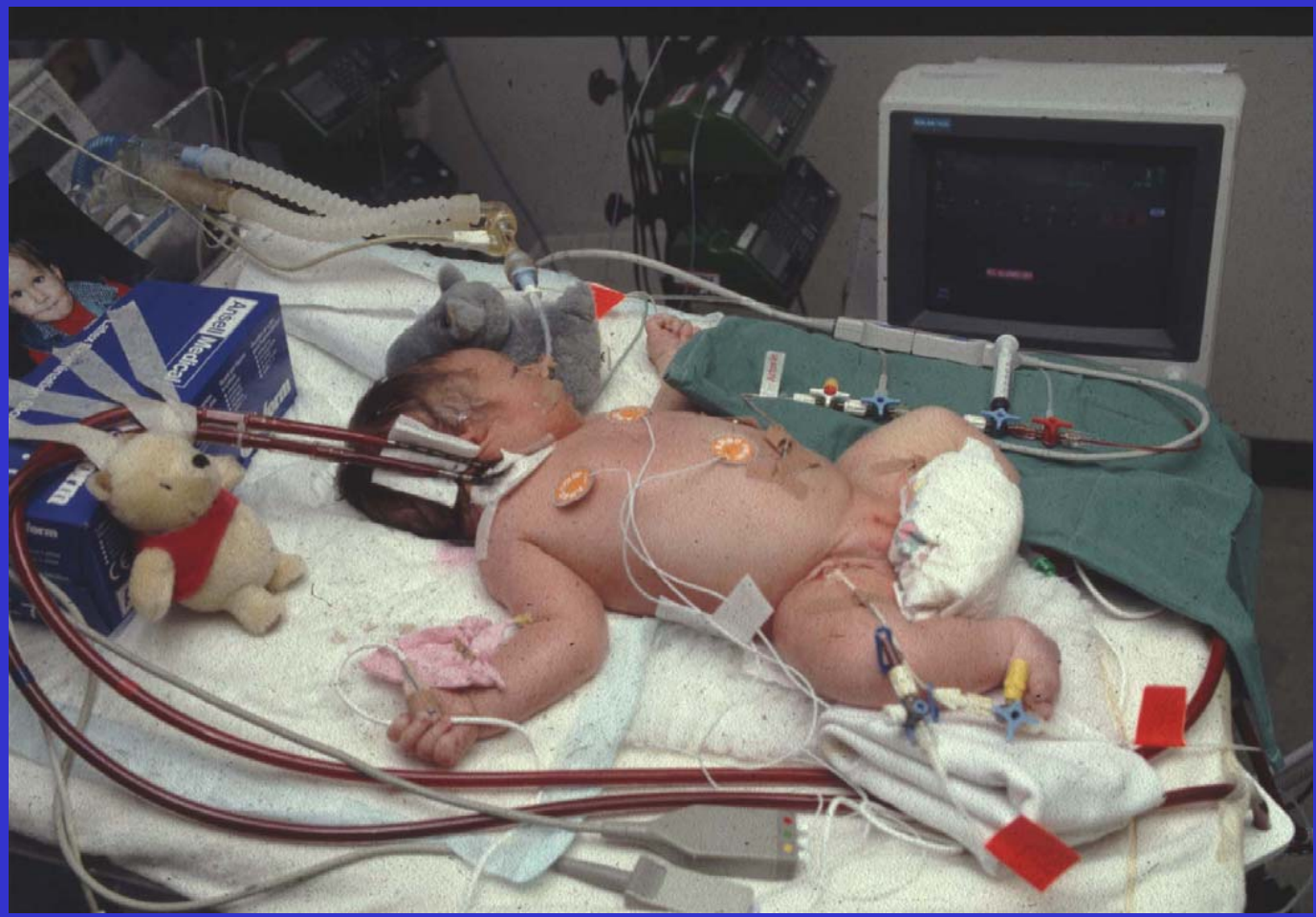
School-age

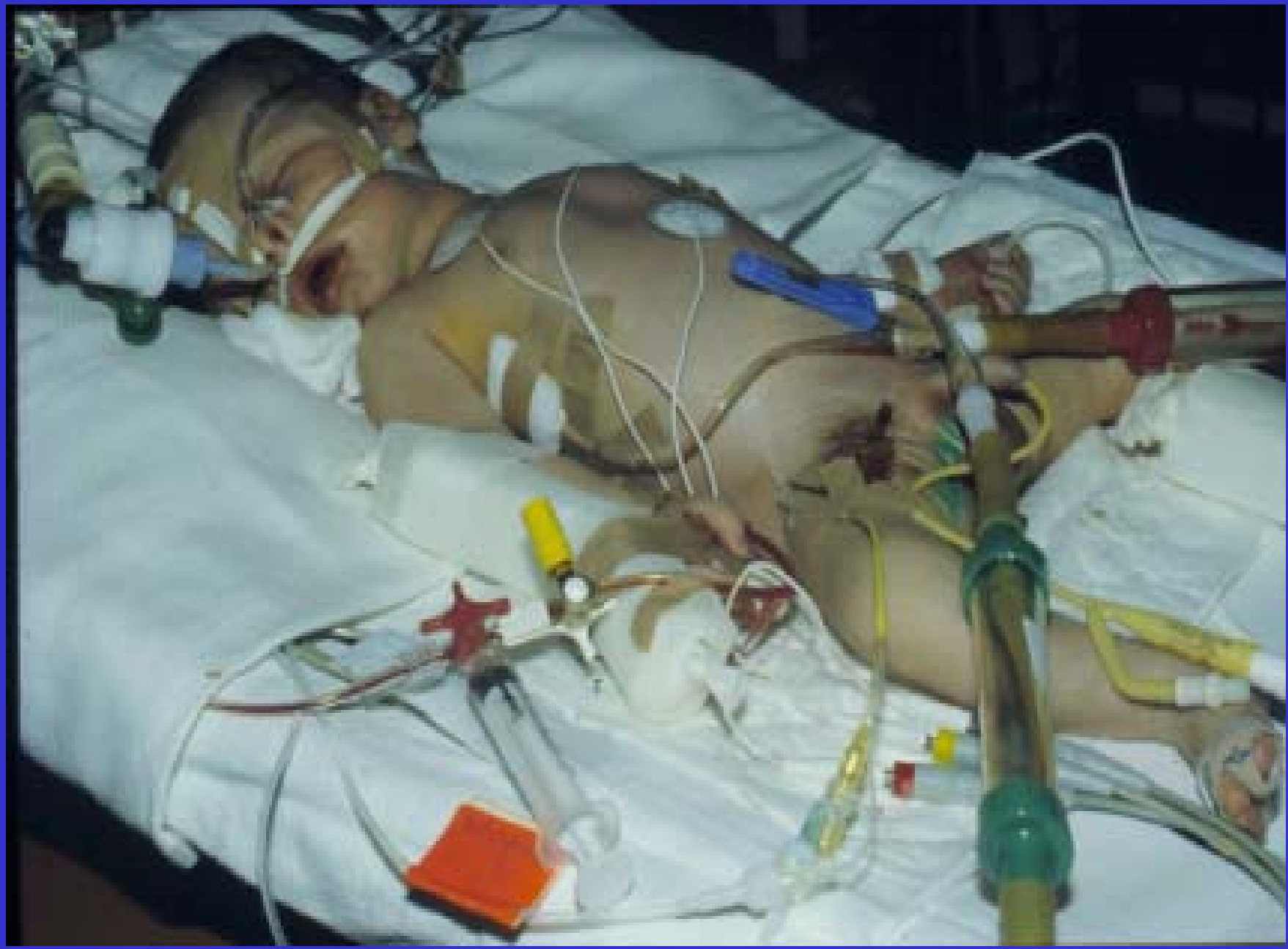
Adolescent

Adult

Determinants of Drug Response in Children

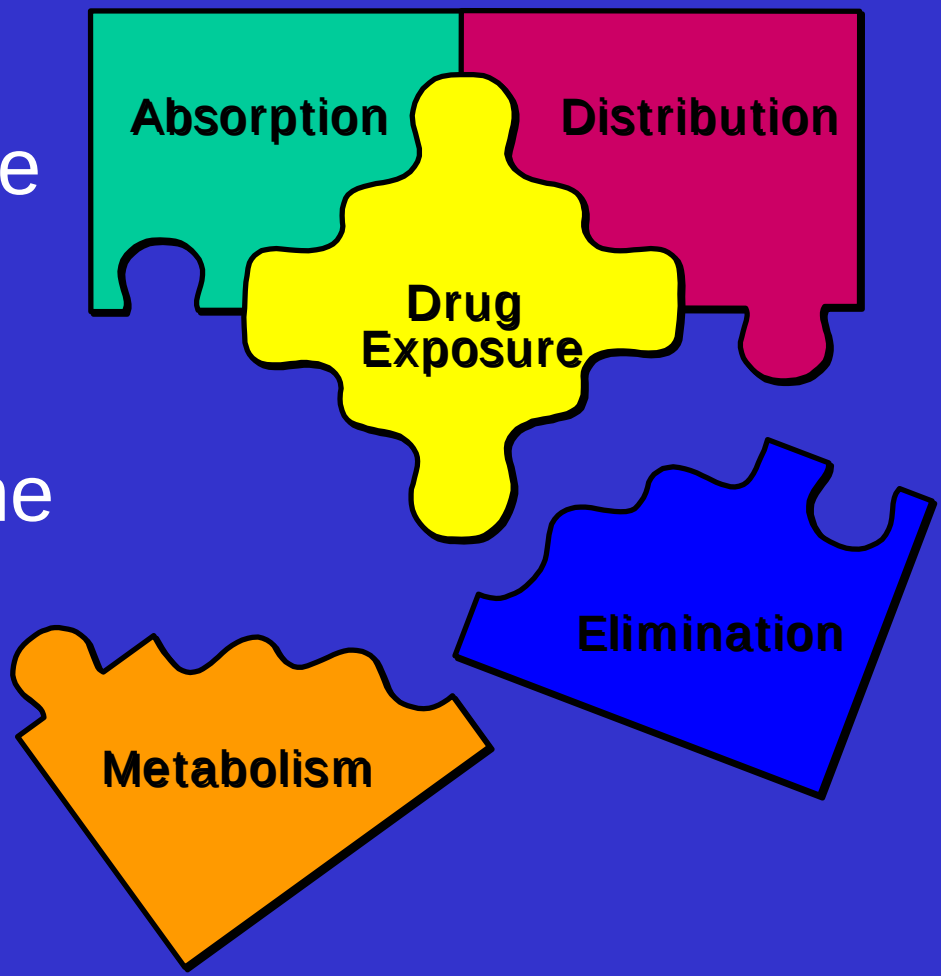




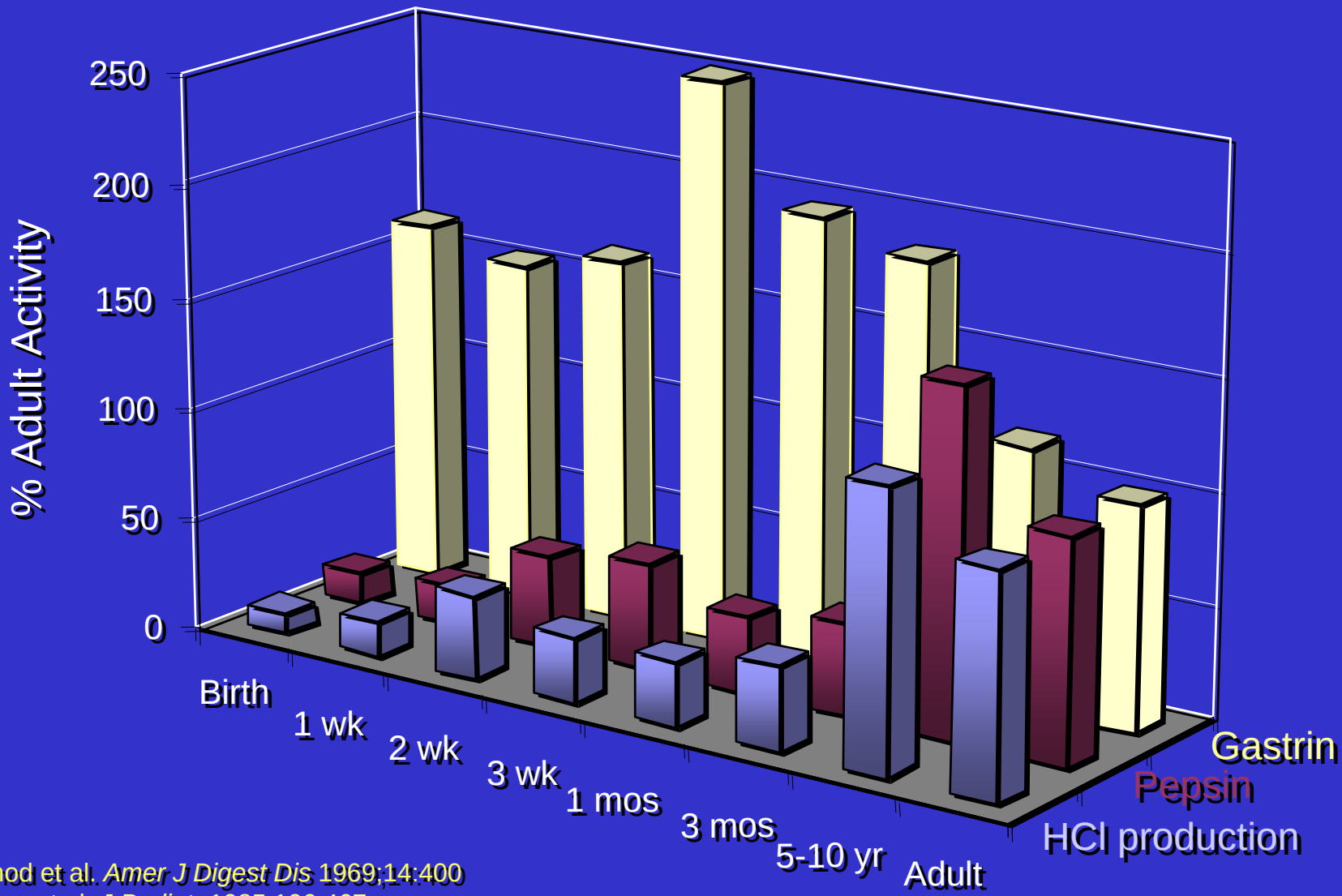


Critical Role of Pharmacokinetics in Pharmacotherapy……

