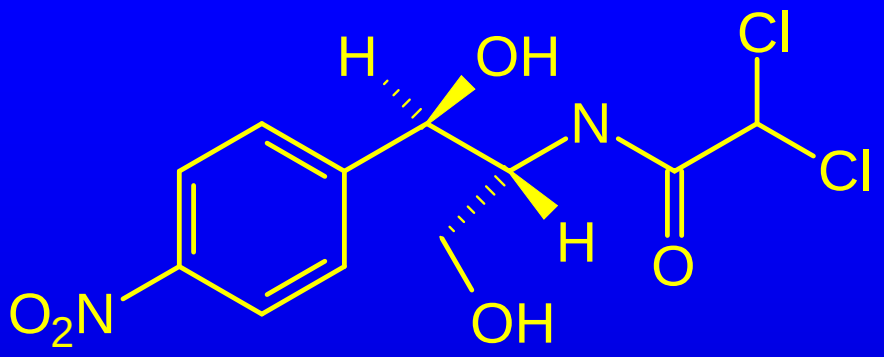
# Developmental Pharmacology

**Scaling adult doses to infants based on body weight or surface area does not account for developmental changes that affect drug disposition or tissue/organ sensitivity.**

**Frank Balis, M.D.**

**February 21, 2008**

# Chloramphenicol




* Natural product of *Streptomyces* (1947)
* Inhibits protein synthesis (bacteriostatic)
* Eliminated by glucuronide conjugation (90%) and renal excretion (<10%)
* Nursery infections treated with high doses

# Chloramphenicol in Infants

* 3320 gm infant, 44 week gestation
* Meconium stained, foul smelling, timing of ROM unknown
* Procaine penicillin (50,00 units) + chloramphenicol (250 mg) IM q8h - 230 mg/kg/day x 72 hr
* Day 4, gray color & cold, moist skin
* Died at 106 hr, 8 hr after onset of vascular collapse

Sutherland, Am J Dis Child 97:761-7, 1959

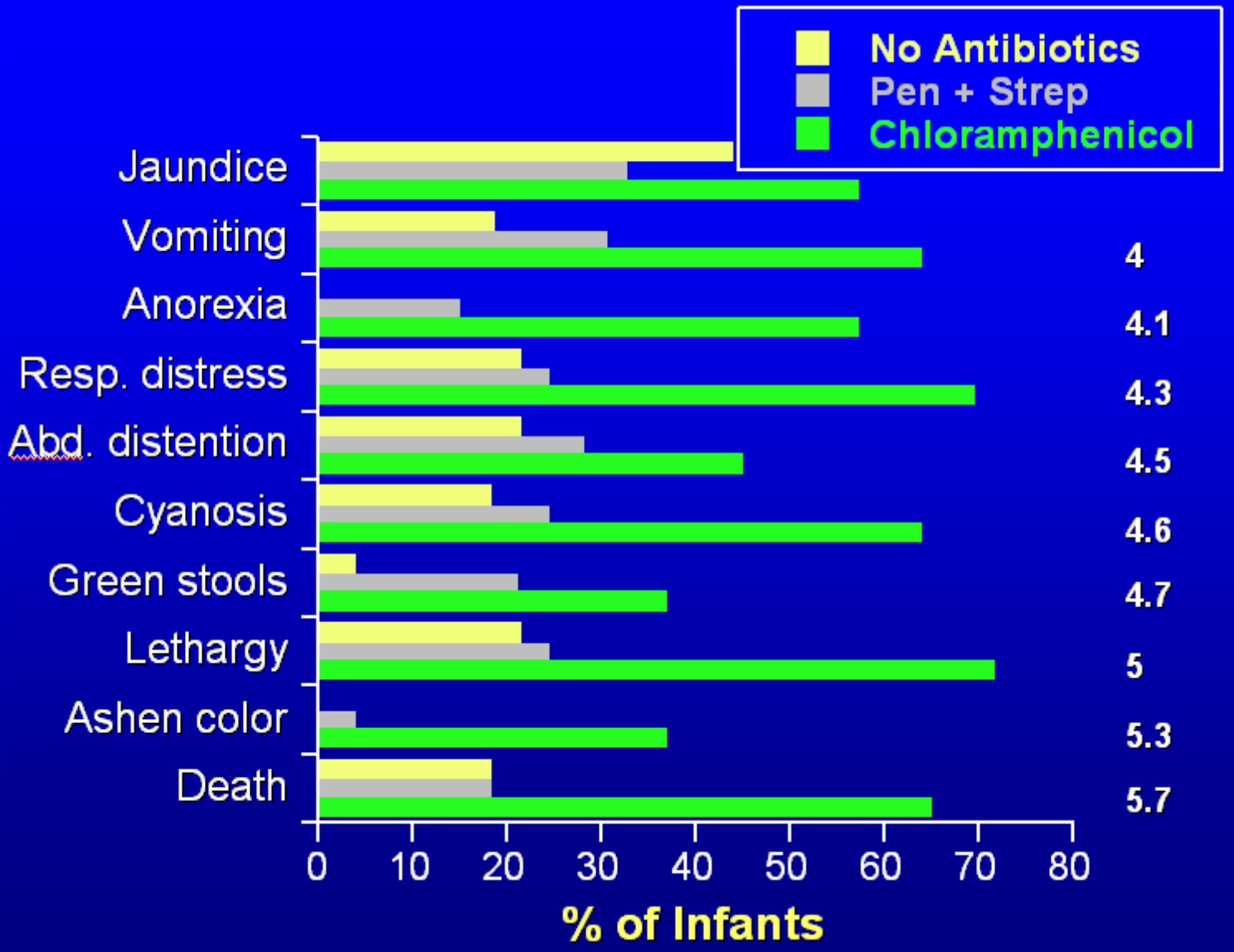
# Chloramphenicol in Premature Infants

## Premature infants born ≥24 hrs after ROM

| | All Infants | | 2001-2500 gm | |
|---|---|---|---|---|
| | n | Deaths | n | Deaths |
| No antibiotics | 32 | 6 | 17 | 1 |
| Pen + strep | 33 | 6 | 24 | 0 |
| Chloramphenicol | 30 | 19 | 16 | 8 |
| Pen + strep + chloramphenicol | 31 | 21 | 15 | 6 |

