WELCOME and INTRODUCTION

Workshop on Regulatory and Scientific Issues related to the Investigation of Medicinal Products intended for Neonatal Use

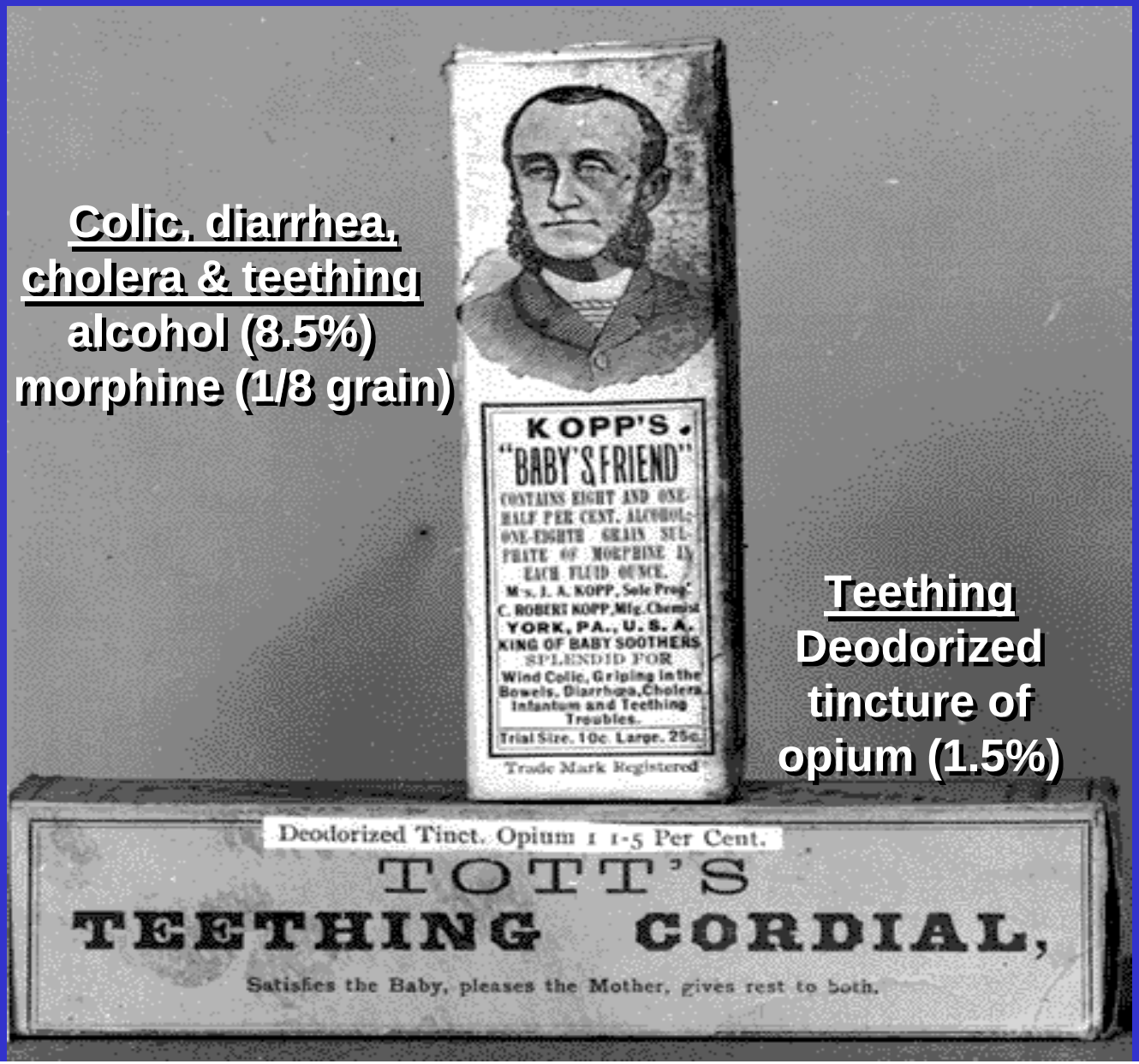
John van den Anker, MD, PhD

Children's National Medical Center, Washington, DC &
Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

11 October 2006

Historical Drug “Development” in Children

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



<u>Teething</u>
Deodorized tincture of opium (1.5%)

Historical Drug “Development” in Children

WHAT IS A LICENSED DRUG?

- Has a product license or marketing authorisation
- issued by the national licensing regulatory bodies
- or the European Medicines Evaluation Agency (EMEA)
- following detailed review of data presented by the drug company

Why was the licensing system introduced?

Origin in ADR's

- 1938 sulfanilamide (107 deaths)
- 1959 chloramphenicol ('grey baby syndrome')
- 1961 thalidomide (phocomelia)

What is a licensed drug?

- **SAFE**
- **EFFECTIVE**
- **HIGH QUALITY**

Examples of unlicensed drugs

- Modifications of licensed drugs
- New drugs/formulations produced under a ‘specials’ manufacturing license
- Drugs which have a license in other countries but not in the UK or France or Germany or the Netherlands or..
- Use of chemicals as drugs

Examples of off label use

Use outside the licensed:

- **Age range**
- **Indications**
- **Dosage recommendations**
- **Route of administration**
- **Contraindications**

Unlicensed and off label drug use in the neonate

- 70 babies
- 455 prescription episodes
- Licensed 35%
- Unlicensed 10%
- Off label 55%

- 90% babies received at least one UL/OL drug
- Conroy S, McIntyre J, Choonara I. Arch. Dis. Child. Fetal Neonatal Ed. 1999;80:F142-5

The Knowledge Gap: Possible Reasons-Still Exist

- Ethical Concerns
- Limited populations for certain diseases
- Difficulties in conducting trials in neonates: logistical to technical reasons
- Lack of infrastructure-improving

The Knowledge Gap: Possible Reasons-Still Exist

- Belief dosing could be determined by weight based calculations (“little children”)
- Lack of accepted endpoints and validated pediatric assessment tools
- Limited marketing potential compared to adults

BPCA: Pediatric Exclusivity Stats (As of July 2006)

- Proposed Pediatric Study Requests 474
- Written Requests issued by FDA 323
- Exclusivity granted for PRODUCT 123
- Number of Determinations 135
- Label changes 114
- Number of patients in requested studies 43,427
- Summaries of Medical/Clinical Pharmacology
  - Summaries on fda.gov/cder/pediatrics 64

www.fda.gov/cder/pediatric/summaryreview.htm

Scientific Trial Issues

- Scientific Issues
  - Extrapolation
  - Bridging Studies
  - Safety Studies: length and type
  - Endpoint & Validation Issues
  - Neonatal population still an issue
  - Need for longer term outcomes for studies (18-24 months)
- Learning from the trials conducted

Neonatal Studies: FDAMA 1999-2002: N=11

• Ranitidine	GERD
• Omeprazole	
• Famotidine	
• Remifentanil	Anesthesia
• Sevofluran	
• Propofol	
• Bisoprolol	Hypertension
• Sotolol	Arrhythmia
• Didanosine	HIV
• Stavudine	
• Lamivudine	

BPCA- Exclusivity Neonatal and Infant Studies: 2002-2005

- Written Requests issued which included the age range: 0-2 years:

  N= 41
- Products with submitted studies for infants less than 4 months of age:

  N=13
- Products with submitted studies for newborns (<1month of age):

  N=9

Neonatal Studies: BPCA N=9

- Ciprofloxacin: Ophthalmic
- Moxifloxacin: Ophthalmic
- Ofloxacin: Conjunctivitis
- Esmolol: Hypertension
- Nelfinavir: HIV
- Fenoldopam: Blood Pressure
- Linezolid: Pneumonia & skin infections
- Nizatidine: GERD
- Argatroban: Thrombosis

BPCA-Off Patent: N=9
Requested Studies for Neonates: 2002-2005

- **Ampicillin:** Sepsis and meningitis
- **Azithromycin:** Chlamydia
- **Azithromycin:** U. urealyticum
- **Dactinomycin:** Wilms, rhabdosarcoma
- **Lorazepam:** Sedation in ICU
- **Meropenem:** Complicated abdominal
- **Morphine:** Analgesia in ICU
- **Nitroprusside:** Reduction of BP
- **Vincristine:** Malignancies

What Pediatric Trials Have Taught (what we were doing before we knew better)

1. Unnecessary Exposure to Ineffective Drugs
2. Ineffective Dosing of an Effective Drug
3. Overdosing of an Effective Drug
4. Undefined Unique Pediatric AE's
5. Effects on Growth and Behavior

ONGOING LESSONS LEARNED

1. PK is more variable, even within the pediatric population, than anticipated
2. Adverse reactions that are pediatric specific will not be defined without pediatric studies
3. Trial designs are being modified as we learn from submitted studies

ONGOING LESSONS LEARNED

4. Ethical issues have to be reassessed from the pediatric perspective
5. Safety studies, of sufficient duration and longer term follow-up studies, remain problematic
6. The present incentive program still leaves many subpopulations unstudied

For the Future: Needs

- More transparency for all pediatric studies and the data from those studies
- Continued development of pediatric endpoints and assessment tools
- Real time inspections of pediatric trials

For the Future: Needs

- Continued development of how to best utilize juvenile animal models
- Better approaches to assess long term safety
- Active surveillance systems focusing on pediatrics
- Studies in Neonates and prematures

OBJECTIVES OF THIS WORKSHOP

- Provide an opportunity for an **in-depth review** and **discussions** between Academia, Regulators, Learned Societies and Health Professionals involved in all aspects related to the investigation of medicinal products in the neonate

OBJECTIVES OF THIS WORKSHOP

- Complementary to the work carried out by the Paediatric Working Party at the EMEA
- Concept papers on the impact of liver, kidney, heart & lung, and brain immaturity when investigating medicinal products in neonates

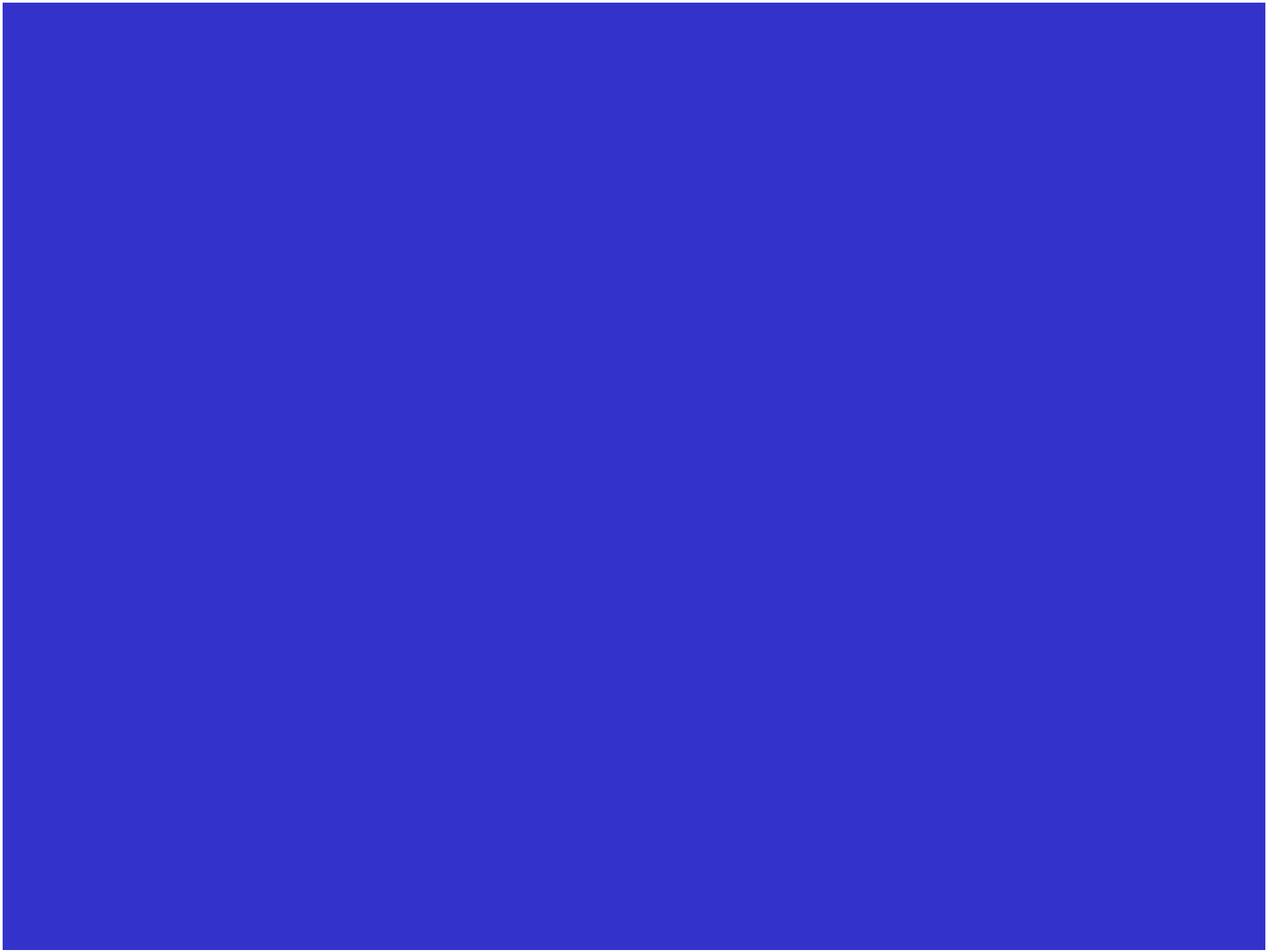
OBJECTIVES OF THIS WORKSHOP

- Preparation of an EMEA guideline for the investigation of medicinal products intended for neonatal use:

- EXISTING CONCEPT PAPERS
- THIS WORKSHOP

PRESENTERS

- Joerg Breitkreutz
- Greg Kearns
- Vineta Fellman
- Pieter Sauer
- Gerard Pons
- Dirk Mentzer
- John van den Anker



Impact of Organ Immaturity on the Investigation of Medicinal Products in the Neonate

John N. van den Anker, MD, PhD, FCP, FAAP

- Evan and Cindy Jones Chair in Pediatric Clinical Pharmacology
- Professor of Pediatrics, Pharmacology and Physiology, The George Washington School of Medicine and Health Sciences
- Professor of Pediatrics, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands


Children's

Designing a Neonatal Protocol

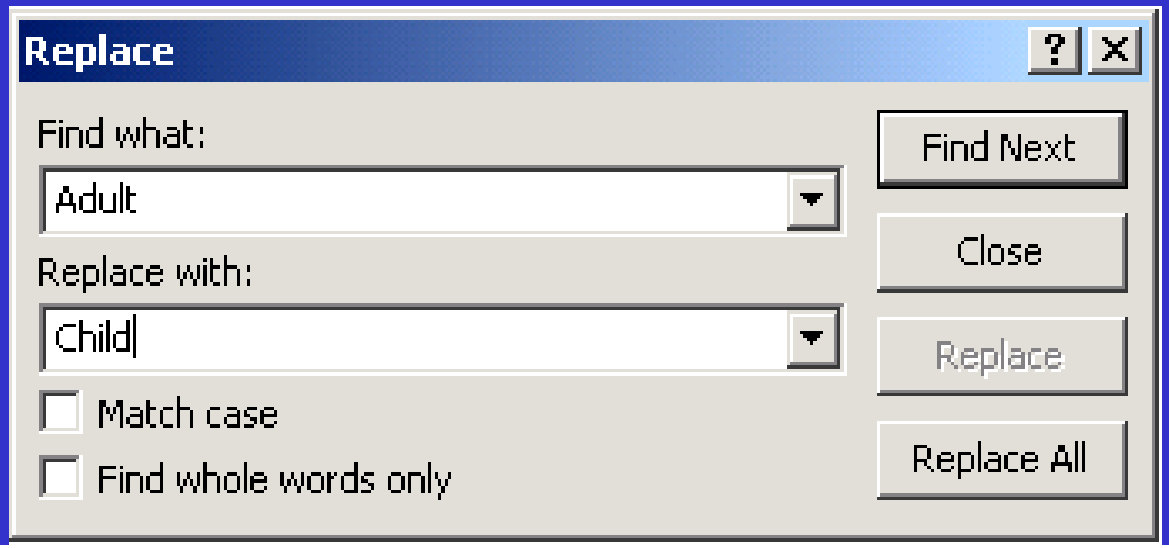
Option 1:

Involve a pediatric trained clinical investigator in the design of the protocol

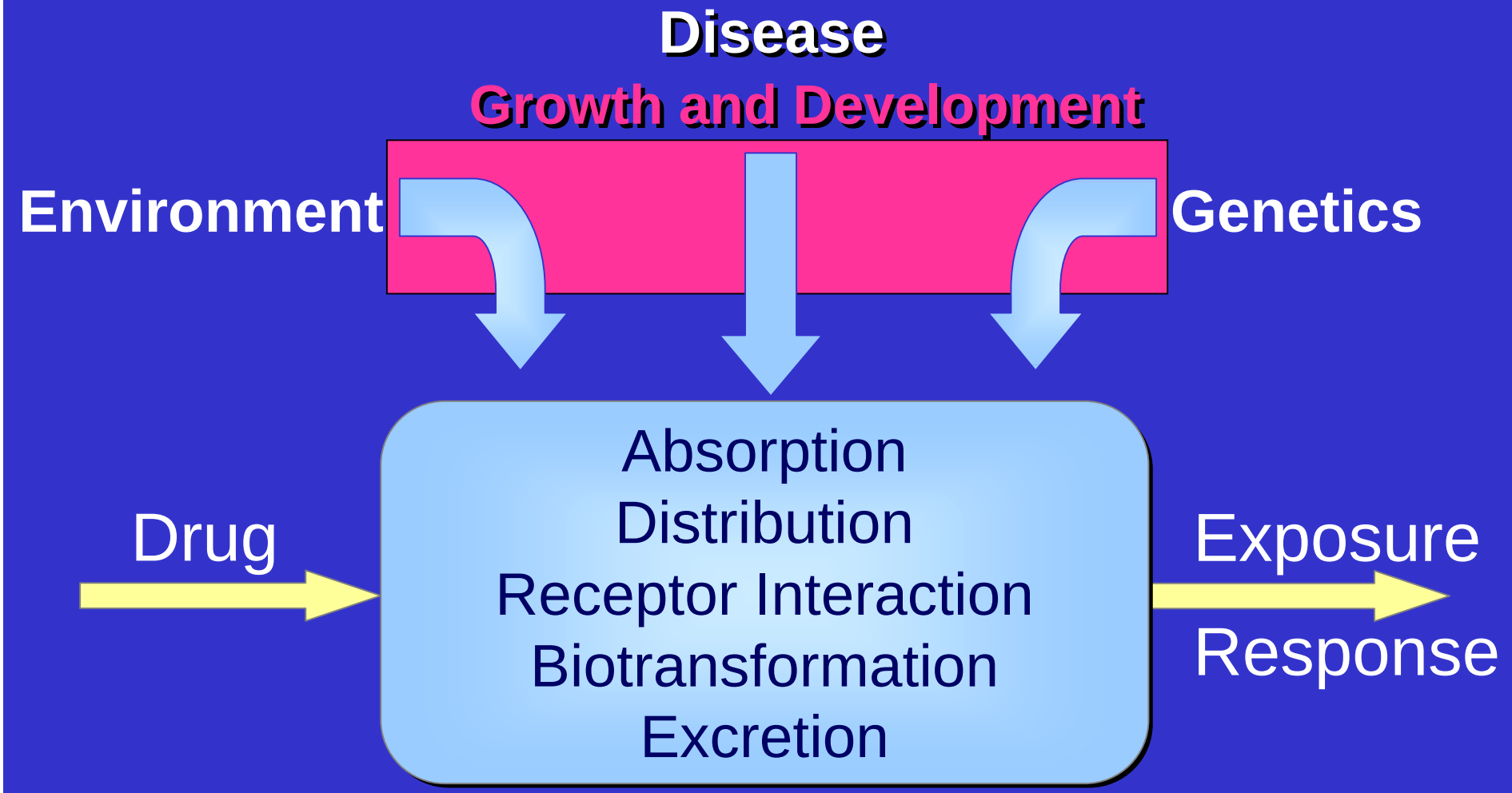
OR

Option 2:

Employ sophisticated in silico algorithms designed to adapt existing adult protocols



Determinants of Drug Response in Neonates



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

Ontogeny ***Pharmacogenetics***

Variability

The Developmental Continuum

Fetus

Newborn

Infant

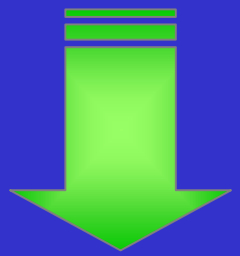
Preschooler

School-age

Adolescent

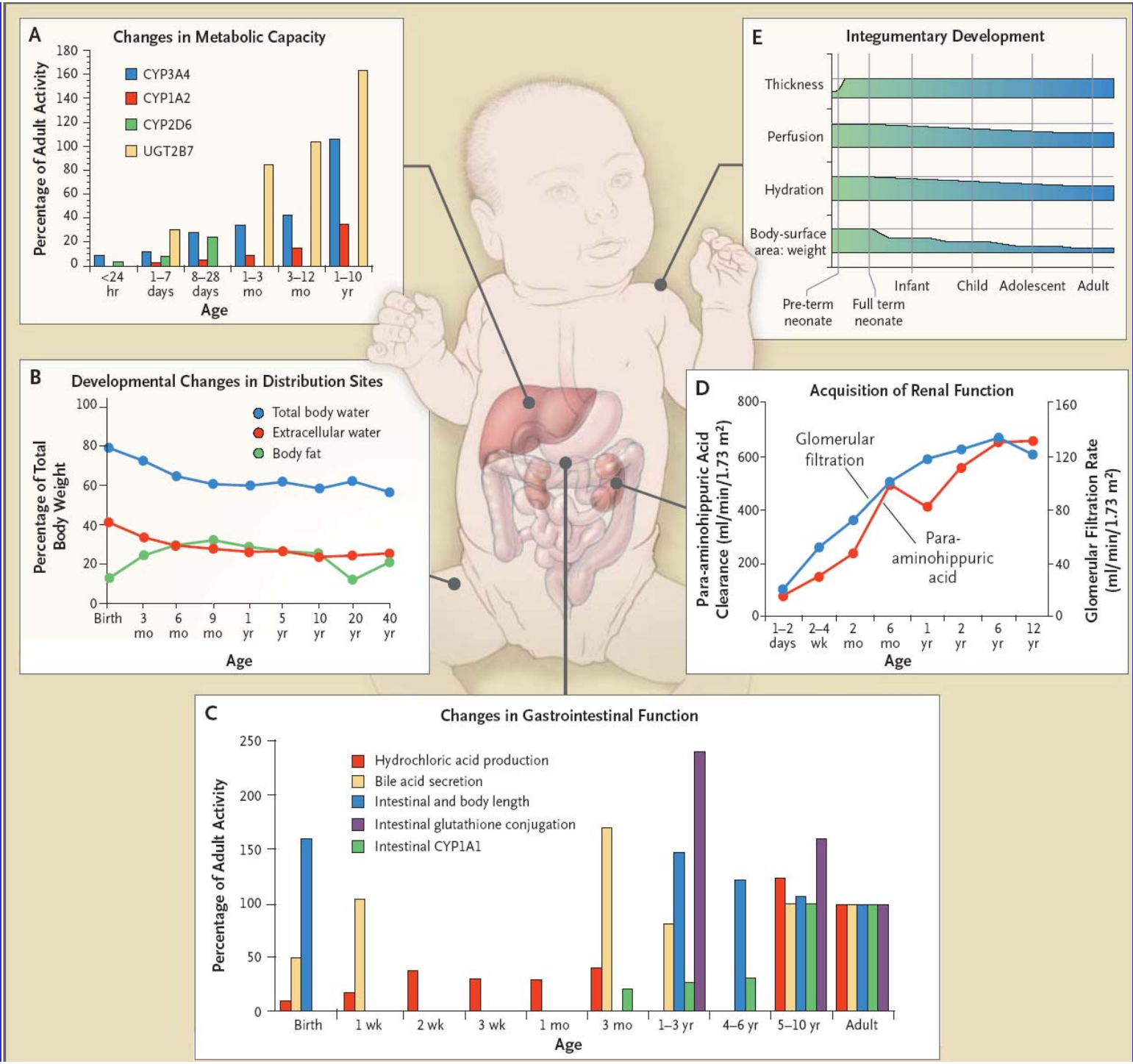
Adult

- 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


A
Changes in Metabolic Capacity
Percentage of Adult Activity
CYP3A4
CYP1A2
CYP2D6
UGT2B7
<24 hr
1–7 days
8–28 days
1–3 mo
3–12 mo
1–10 yr
Age
B
Developmental Changes in Distribution Sites
Percentage of Total Body Weight
Total body water
Extracellular water
Body fat
Birth
3 mo
6 mo
9 mo
1 yr
5 yr
10 yr
20 yr
40 yr
Age
C
Changes in Gastrointestinal Function
Percentage of Adult Activity
Hydrochloric acid production
Bile acid secretion
Intestinal and body length
Intestinal glutathione conjugation
Intestinal CYP1A1
Birth
1 wk
2 wk
3 wk
1 mo
3 mo
1–3 yr
4–6 yr
5–10 yr
Adult
Age
D
Acquisition of Renal Function
Para-aminohippuric Acid Clearance (ml/min/1.73 m²)
Glomerular Filtration Rate (ml/min/1.73 m²)
Glomerular filtration
Para-aminohippuric acid
1–2 days
2–4 wk
2 mo
6 mo
1 yr
2 yr
6 yr
12 yr
Age
E
Integumentary Development
Thickness
Perfusion
Hydration
Body-surface area: weight
Pre-term neonate
Full term neonate
Infant
Child
Adolescent
Adult