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

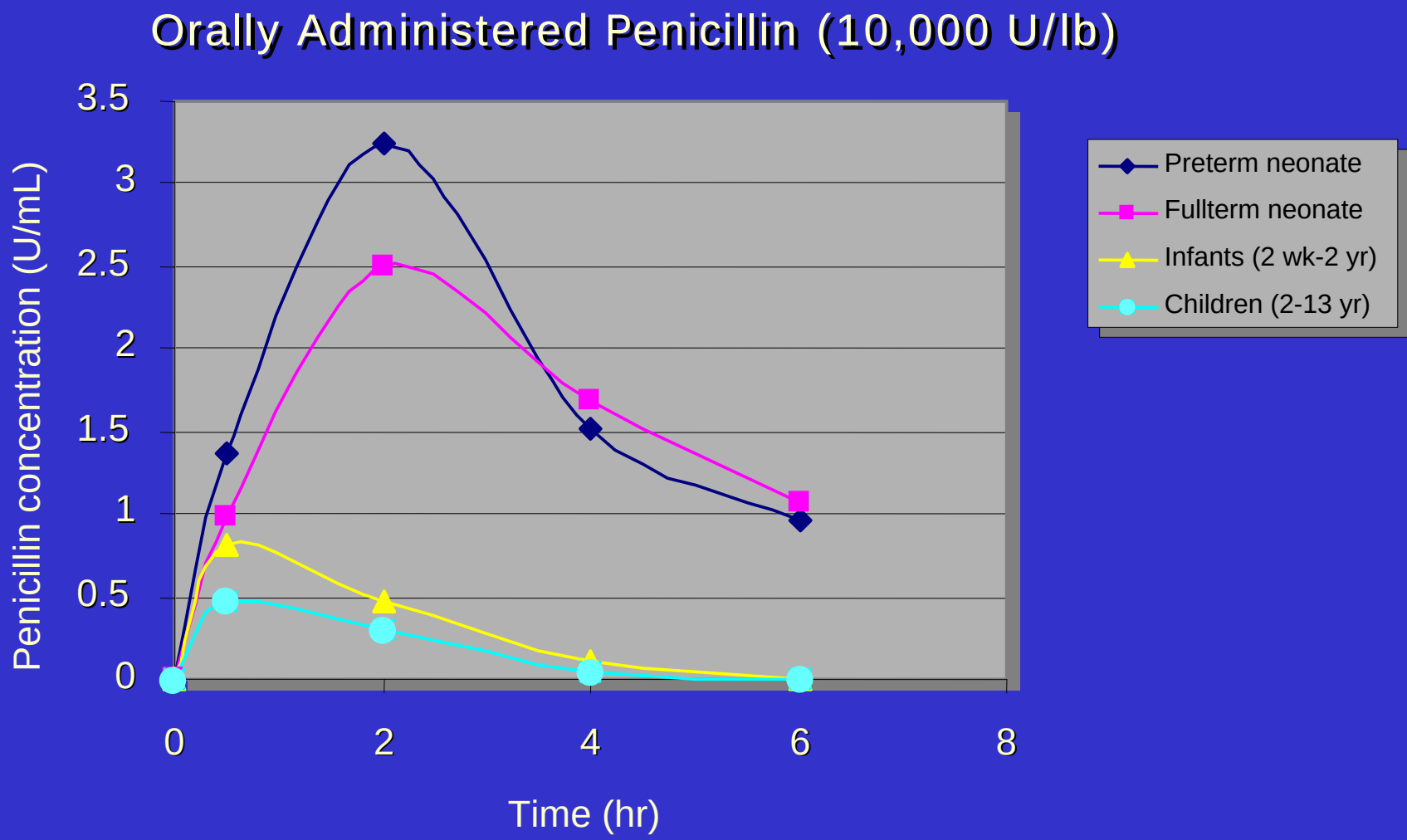


Drug Absorption
Developmental Changes in Gastric pH



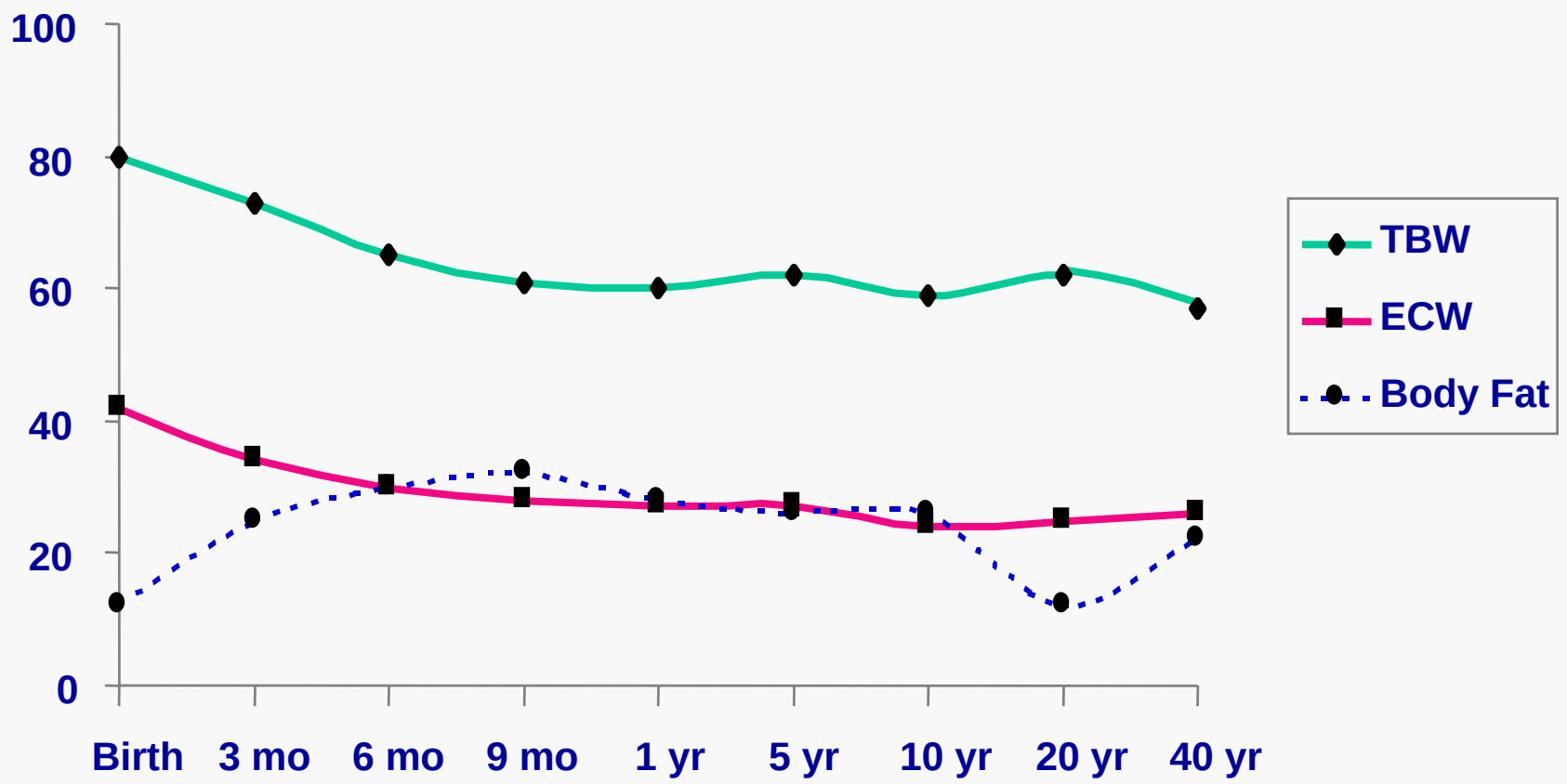
Agunod et al. *Amer J Digest Dis* 1969;14:400
Mozam et al. *J Pediatr* 1985;106:467
Rodgers et al. *J. Pediatr Surg* 1978;13:13

