# Barriers to Drug Development in Pediatrics

## Dose-Finding & Bioavailability: Guessing

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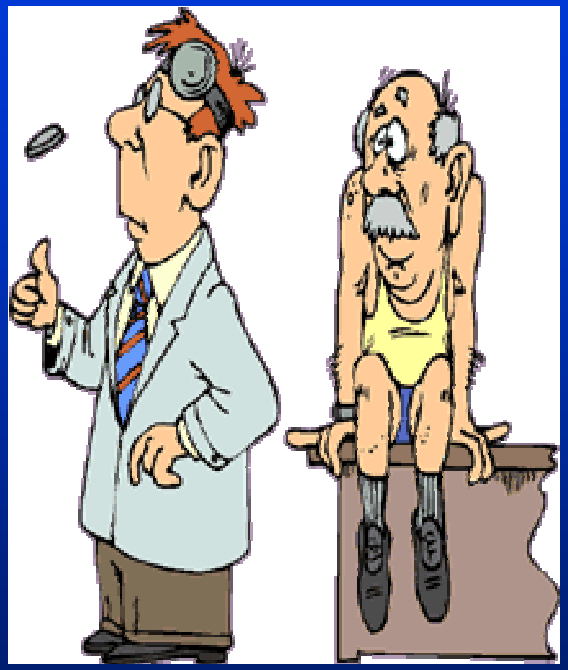
# Dose-Finding & Bioavailability: Guessing Which Model(s) Do We Use in Pediatrics?


Las Vegas



Medical Experience
Limited Literature

Physiologic
Reasoning

# Dose-Finding & Bioavailability: Guessing Which Model(s) Do We Use in Pediatrics?

## Missing Link: Rigorous Prospective Study

- About 2/3 of drugs are not labeled for pediatric patients, so the label often doesn't help
- Studies that are often used for pediatric dose estimation are:
  - too small
  - wrong patient population by age or disease
  - non-existent

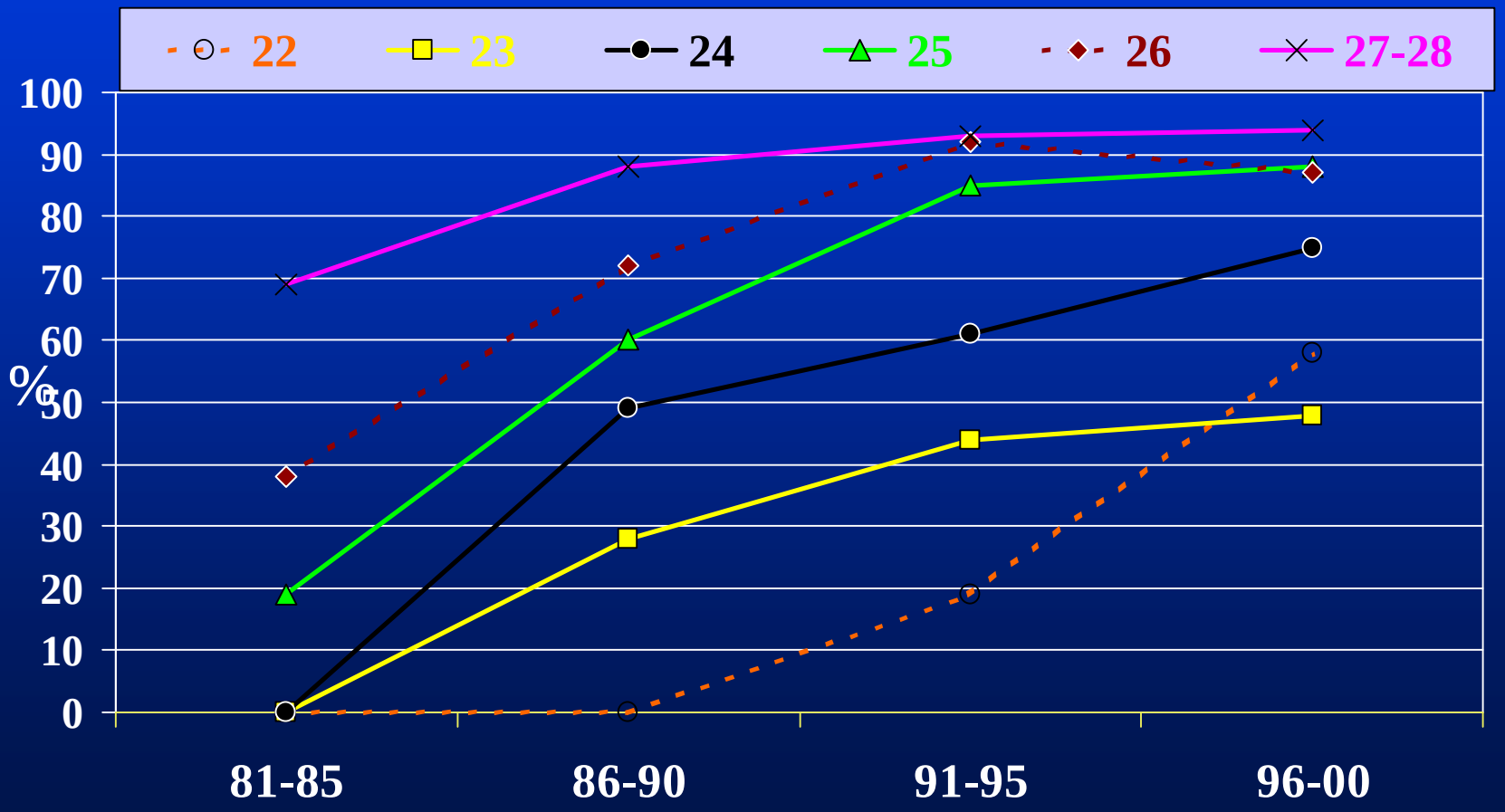
# Lessons Learned From Therapeutic Misadventures In the NICU