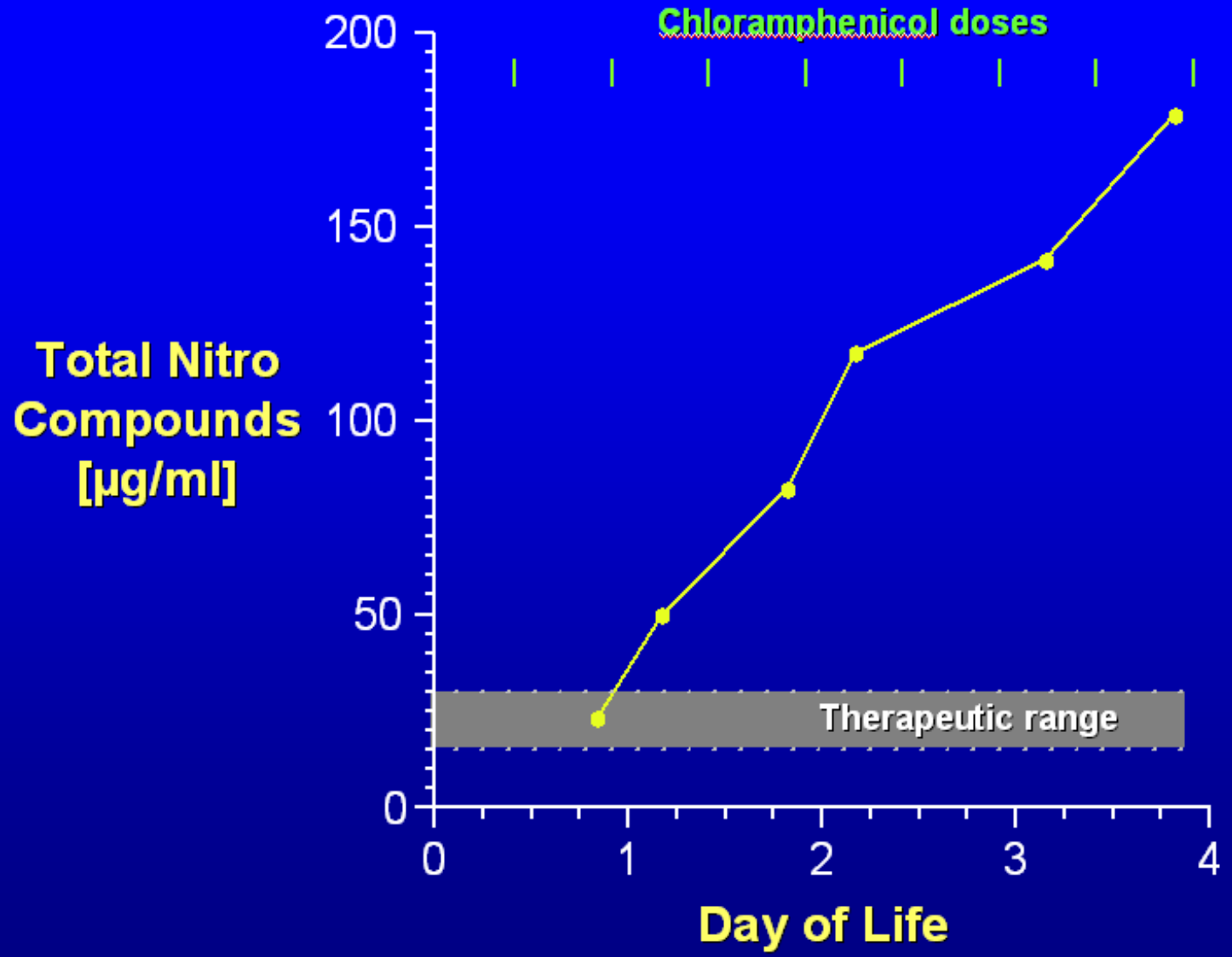
Burns et al., NEJM 261:1318-21, 1959

# Gray Baby Syndrome



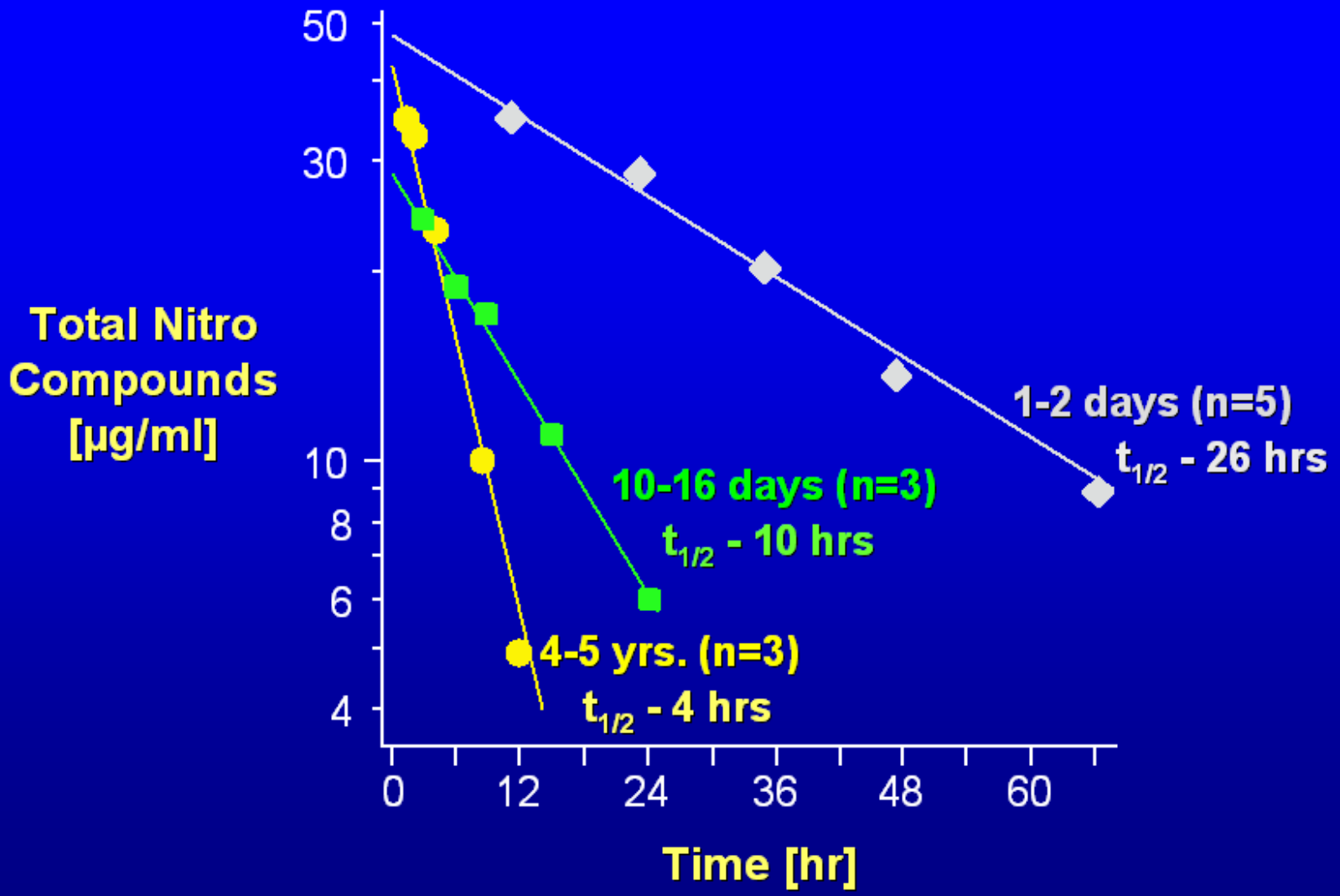

Burns et al., NEJM 261:1318-21, 1959

# Chloramphenicol Blood Levels



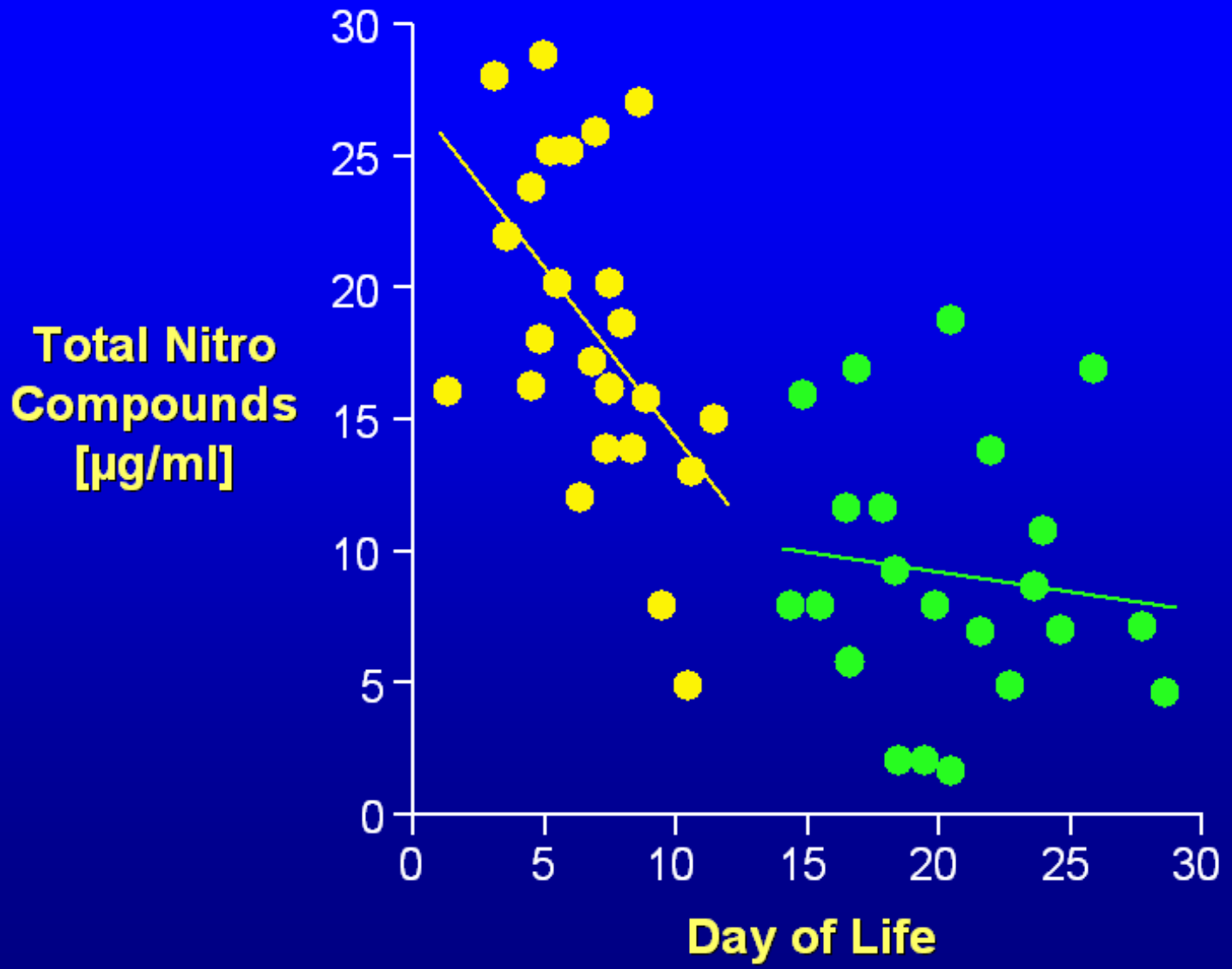

Burns et al., NEJM 261:1318-21, 1959

# Chloramphenicol Pharmacokinetics




Weiss et al., NEJM 262:787-94, 1960

# Repeated Administration

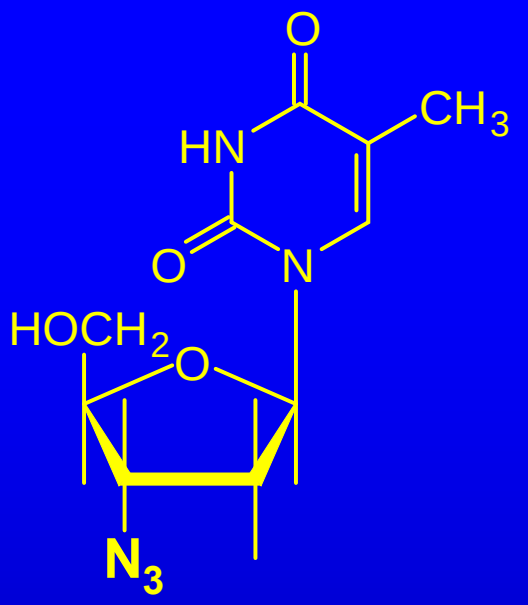



Weiss et al., NEJM 262:787-94, 1960

# Drug Use in Infants and Children

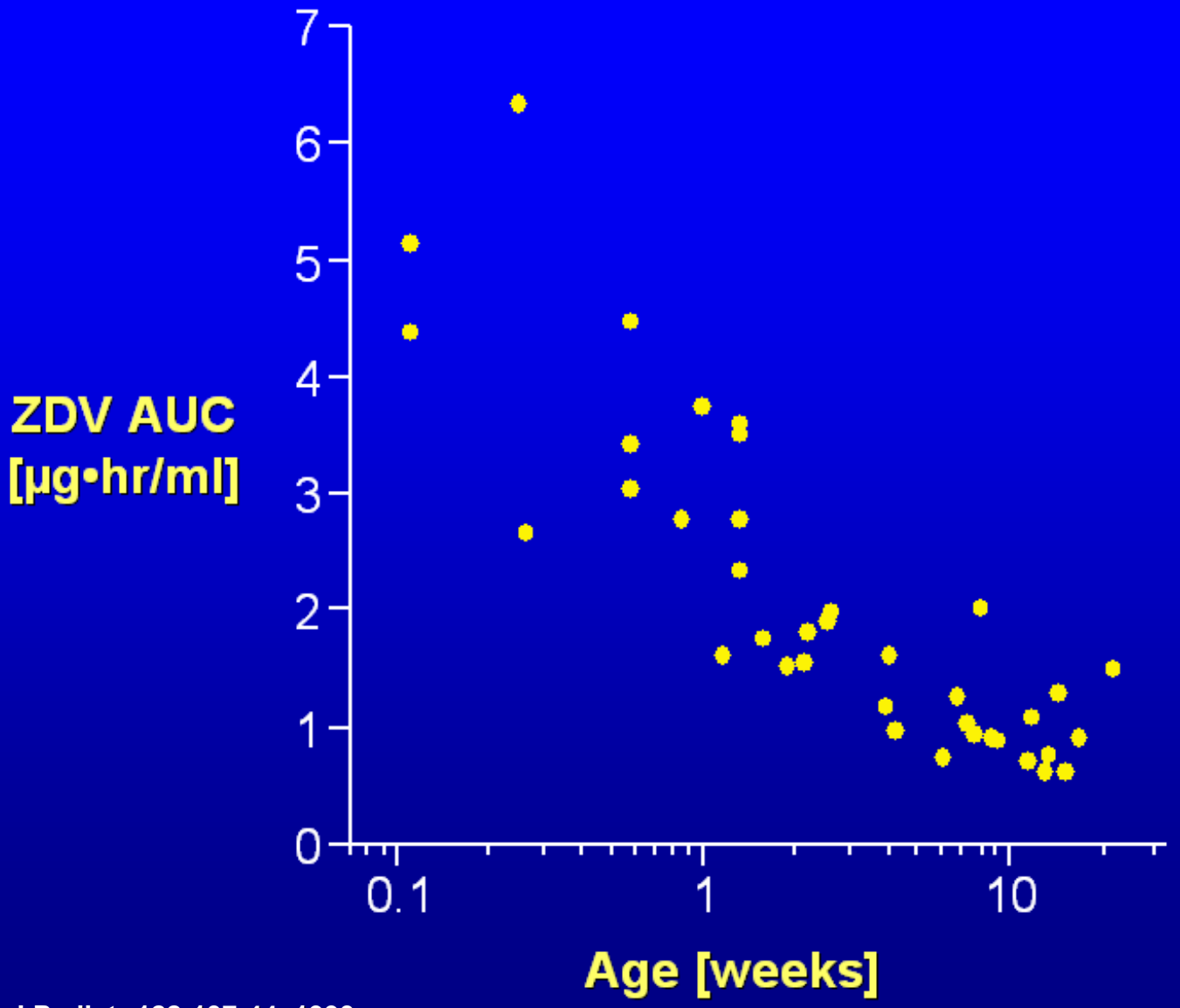
* Scaling adult doses based on body weight or surface area does not account for developmental changes that affect drug disposition or tissue/organ sensitivity.
* Pharmacologic impact of developmental changes are often discovered when unexpected or severe toxicity in infants and children leads to detailed pharmacologic studies.
* Therapeutic tragedies could be avoided by performing pediatric pharmacologic studies during the drug development process (before wide-spread use of agents in infants and children).

# Zidovudine




* Synthetic nucleoside analog
* Inhibits HIV reverse transcriptase
* Eliminated by glucuronide conjugation (67%) and renal excretion (33%)
* Perinatal therapy to prevent HIV transmission

# Zidovudine in the Newborn




Boucher et al., J Pediatr 122:137-44, 1993

# Zidovudine in Newborns

| Group | Age (days) | Clearance (ml/min/kg) | $t_{1/2}$ (hr) | F (%) |
|---|---|---|---|---|
| Preterm | 5.5 | 2.5 | 7.2 | |
| | 17.7 | 4.4 | 4.4 | |
| Term | [2] 14 | 10.9 | 3.1 | |
| | >14 | 19.0 | 1.9 | |

| Age Group | Clearance (ml/min/kg) | $t_{1/2}$ (hr) | F (%) |
|---|---|---|---|
| 1-13 yrs | 24 | 1.5 | 68 |
| Adults | 21 | 1.1 | 63 |

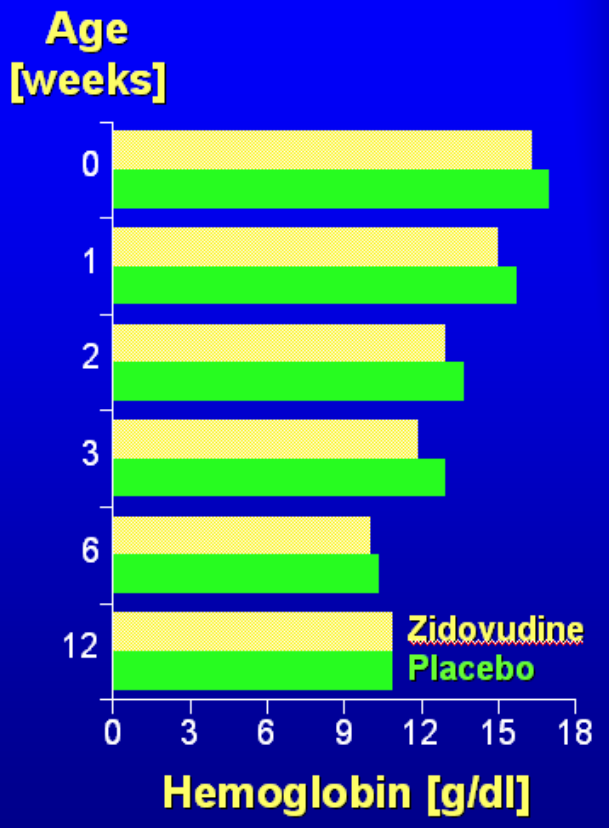
Boucher et al., J Pediatr 125:642-9, 1994
Mirochnick et al., Antimicrob Agents Chemother 42:808-12, 1998
Balis et al., J Pediatr 114:880-4, 1989
Klecker et al., Clin Pharmacol Ther 41: 407-12, 1987

# Prevention of Vertical Transmission

* Randomized, double-blind, placebo controlled trial
* Rate of vertical transmission was the primary endpoint
* Zidovudine/placebo regimen
  - Mothers: 100 mg of ZDV antepartum orally, 5 times daily, and then continuous infusion of 1 mg/kg/hr during labor and delivery
  - Infants: 2 mg/kg orally every 6 hours for 6 weeks, beginning 8-12 hours after birth.

# Prevention of HIV Transmission

| | Zidovudine | Placebo |
|---|---|---|
| | AGE >32 WEEKS | |
| Number | 121 | 127 |
| HIV-infected | 9 | 31 |
| Rate (%) | 7.4 | 24.4 |
| | AGE ³ 1 YEAR | |
| Number | 83 | 89 |
| HIV-infected | 7 | 20 |
| Rate (%) | 8.4 | 22.5 |




Connor et al., NEJM 331:1173-80, 1994

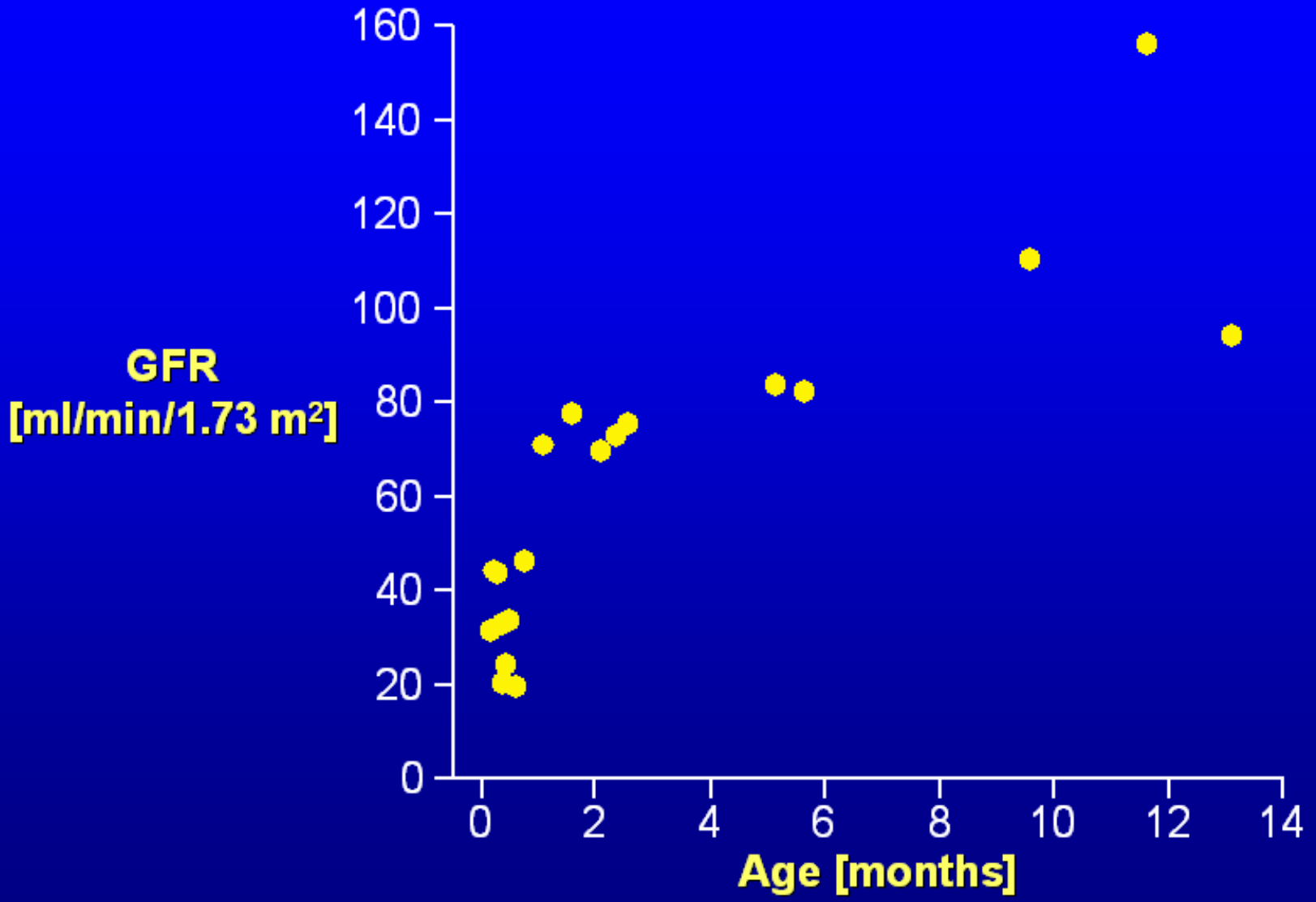
# Ontogeny and Pharmacology

* Excretory organ (liver and kidneys) development has the greatest impact on drug disposition (pharmacokinetics)
* The most dramatic changes occur during the first days to months of life
* Anticipate age-related differences in drug disposition based on knowledge of ontogeny
* Effect of ontogeny on tissue/organ sensitivity to drugs (pharmacodynamics) is poorly studied
* Disease states may alter a drug's PK/PD