Selecting the population

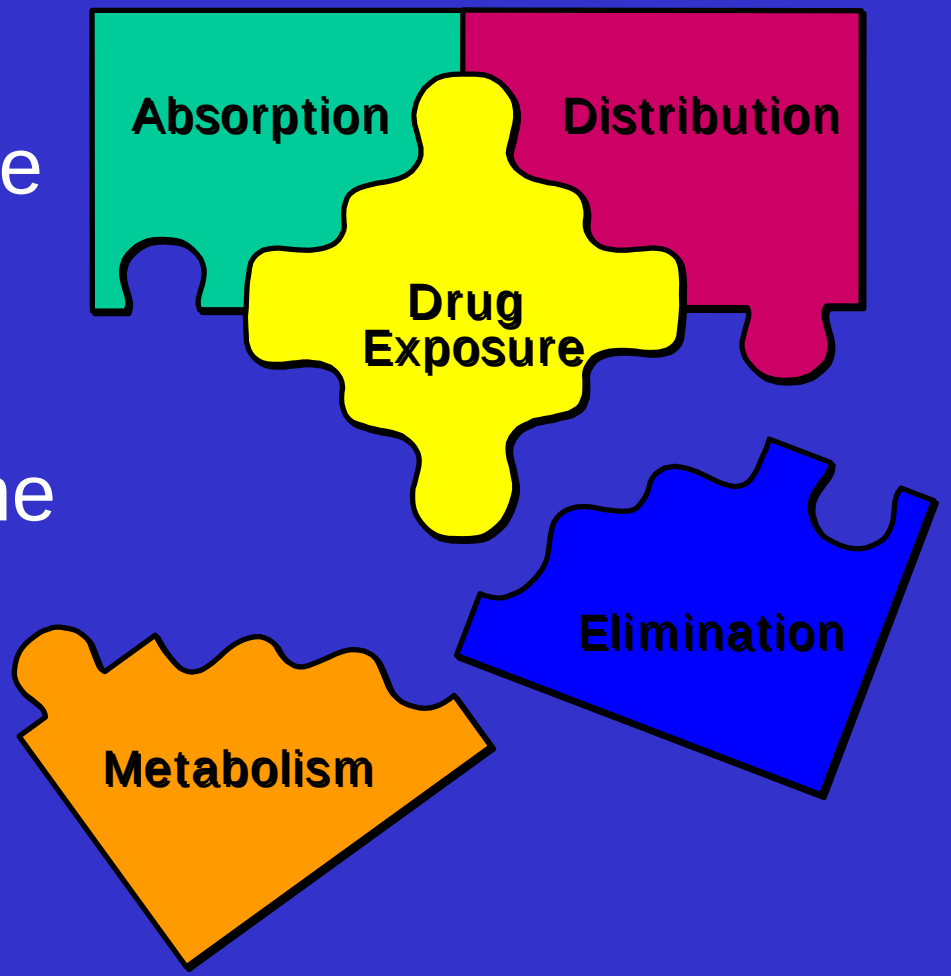
All neonates are not created equal

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

These will increase variability
in outcome measures

Critical Role of Pharmacokinetics in Pharmacotherapy……

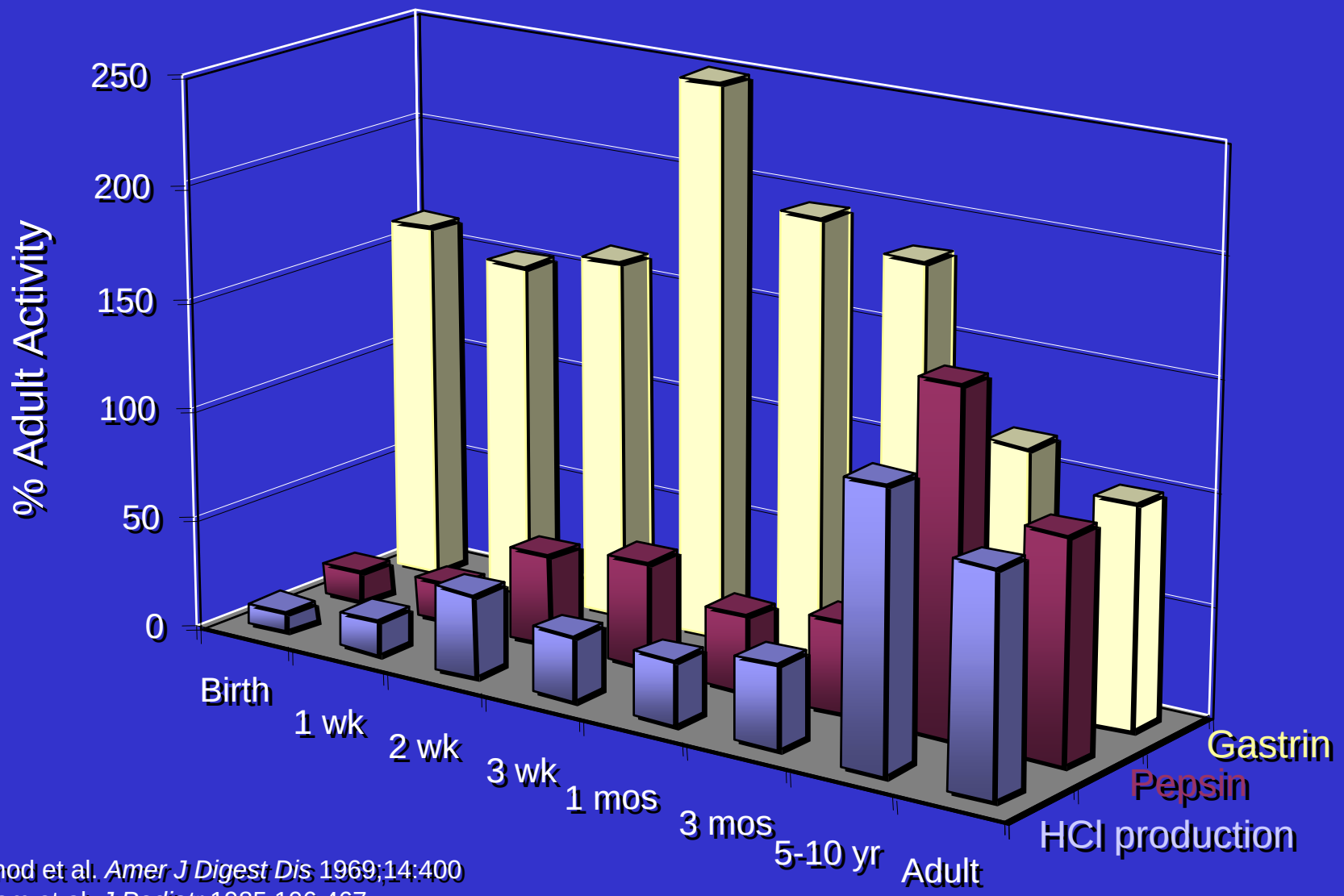
- The combination of ADME dictate exposure which dictates dose.
- Exposure along with the interaction with therapeutic targets (e.g., receptors) dictates response.



Getting the drug in…

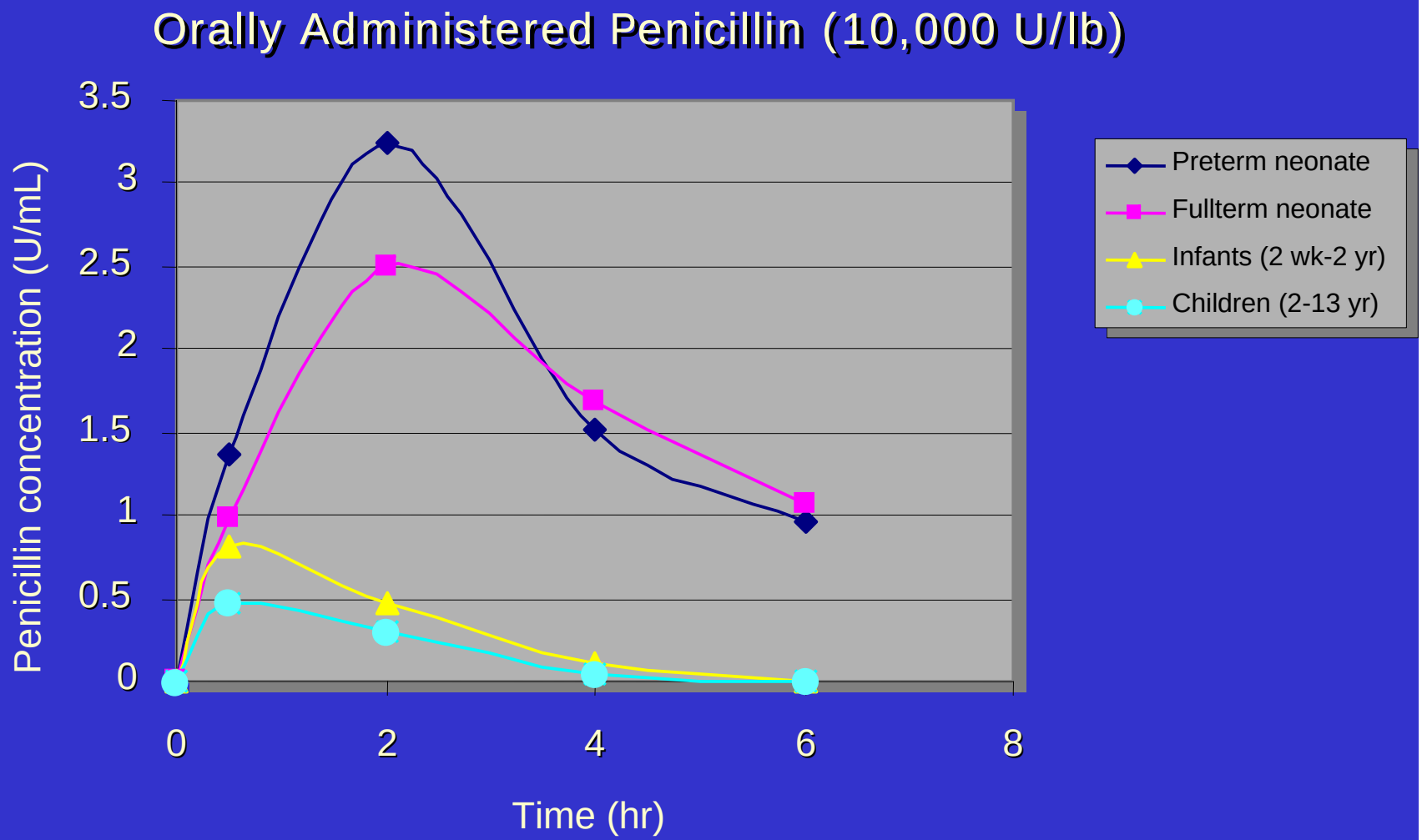
- Can the adult dosage form be administered without modification?
- Does the existing adult dosage form require modification?
- **Have you considered age dependent changes in physiology that influence absorption?**

Drug Absorption
Developmental Changes in Gastric pH

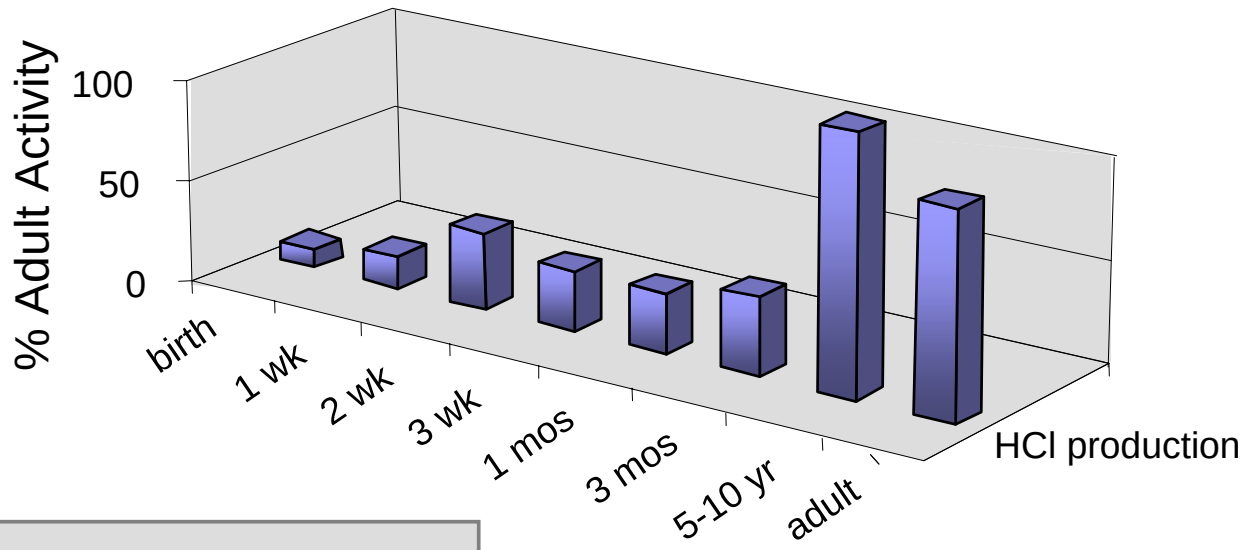


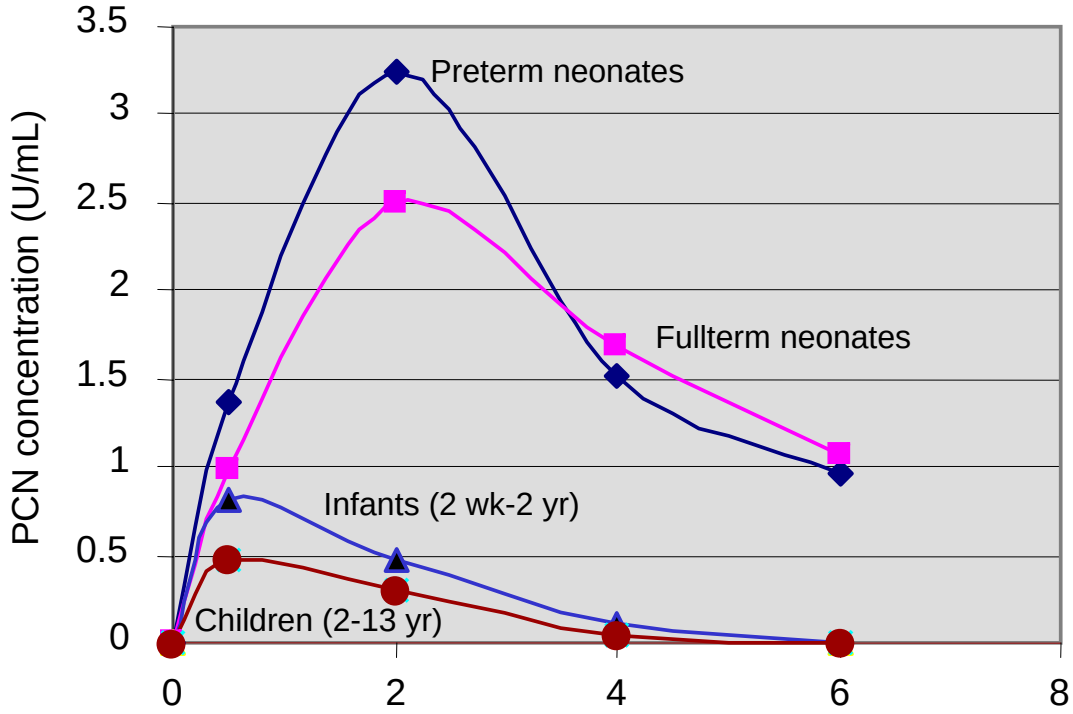
Agunod et al. *Amer J Digest Dis* 1969;14:400
Mozam et al. *J Pediatr* 1985;106:467
Rodgers et al. *J. Pediatr Surg* 1978;13:13