- Newer the drug, the less it will be studied in pediatric populations—exception for surfactant
- Smaller and sicker the patient, the more drugs are used and the less the drugs will have been studied
- "Innovative care" becomes the rule rather than the exception in the critically ill NICU and PICU patients
- Dosages are often derived from experience in a different pediatric population with modifications for physiologic differences

# Large Challenges Inversely Proportional to Size

# Increasing Survival of Prematures 1981-2000
# University of Utah Tertiary NICU

## Weeks Gestation at Birth



# Measures of Kinetics, Dosing, Efficacy Moving Targets in Newborns

- Survival at gestations of 23-24 weeks are increasing
- Studies in moderately preterm newborns with gestations of 30 weeks and above may not be relevant to today's prematures
- Physiologic differences related to extreme immaturity may not predict kinetics or the response to the same concentration of drug that is effective in the more mature newborn

# Labeling: Surrogate Marker for Study

## Drug Labels

- Labeling is based on careful study
- Lack of labeling often reflects lack of study
- Lack of study may slow, but seldom stops treatment using dosages based on experience, physiology, adults, luck
- Sometimes we practice like cowboys and prescribe from the hip

# Tolazoline for PPHN
# Treatment Unguided by Kinetics

- PPHN mortality in the 1970's around 30%
- Tolazoline increased paO2 initially in 60-69% of newborns with PPHN; mortality was unchanged
- Tolazoline (Priscoline), a structural analog of histamine and catecholamines, releases histamine, a potent simulus to gastric acid secretion
- Gastric perforations, hypotension, oliguria, thrombocytopenia (Ward: Clin Perinatol 1984;11:703)

# Persistent Pulmonary Hypertension of the Newborn (PPHN) & Tolazoline Treatment

- 1961: Tolazoline described by cardiologists as an "Effective Pulmonary Vasodilator"

  Grover et al. Am Heart J 61:5, 1961

  - 8 children with VSD's selected for report since PVR decreased > SVR after 1 mg/kg doses
  - Not a study, not randomized, single dose tested

- 1969: first description of PPHN in 2 neonates

  - 1 patient treated (ped cardiologist) with tolazoline & paO2 increased, neither survived