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

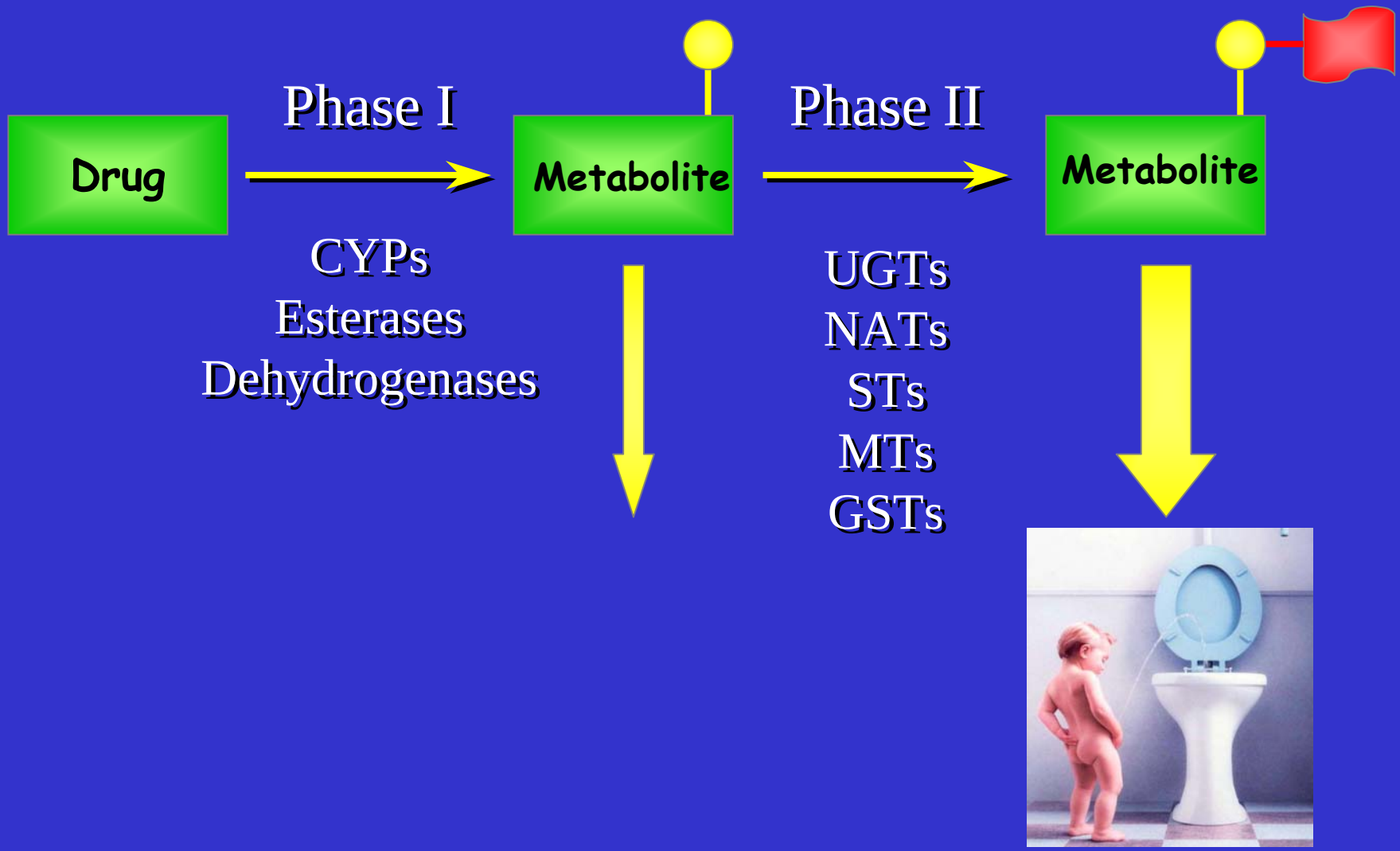


Impact of Age on Linezolid Pharmacokinetics

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%

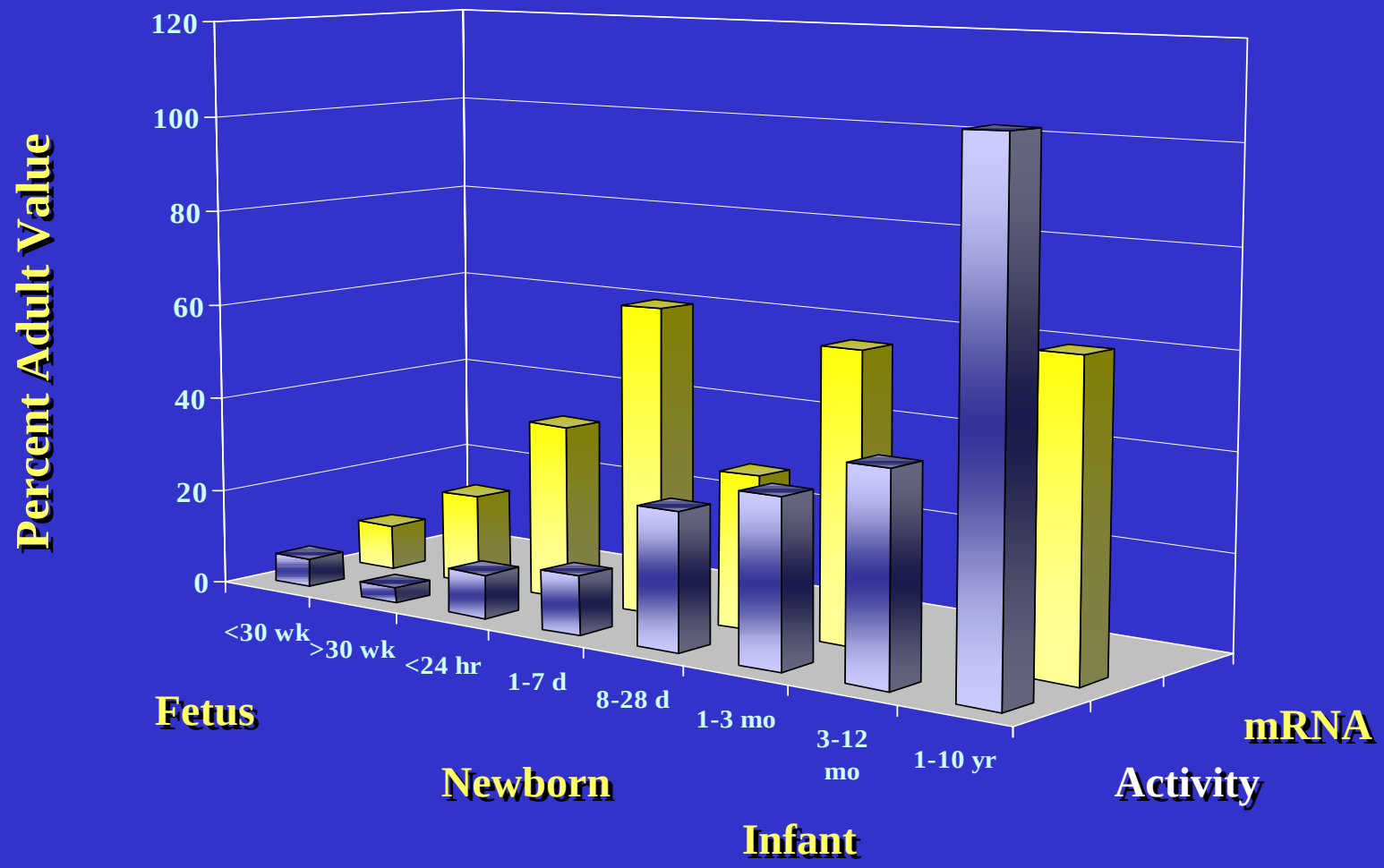
Kearns, Jungbluth, Abdel-Rahman, Hopkins, Welshman, Grzebyk, Bruss, van den Anker. Clin Pharmacol Ther 2003;74:413-22.

Drug Biotransformation



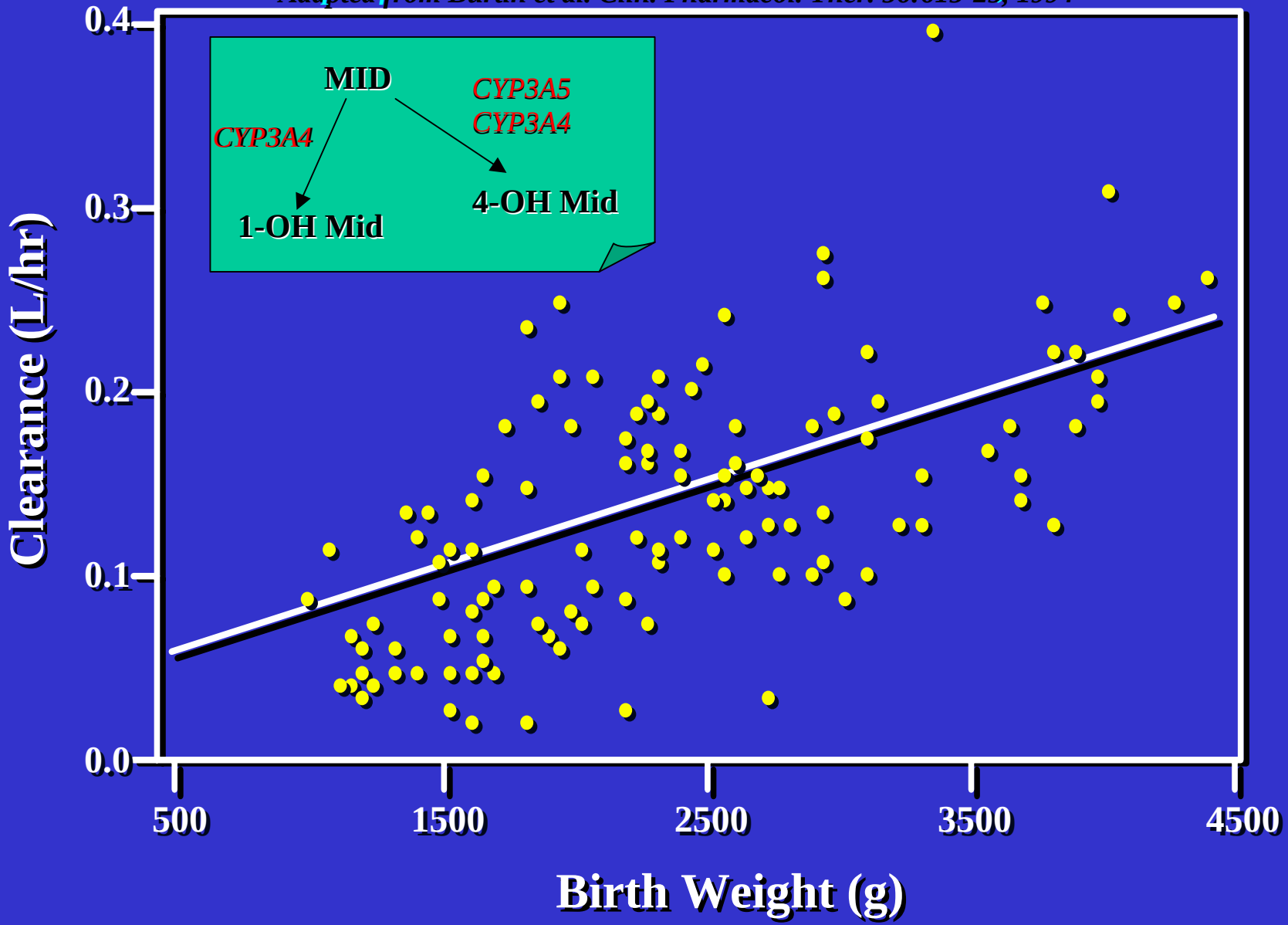
Ontogeny of CYP3A4

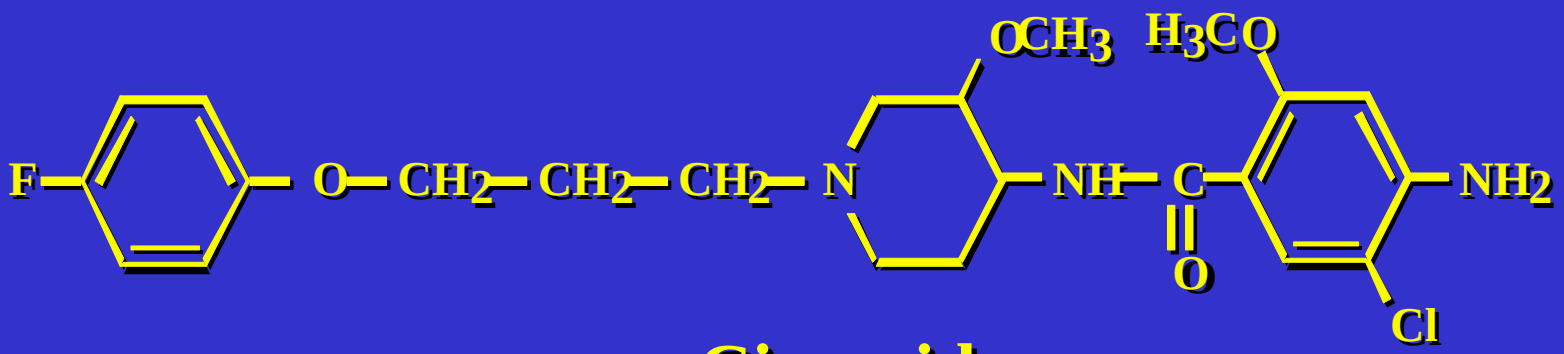
From Lacroix D et al. *Eur. J. Biochem.* 247: 625-634, 1997



Midazolam Clearance in Neonates

Adapted from Burtin et al. Clin. Pharmacol. Ther. 56:615-25, 1994





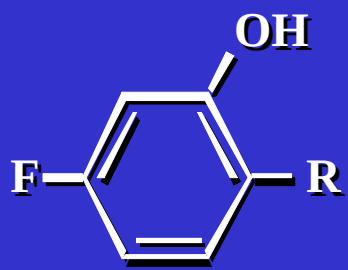
Cisapride

CYP3A4

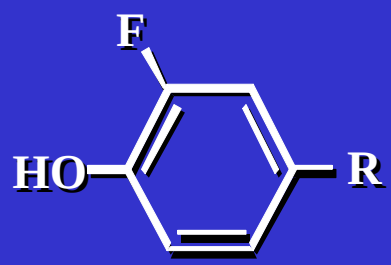
CYP3A4

CYP2B6

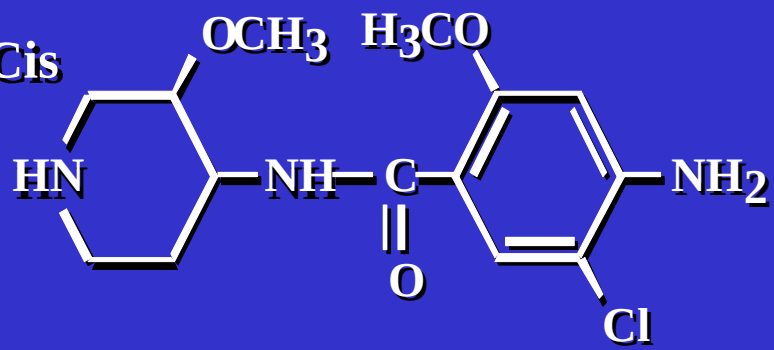
CYP3A4



4-F-2-OH-Cis



3-F-4-OH-Cis



Norcisapride

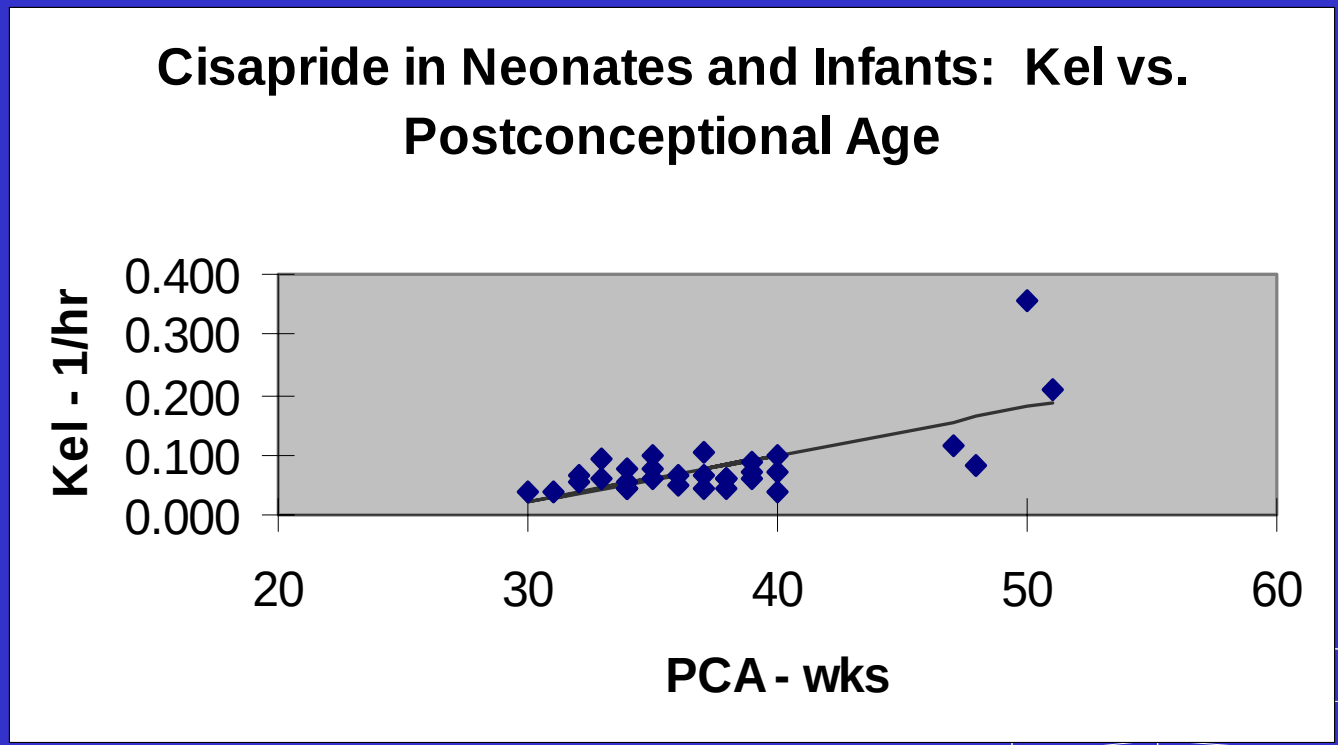
Single-Dose (0.2 mg/kg) Pharmacokinetics of Cisapride in Neonates and Young Infants