Developmental Alterations in Intestinal Drug Absorption
Influence of Higher Gastric pH



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





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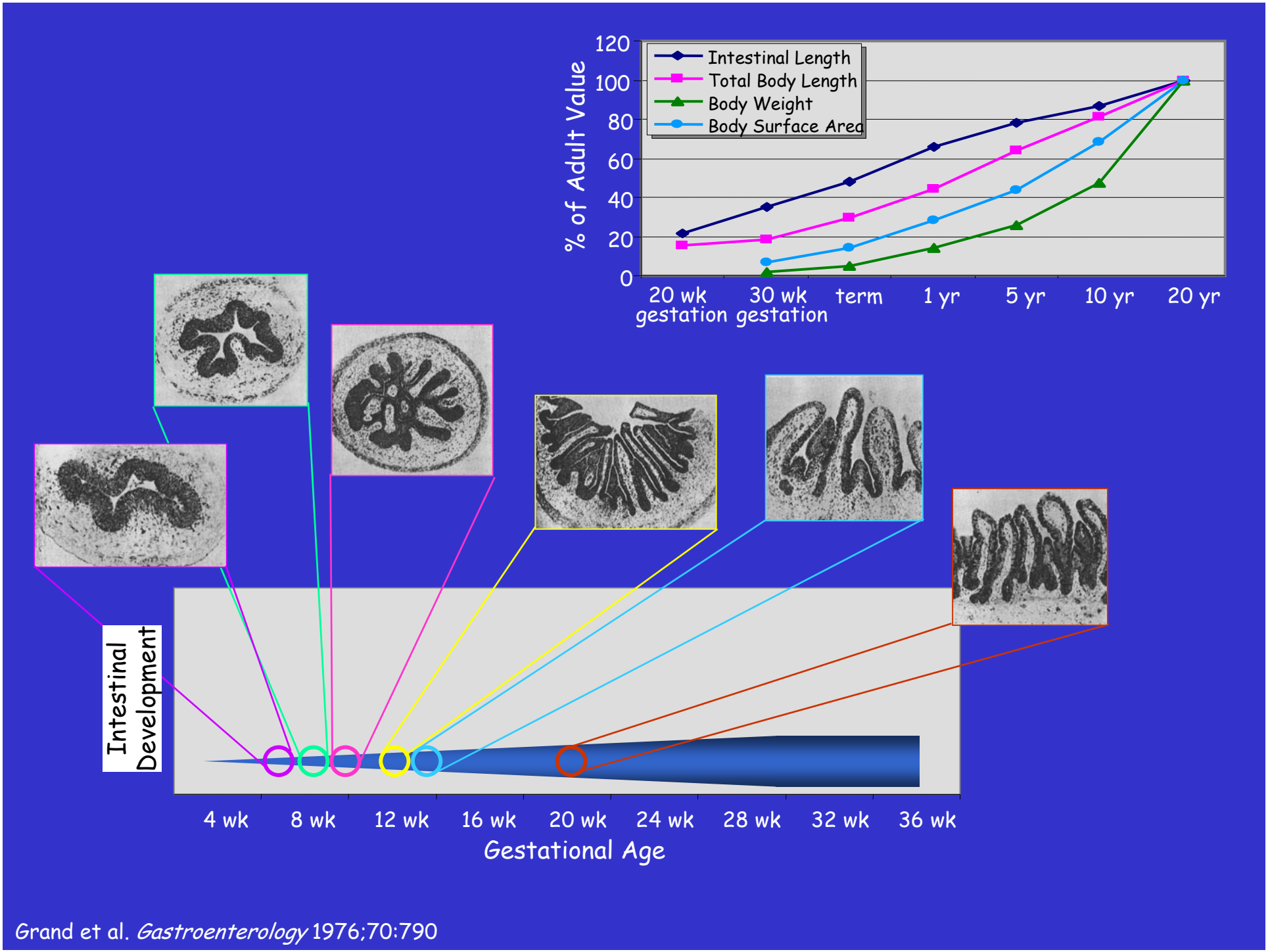
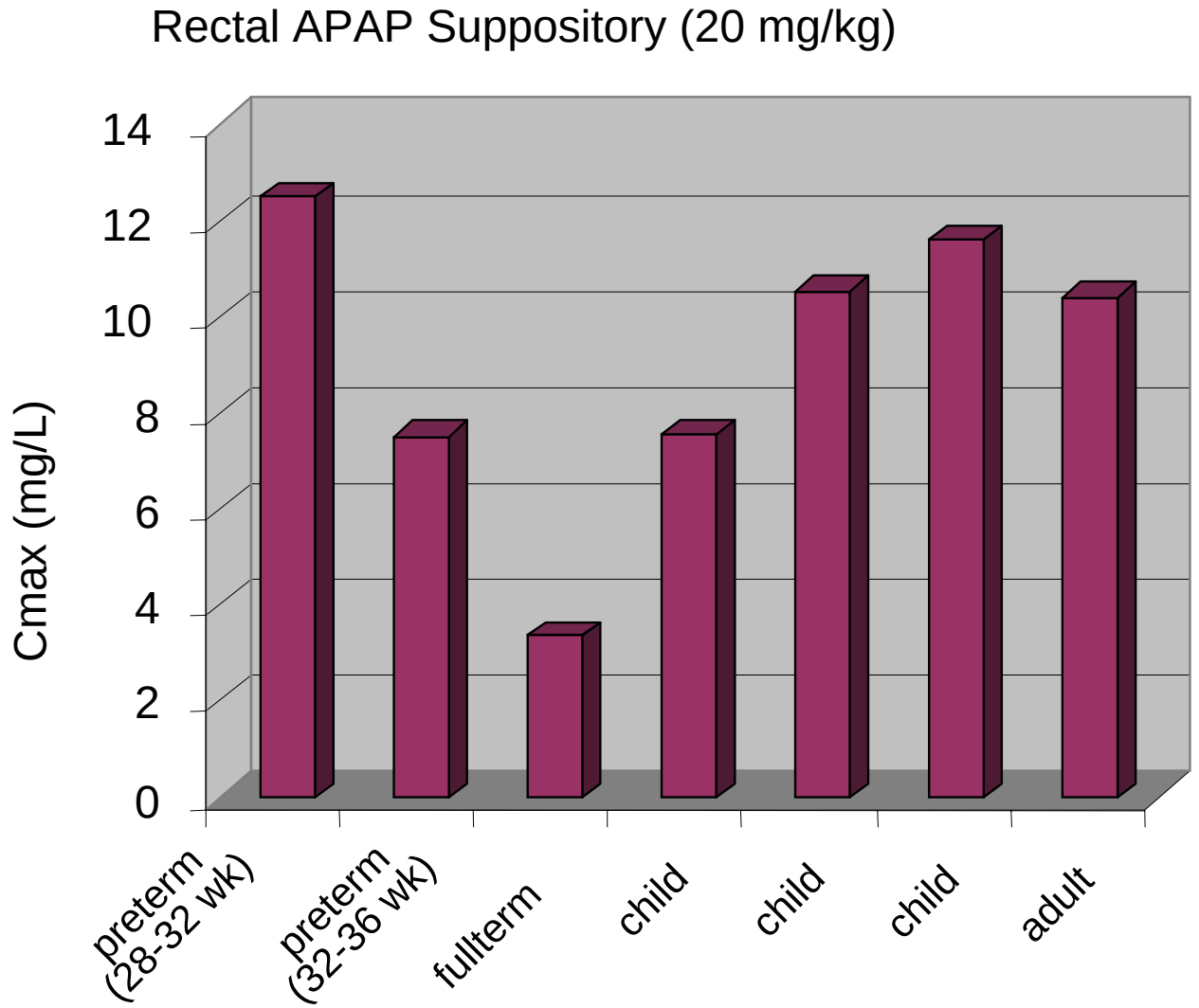
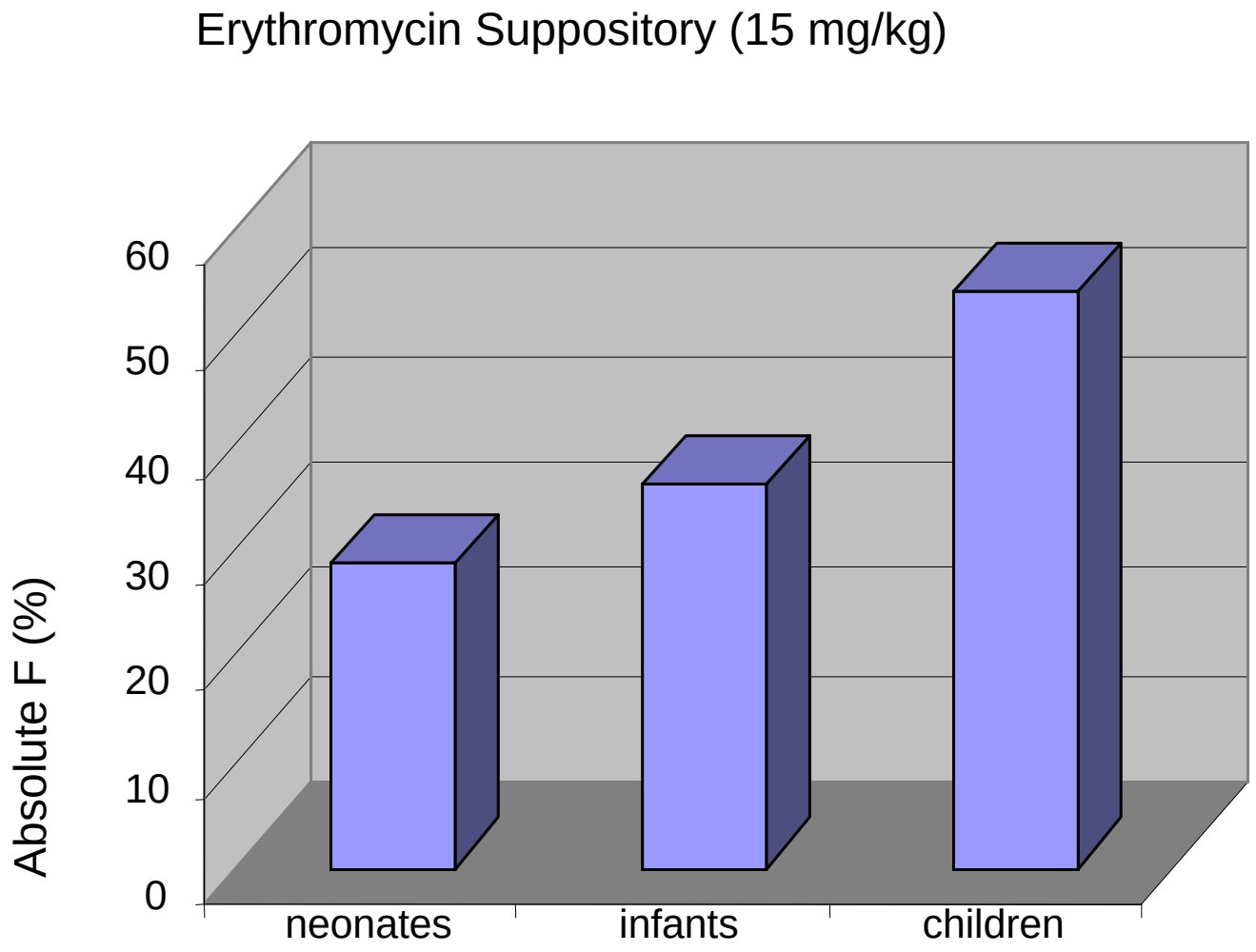
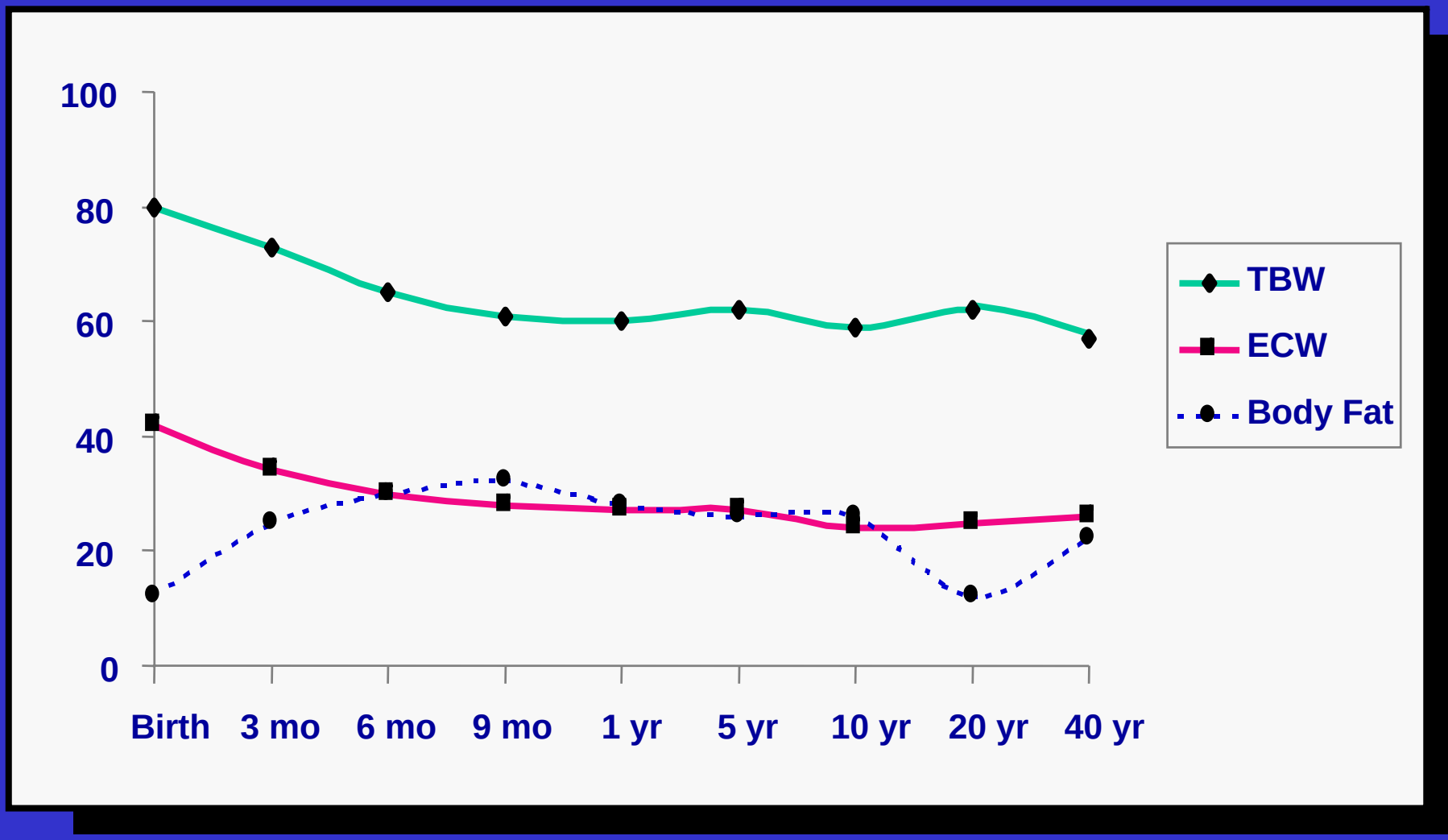