  Gersony et al. Circulation 1969; 40 (suppl III): 87

# Tolazoline Dose Escalation Without Guidance of pK, pD Study

## Tolazoline (Priscoline) Dose Inflation

| | | |
|---|---|---|
| **Pulse Doses** | **1961** | **1.0 mg/kg** |
| | **1965** | **2.0 mg/kg** |
| | **1980** | **5.0 mg/kg** |
| **Infusion Doses** | **1976** | **1.0-2.0 mg/kg/hr** |
| | **1979** | **10 mg/kg/hr** |

**"8 of the non-responders died in a hypotensive state while receiving tolazoline"** **J Pediatr 95:595, 1979**

Dose Guessing: If a little is good and the effect is transient, repeat & increase the dose

# Tolazoline Kinetics Vary Widely With Renal Function; May be Lethal

1982: first report of tolazoline kinetics in newborns (3 years after reports of infusions of 10 mg/kg/hr)

Half-life in newborns varies from 3.3 to 33 hr

Monin et al. Dev Pharmacol Ther 4 (suppl 1):124, 1982

1986: Elimination ceases when urine output stops

Half-life increases with oliguria

Concentrations during infusions to oliguric neonates reach levels that are lethal to lambs

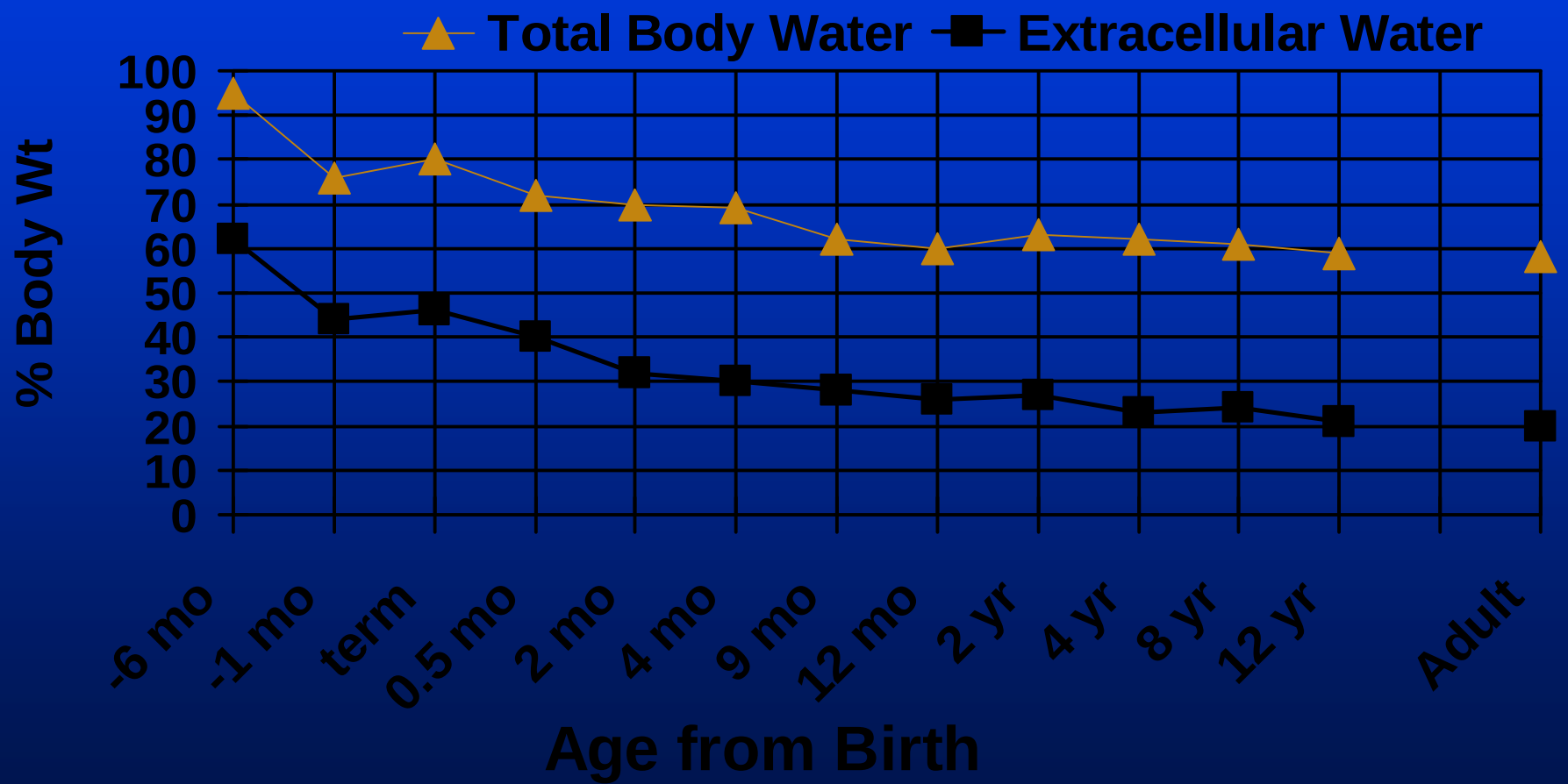
Ward et al: Pediatrics 1986;77:307

# Dose Guessing: Distribution
## Physiology and Developmental Pharmacology

$$\text{Concentration} = \frac{\text{Dose (mg/kg)}}{\text{aVD (L/kg)}}$$

- **Distribution can vary widely during infancy, both for polar and for non-polar drugs**
  - **Greatest change in total body water occurs during fetal development**
  - **Acquisition of body fat increases with varying rates, but generally faster than is healthy**