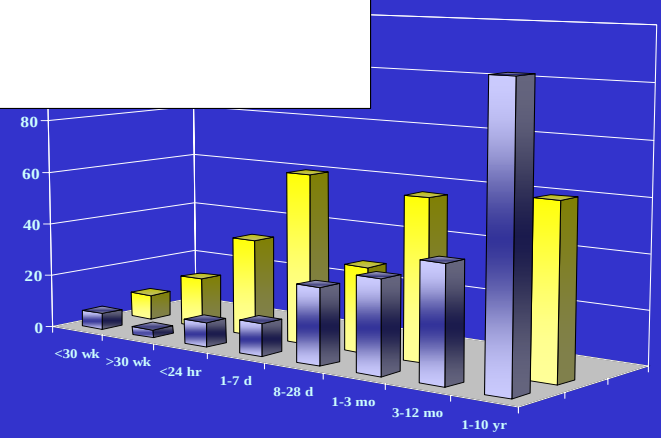
	Postconceptional Age		
	28-36 wks. (n = 17)	36-42 wks. (n = 13)	42-54 wks. (n = 5)
Cmax (ng/ml)	30.0(17.5)	23.3(11.7)	44.5(19.5)
Tmax (hr)	5.0(2.6)	4.3(3.3)	2.2(1.1)
T1/2 (hr)	11.6(3.0)	11.5(3.0)	4.8(3.0)
AUC (ng/ml*hr)	568(257)	362(198)	364(249)
VDss/F (L/kg)	7.4(4.7)	12.7(9.1)	4.1(1.5)
Cl/F (L/hr/kg)	0.45(0.26)	0.75(0.46)	0.85(0.69)

Kearns, Robinson, Wilson-Costello, Knight, Ward, van den Anker. *Clin Pharmacol Ther* 2003;74:312-325

-Data expressed as mean (S.D.)

Impact of Development on Cisapride Elimination in Infants





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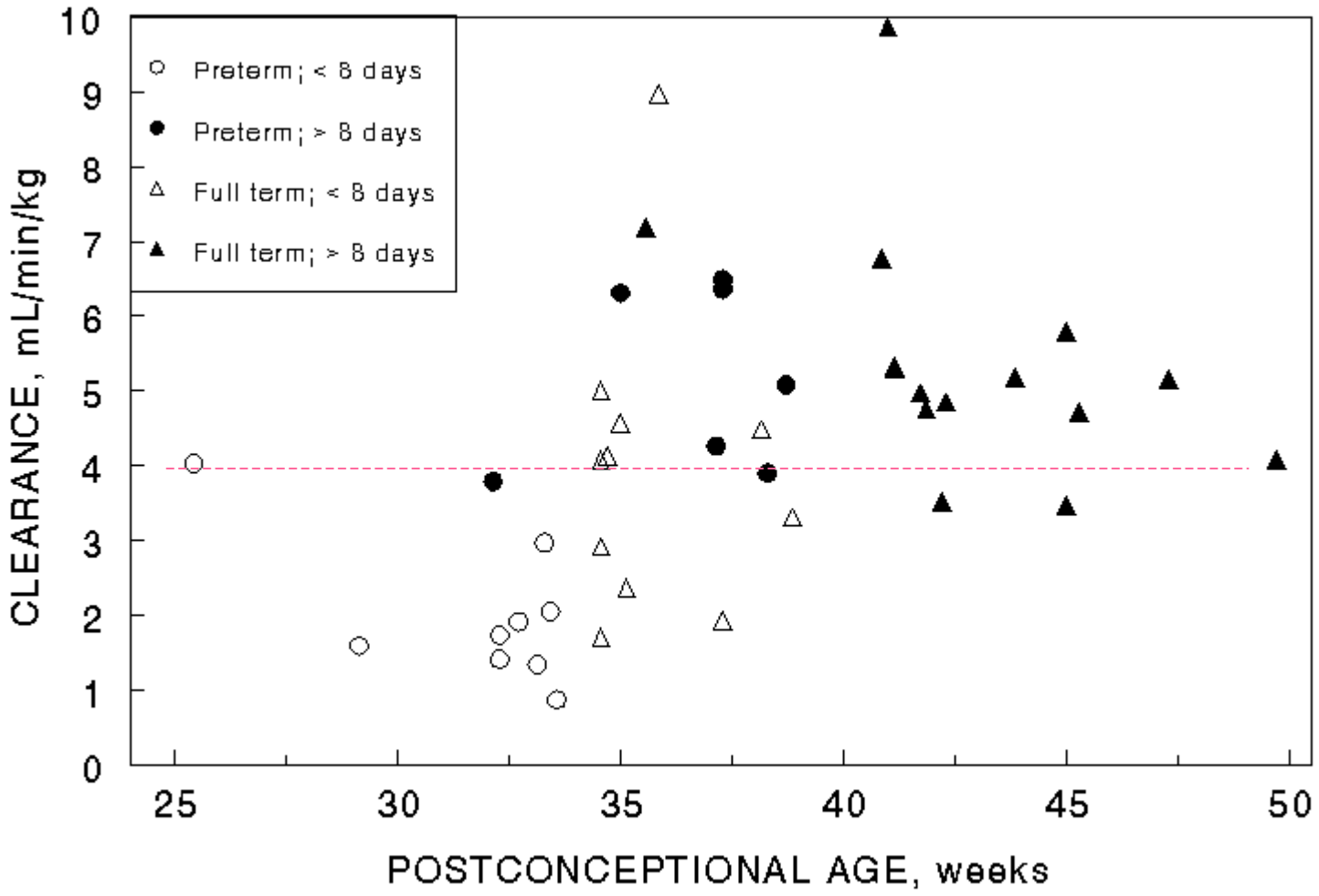
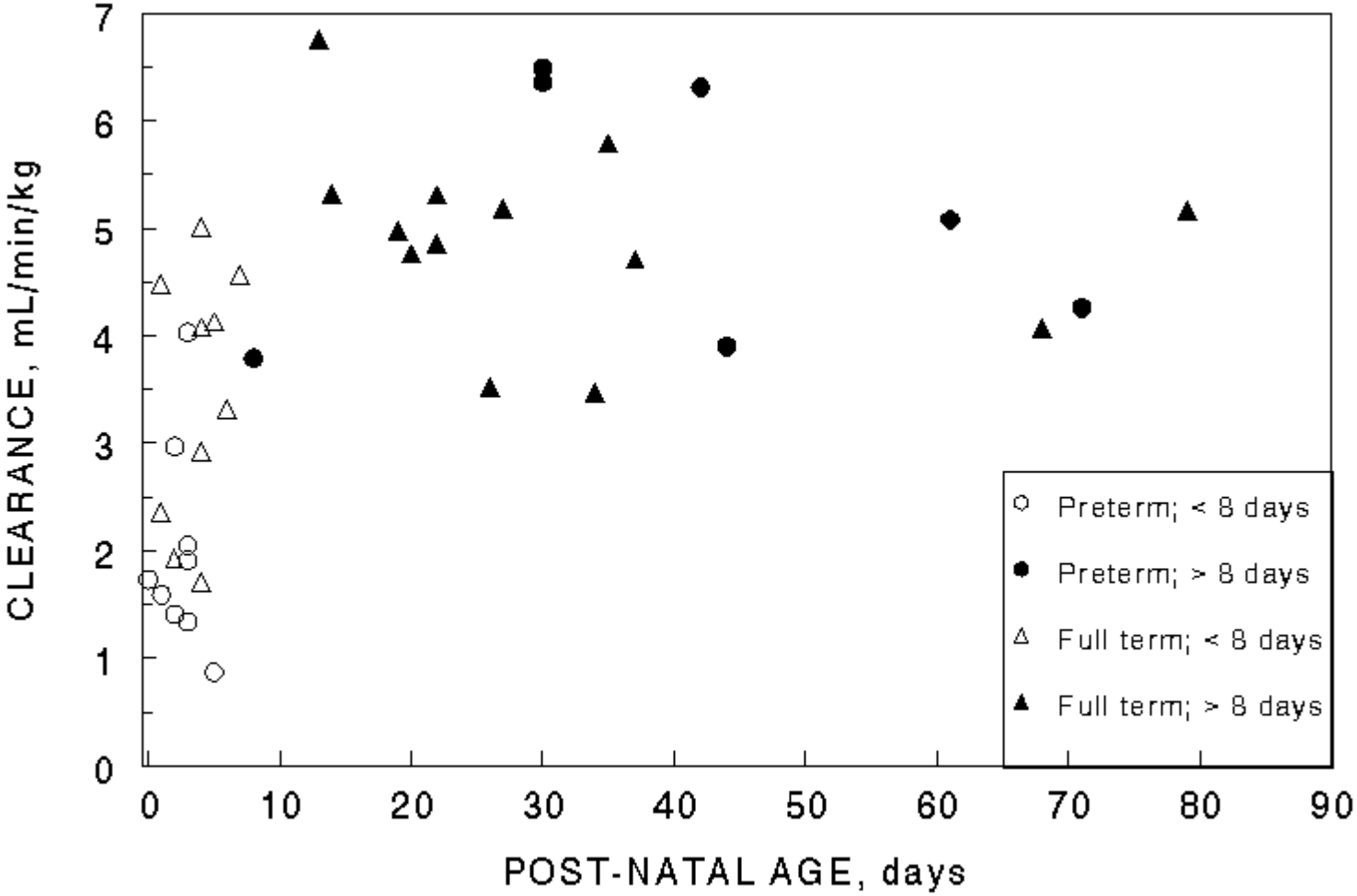
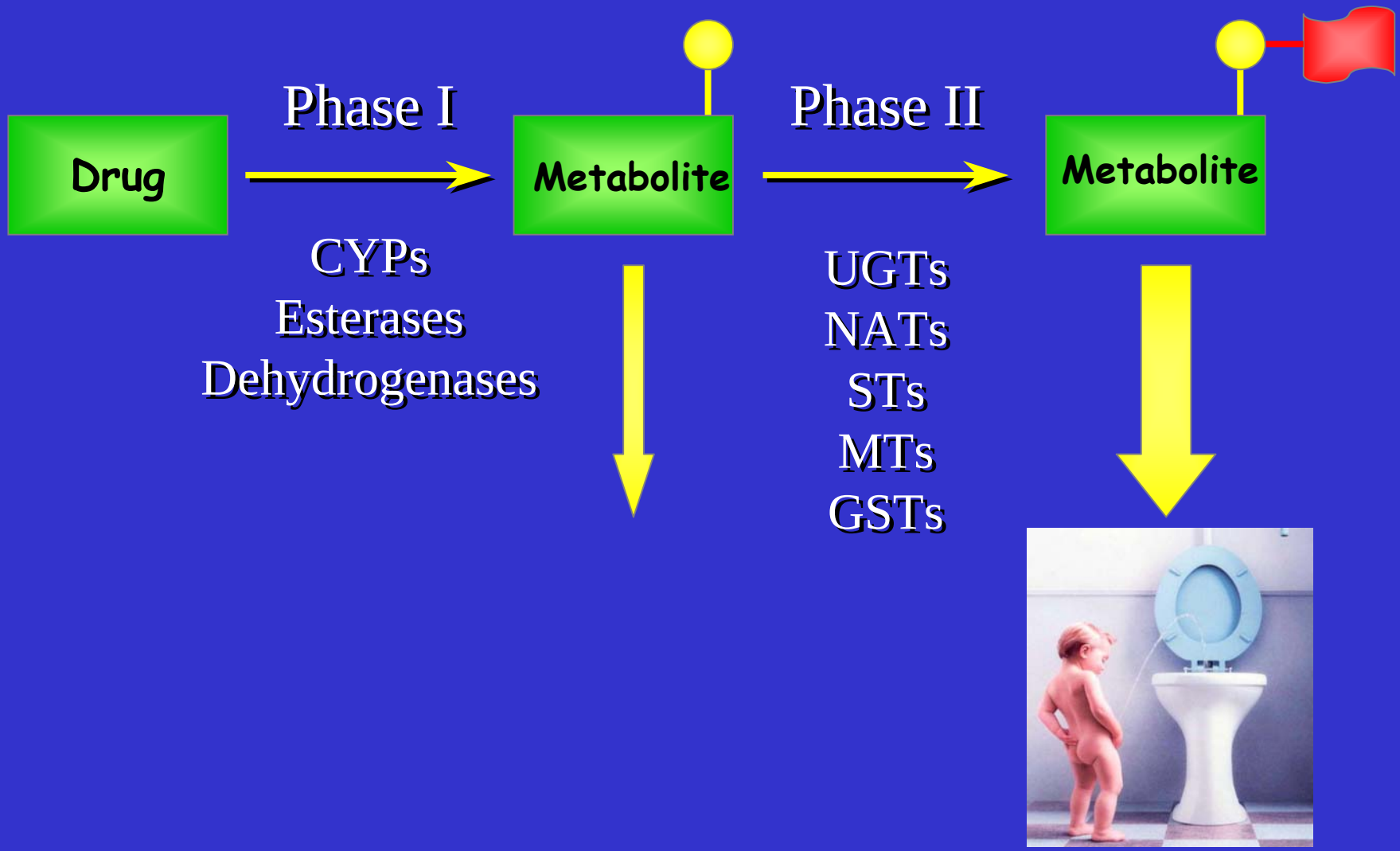
Linezolid Plasma Clearance Association with PCA



