# Drug Absorption and Disposition in Children:

## Physiologic Changes in the Developing Digestive Tract

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Children's Mercy Kansas City

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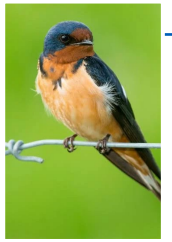
# Objectives

- Review developmental changes in the maturing pediatric digestive tract & their relevance to pharmacology
- Discuss influences of diet, disease and the microbiome on drug absorption/disposition
- Provide clinical examples and identify gaps in knowledge

# Factors Influencing Oral Absorption



## Pre-stomach factors

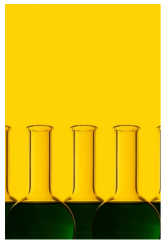
- Swallowing
- Esophagus

## Stomach Factors

- pH
- Volume
- Emptying Time

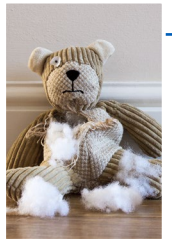
## Intestine Factors

- Microbial Colonization
- Motility
- Surface Area
- Luminal Contents
- Drug Transport



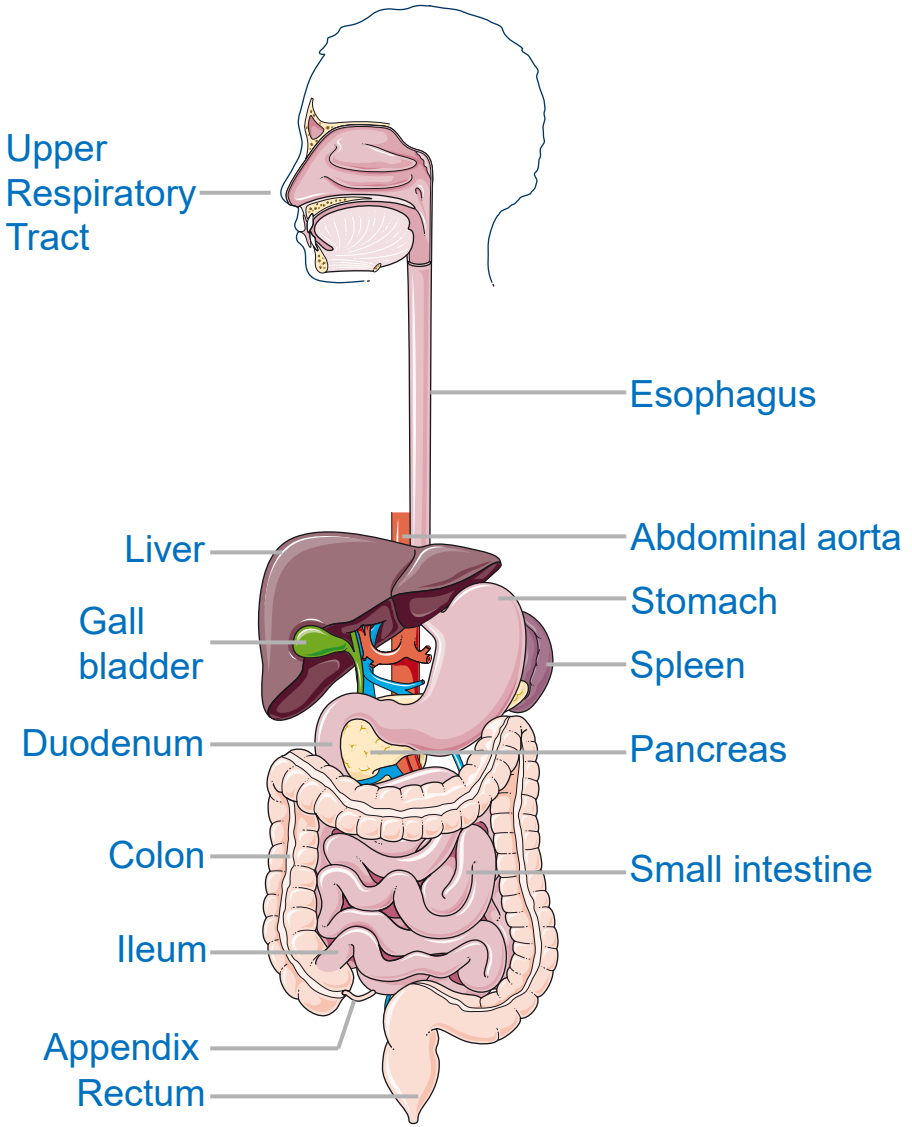
## Hepatobiliary Factors

- Biliary function
- Drug Metabolism



## All

- Disease effects

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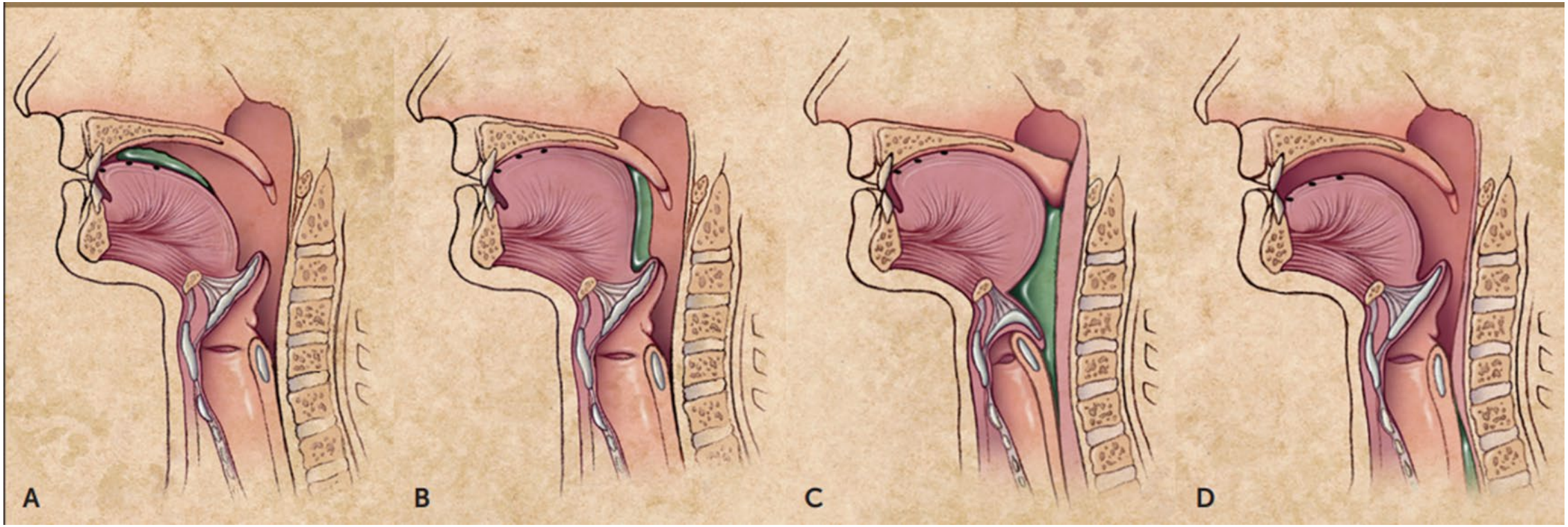
# Pre-stomach

Photo: “The Land Between”