# Changes in Body Water Compartments Fetus to Adult

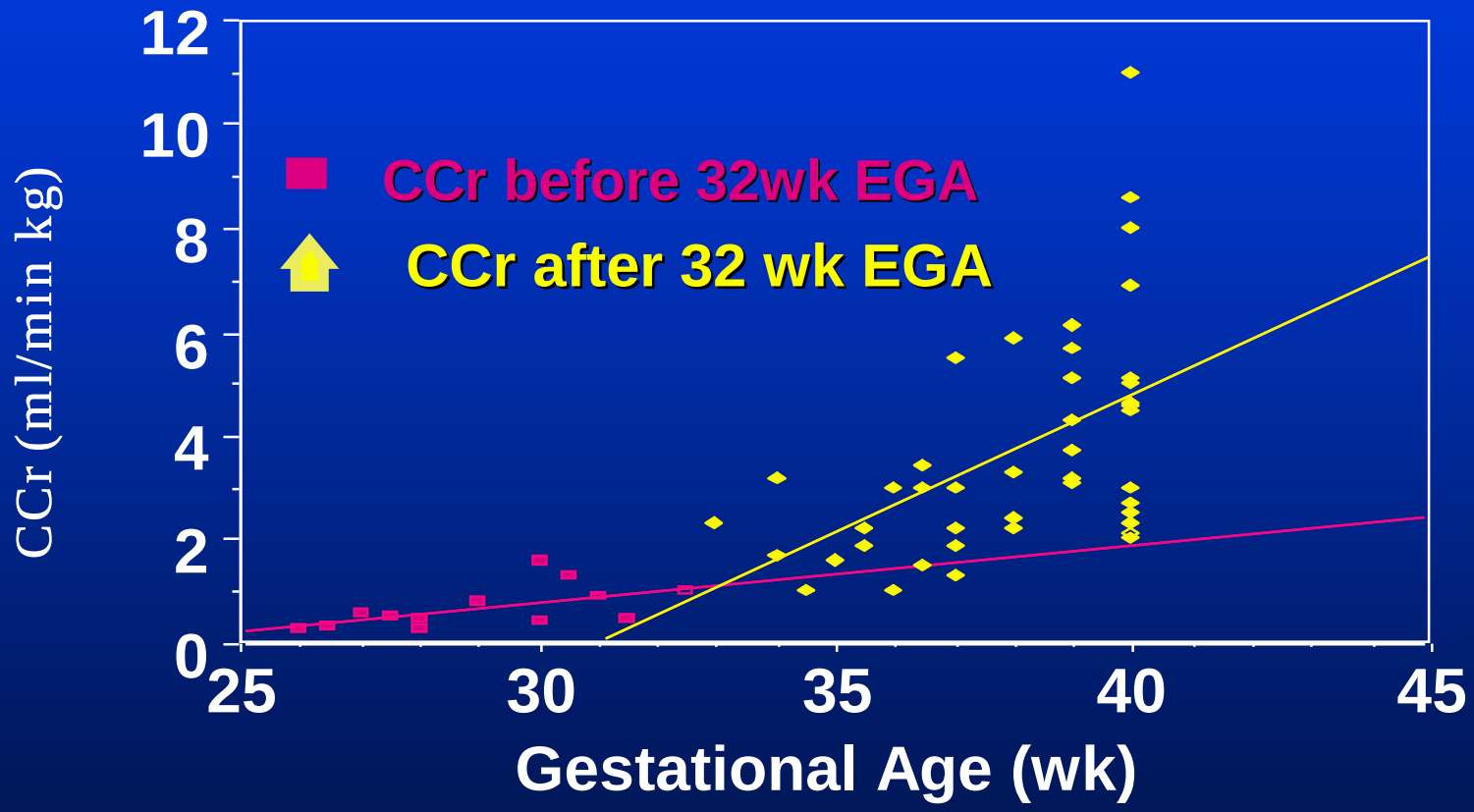



Friis-Hansen. Pediatrics 1961;28:169. ibid 1971;47:267

# Dose Guessing: Renal Clearance
## Physiology and Developmental Pharmacology

- **Pathways of clearance should be known from studies in older patients**
  - **Renal (glomerular vs tubular) maturation is relatively well studied maturation**

# Developmental Change in Glomerular Filtration Rate (GFR)




Redrawn from: Engle WD, Arant BS, Jr: Kidney Int 1983;24:360

# Digoxin Developmental Kinetics
## (15 neonates 29-40 wks)

**Digoxin is eliminated largely (90%) by renal excretion**

| Weight | Clearance (ml/min/1.73 $m^2$) |
|---|---|
| 0.8 - 1.0 kg | 22.5 ± 5.5 |
| 1.0 - 1.5 kg | 29.5 ± 5.6 |
| 1.5 - 2.3 kg | 59.0 ± 16.2 |