# Renal Ontogeny

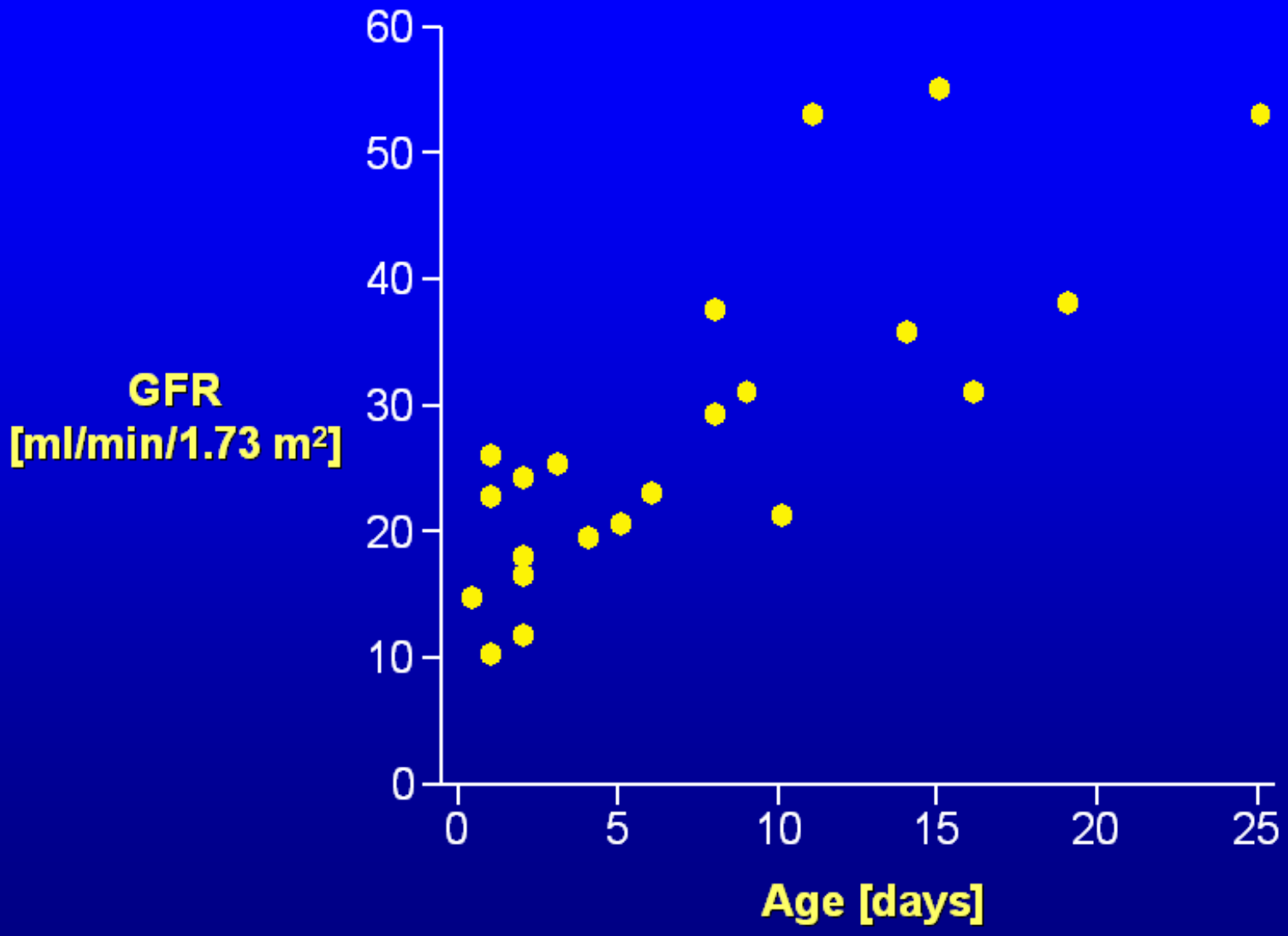
* **Glomerular filtration rate**
  - **Low at birth**
    * Full term newborn - 10-15 ml/min/$m^2$
    * Premature - 5-10 ml/min/$m^2$
  - **GFR doubles by 1 week of age**
  - **Adult values by 6-12 months of age**
* **Tubular function**
  - **Secretory function impaired at birth**
  - **Glomerulotubular imbalance**
  - **Adult values by 1 year of age**

# Glomerular Filtration Rate



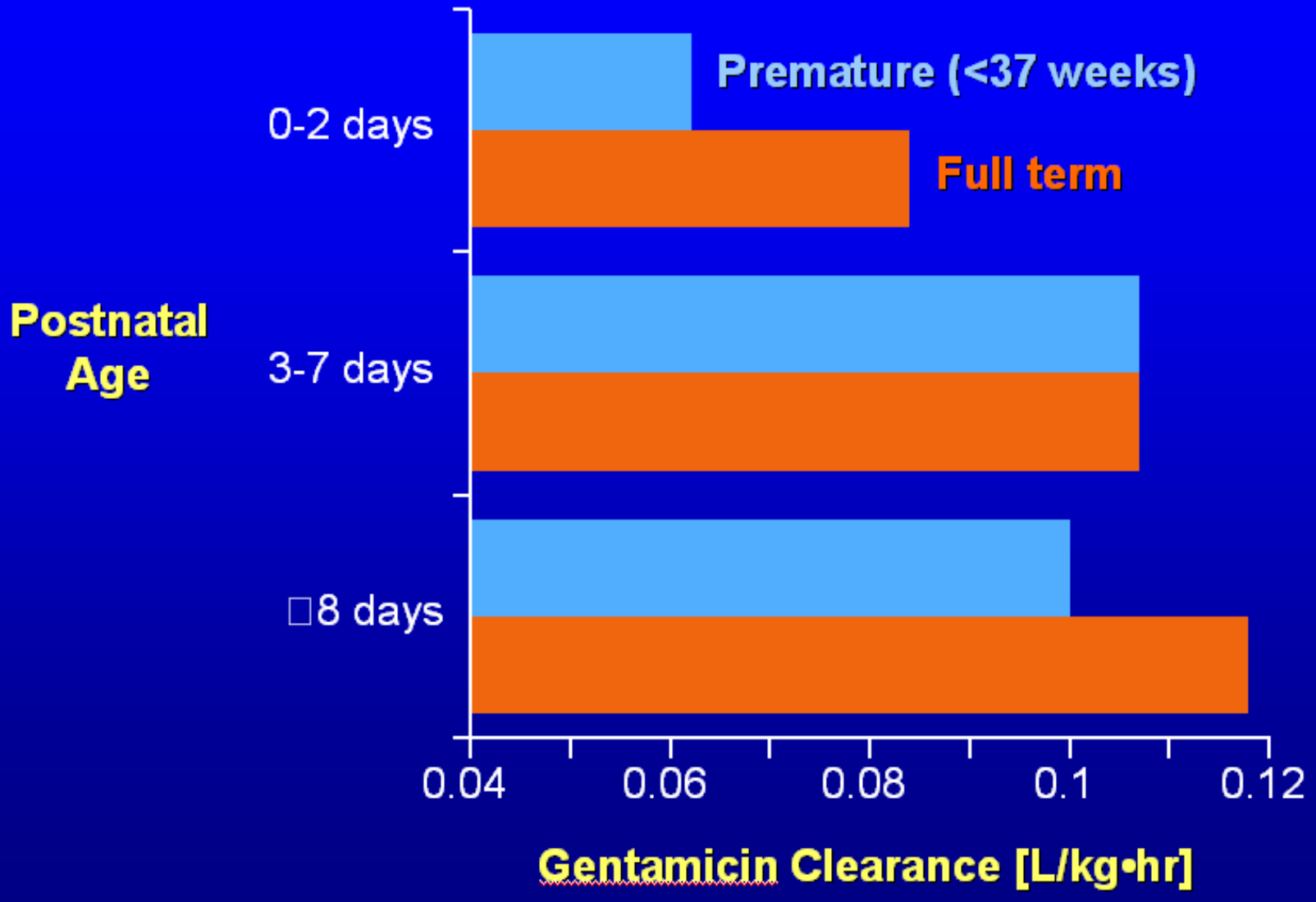

Aperia, Acta Pædiatr Scand 64:393-8, 1975

# GFR in Infants




Guignard, J Pediatr 87:268-72, 1975

# Gentamicin Clearance




Pons, Ther Drug Monit 10:421-7, 1988

# Hepatic Ontogeny

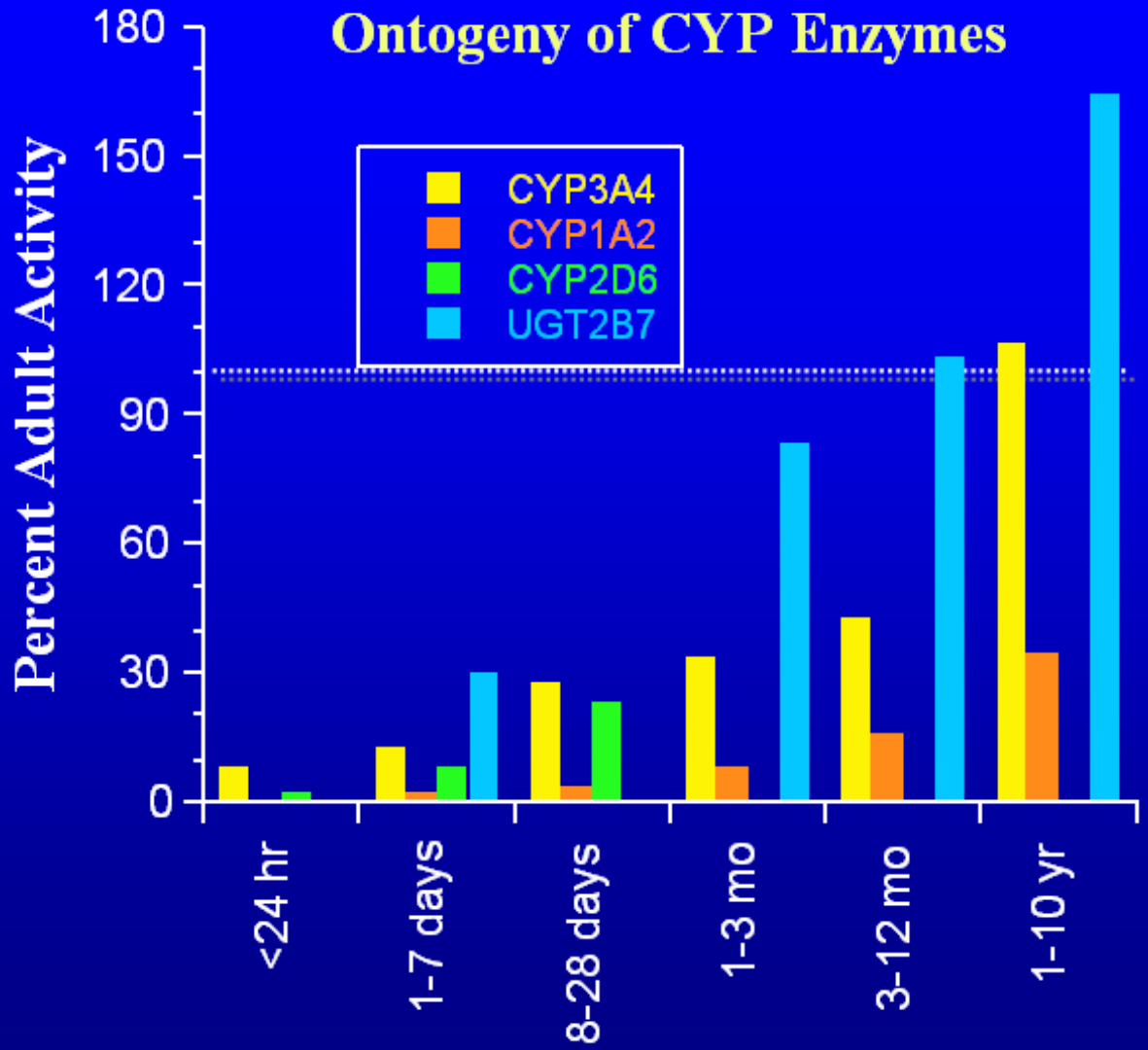
* **Phase 1 (oxidation, hydrolysis, reduction, demethylation)**
  - **Activity low at birth**
  - **Mature at variable rates**
    * Oxidative metabolism increases rapidly after birth
    * Alcohol dehydrogenase reaches adult levels at 5 yrs
  - **Activity in young children exceeds adult levels**
* **Phase 2 (conjugation, acetylation, methylation)**
  - **Conjugation:**
    * Glucuronidation ↓ at birth
    * Sulfatation ↑ at birth
  - **Acetylation ↓ at birth, "fast" or "slow" phenotype by 12-15 mo.**

# Cytochrome P450 (CYP) Enzymes

* Superfamily of Phase 1 enzymes (oxidation, demethylation)
* Nomenclature:

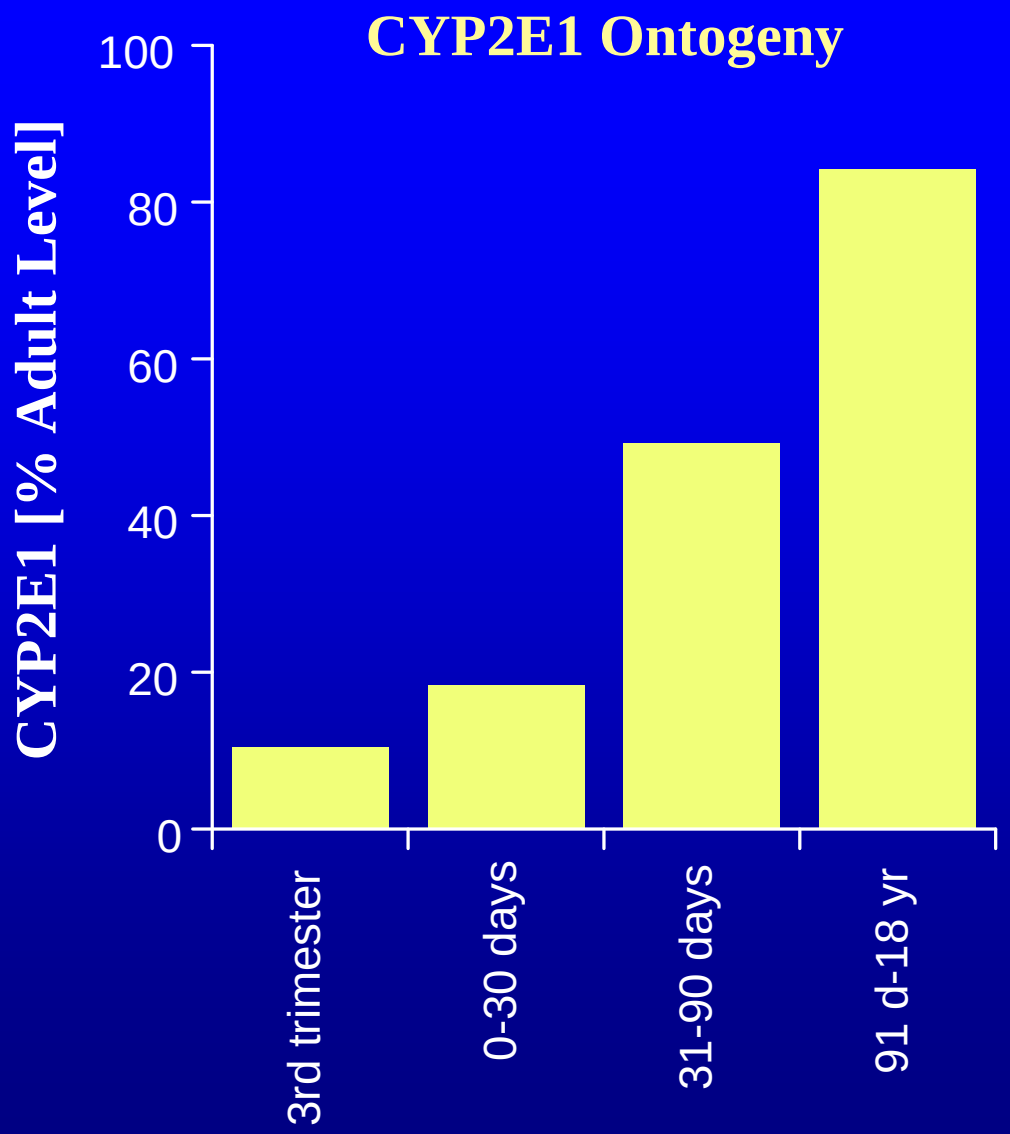

* 17 Families and 39 subfamilies in humans
* CYP1, CYP2, CYP3 are primary drug metabolizing enzymes
* Half of all drugs metabolized by CYP3A subfamily
* CYP3A4 is most abundant hepatic P450 enzyme and metabolizes at least 50 drugs