# Swallowing is the first step to GI absorption

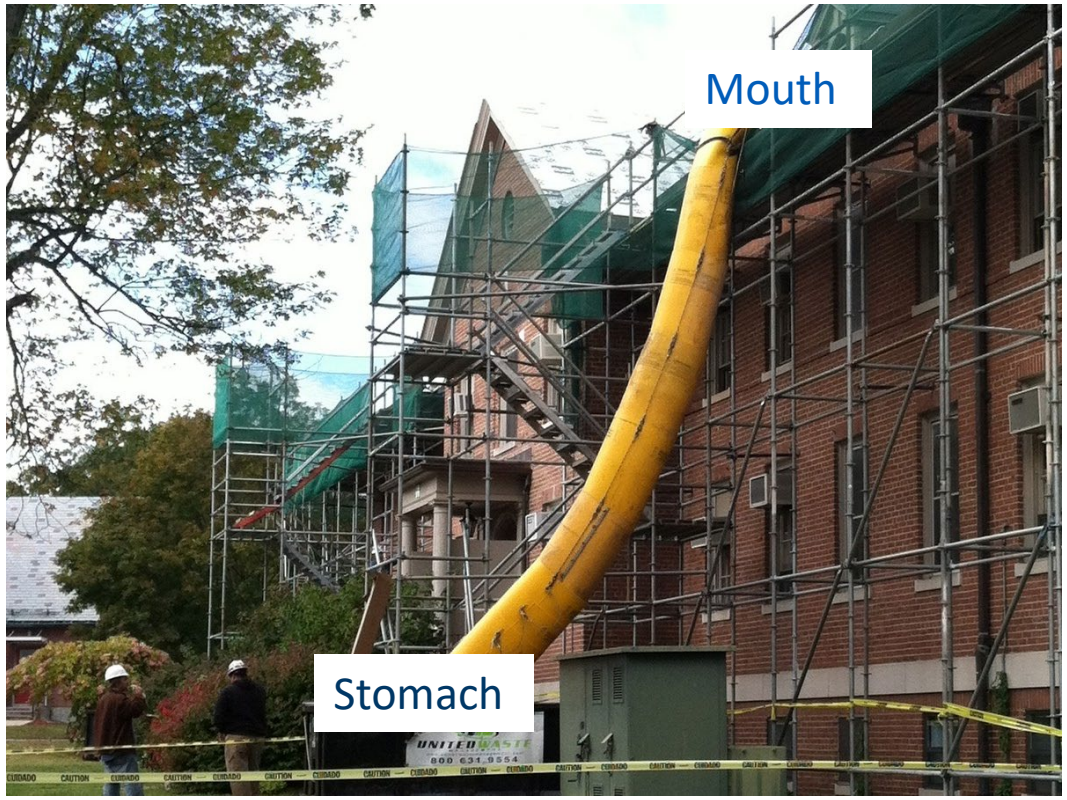


# Sensory development and food acceptance change in childhood

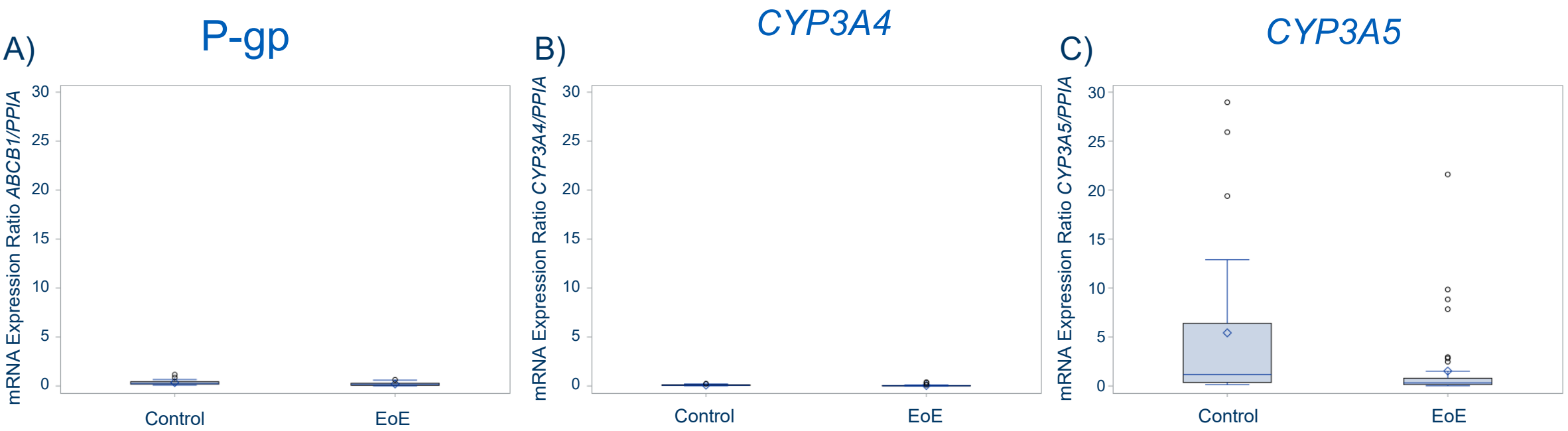

Lawless *J Am Diet Assoc* 1985;85:577

# The esophagus is a challenging environment for drug targeting

- Saliva coated
- Swallowing/peristalsis
- Poor uptake
- Rapid transit time
- Variable length