Collins-Nakai: Dev Pharmacol Ther 4:61, 1982

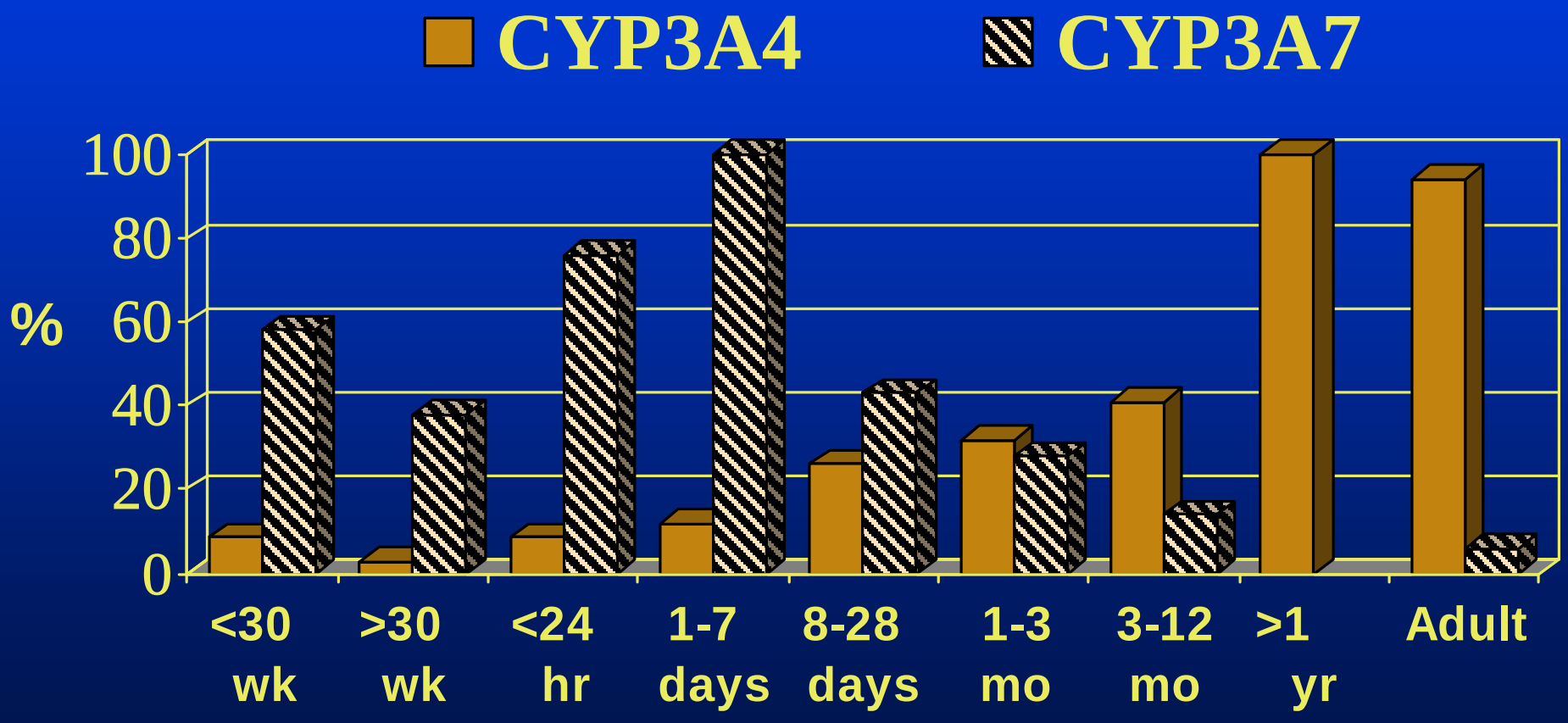
# Maturation of Renal Function

- Glomerular function normalized to BSA (normalization to body wt is less well accepted) approaches adult function by 6-12 months
- Tubular function lags behind GFR, but reaches adult function by 12 months
  - Particularly important for active transport of strong acids, bases