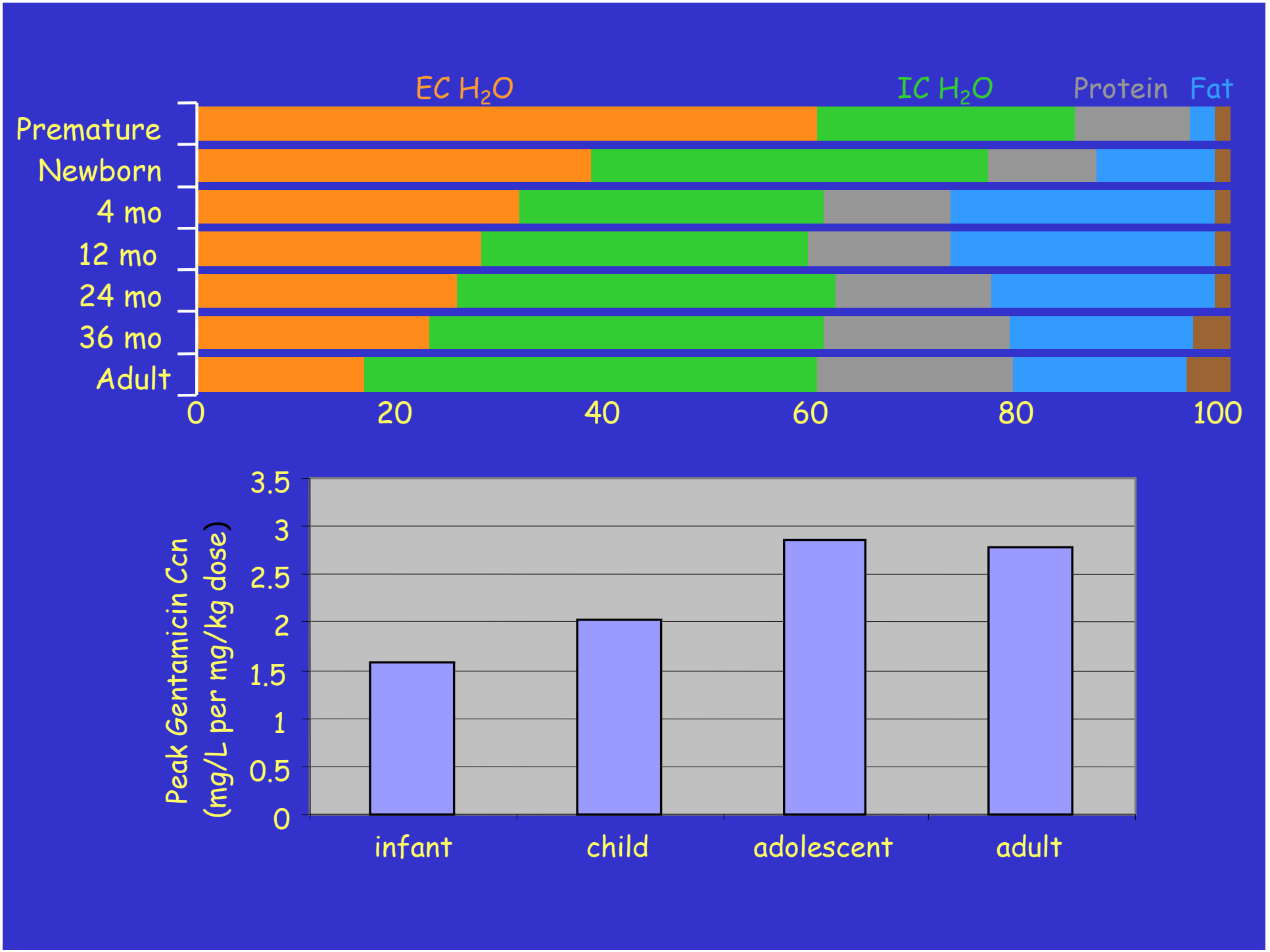
Grand et al. *Gastroenterology* 1976;70:790


Rectal APAP Suppository (20 mg/kg)
Cmax (mg/L)
14
12
10
8
6
4
2
0
preterm (28-32 wk)
preterm (32-36 wk)
fullterm
child
child
child
adult


Erythromycin Suppository (15 mg/kg)
Absolute F (%)
60
50
40
30
20
10
0
neonates
infants
children

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

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;74:413-422

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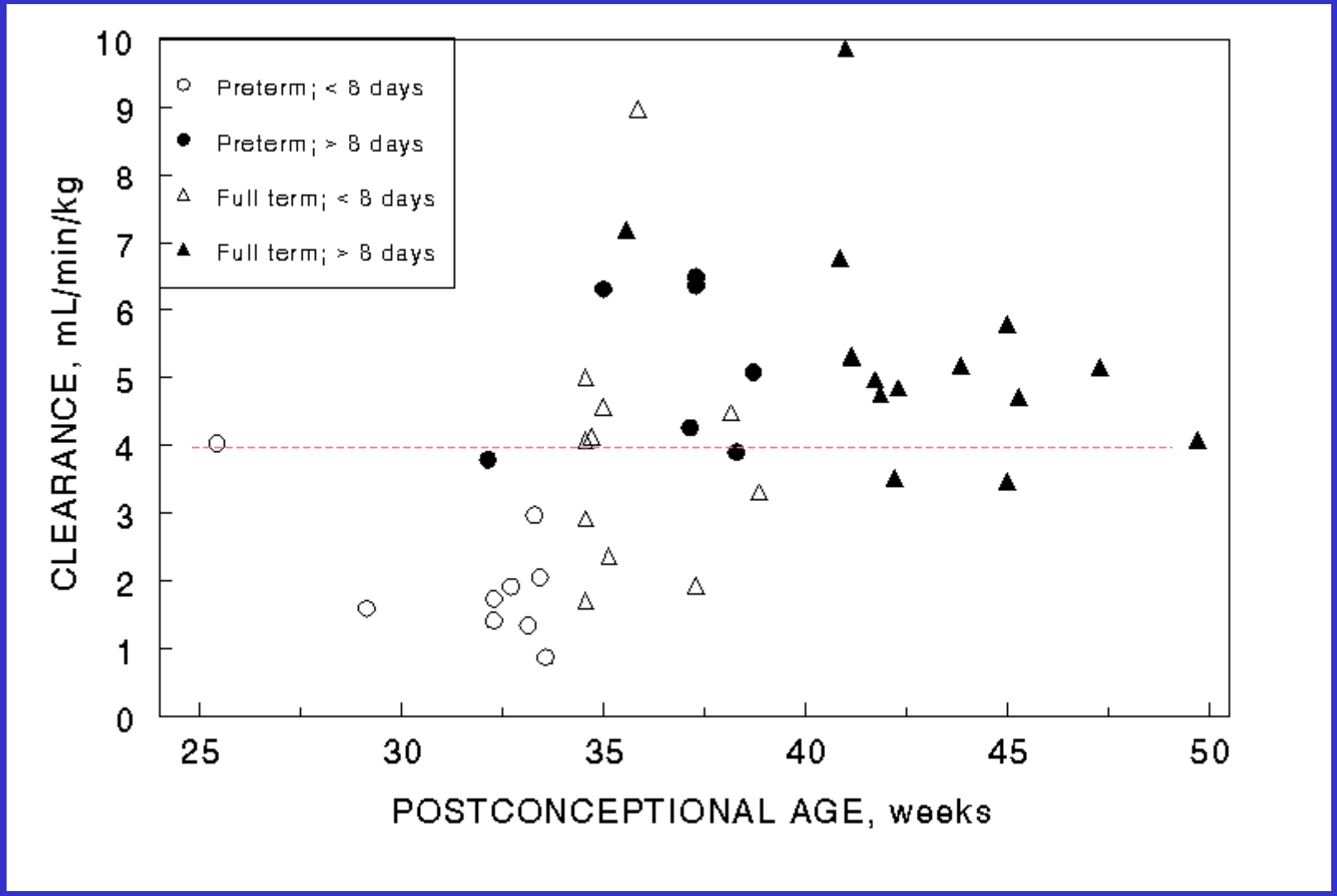
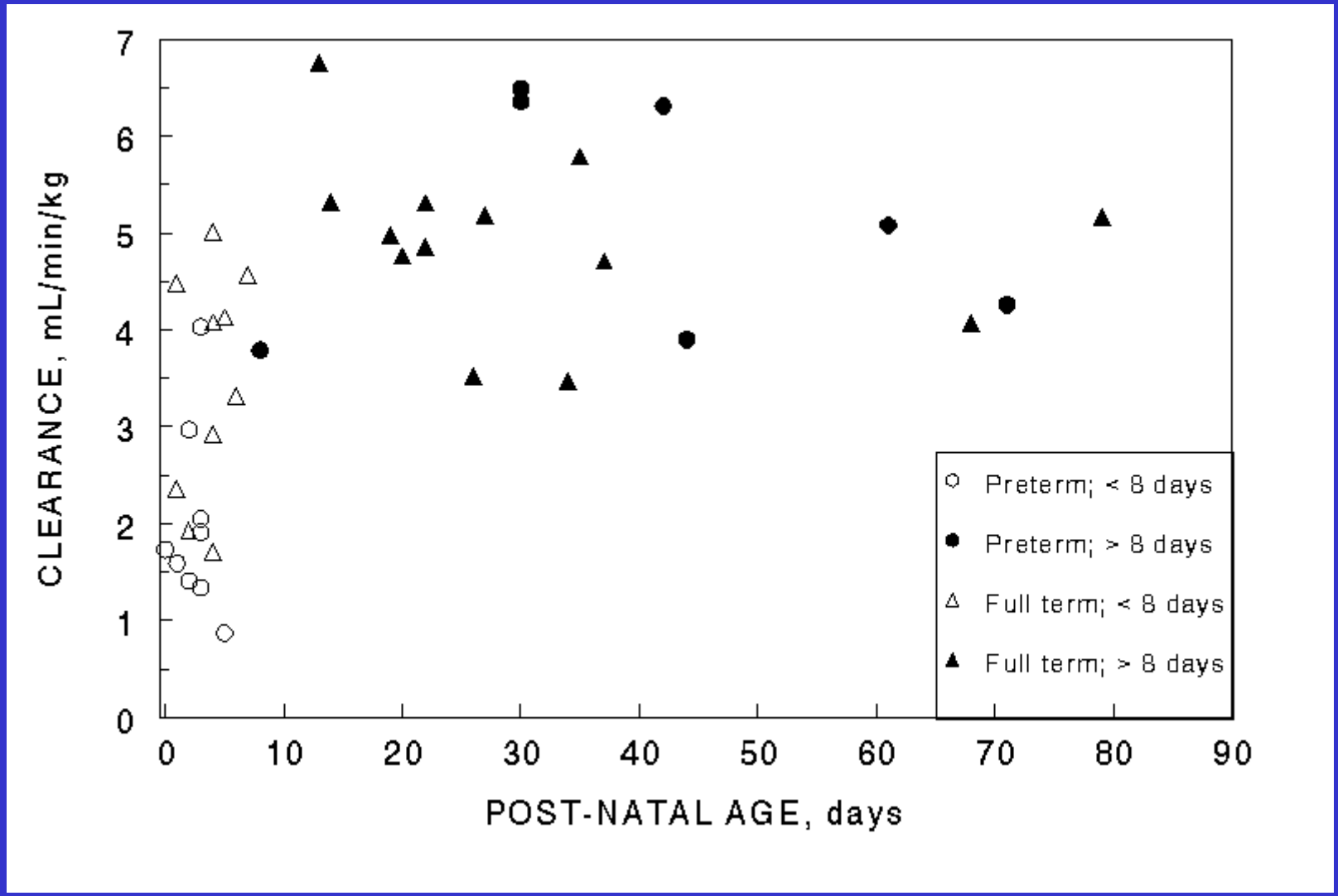
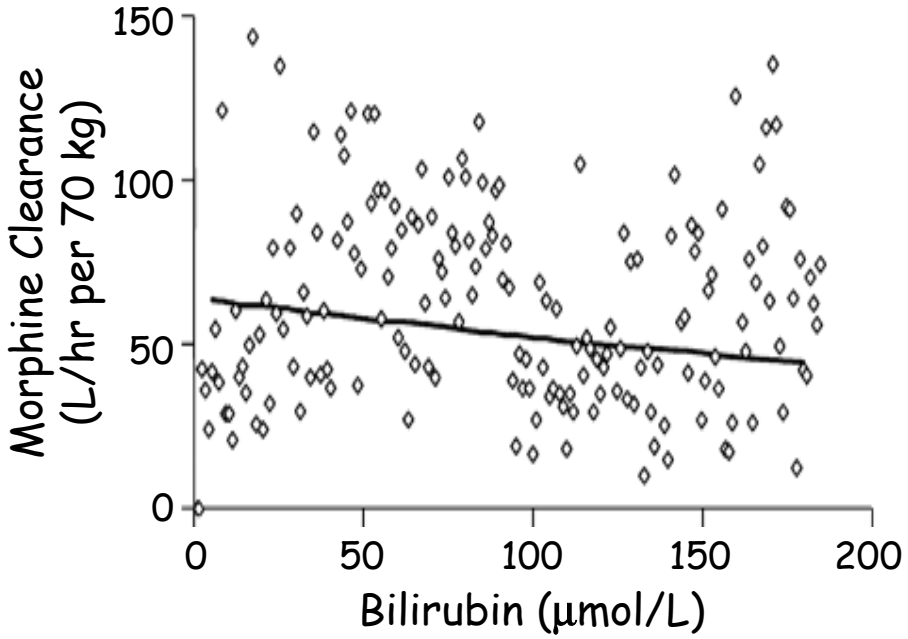
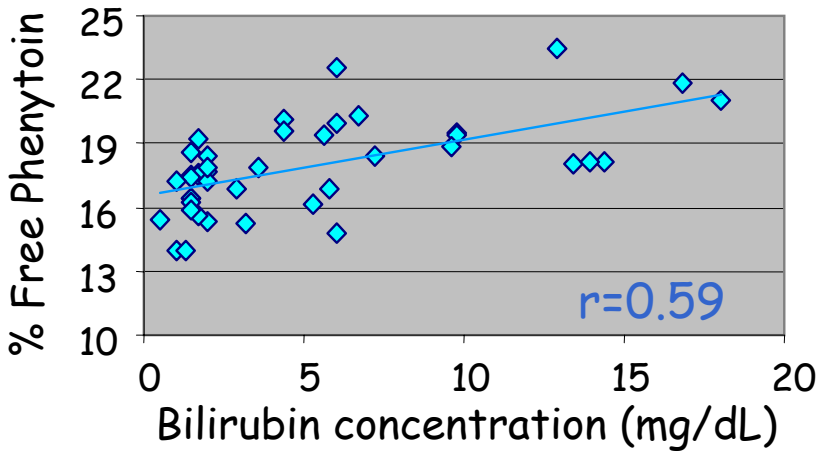
Linezolid Plasma Clearance Association with PCA