Linezolid Plasma Clearance Association with PNA



Drug Biotransformation



NEWBORN RENAL FUNCTION

- **Very low Glomerular Filtration Rate (GFR)**
- **Delicate balance between vasoconstrictor and vasodilatory renal forces**
- **Low mean arterial pressure and high intrarenal vascular resistance**
- **Limited postnatal renal functional adaptation to endogenous or exogenous stress**

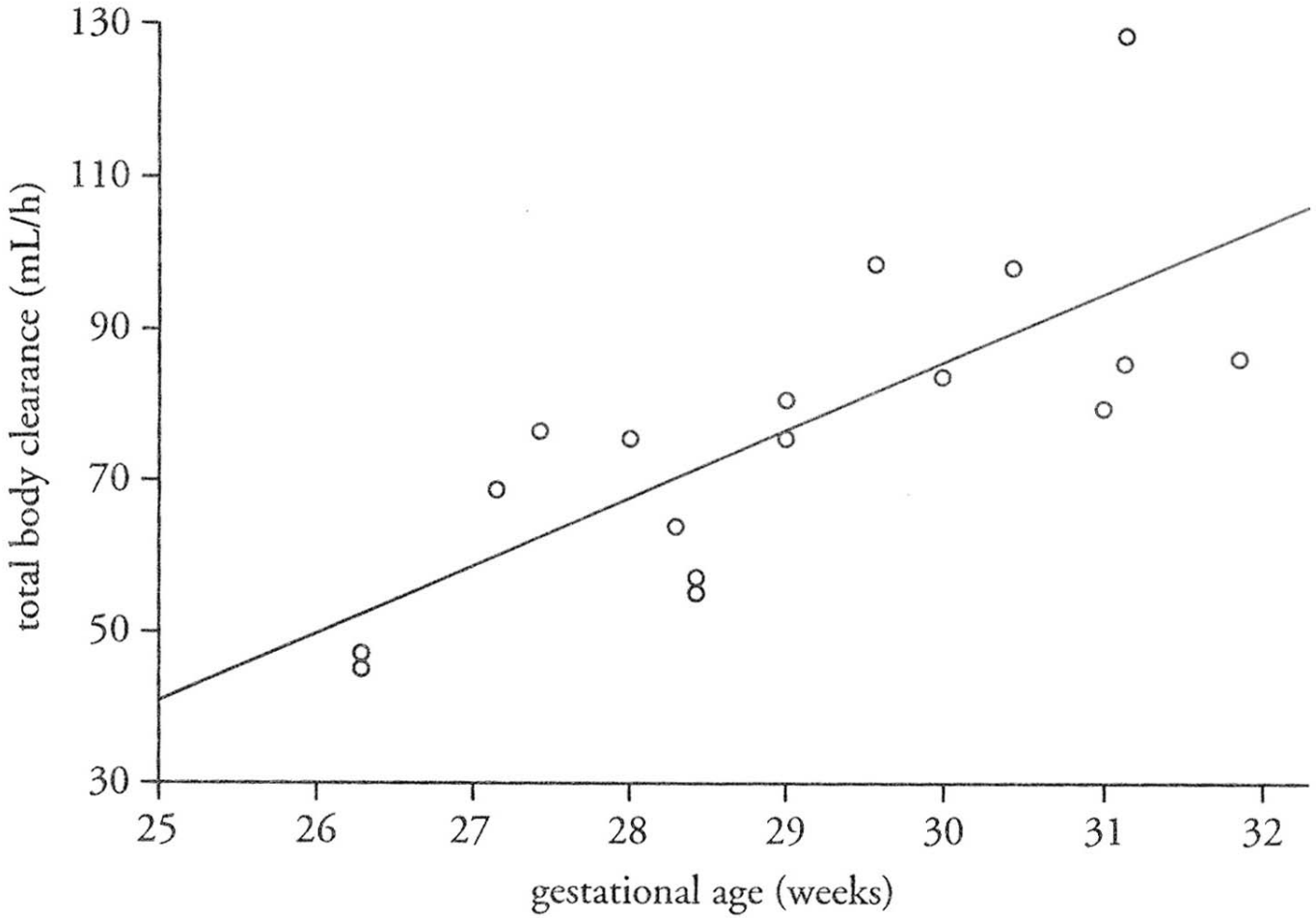


Figure 2. Linear regression analysis of total body clearance of amoxicillin (mL/h) versus gestational age (weeks) in 17 preterm infants on day 3 after birth ($r=0.75$, $p<0.001$, $y=8.88x-181.2$)

Huisman-de Boer JJ, van den Anker JN, et al. Antimicrob Agents Chemother 1995;39:431-4.

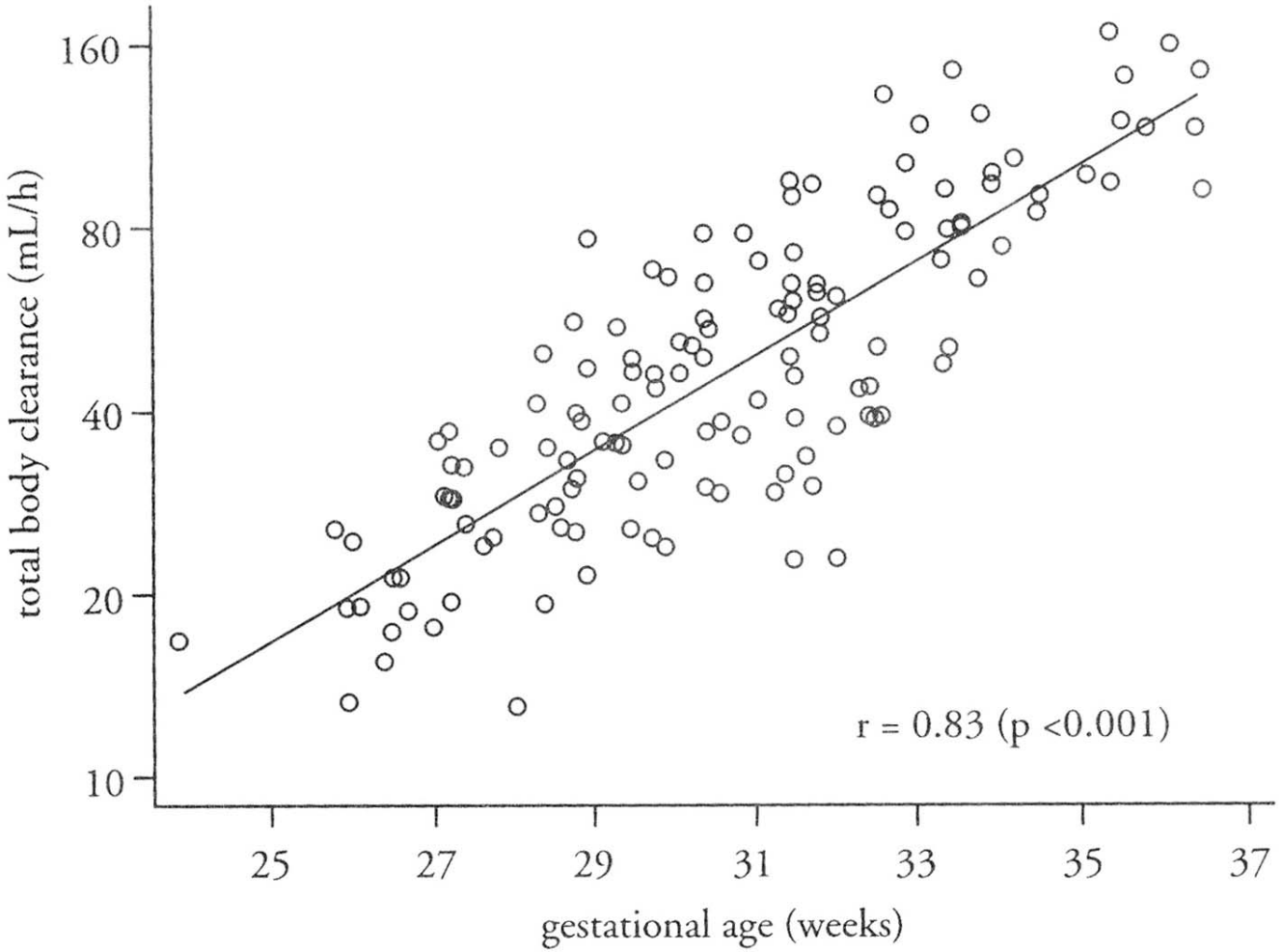
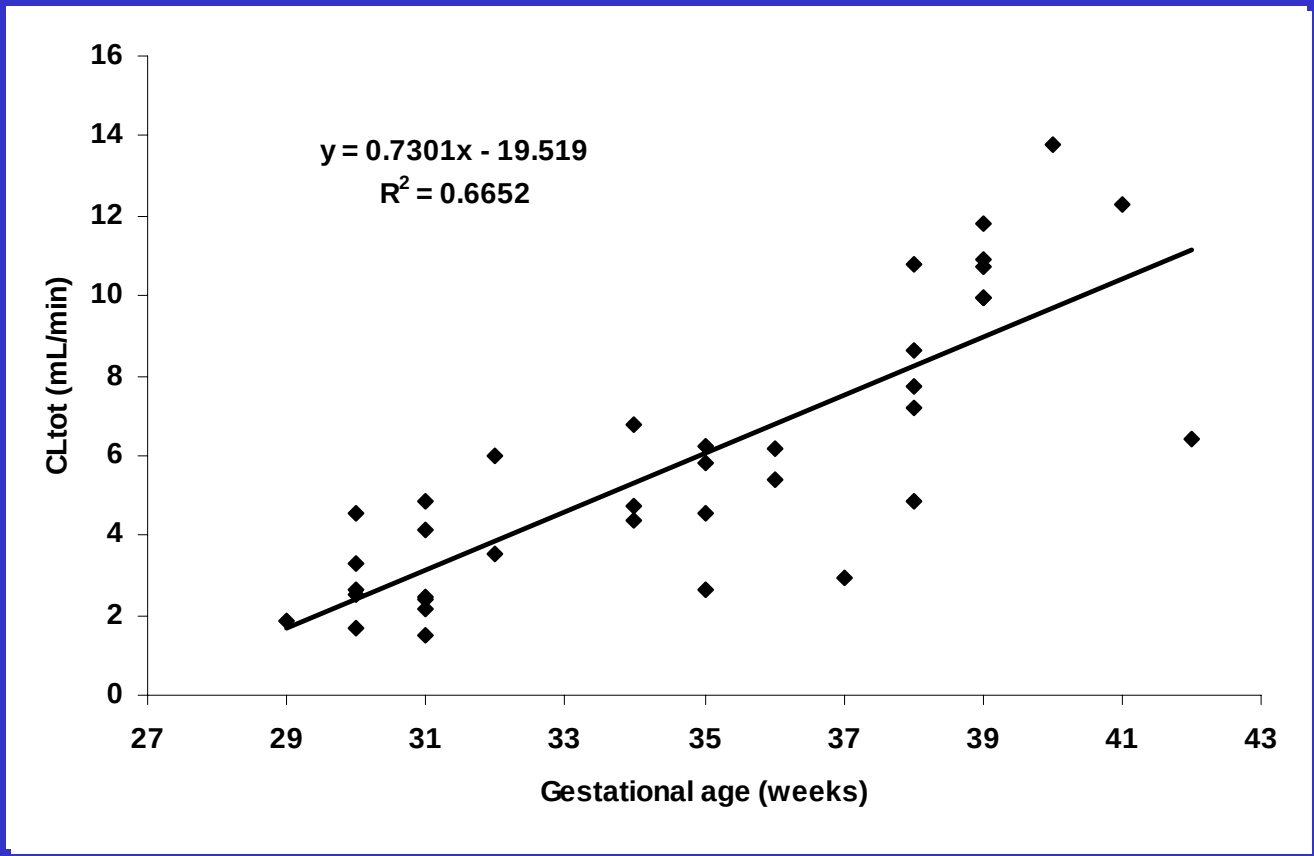


Figure 1. **Linear regression analysis of total body clearance of ceftazidime (mL/h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth. Note the logarithmically transformed vertical axis**