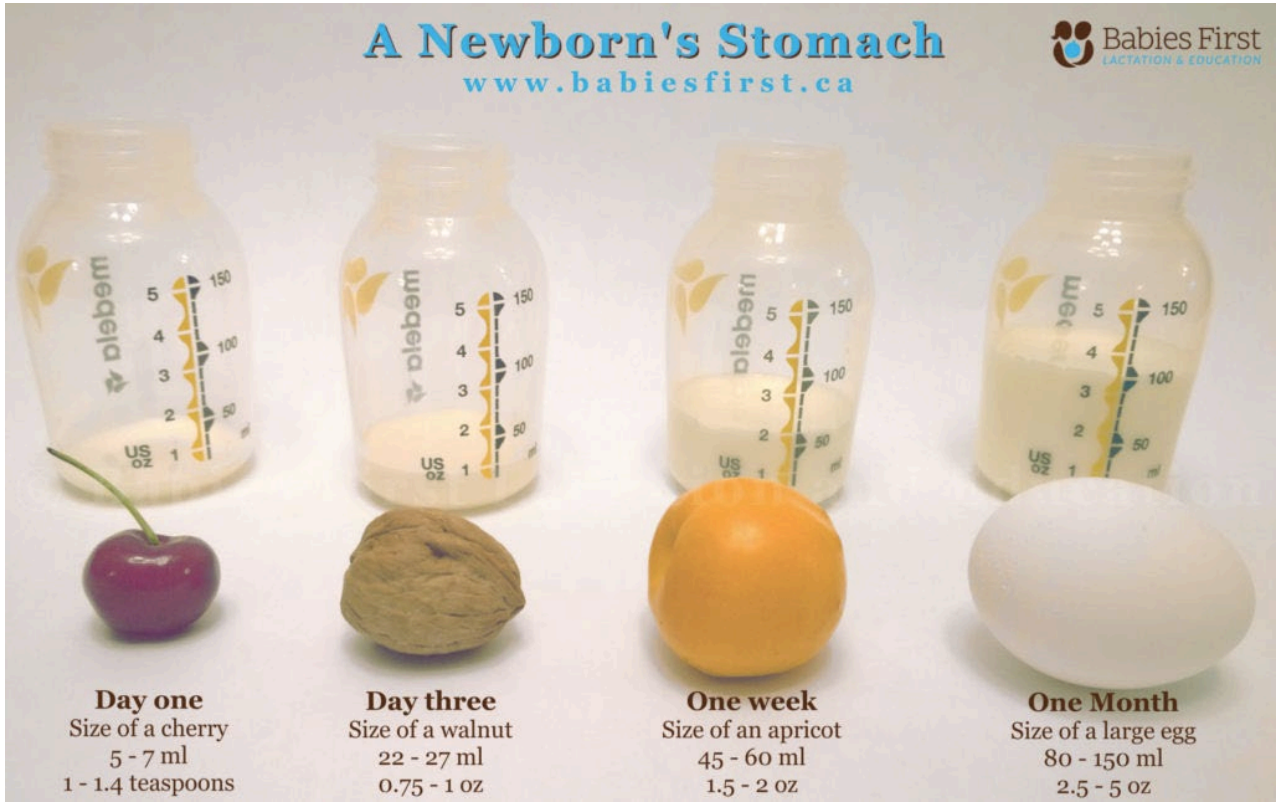
# Esophageal mucosa expresses *CYP3A5* mRNA (but not *CYP3A4*)