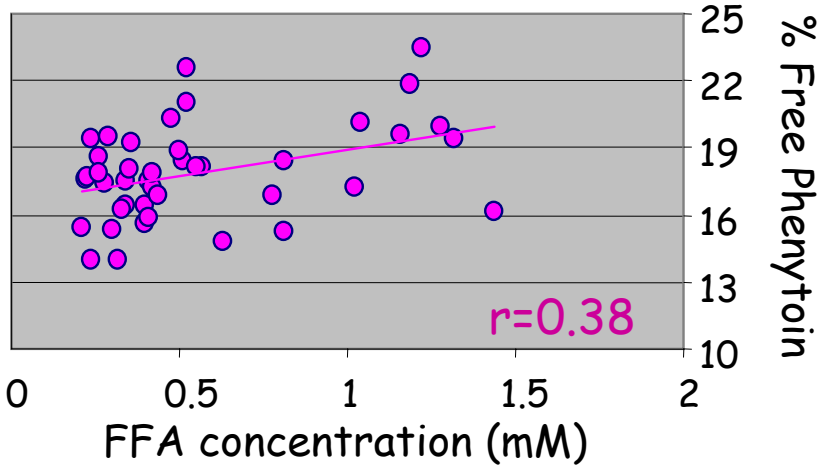


Linezolid Plasma Clearance Association with PNA





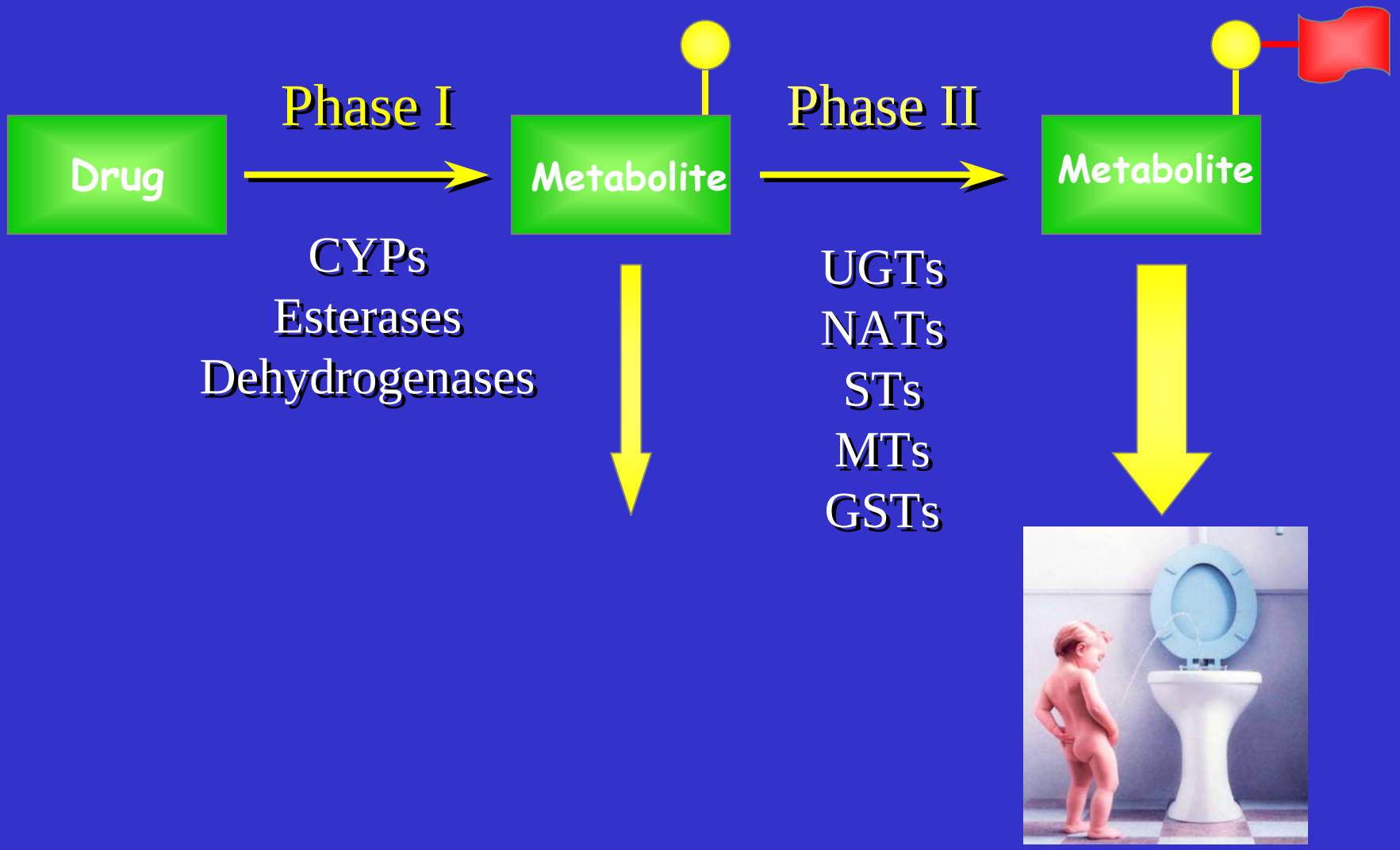


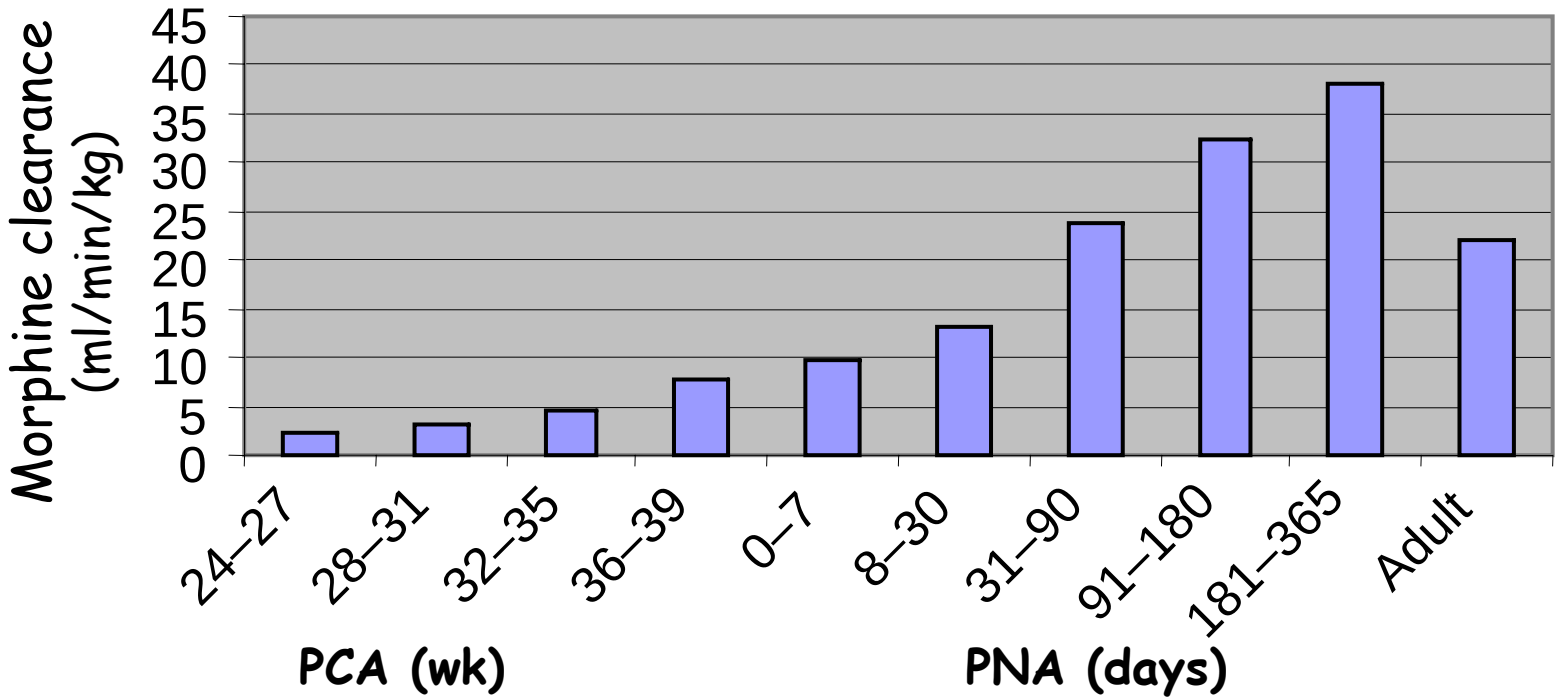


Bouwmeester et al. Br J Anaesth. 2004;92:208-17
Le Guennec and Billon, Pediatrics 79:264-268, 1987