# CYP Ontogeny

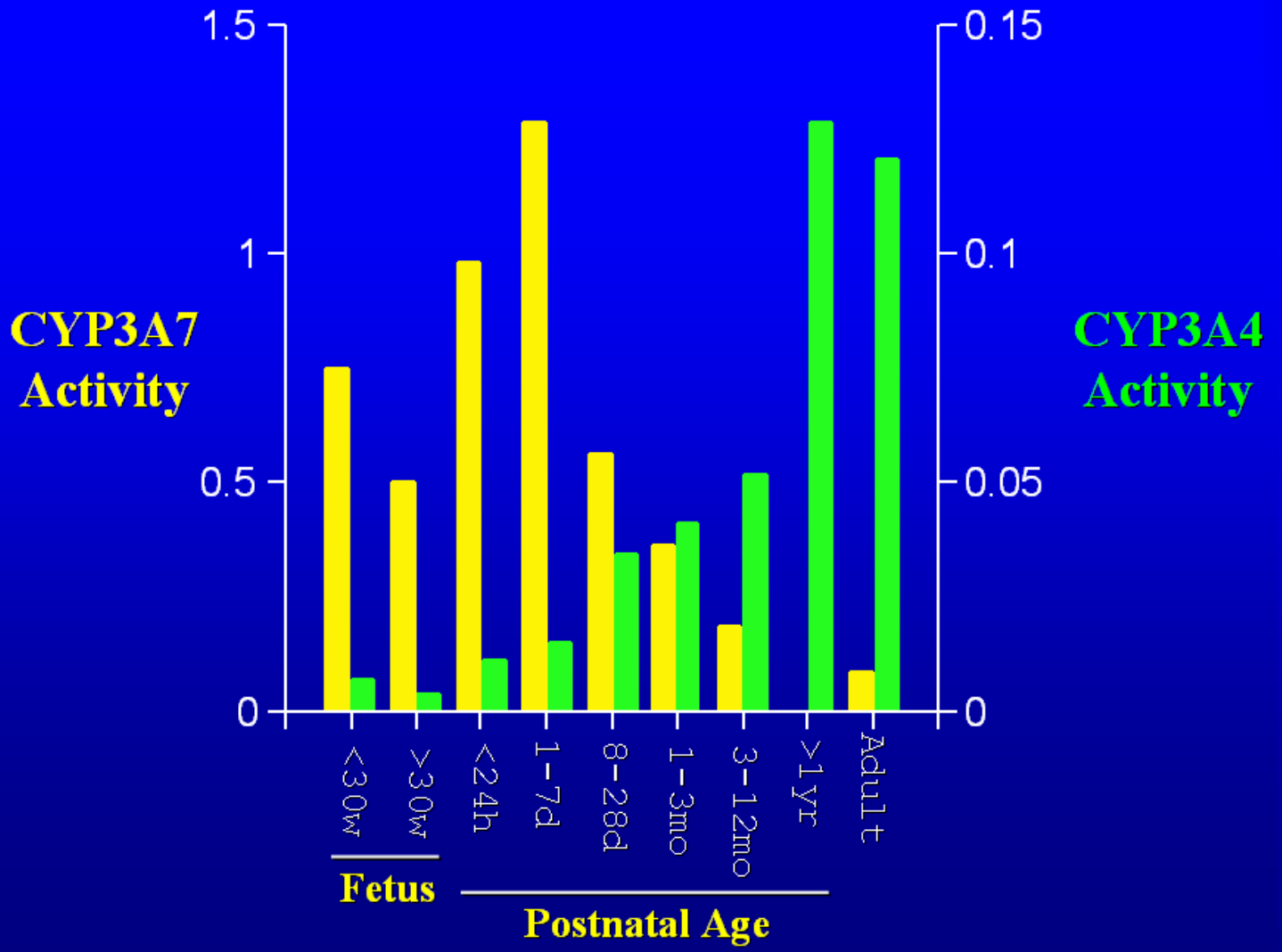



Kearns GL et al. NEJM 349: 1157, 2003

# CYP2E1 Ontogeny

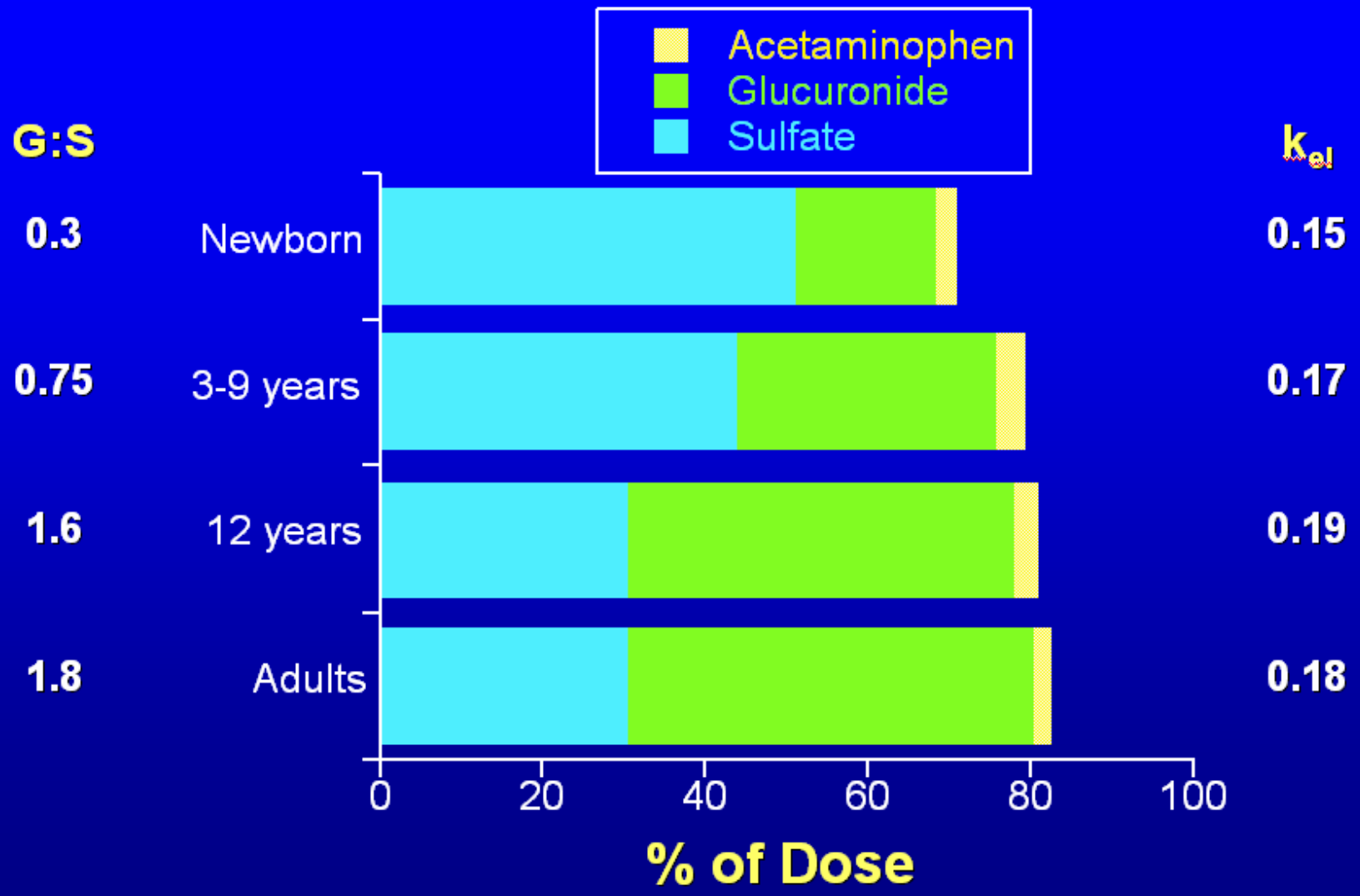


# CYP3A Ontogeny



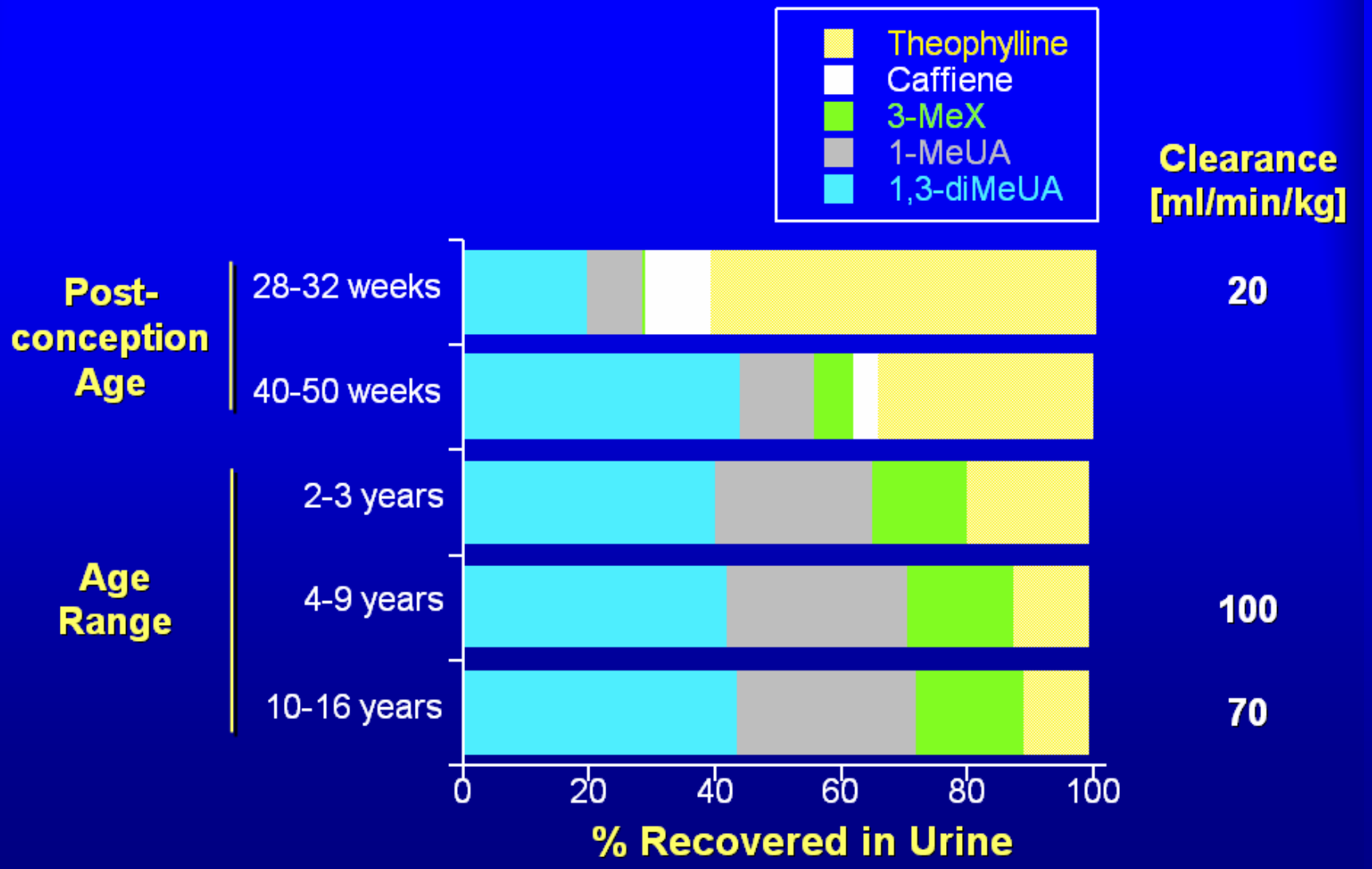

LaCroix D et al. Eur J Biochem 247:625, 1997

# Acetaminophen Metabolism




Miller et al., Clin Pharmacol Ther 19:284-94, 1976

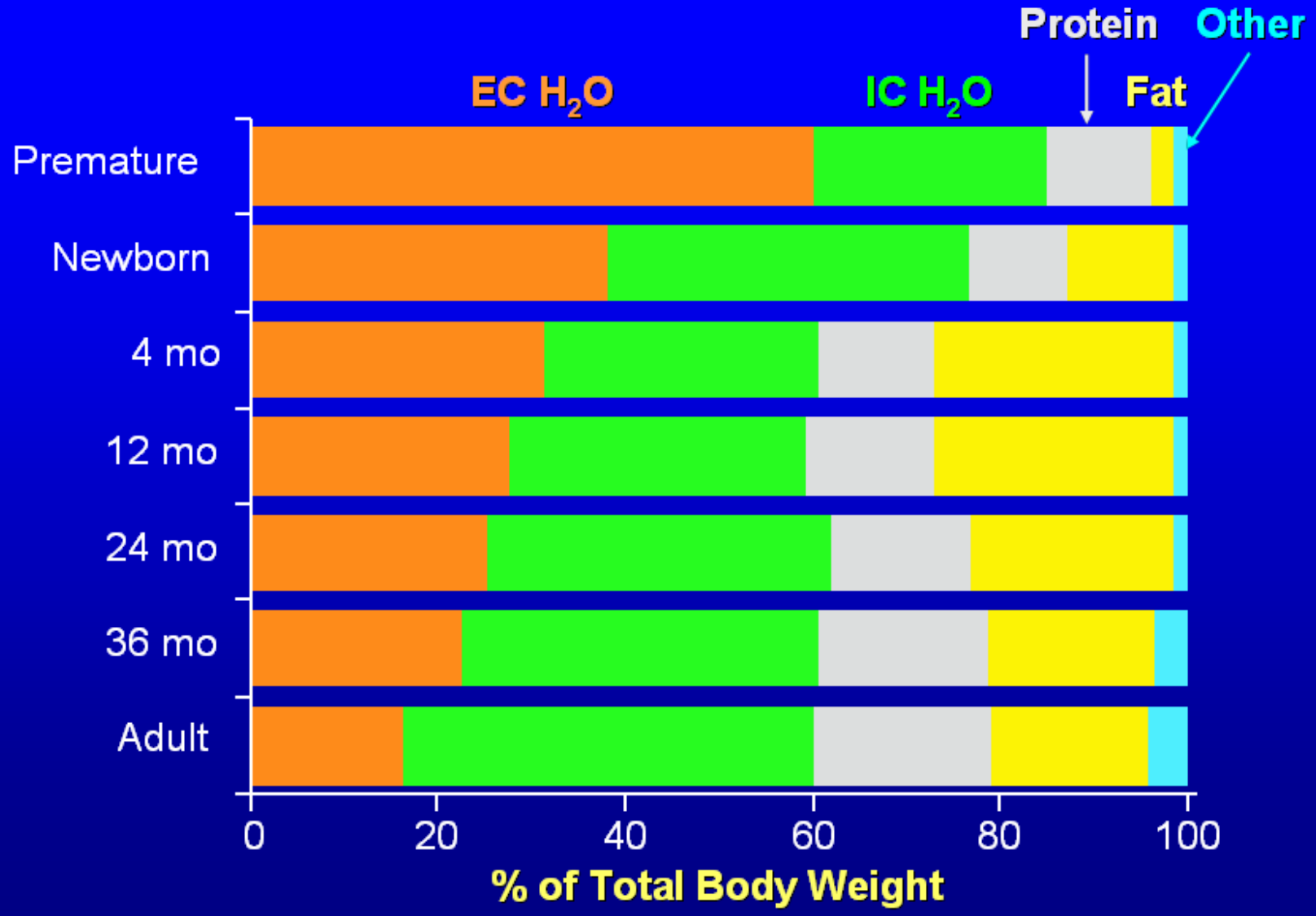
# Theophylline Urinary Metabolites



# Factors Affecting Drug Distribution

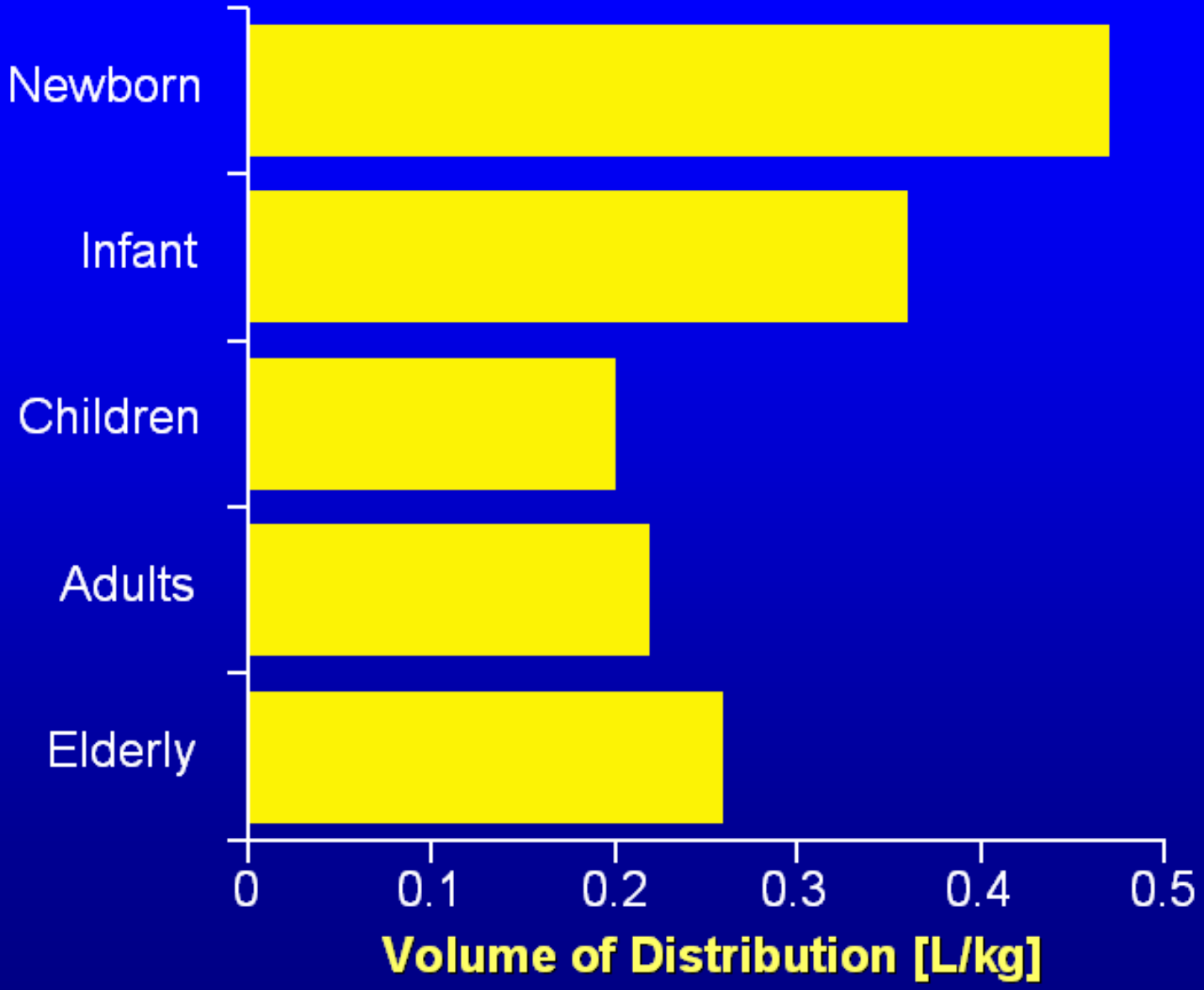
* Physicochemical properties of the drug
* Cardiac output/Regional blood flow
* Degree of protein/tissue binding
* Body composition
  - Extracellular water
  - Adipose tissue

# Ontogeny of Body Composition




Kaufman, Pediatric Pharmacology (Yaffe & Aranda, eds) pp. 212-9, 1992

# Volume of Distribution of Sulfa




Routledge, J Antimicrob Chemother 34 Suppl A:19-24, 1994

# Tissue and Organ Weight

| | % of Total Body Weight | | |