Manuscript under review

# Stomach

# Stomach size changes vastly during newborn period and early childhood

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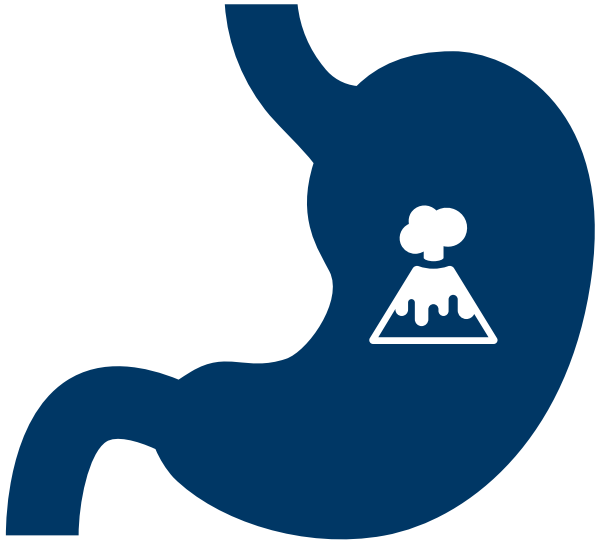
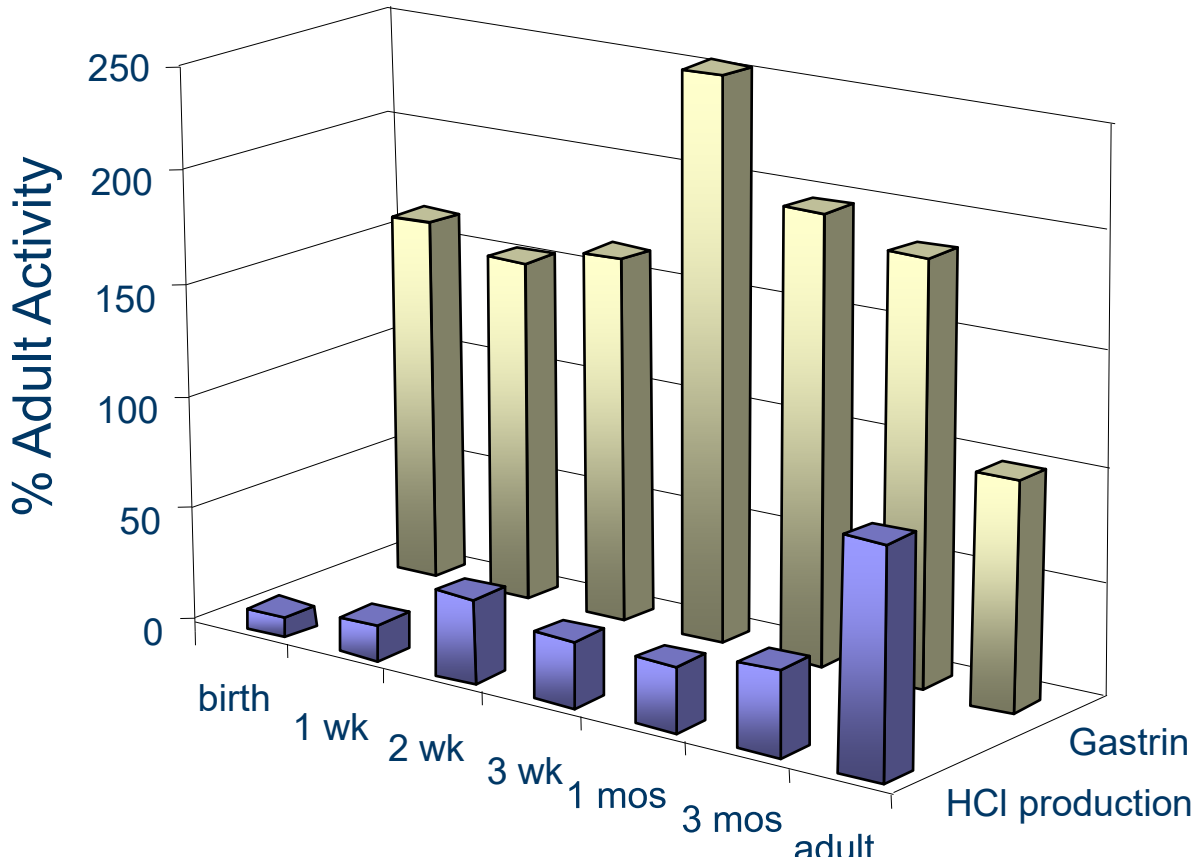
# Almost half of 4 months infants reflux once per day—up to 10% of feed volume




Martin, AJ et al. Pediatrics. 2002; 109
Nelson, SP et al Arch Pediatr Adolesc Med. 2000; 154
Singendonk, M et al. JPGN. 2019; 68
Chen, PL et al. J Hum Lact. 2017; 33
Okimoto, E et al. J Gastroenterol Hepatol. 2015; 30