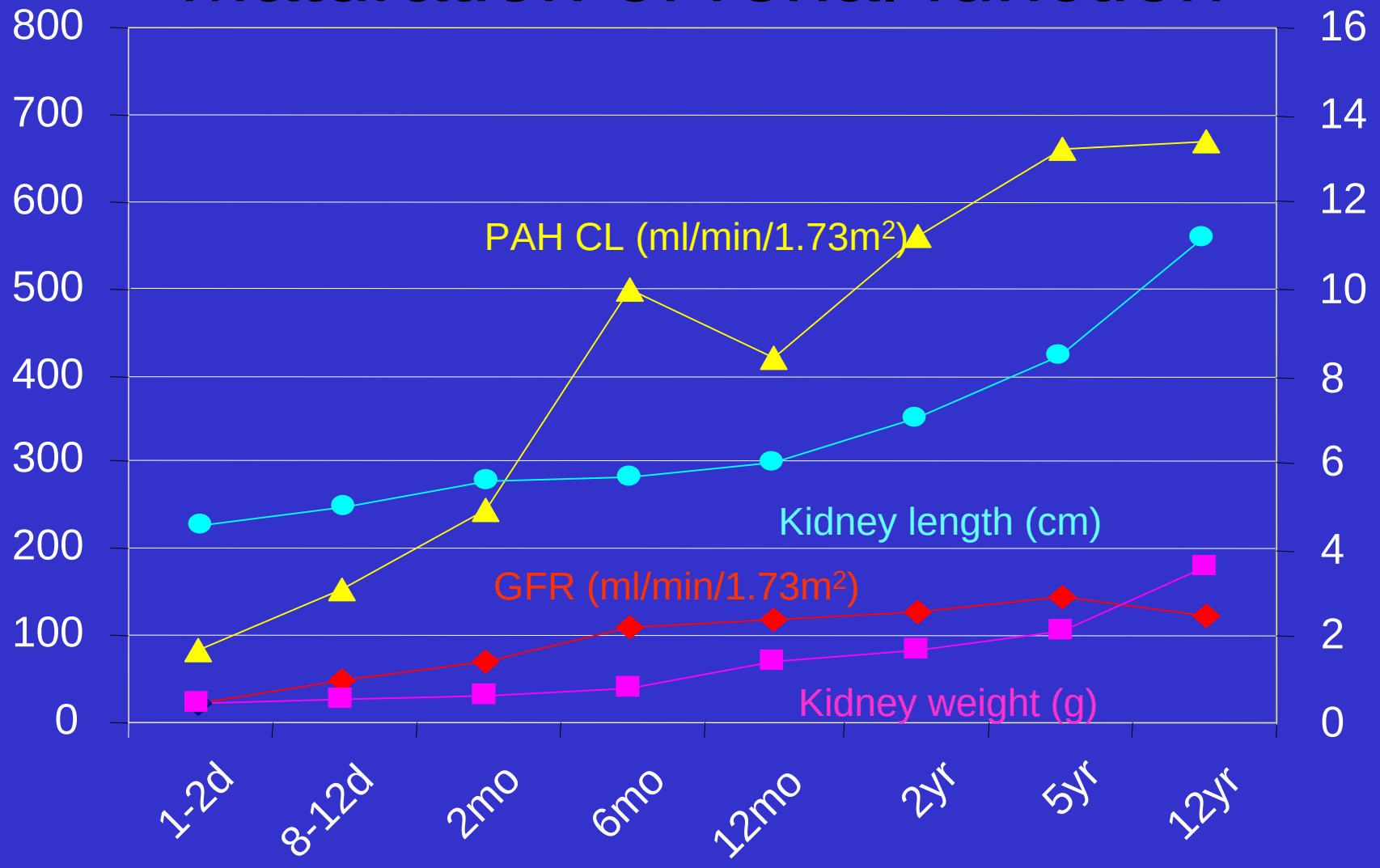
Fredholm et al. *Pediatr Res* 1975;9:26

Drug Biotransformation




Morphine clearance
(ml/min/kg)
45
40
35
30
25
20
15
10
5
0
24–27
28–31
32–35
36–39
0–7
8–30
31–90
91–180
181–365
Adult
PCA (wk)
PNA (days)

Maturation of renal function



From John TR, Moore WM, Jeffries JE (eds.), Children are Different: Developmental Physiology, 2nd edition, Ross Laboratories, 1978

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

HOW TO MEASURE GLOMERULAR FILTRATION RATE

- Clearance of exogenously infused inulin
- Clearance of creatinine
- Serum creatinine
- Cystatin C
- Clearance of aminoglycosides

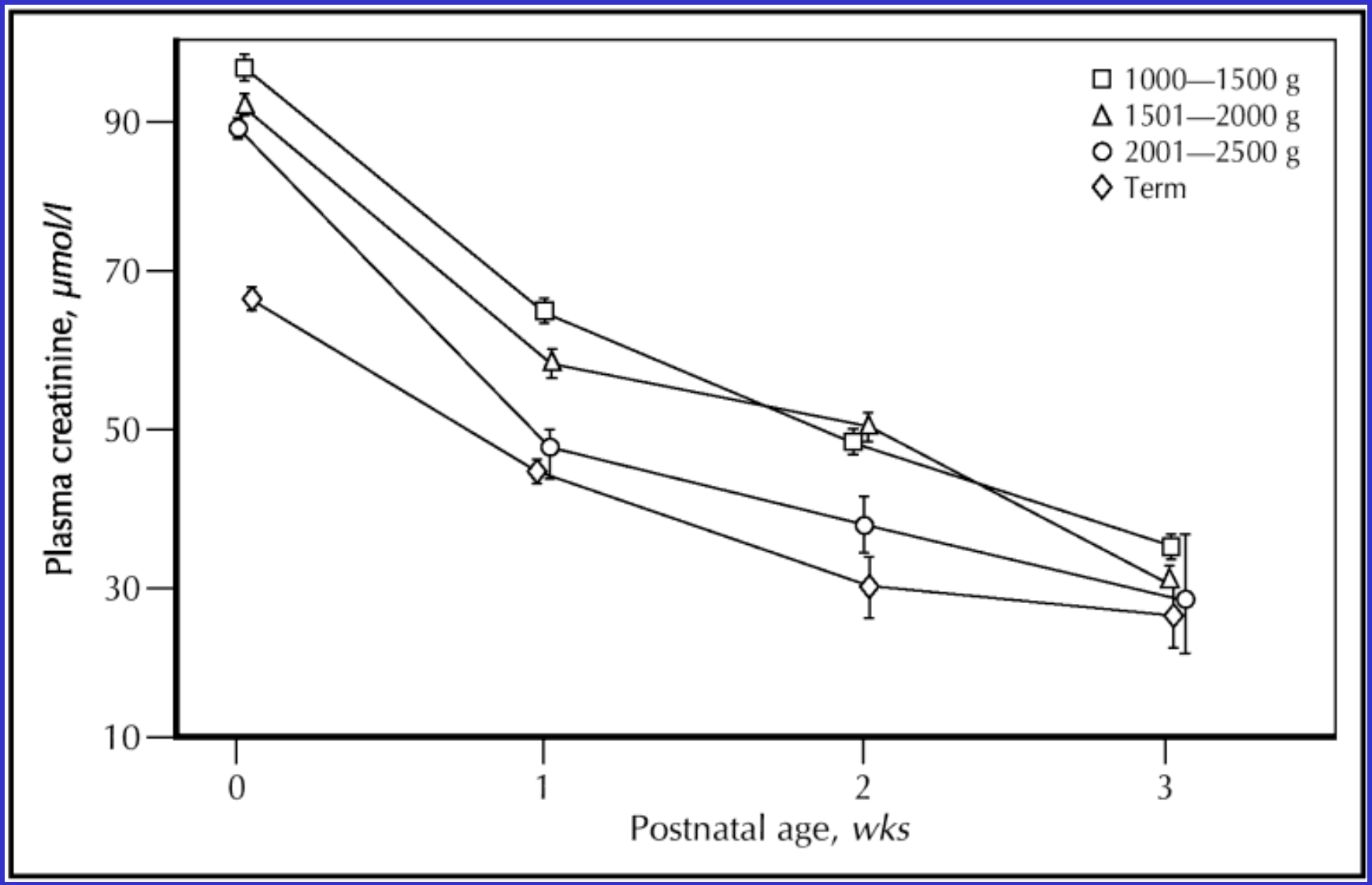


Figure 1. Plasma creatinine concentration in the first weeks of life of neonates with various birth weights The plasma creatinine inversely correlates with body weight (and gestational age) during the first days of life. It reaches steady neonatal levels by 3 to 4 weeks of life. Adapted with permission [17].

From: Drukker: Curr Opin Pediatr, Volume 14(2).April 2002.175-182

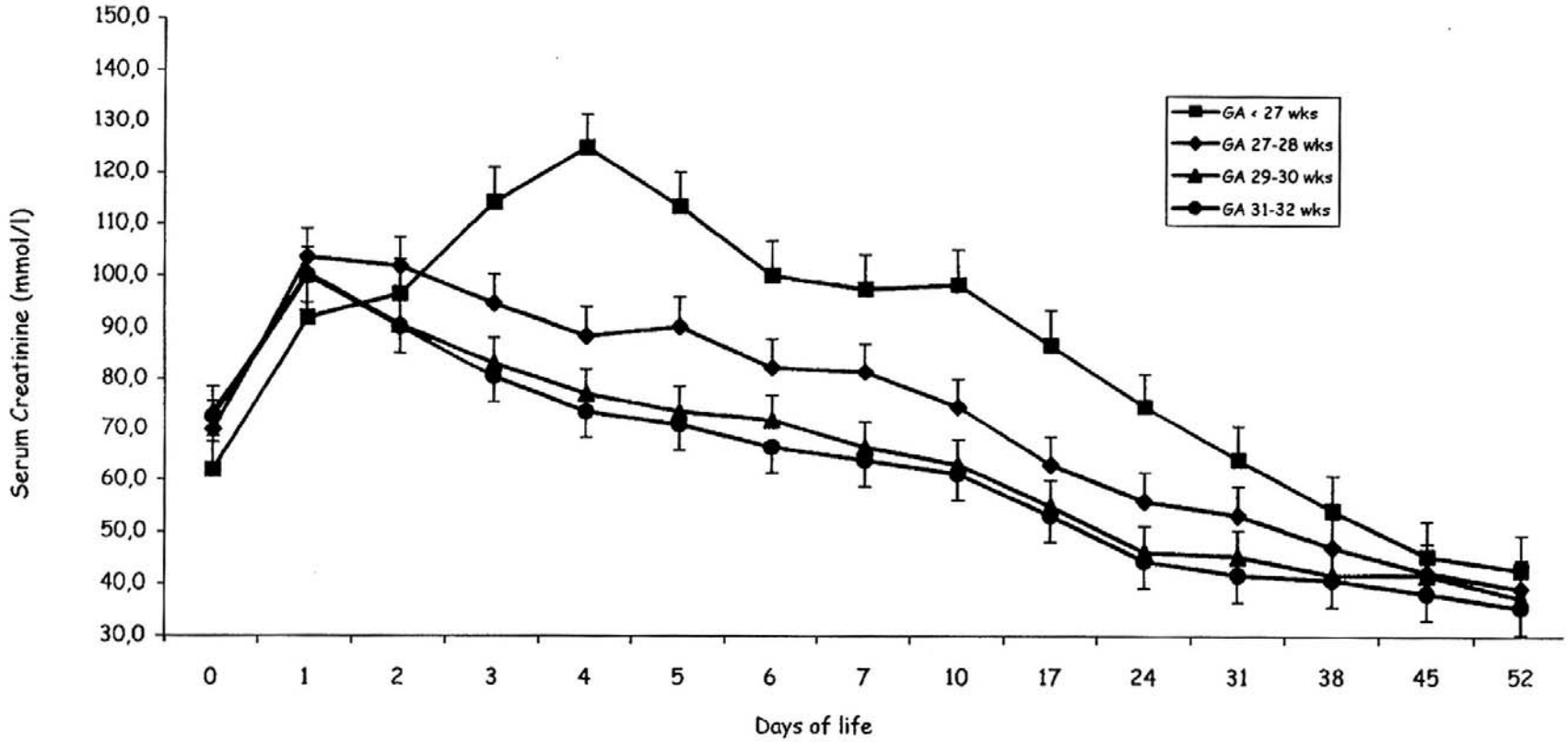


Fig. 1 Serum creatinine concentration (μmol/l) during the study period; values are given as mean and standard error

AMIKACIN ADMINISTRATION in NEONATES : PHARMACOKINETIC VARIABLES

	Vd (L/kg)	Half - life (h)	Cl (ml/kg/h)
	mean ± 1 sd	mean ± 1 sd	mean ± 1 sd
<28 w	0.700 ± 0.151	12.20 ± 3.83	0.73 ± 0.148
28 - < 31 w	0.660 ± 0.120	8.40 ± 1.36	0.87 ± 0.127
31 - < 34 w	0.614 ± 0.013	7.71 ± 0.31	0.98 ± 0.025
34 - < 37 w	0.573 ± 0.013	6.77 ± 0.32	1.09 ± 0.061
37 - 41 w	0.520 ± 0.021	5.55 ± 0.49	1.15 ± 0.036

Langhendries et al, Med Mal Infect,1993;23:44

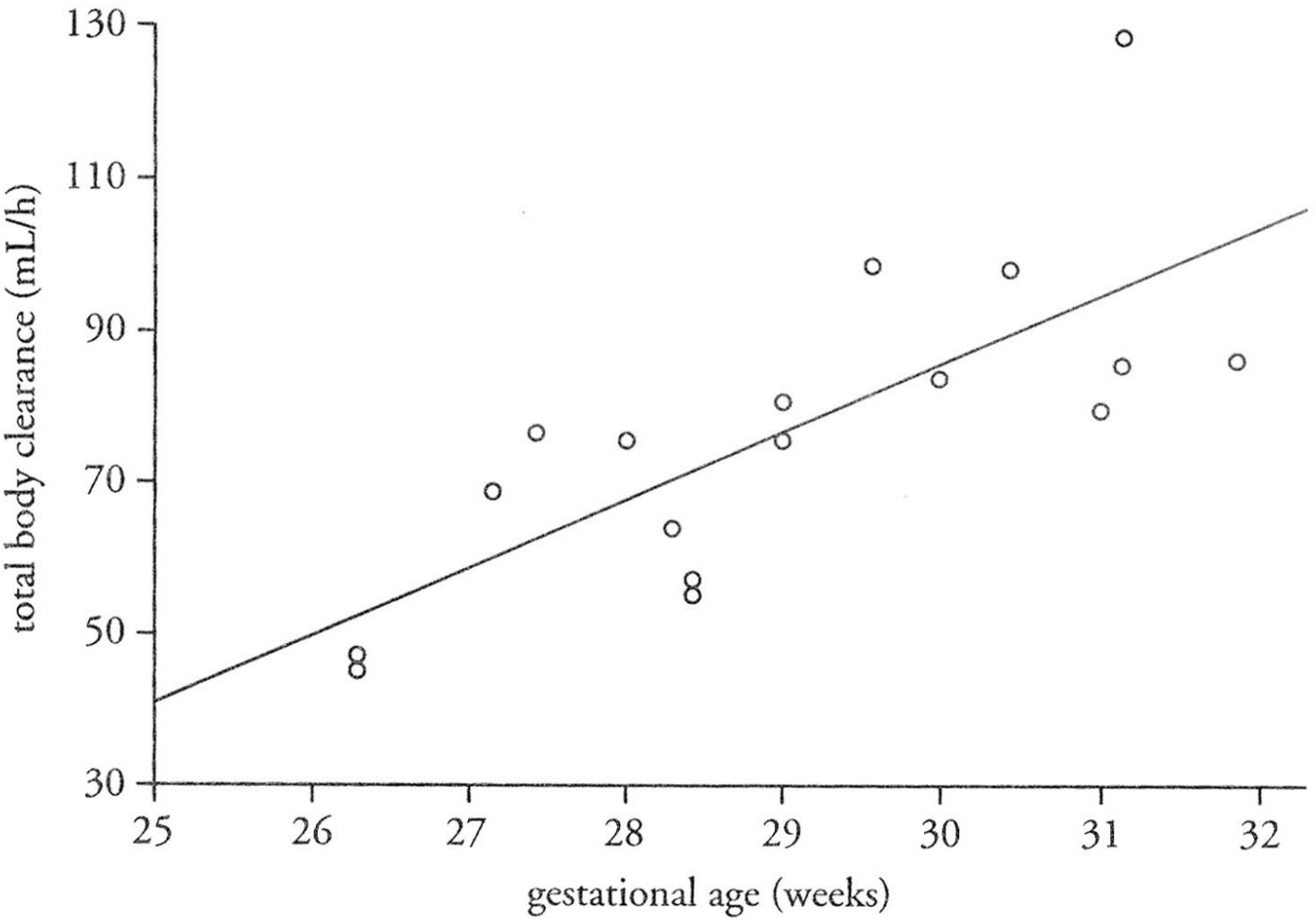


Figure 2. **Linear regression analysis of total body clearance of amoxicillin (mL/h) versus gestational age (weeks) in 17 preterm infants on day 3 after birth ($r=0.75$, $p<0.001$, $y=8.88x-181.2$)**