|---|---|---|---|
| | Fetus | Newborn | Adult |
| Skeletal muscle | 25 | 25 | 40 |
| Skin | 13 | 4 | 6 |
| Skeleton | 22 | 18 | 14 |
| Heart | 0.6 | 0.5 | 0.4 |
| Liver | 4 | 5 | 2 |
| Kidneys | 0.7 | 1 | 0.5 |
| Brain | 13 | 12 | 2 |

# Plasma Proteins

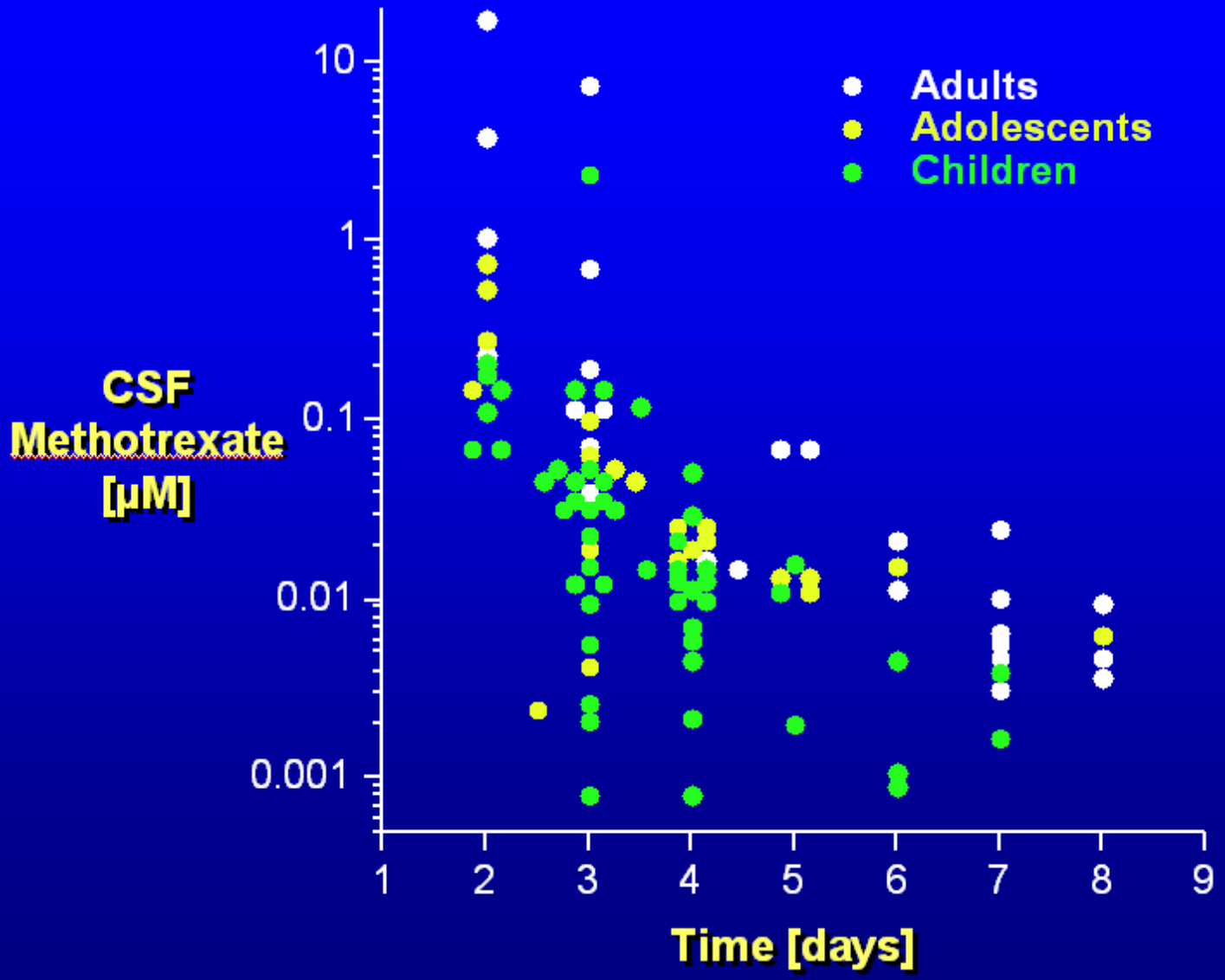
| | Change from Adult Values | | |
|---|---|---|---|
| | Newborn | Infant | Child |
| Total protein | ↓ | ↓ | = |
| Albumin | ↓ | = | = |
| $\alpha_1$-Acid glycoprotein | ↓ | | = |
| Fetal albumin | Present | Absent | Absent |
| Globulin | ↓ | ↓ | = |

# Protein Binding in Cord and Adult Plasma

| | Plasma Protein Binding (%) | |
|---|---|---|
| | Cord | Adult |
| Acetominophen | 36.8 | 47.5 |
| Chloramphenicol | 31 | 42 |
| Morphine | 46 | 66 |
| Phenobarbital | 32.4 | 50.7 |
| Phenytoin | 74.4 | 85.8 |
| Promethazine | 69.8 | 82.7 |
| | 30.2 | 17.3 |

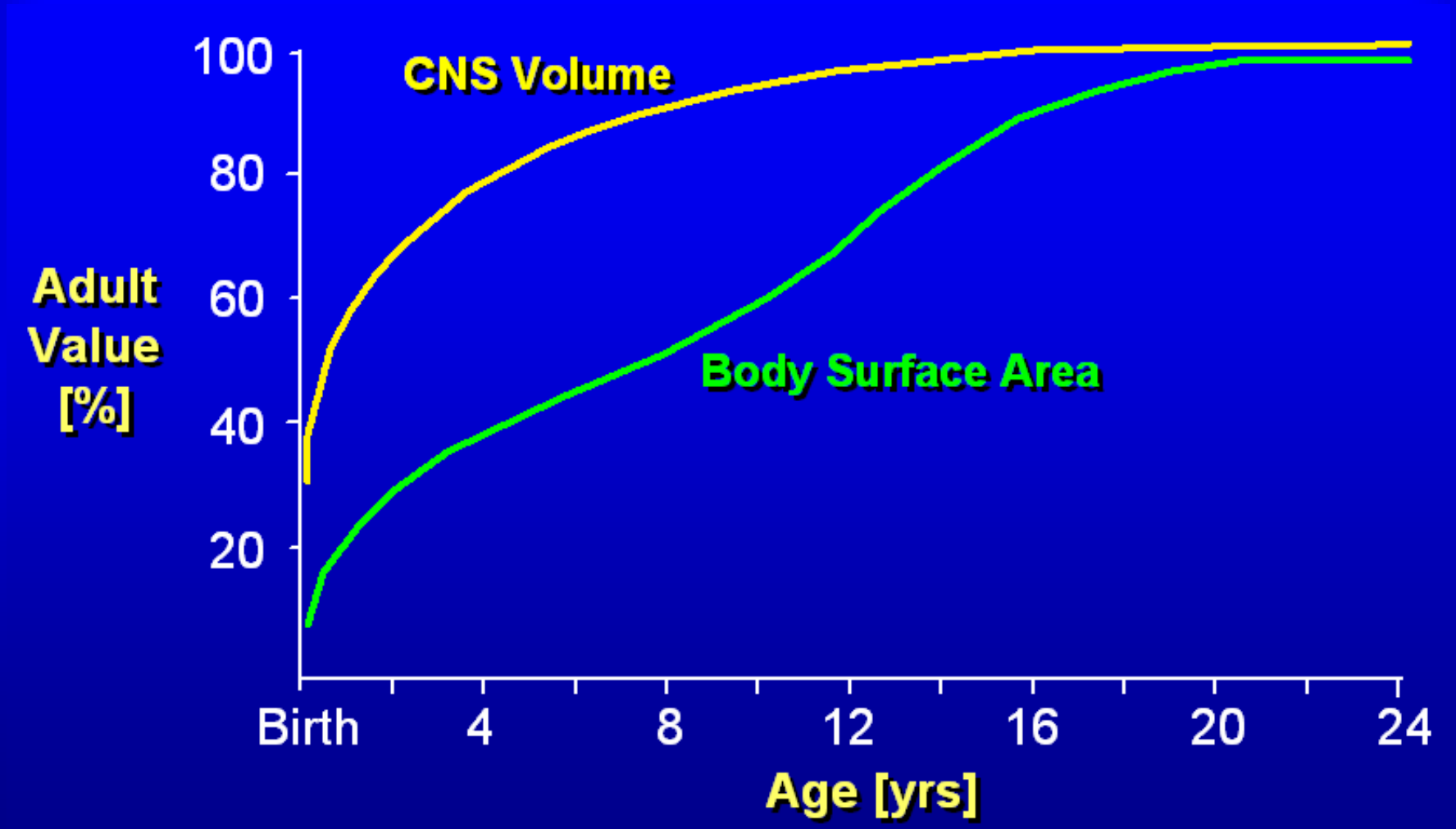
Kurz et al., Europ J Clin Pharmacol II:463-7, 1977