# Gastric acid production is lower than adults in neonates and increases with growth





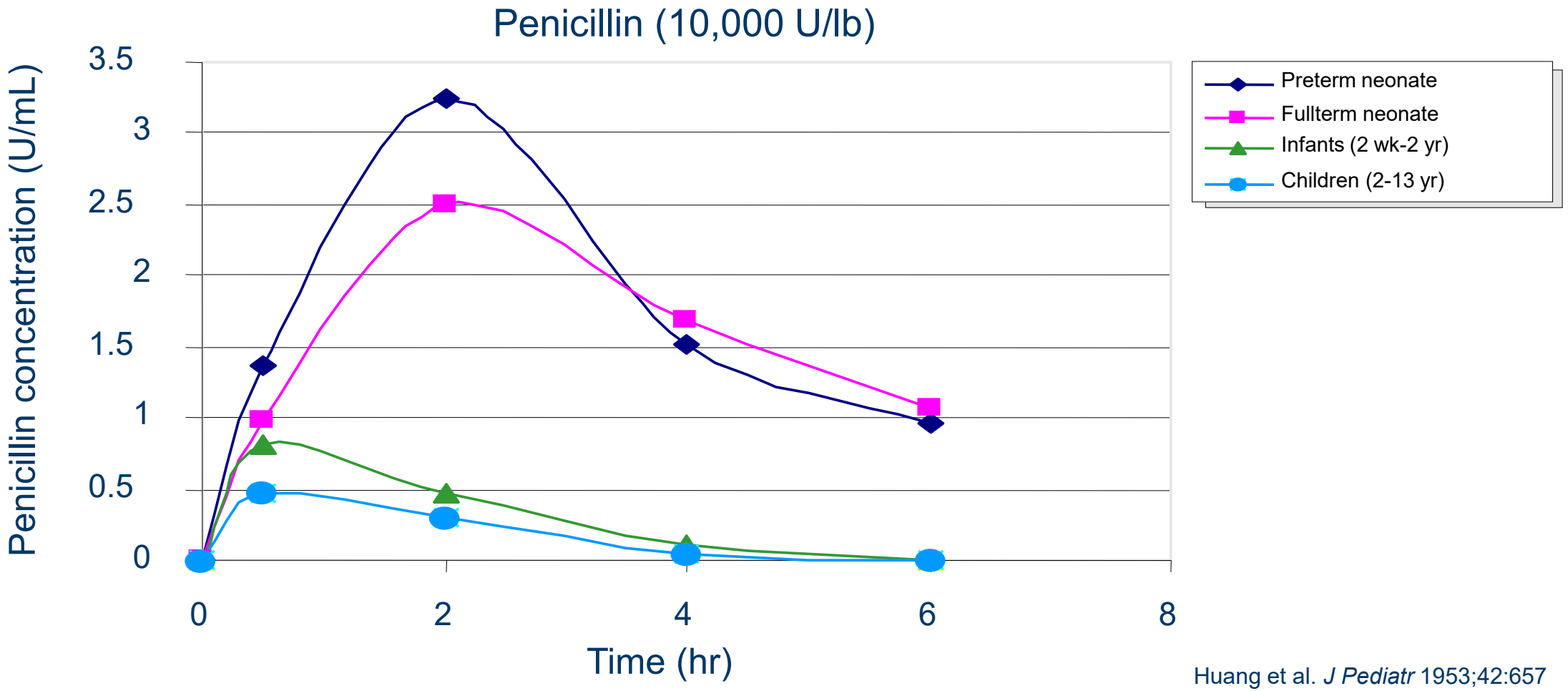
Yu et al. *AAPS J* 2014;16:1162

Agunod et al. *Amer J Digest Dis* 1969;14:400

Mozam et al. *Ann Surg* 1984;199:389

Rodgers et al. *J. Pediatr Surg* 1978;13:13

# Oral penicillin exposure is higher in neonates than older children due to higher neonate stomach pH




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

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# Diet content and frequency changes rapidly in the first year of life (and beyond)

## Newborn

- 8-12 meals

## 1 month

- 6-8 meals

## 6 months

- 4-6 meals
- Start table foods

## 7-8 months

- 3-5 meals

## Toddler

- 3 meals
- 3 snacks

## Adolescent

- ???