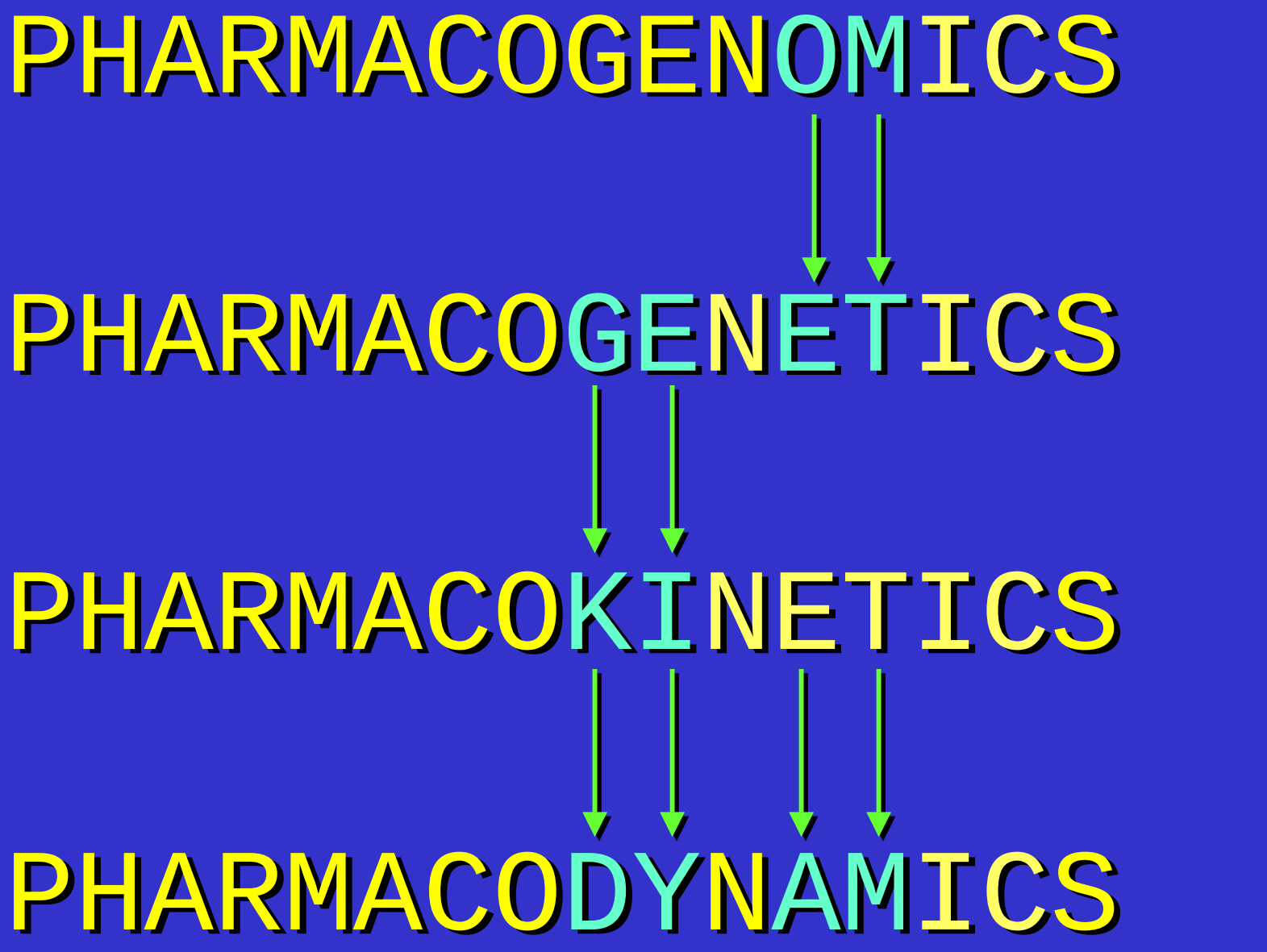
Van den Anker JN, et al. Clin Pharmacol Ther 1995;58:650-9.

Meropenem pharmacokinetics in the newborn



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

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


PHARMACOGENOMICS
PHARMACOGENETICS
PHARMACOKINETICS
PHARMACODYNAMICS

Leeder, 2002

PHARMACOGENETICS

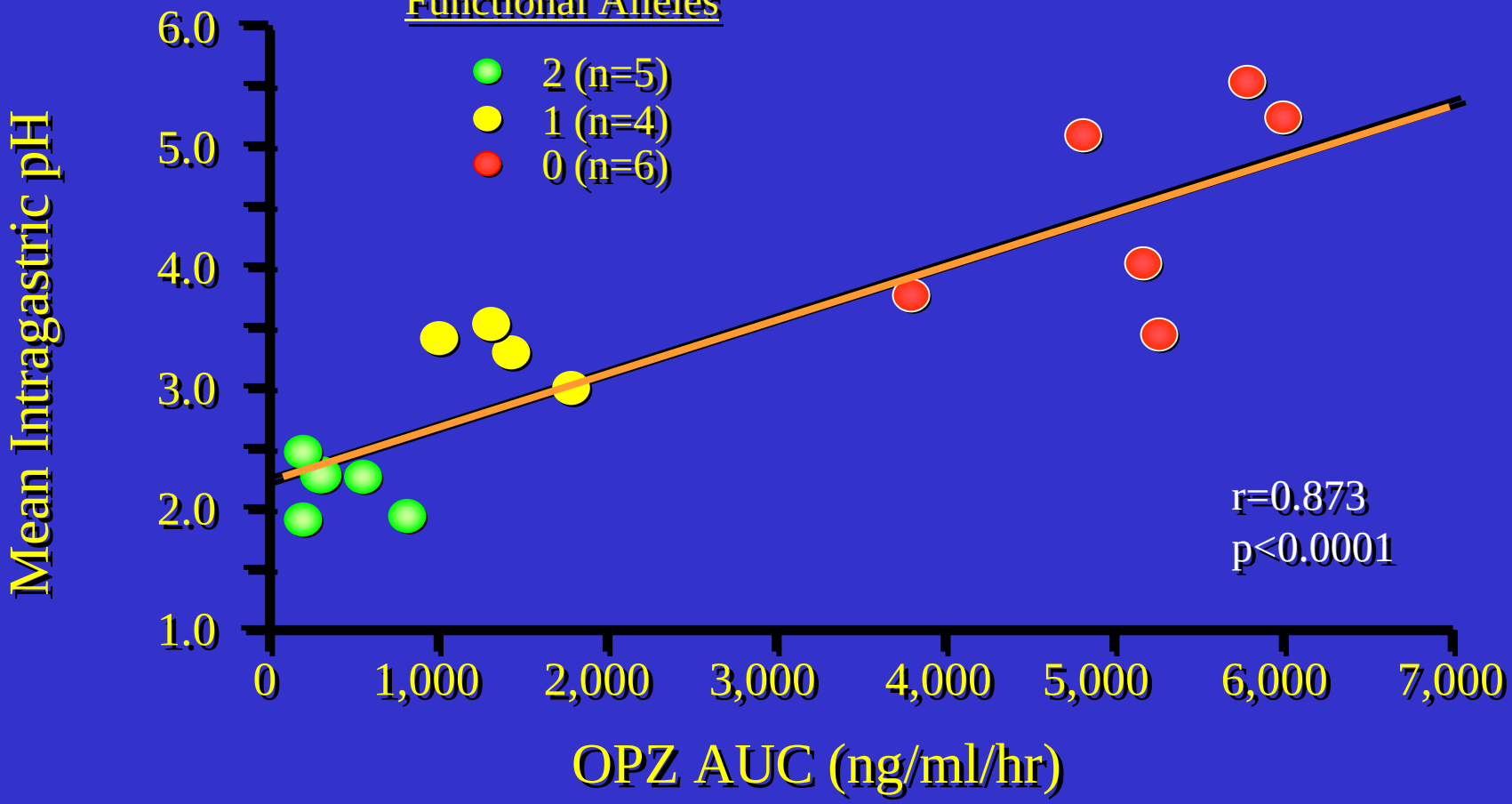
The study of the role of genetic factors in drug disposition, response and toxicity - relating variation in human genes to variation in drug responses at the level of the individual patient (the right drug for the right patient)

CYP2C19 Pharmacogenetics

- 1984: Unusual sedation in a subject receiving anticonvulsant mephenytoin
- 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

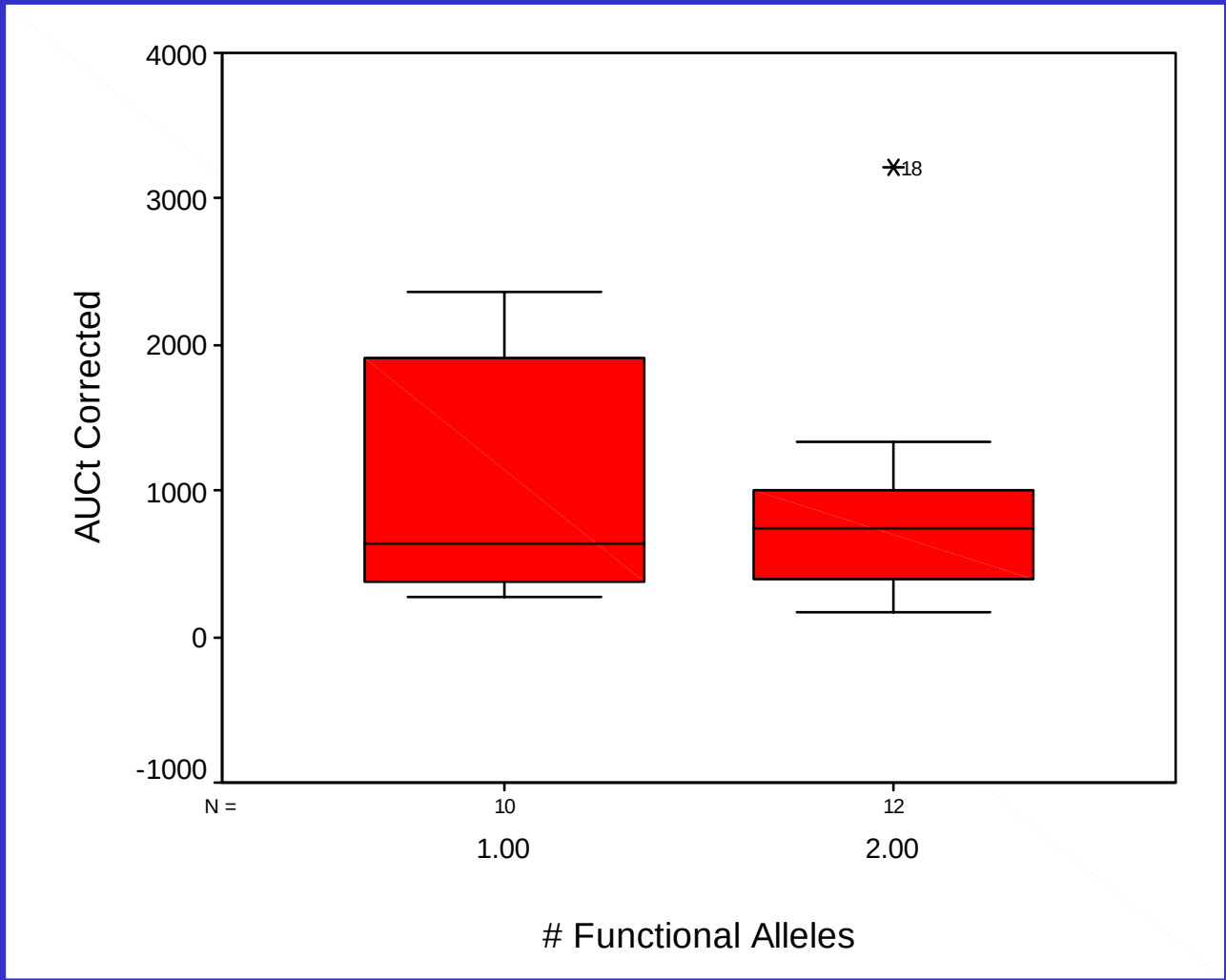
Impact of CYP2C19 Pharmacogenetics on Omeprazole PK and PD……..