# CSF MTX and Age




Bleyer, Cancer Treat Rep 61:1419-25, 1977

# CNS Growth and Development



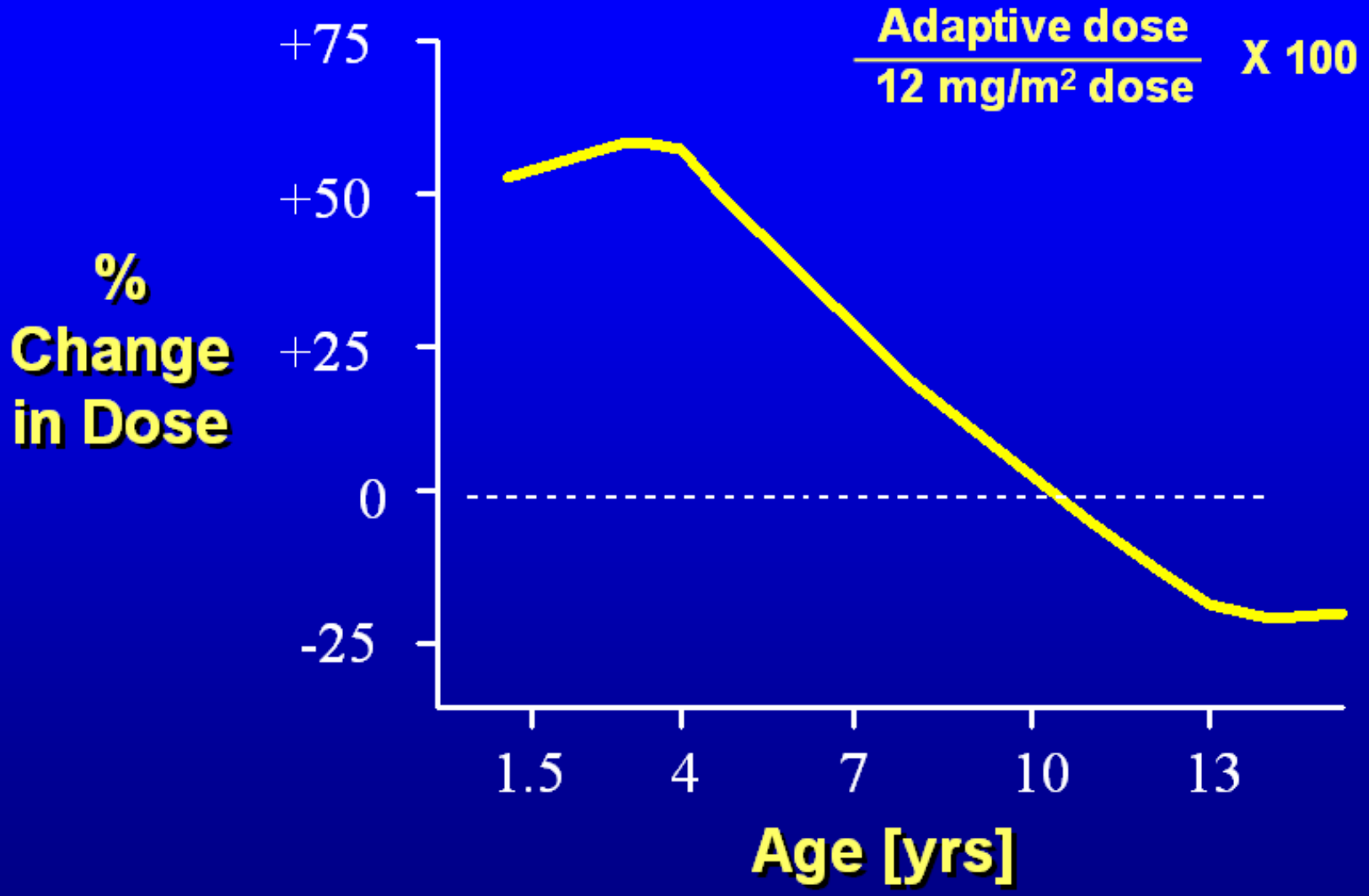

Bleyer, Cancer Treat Rep 61:1419-25, 1977

# Adaptive IT MTX Dosing Regimen

| Age [yrs] | MTX Dose [mg] |
|---|---|
| <1 | 6 |
| 1 | 8 |
| 2 | 10 |
| ³ 3 | 12 |

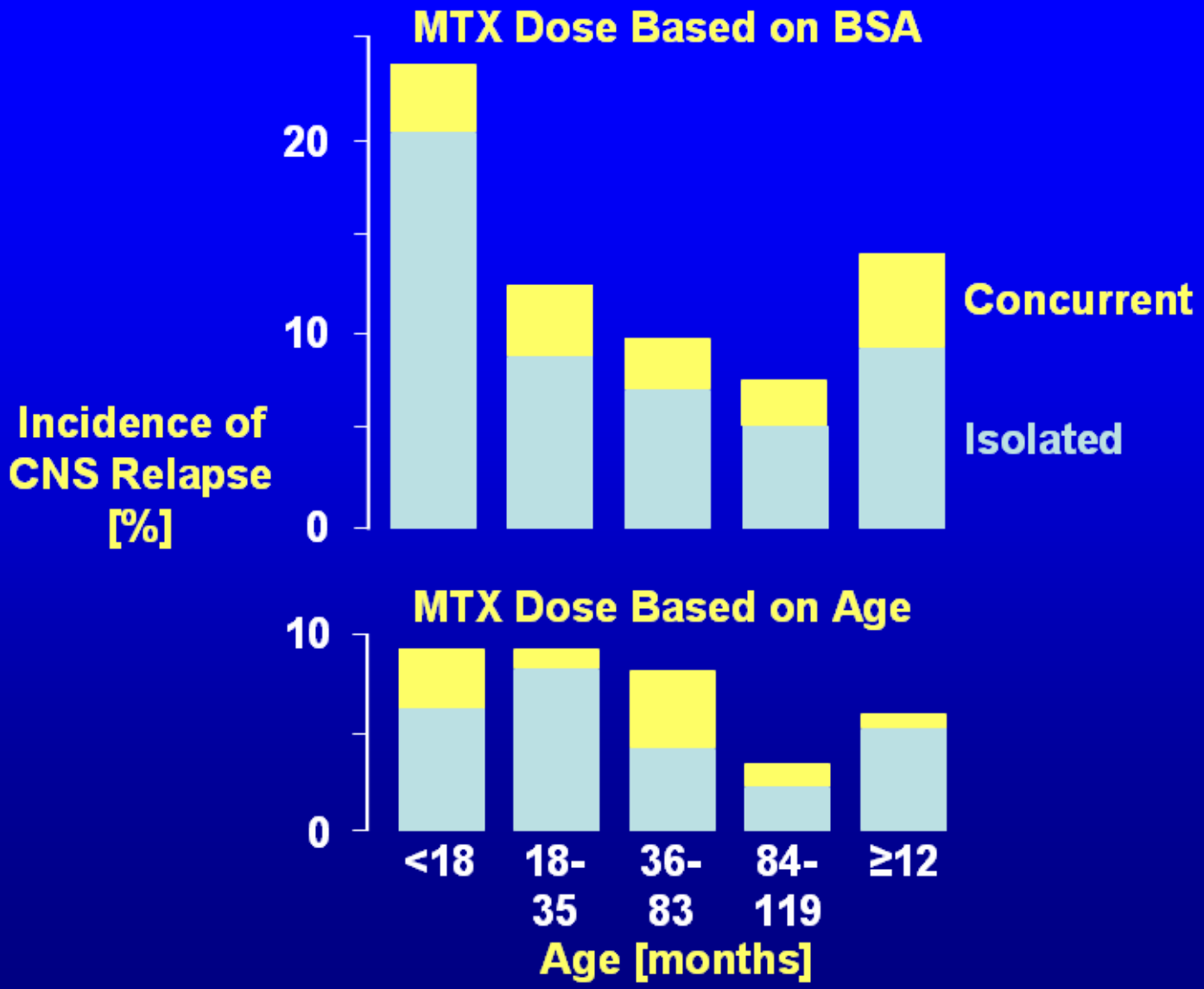
Bleyer, Cancer Treat Rep 61:1419-25, 1977

# Dose Change with Adaptive Regimen




Bleyer, J Clin Oncol 1:317-25, 1983

# Effect of Adaptive IT Dosing on Outcome




Bleyer, J Clin Oncol 1:317-25, 1983

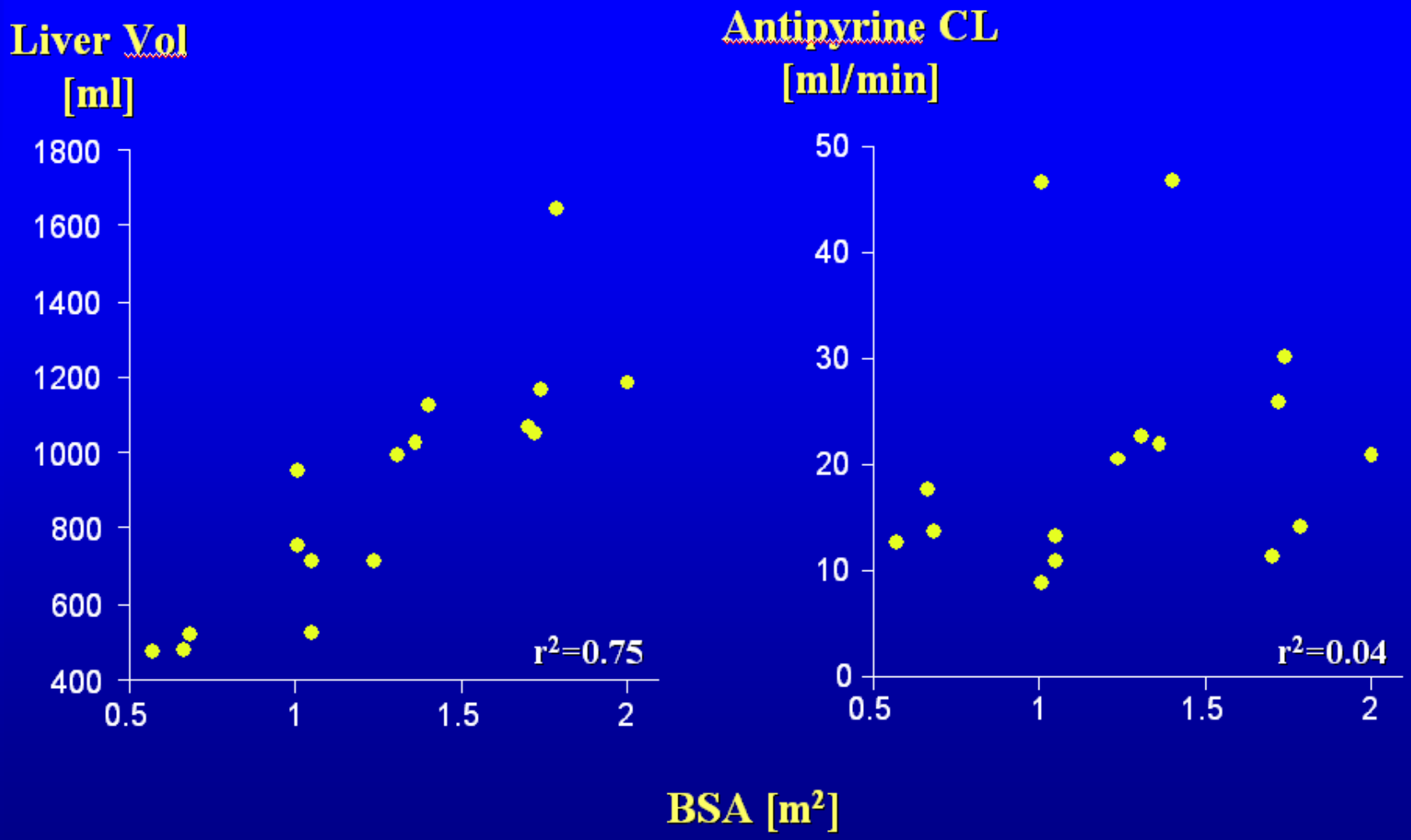
# Dosing Based on Body Surface Area

* BSA = 2-dimensional surface area of the skin
* Estimated from formulas using weight & height
* Correlation between BSA and kidney/liver function is weak
* BSA dosing evolved from scaling doses from animals to humans (toxicology)

| Species | Wt [kg] | BSA [$m^2$] | Dose [mg] | Dose [mg/kg] | Dose [mg/$m^2$] |
|---|---|---|---|---|---|
| Mouse | 0.018 | 0.0075 | 0.027 | 1.5 | 3.6 |
| Rat | 0.25 | 0.045 | 0.125 | 0.5 | 2.8 |
| Infant | 8 | 0.4 | 1.25 | 0.15 | 3.1 |
| Child | 20 | 0.8 | 2.5 | 0.12 | 3.1 |
| Adult | 70 | 1.85 | 5.0 | 0.07 | 2.7 |