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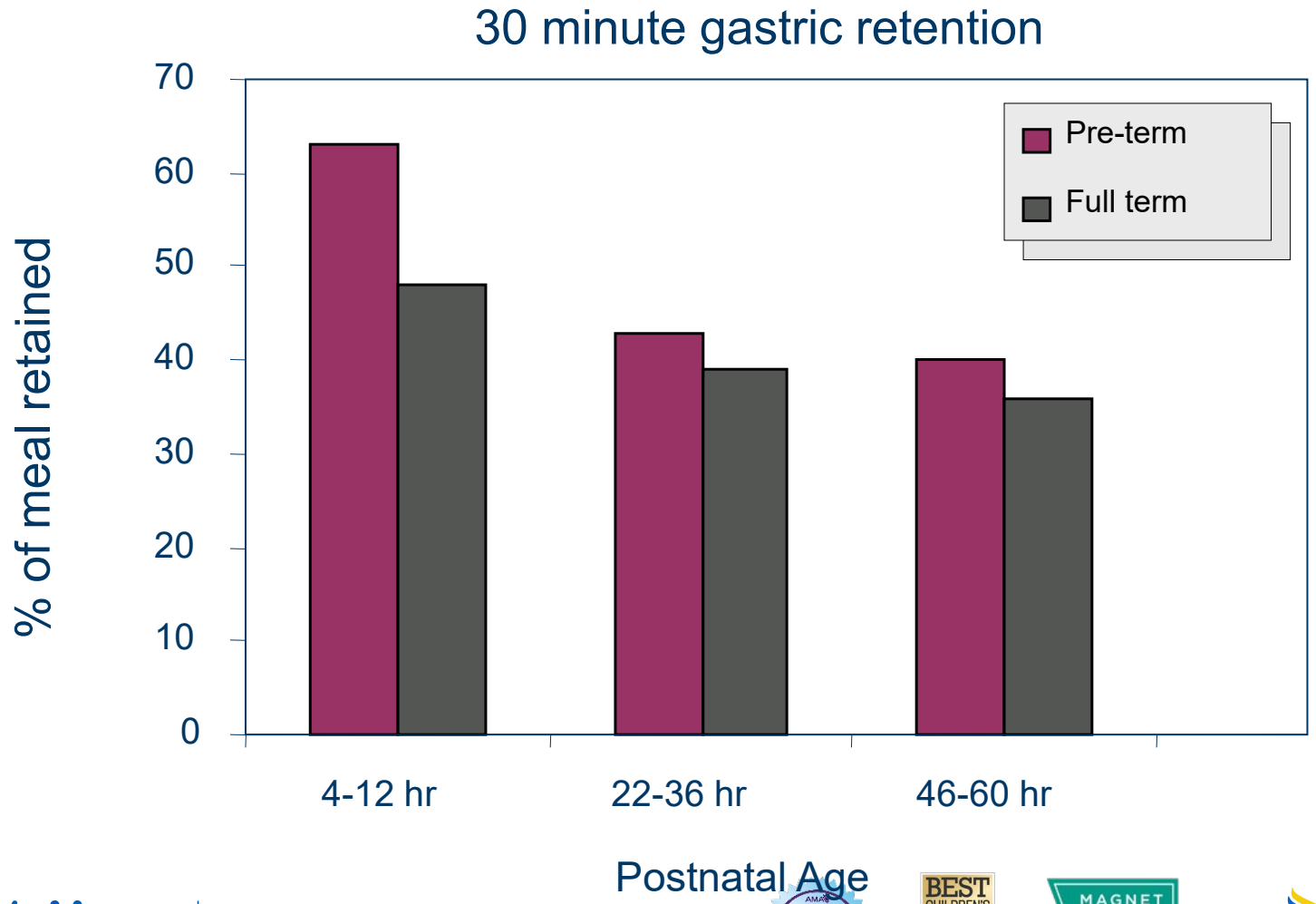
# Gastric emptying rates increase with age (minimally)