# Dose Guessing: Metabolism
## Physiology and Developmental Pharmacology

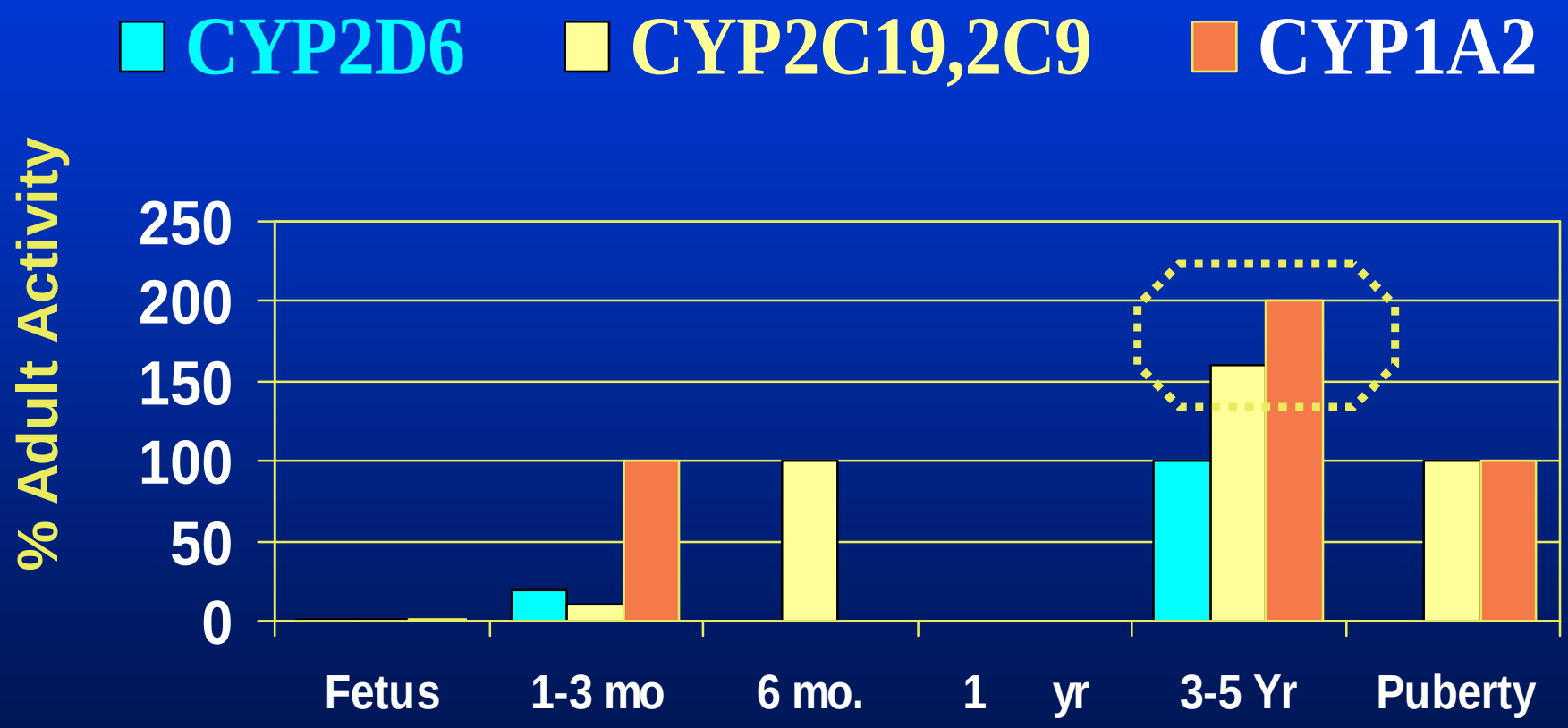
- **Pathways of biometabolism should be known from studies in older patients**
  - **Hepatic enzyme maturation is not known as well, because it is more complex and more variations are recognized each year**
  - **Ethnically distributed variations in activity**
  - **Inherited variations in single enzymes**