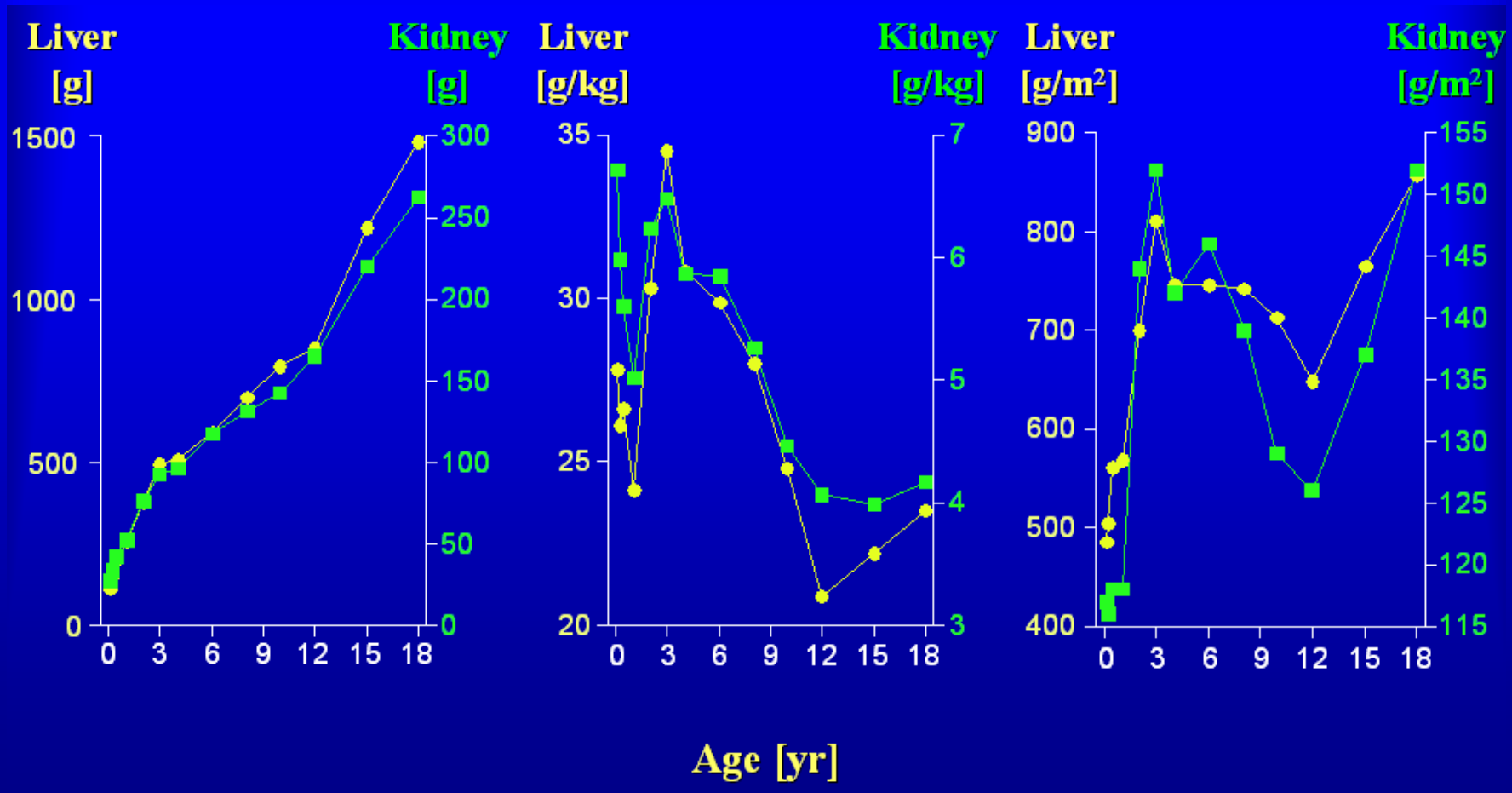
Pinkel, Cancer Res 18:853, 1958

# Liver Function (Children)

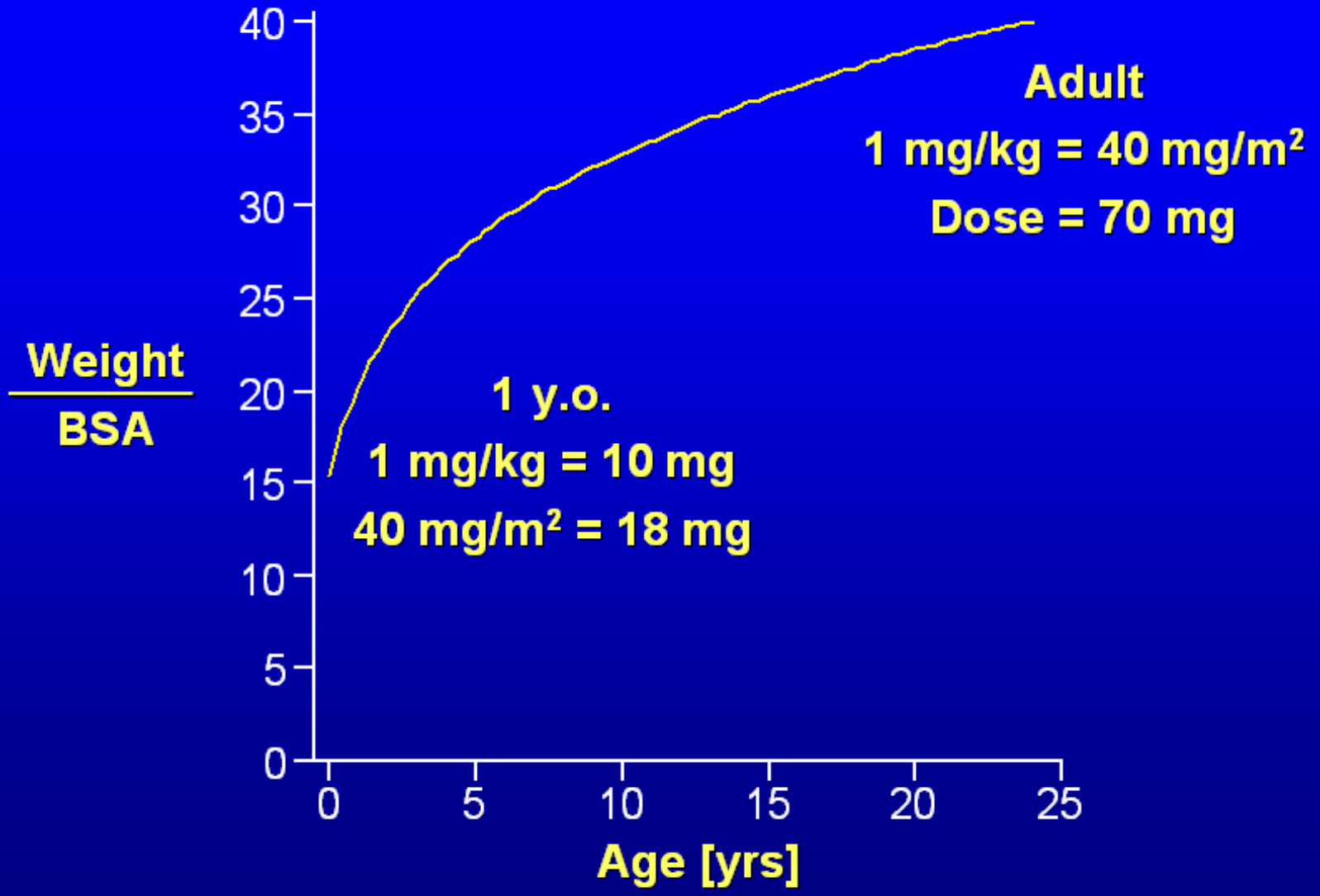



Murry et al. Drug Metab Disp 23:1110, 1995

# Excretory Organ Growth



# Body Weight:Surface Area

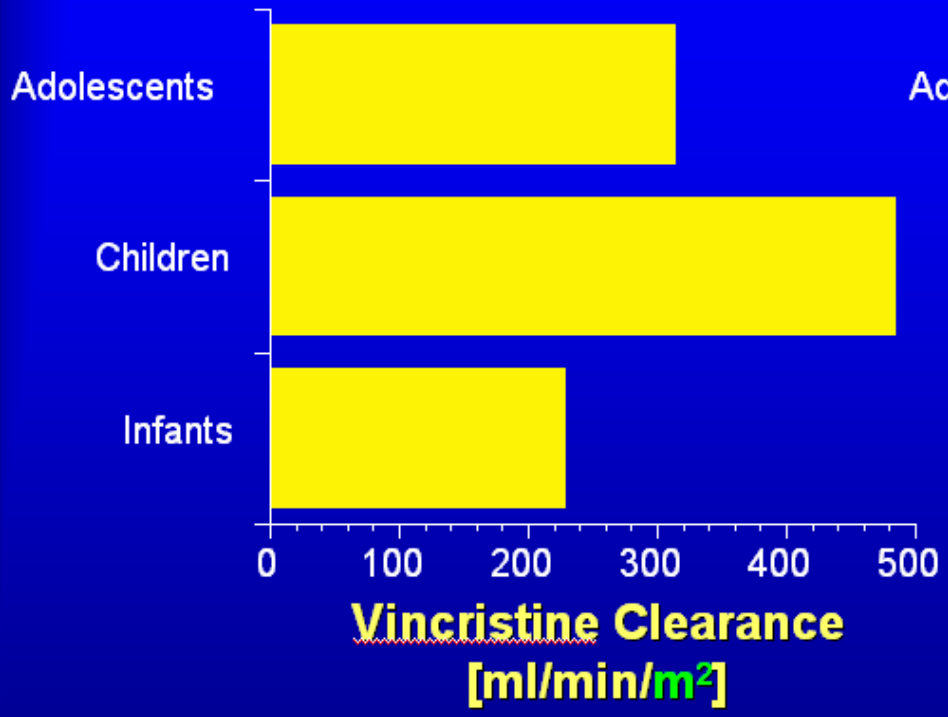


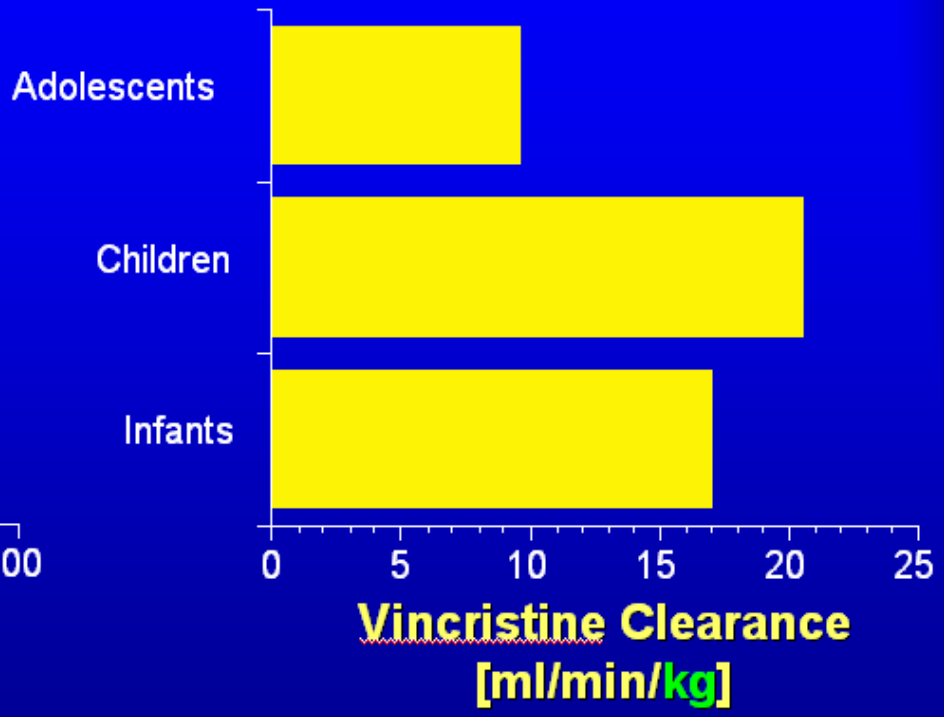
# Anticancer Drug Clearance

| Drug | Route of Elimination | $CL_{infants}$ *vs* $CL_{children}$ | Dosing |
|---|---|---|---|
| Methotrexate | R | ↓ (15%) | No adjustments |
| Mercaptopurine | M | ND | No adjustments |
| Vincristine | M | ↓ (/$m^2$) | <1 yo, dose/kg |
| VM26/VP16 | M | ND (/$m^2$) | No adjustments (/$m^2$) |
| Doxorubicin | B, M | ↓ (/$m^2$) | <2 yo, dose/kg or ↓dose/$m^2$ |
| Cytarabine | M | ND | No adjustment |