Omeprazole PK After a Single 20 mg Oral Dose)



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

Lack of an Effect of *CYP2C19* Genotype on Omeprazole Exposure in Pediatric EMs



Kearns, Andersson, James, Li, Gaedigk, Kraynak, Kuczmanski, Ramabadran, van den Anker. *J Clin Pharmacol;2003:43:840-848*

CYP2D6 Pharmacogenetics

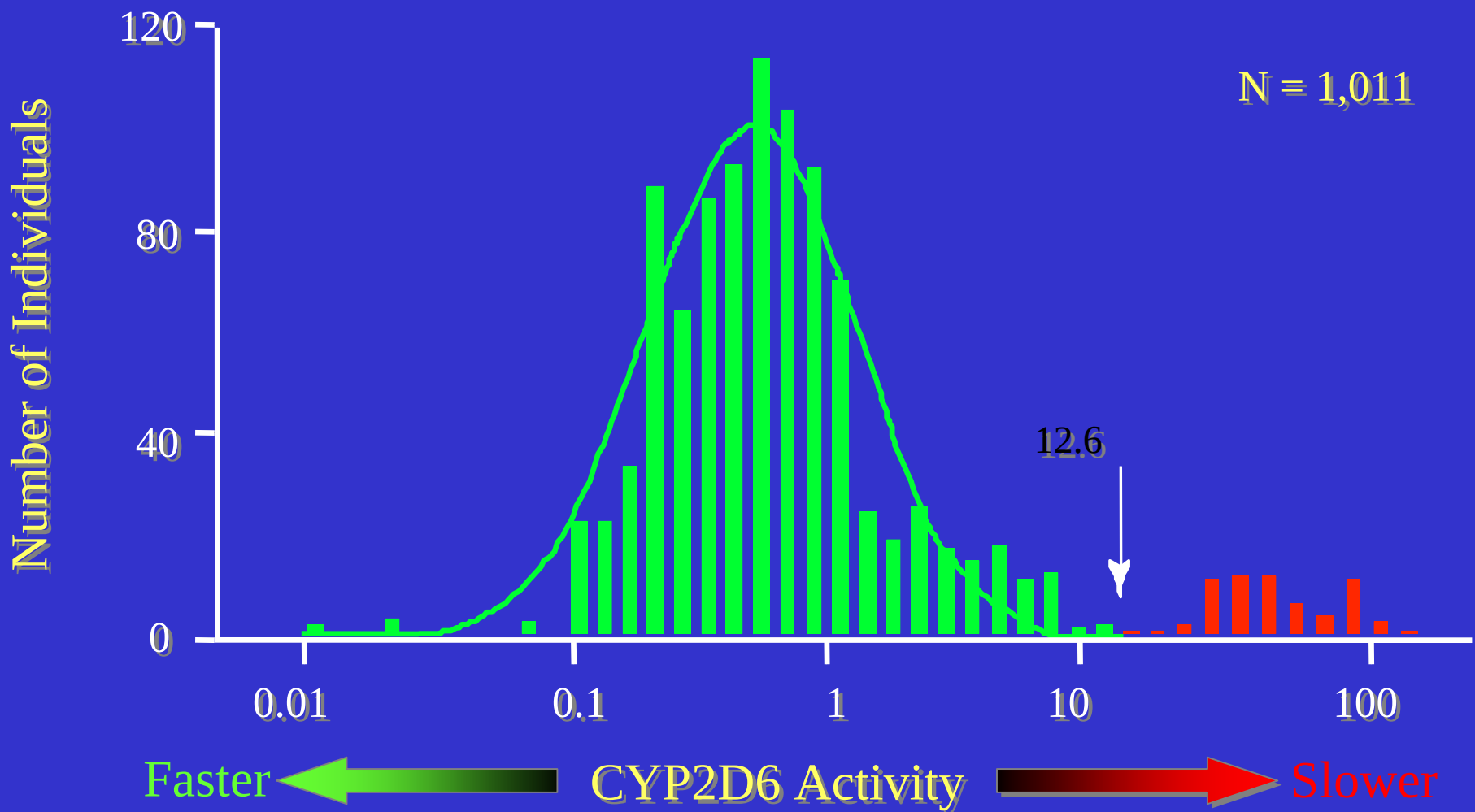
"Functional" overdose

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)

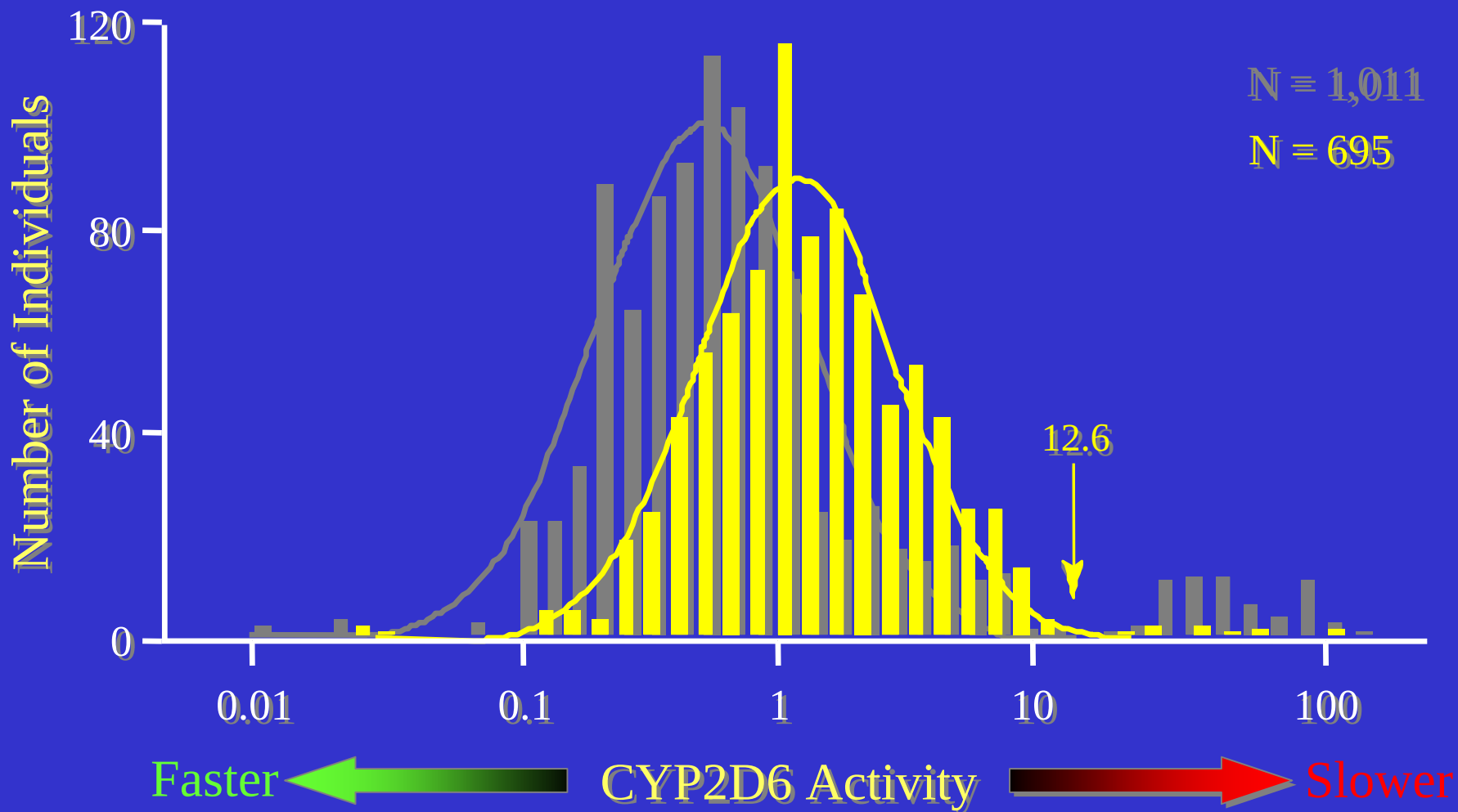
CYP2D6 Pharmacogenetics: Caucasians

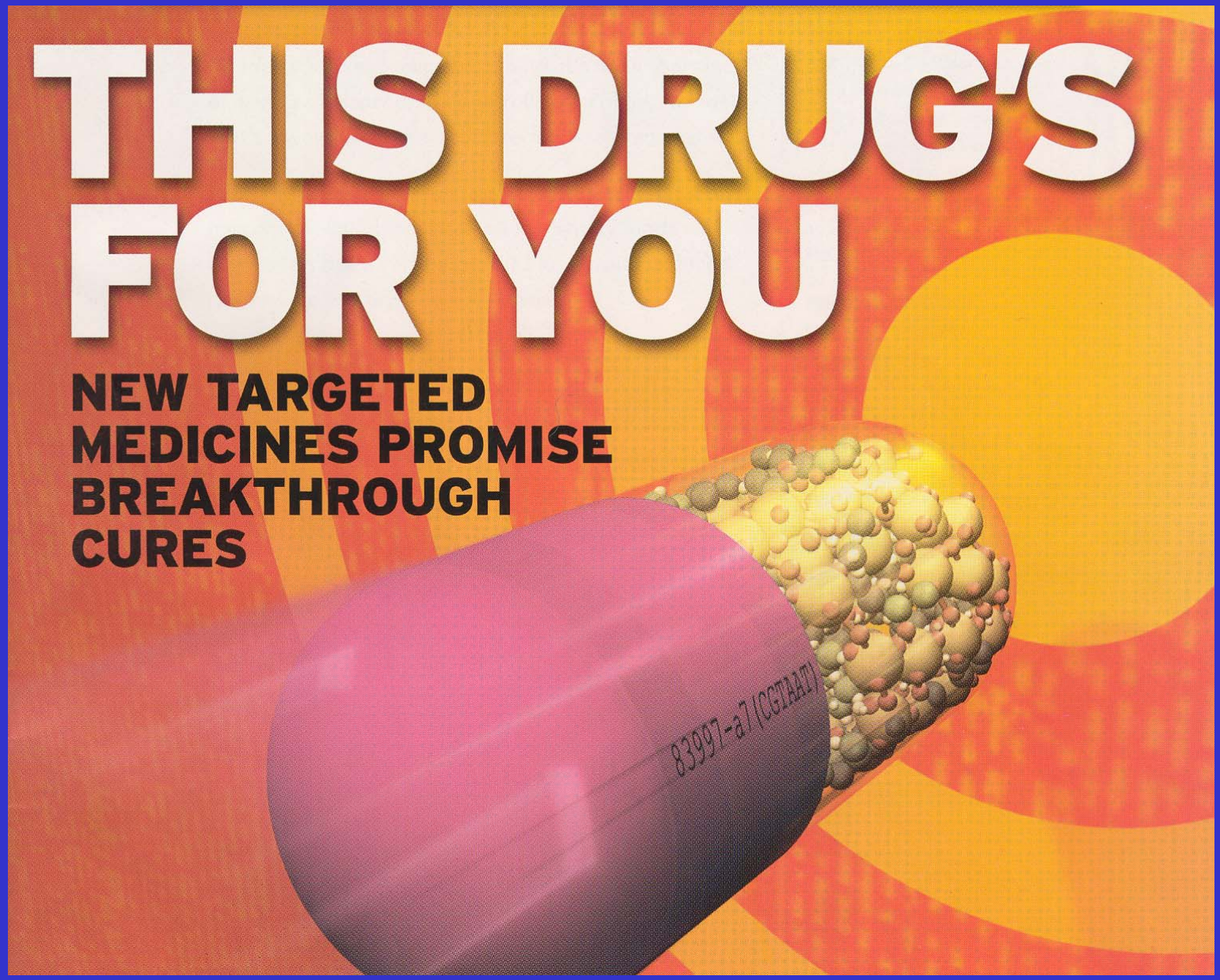
Bertilsson *et al.* Clin. Pharmacol. Ther. 51:288-97, 1992



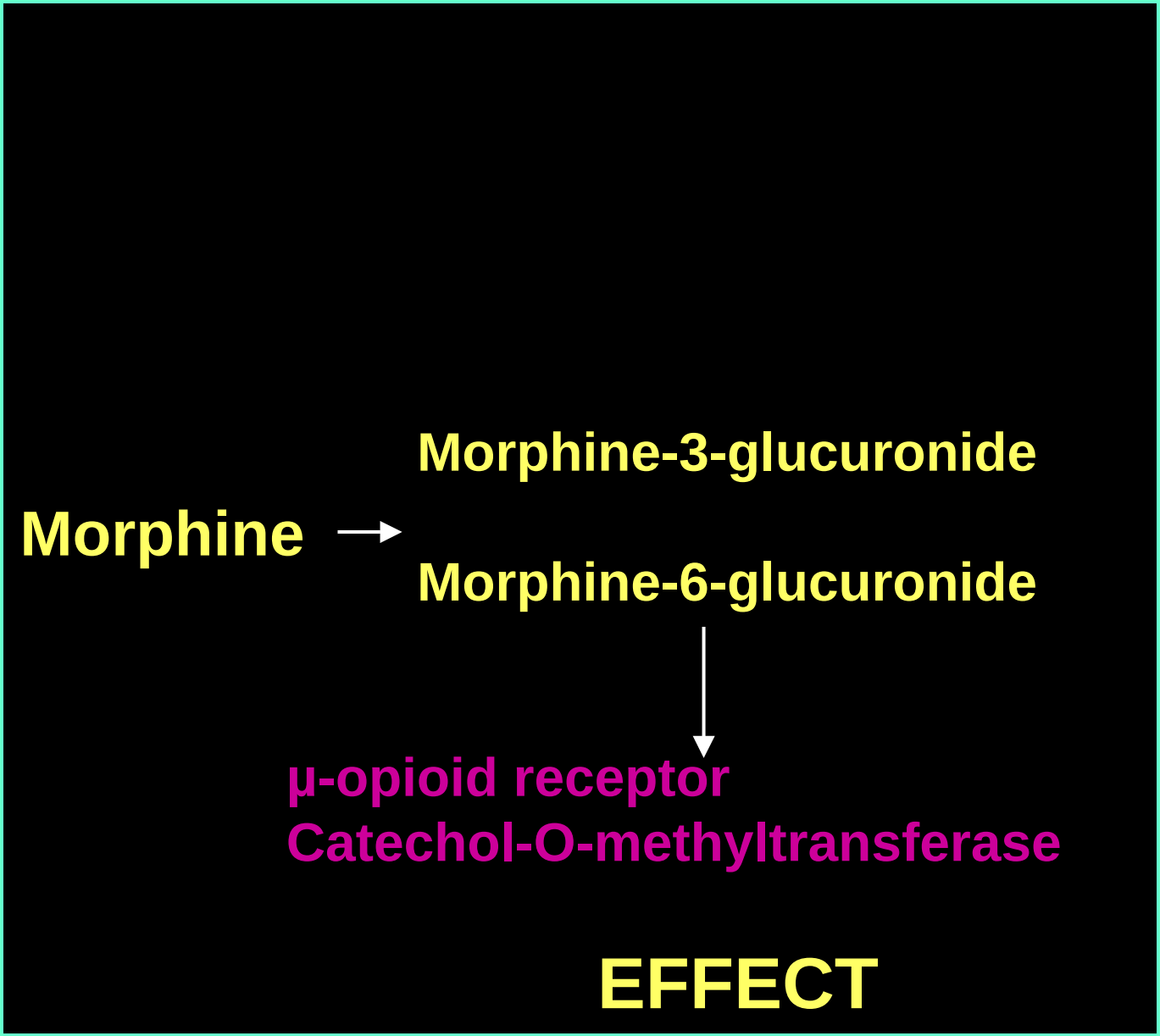
CYP2D6 Activity: Chinese

Bertilsson *et al.* Clin. Pharmacol. Ther. 51:288-97, 1992





U.S. News and World Report, 14 January 2003


Morphine-3-glucuronide
Morphine
Morphine-6-glucuronide
μ-opioid receptor
Catechol-O-methyltransferase
EFFECT