# Cytochrome P450 3A (CYP3A) Switch CYP3A7 (Fetal) TO 3A4 (Adult) After Birth




Eur J Biochem 1997;147:625

# Maturational Patterns of CYP's Need More Study




Redrawn from Leeder et al: Ped Clin North Amer 1997;44:55

# Clearance vs Maturation Likely to Guess Wrong

Data in next slide from:

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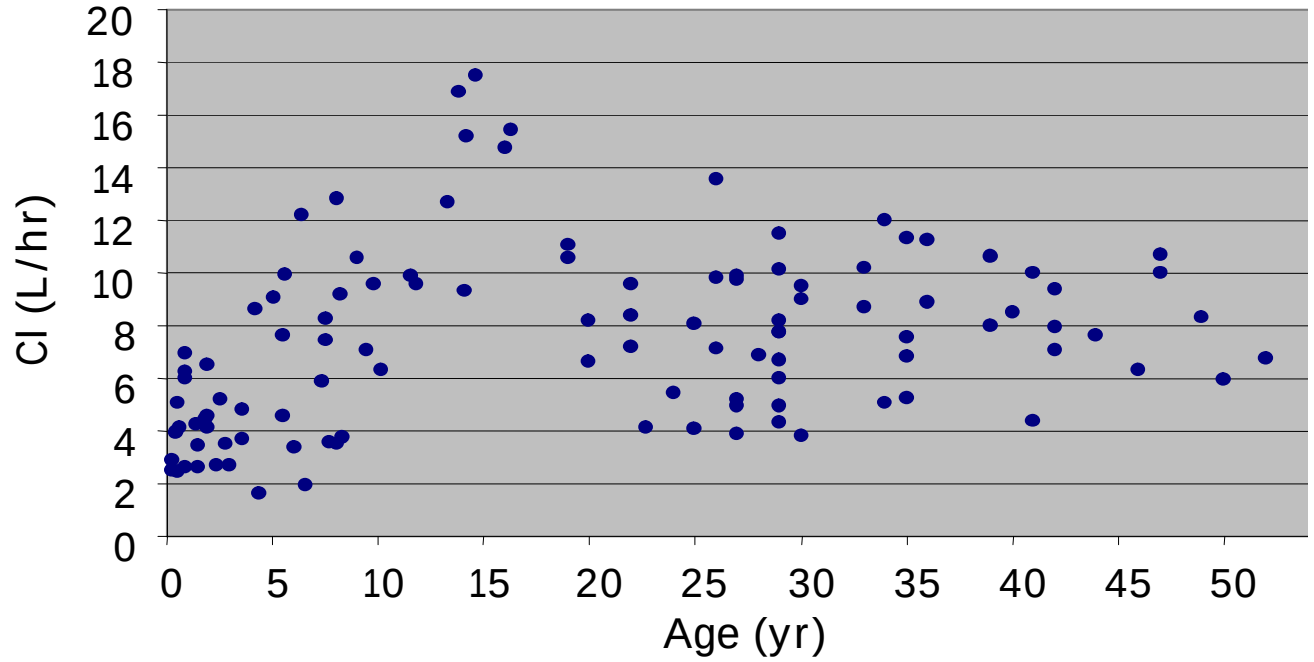
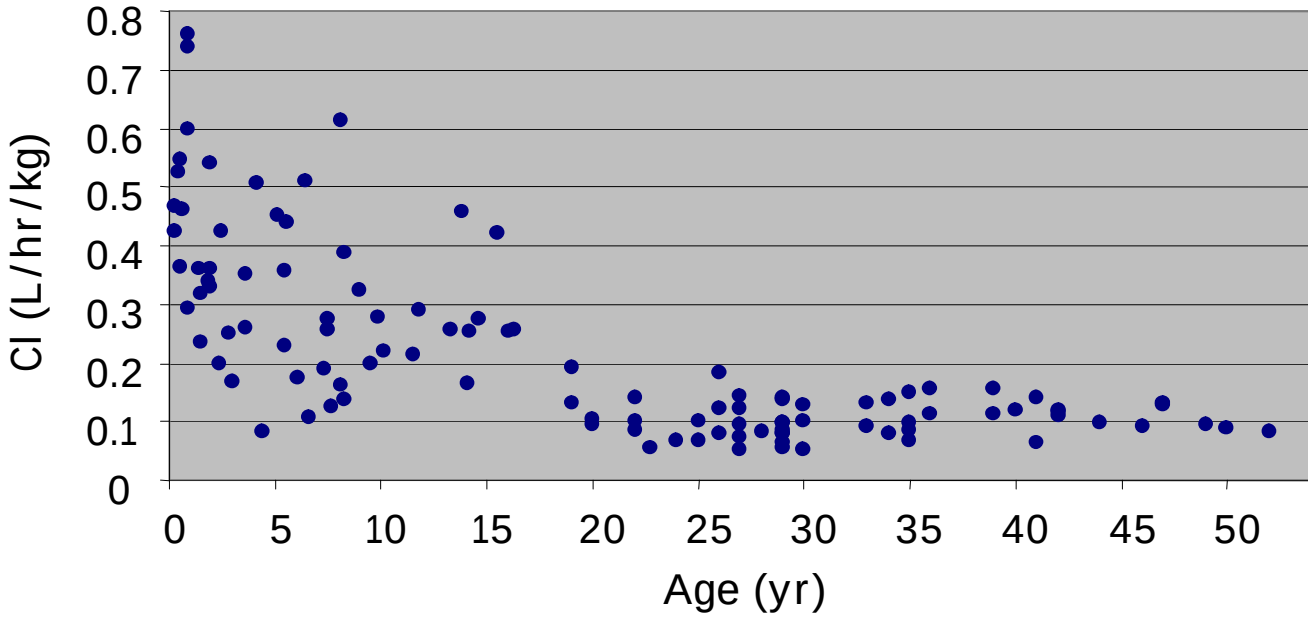
Study Report:
Total body clearance is lowest in infants, increasing through adolescence and then decreasing into adulthood.

Outcomes:
- correction of clearance for weight suggests that clearance is highest in the youngest population and decreases in a non-linear fashion with increasing age.



# From Dose Guessing to Informed Prescribing More Study

- Continue clinical study of kinetics, safety & efficacy of new and older off-patent drugs often used in peds
- Increase translational study of developmental variations in drug effects and in drug metabolism

Lend a helping hand with better informed drug therapy