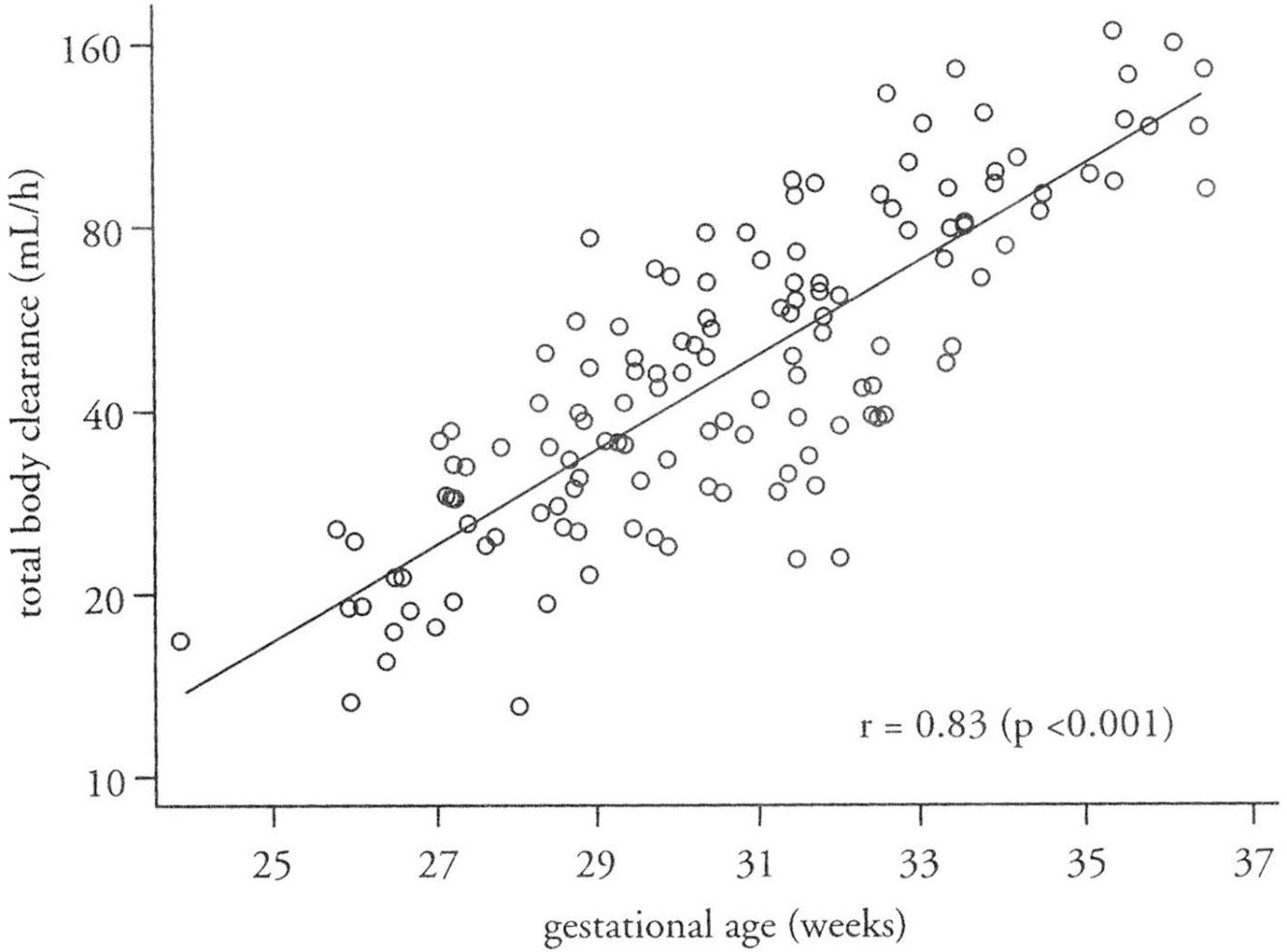


Figure 1. Linear regression analysis of total body clearance of ceftazidime (mL/h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth. Note the logarithmically transformed vertical axis

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

Table 2. **Pharmacokinetic parameters of ceftazidime and inulin clearances of infants with severe asphyxia and in control infants without asphyxia**[a]

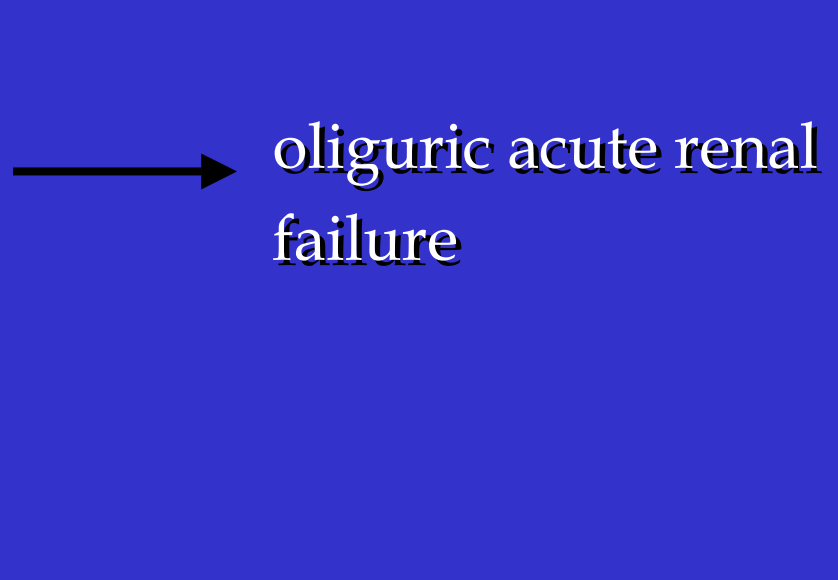
	Asphyxiated (n=10)	Controls (n=9)	P-value
CL (mL/h)	128.4 ± 25.1	205.7 ± 55.4	<0.001
CL (mL/h/kg)	40.9 ± 6.1	60.8 ± 8.3	<0.001
V (mL)	1090 ± 304	1132 ± 258	NS
V (mL/kg)	344 ± 79	336 ± 46	NS
$t_{1/2}$ (h)	5.86 ± 1.13	3.85 ± 0.40	<0.001
CL_{in} (mL/h)	188.4 ± 25.5	284.2 ± 53.1	<0.001
CL_{in} (mL/min)	3.14 ± 0.43	4.73 ± 0.89	<0.001

[a]Values are mean ± SD

Abbreviations: CL, total body clearance; V, apparent volume of distribution; $t_{1/2}$, serum half-life, CL_{in}, inulin clearance; NS, not significant

NEWBORN RENAL FUNCTION

- Aspirin
- Indomethacin
- Ibuprofen
- Rofecoxib



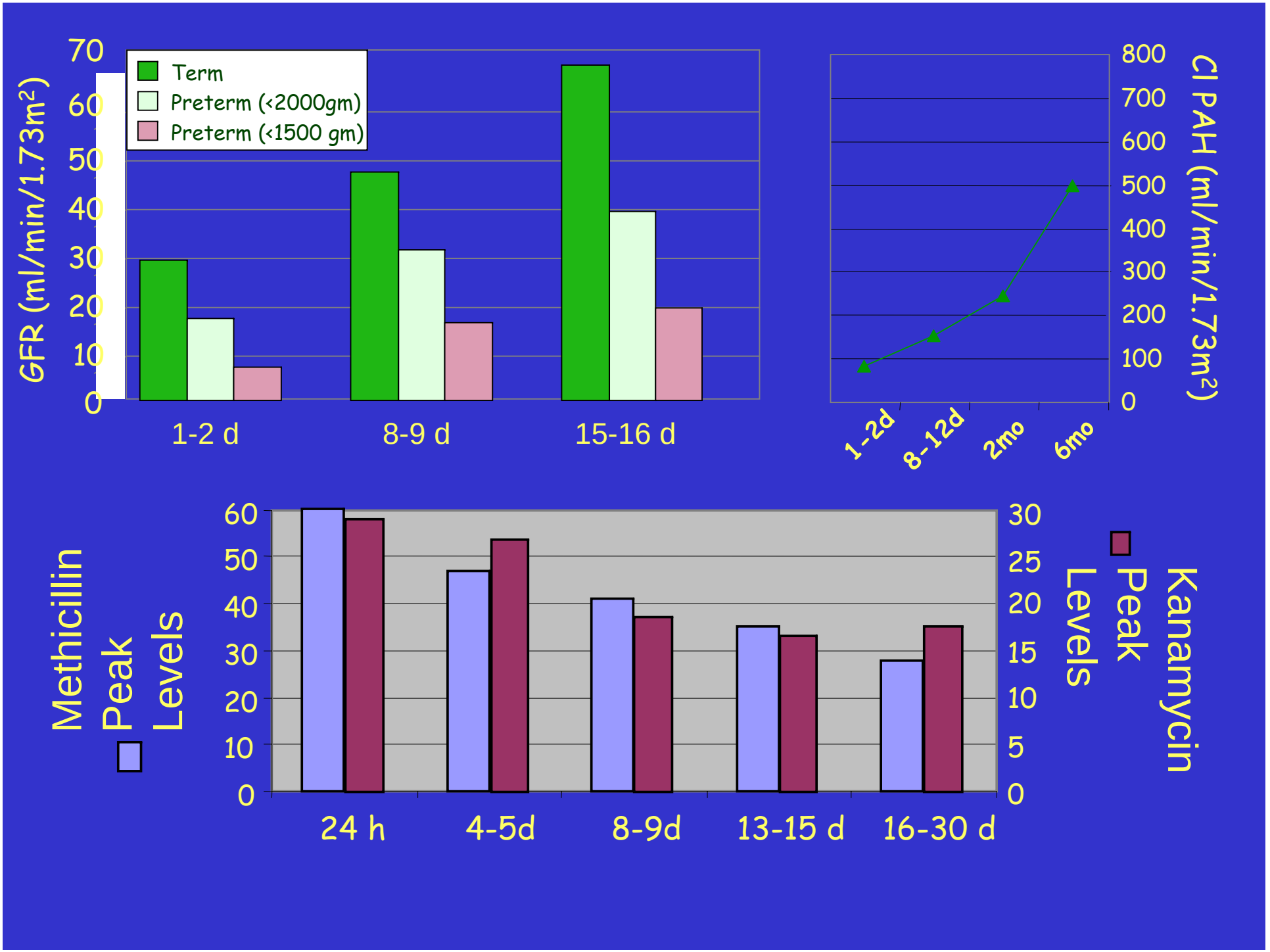
NEWBORN RENAL FUNCTION

- Corticosteroids:
  - increases Mean Arterial Blood Pressure, improves cardiovascular status
  - increases Renal Blood Flow
  - increases functional glomerular surface area available for filtration
  - increases glomerular filtration of the single nephron

Table 3. **The effect of gestational age and prenatal exposure to betamethasone or indomethacin on GFR values at day 3 after birth**[a]

	regression coefficient			p-value
Gestational age (weeks)	+0.035	(± 0.005)	mL/min/week	p <0.001
Indomethacin[b]	-0.15	(± 0.03)	mL/min	p <0.001
Betamethasone[b]	+0.11	(± 0.03)	mL/min	p <0.001

[a]Values are mean increase (± SEM)
[b]prenatal exposure versus no prenatal exposure


GFR (ml/min/1.73m²)
70
60
50
40
30
20
10
0
Term
Preterm (<2000gm)
Preterm (<1500 gm)
1-2 d
8-9 d
15-16 d
CI PAH (ml/min/1.73m²)
800
700
600
500
400
300
200
100
0
1-2d
8-12d
2mo
6mo
Methicillin Peak Levels
60
50
40
30
20
10
0
24 h
4-5d
8-9d
13-15 d
16-30 d
30
25
20
15
10
5
0
Kanamycin Peak Levels

Exposure-Response Relationships Result from Age Dependent Drug Disposition and Action……

- Differences in extravascular absorption rate and extent
- Altered body composition influences distribution
- Marked ontogeny of drug metabolizing enzymes and transporters
- Dynamic influence of development on renal function
- Impact of development on drug action / effect

Therapeutic Response Along the Developmental Continuum

A function of the developmental processes that influence drug disposition and interaction with therapeutic targets

The need for drug studies in neonates

- 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

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)