- **μ-opioid receptor gene (OPRM)**

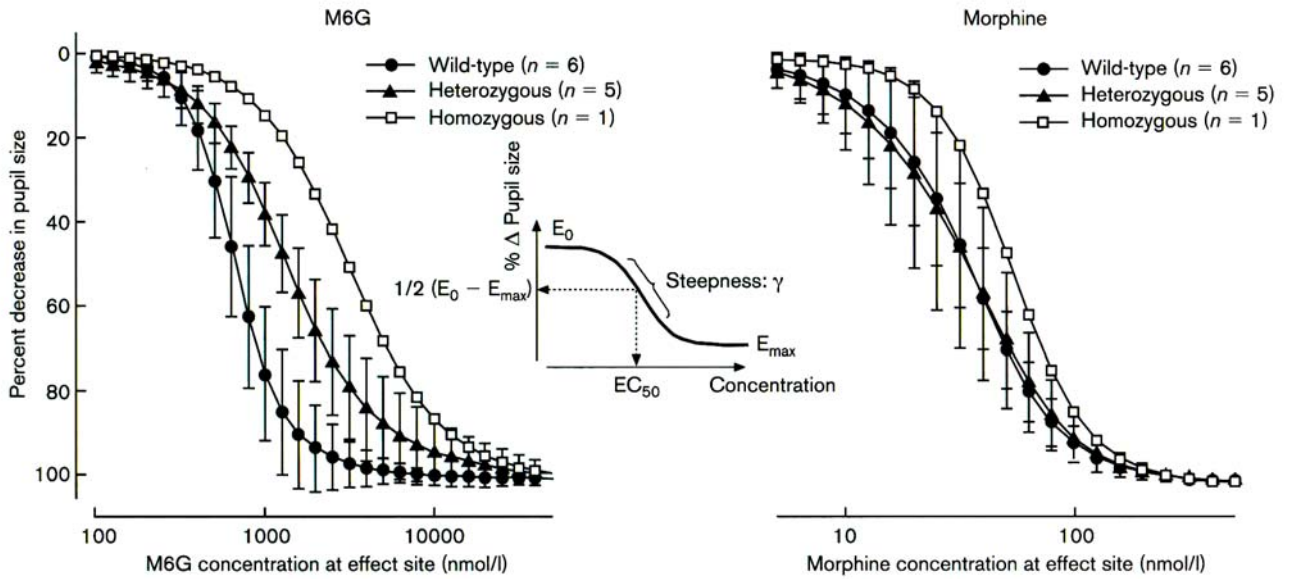
  The genetic polymorphism A118G of the human μ-opioid receptor gene decreases effect of morphine-6-glucuronide
  Lotsch et al 2002, Pharmacogenetics 12:3-9

μ-opioid receptor gene

The genetic polymorphism A118G of the human μ-opioid receptor gene decreases effect of morphine-6-glucuronide

Lotsch et al 2002, Pharmacogenetics 12:3-9

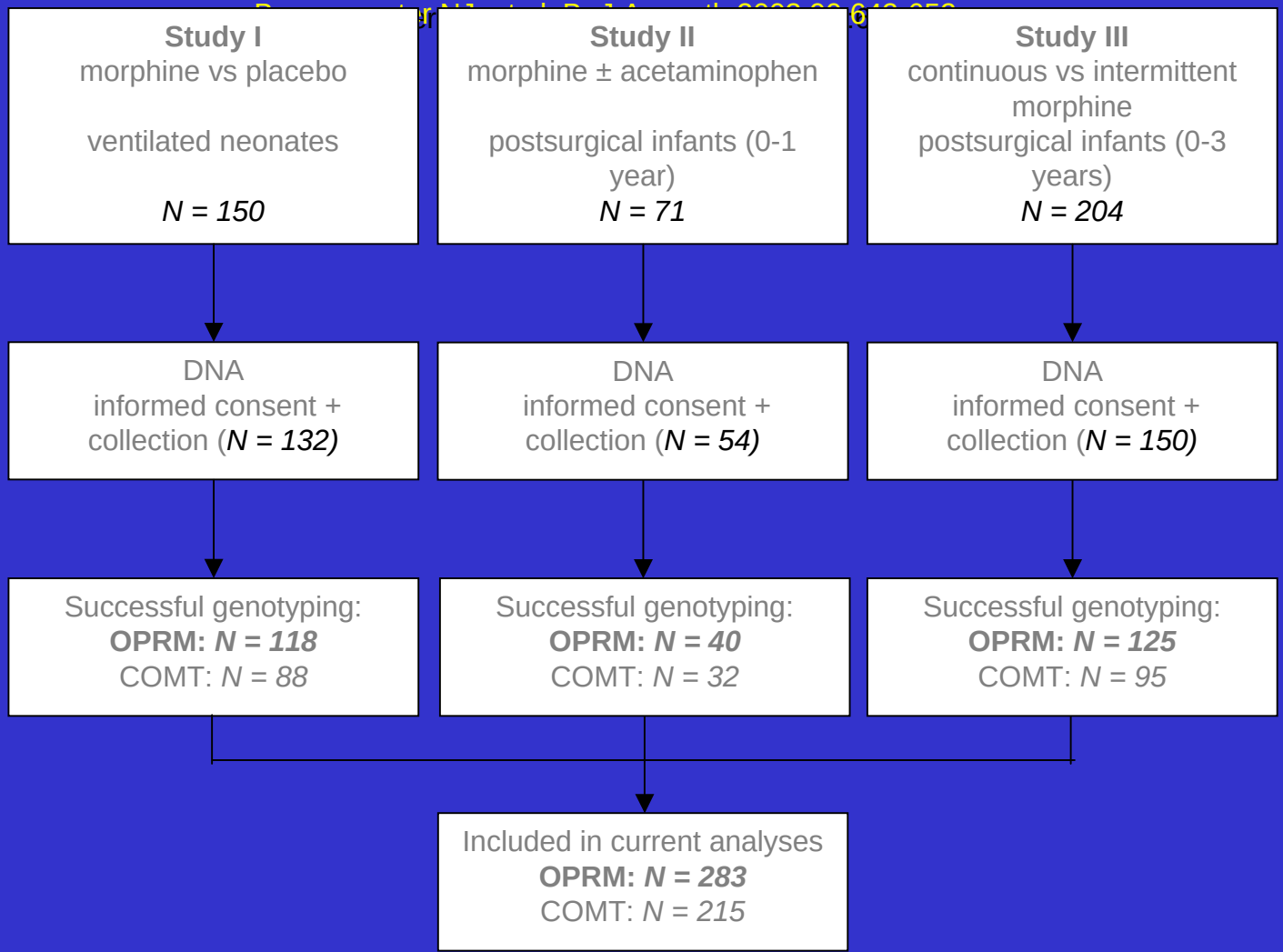
Fig. 2



Concentration effect relationship of M6G and morphine in subjects with the A118G SNP in the μ-opioid receptor gene and wild-type subjects. The curves were calculated from the individual estimates of the parameters of the sigmoid E_{max} pharmacodynamic model (Table 1) that described the dose–response relationship. They represent the mean ± SD per group. While the SNP resulted in a right shift of the curve for M6G, indicating lower potency, it had no effect on the potency of morphine. A schematic drawing of the E_{max} model with indication of the parameters from equation 1 is also given.

OPRM and COMT

Simons SH, et al. JAMA 2003;290:2419-2427



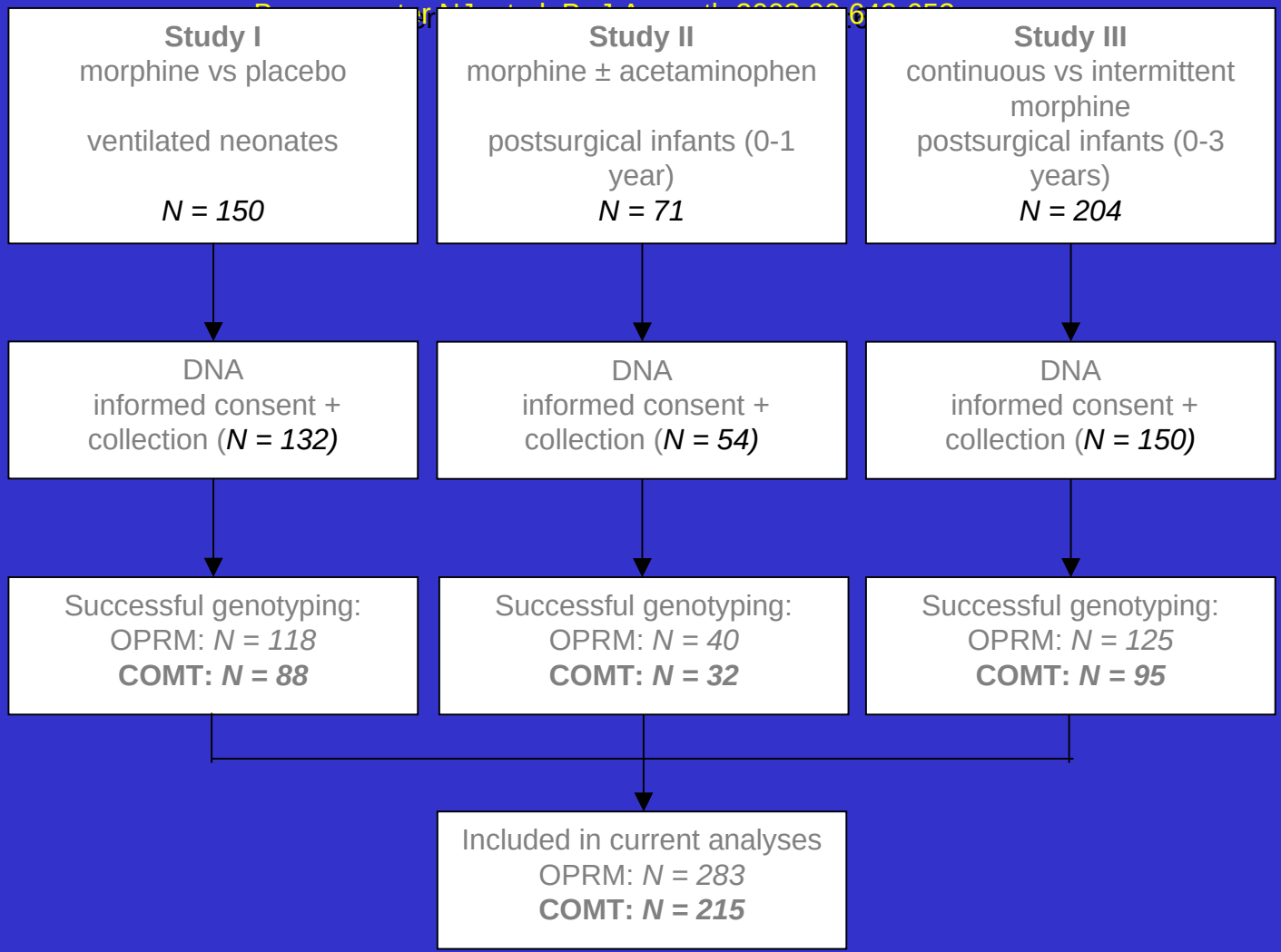
μ-opioid receptor gene (OPRM)

	Study I	Study II	Study III	Total
OPRM gene ($asn^{40}asp$)				
Wild type	84	30	100	214
Heterozygous	30	9	24	63
Homozygous	4	1	1	6
Total	**118**	**40**	**125**	**283**

Simons, et al .
Ped Research 2004;55:275A

OPRM and COMT

Simons SH, et al. JAMA 2003;290:2419-2427



Catechol-O-methyl transferase (COMT)

COMT is an enzyme that metabolises catecholamines that work as neurotransmitters.

The Val158Met variant
influences the human experience of pain:

patients with Met/Met variant
experience more pain

(Zubieta 2003, Science)

Catechol-O-methyl transferase (COMT)

	Study I	Study II	Study III	Total
COMT gene (val^{158}met)				
Wild type	21	7	26	54
Heterozygous	47	17	41	105
Homozygous	20	8	28	56
Total	**88**	**32**	**95**	**215**

Simons, et al.
Ped Research 2004;55:275A

Future perspectives:
The Perfect Neonatal Pain Assessment Instrument

The need for drug studies in children

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

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)