McLeod et al., Br J Cancer 66 (Suppl. 18):S23-S29, 1992

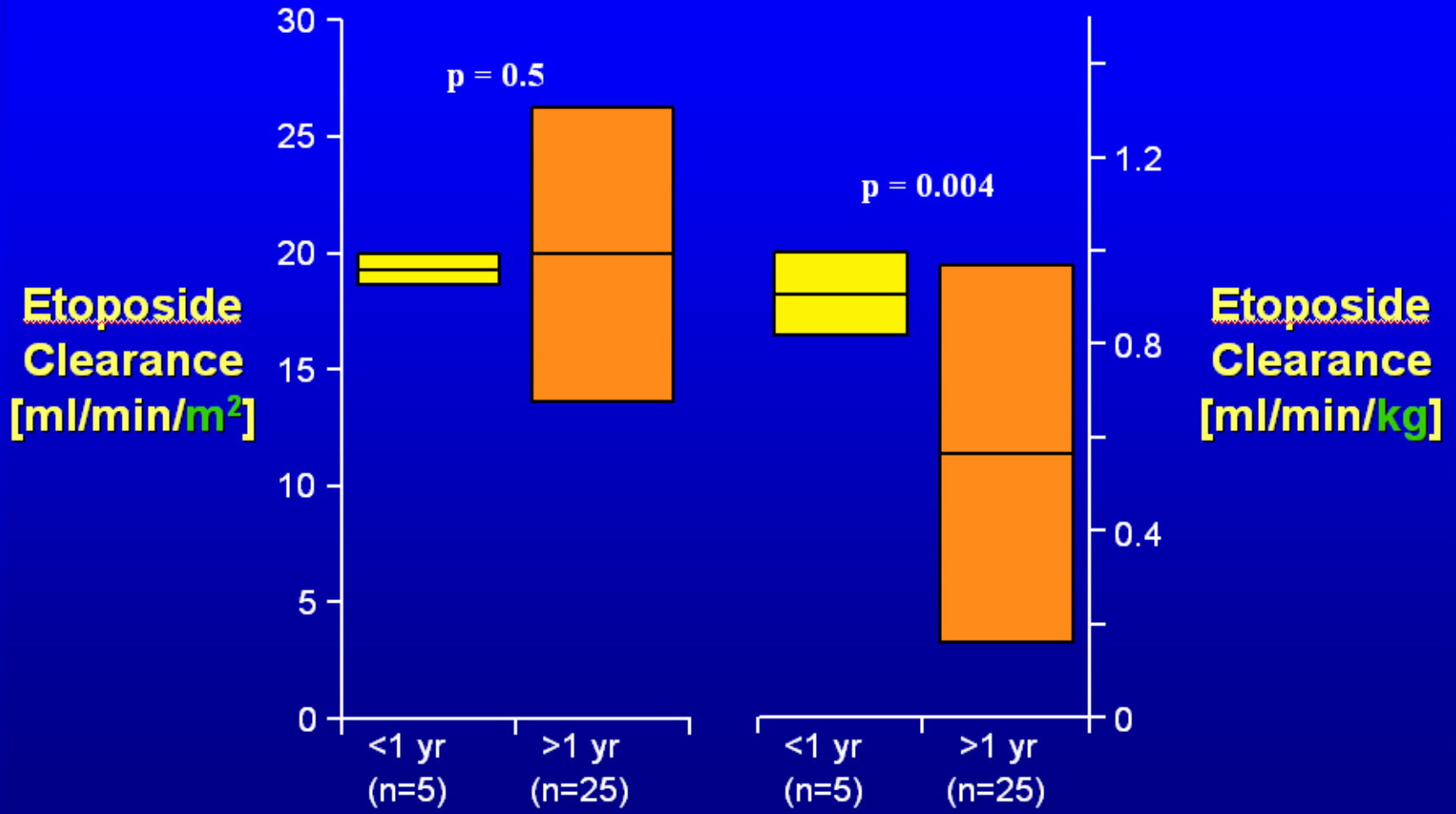
# Vincristine Clearance



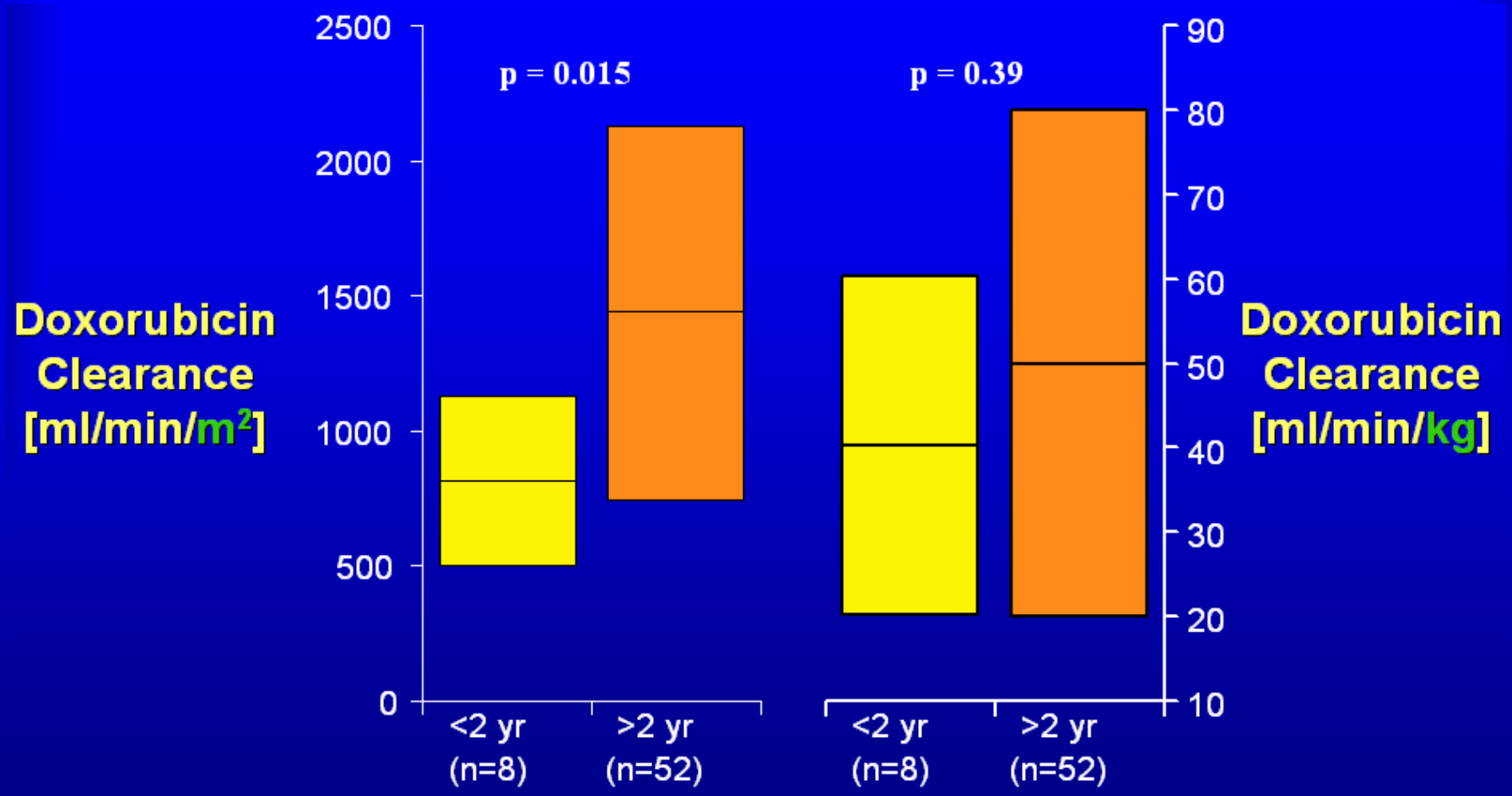




Crom et al., J Pediatr 125:642-9, 1994

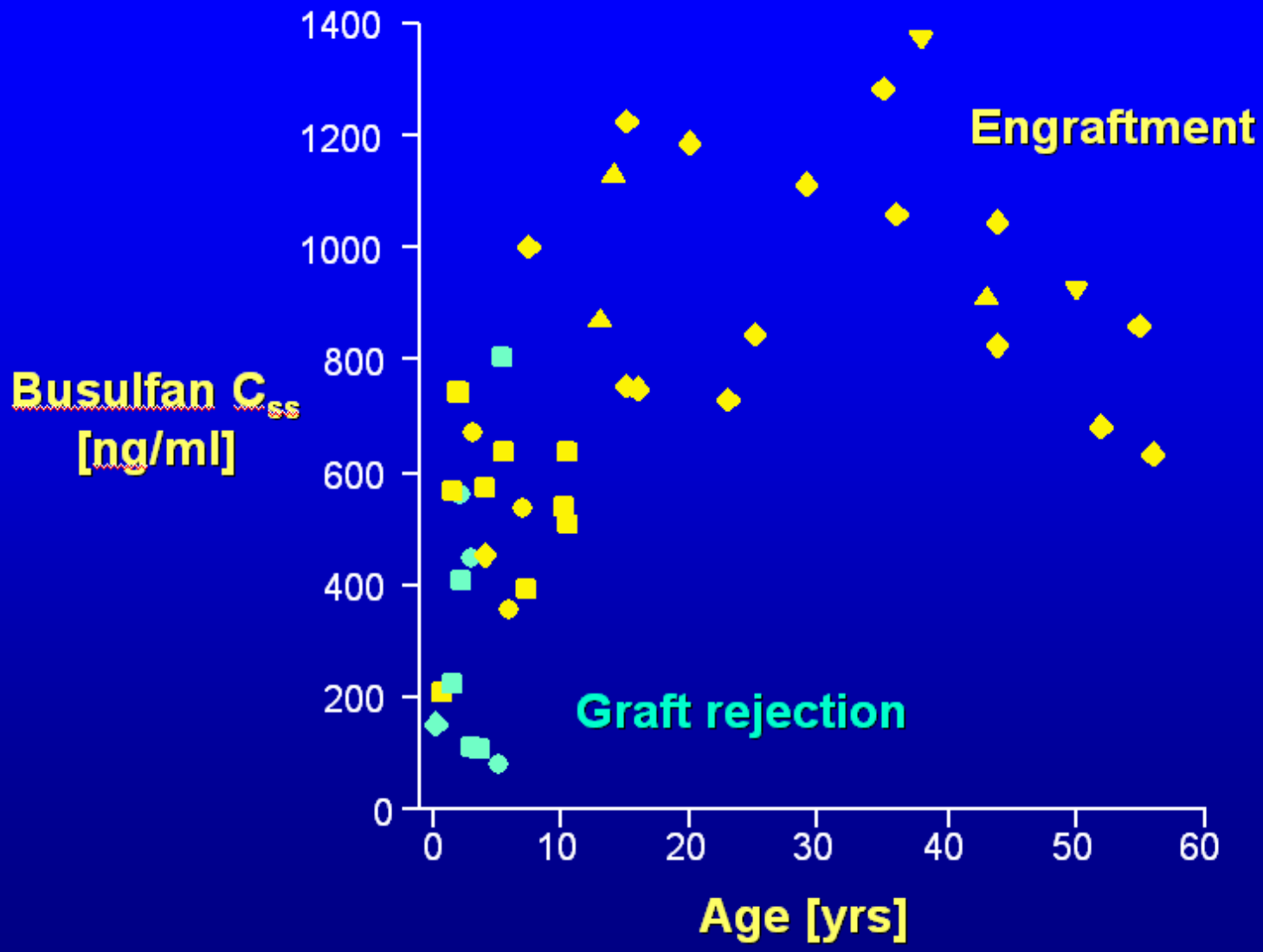
# Etoposide Clearance



# Doxorubicin Clearance

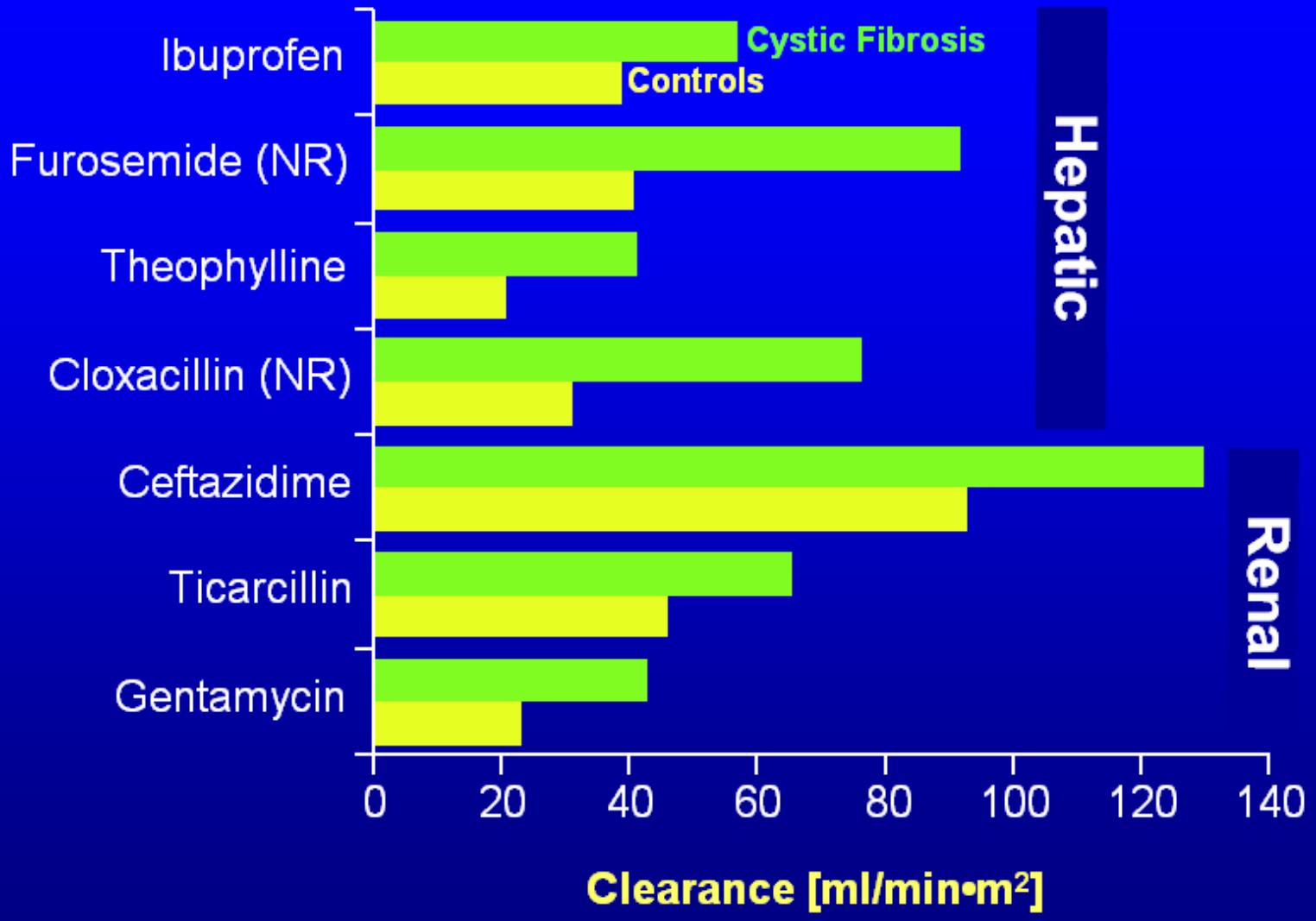


# Oral Busulfan (16-30 mg/kg)




Slattery et al., Bone Marrow Transplant 16:31, 1995

# Drug Clearance in Cystic Fibrosis




Rey, Clin Pharmacokinet 35:313-29, 1998

# Retinoids

| | ≤12 Yr. | >12 Yr | Adult |
|---|---|---|---|
| **ATRA** | | | |
| MTD | 60 mg/m²/d | 90 mg/m²/d | 150 mg/m²/d |
| DLT | Pseudotumor cerebri | HA and PC | Dermatologic |
| **9-cis-RA** | | | |
| MTD | 35 mg/m²/d | 85 mg/m²/d | 140 mg/m²/d |
| DLT | Pseudotumor cerebri | HA and PC | HA, diarrhea, dermatologic |

# Conclusions

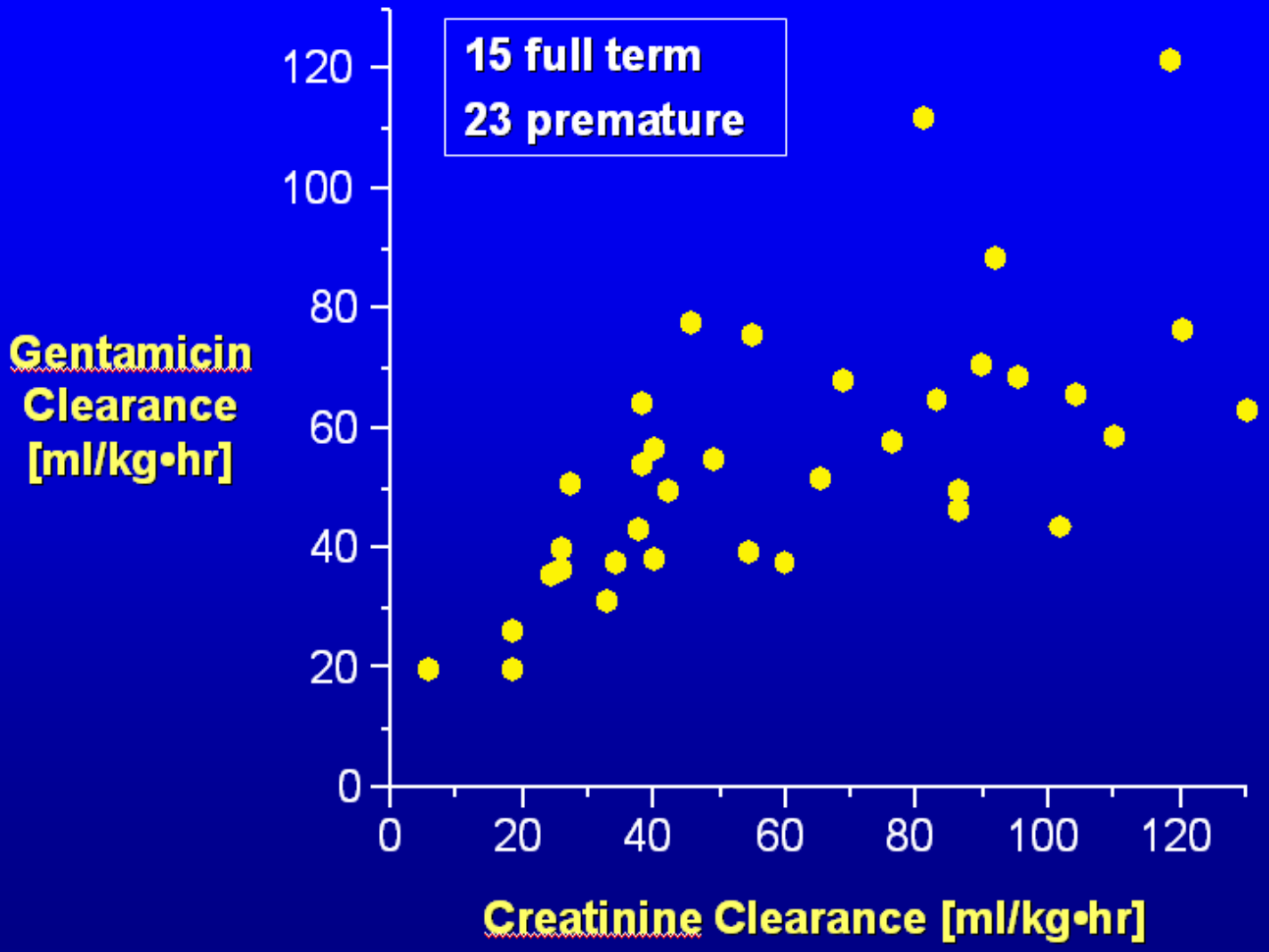
* Infants (esp. newborns) may have reduced capacity to eliminate drugs
* Anticipate the effects of ontogeny on drug disposition based on route of elimination
* More systematic pharmacokinetic studies of drugs in infants are needed
* Tissue sensitivity to the toxic effects of drugs may be age-dependent

# Cytochrome P450 Enzymes

| Present in fetus | Appear after birth | Appear 3-4 months of age |
|---|---|---|
| CYP3A7* | CYP2D6 | CYP1A2 |
| CYP1A1 | CYP3A4* | |
| CYP3A5 | CYP2C9 | |
| | CYP2C18/19 | |
| | CYP2E1 | |

* Most abundant form

# Gentamicin in the Newborn




Koren et al., Clin Pharmacol Ther 38:680-5, 1985