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

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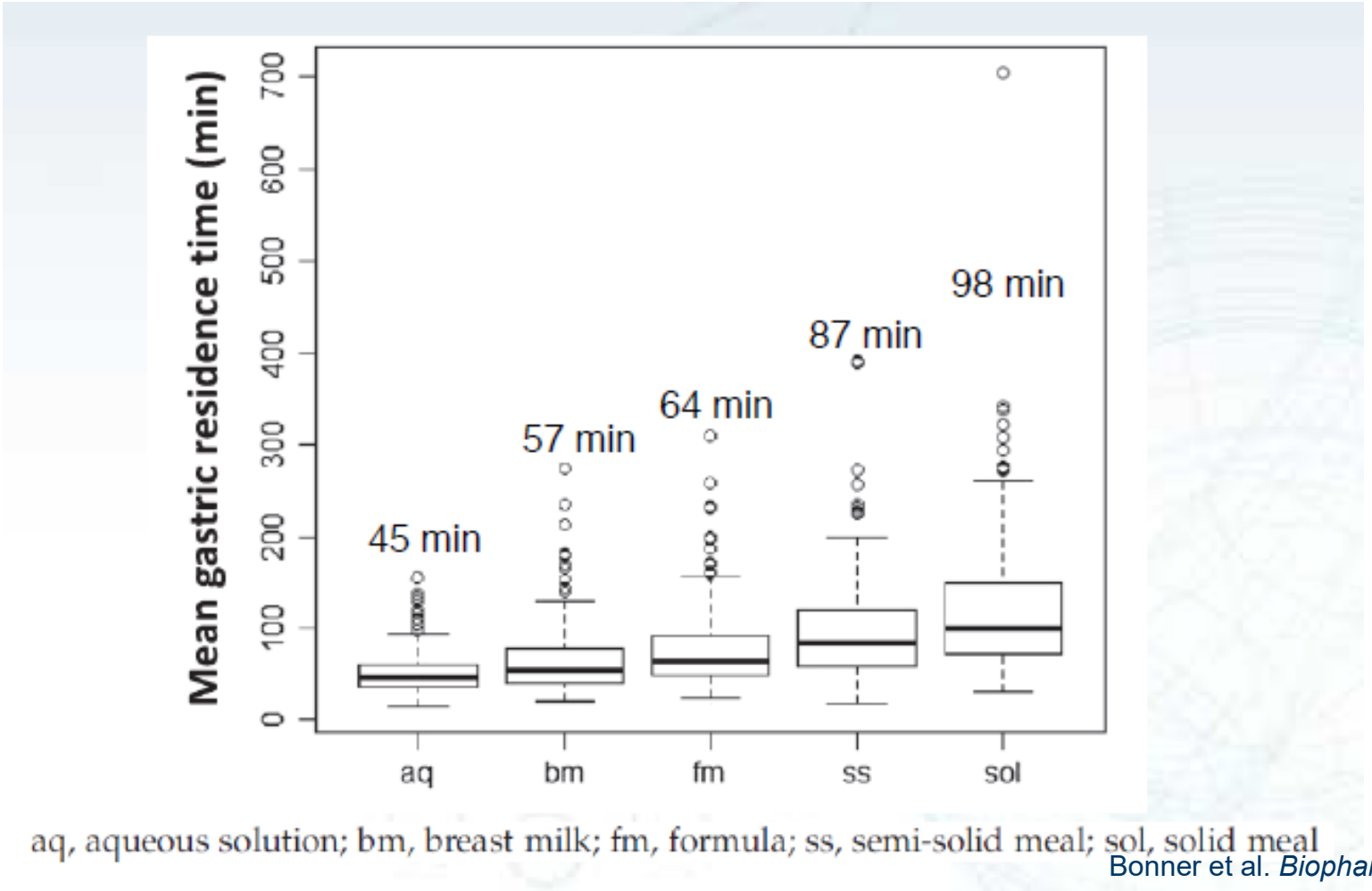
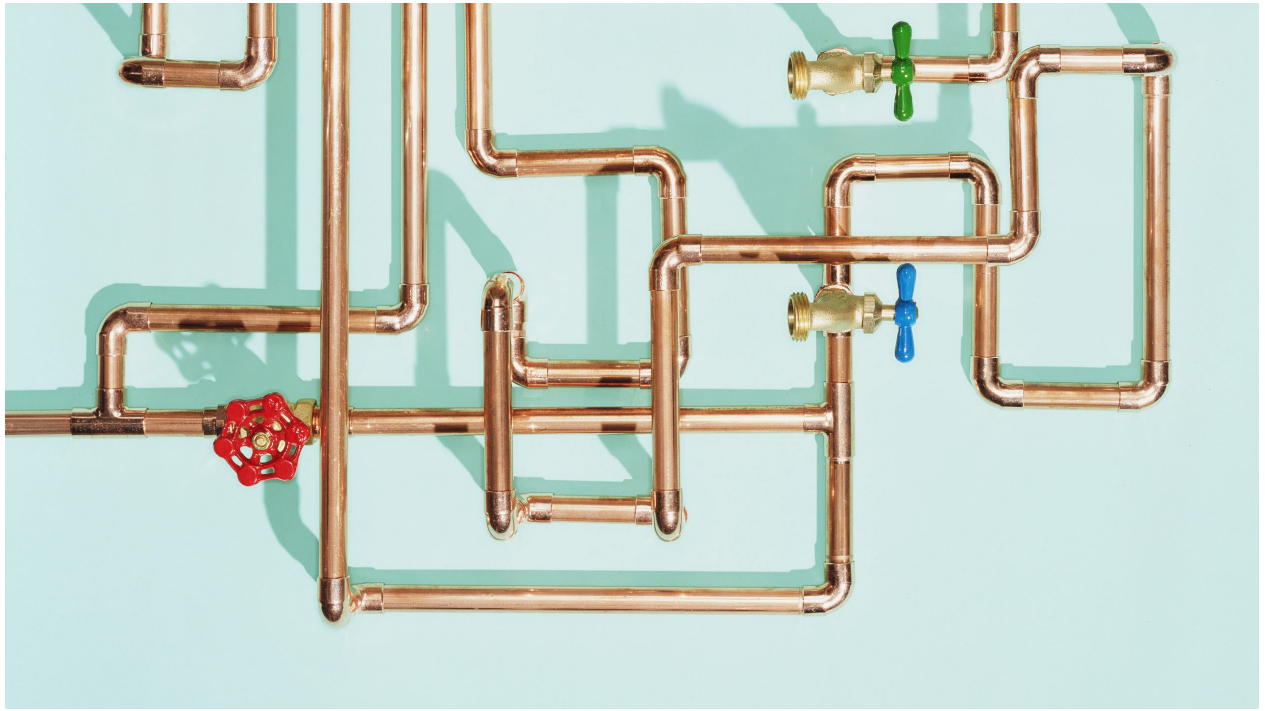
# Meal type influences gastric emptying



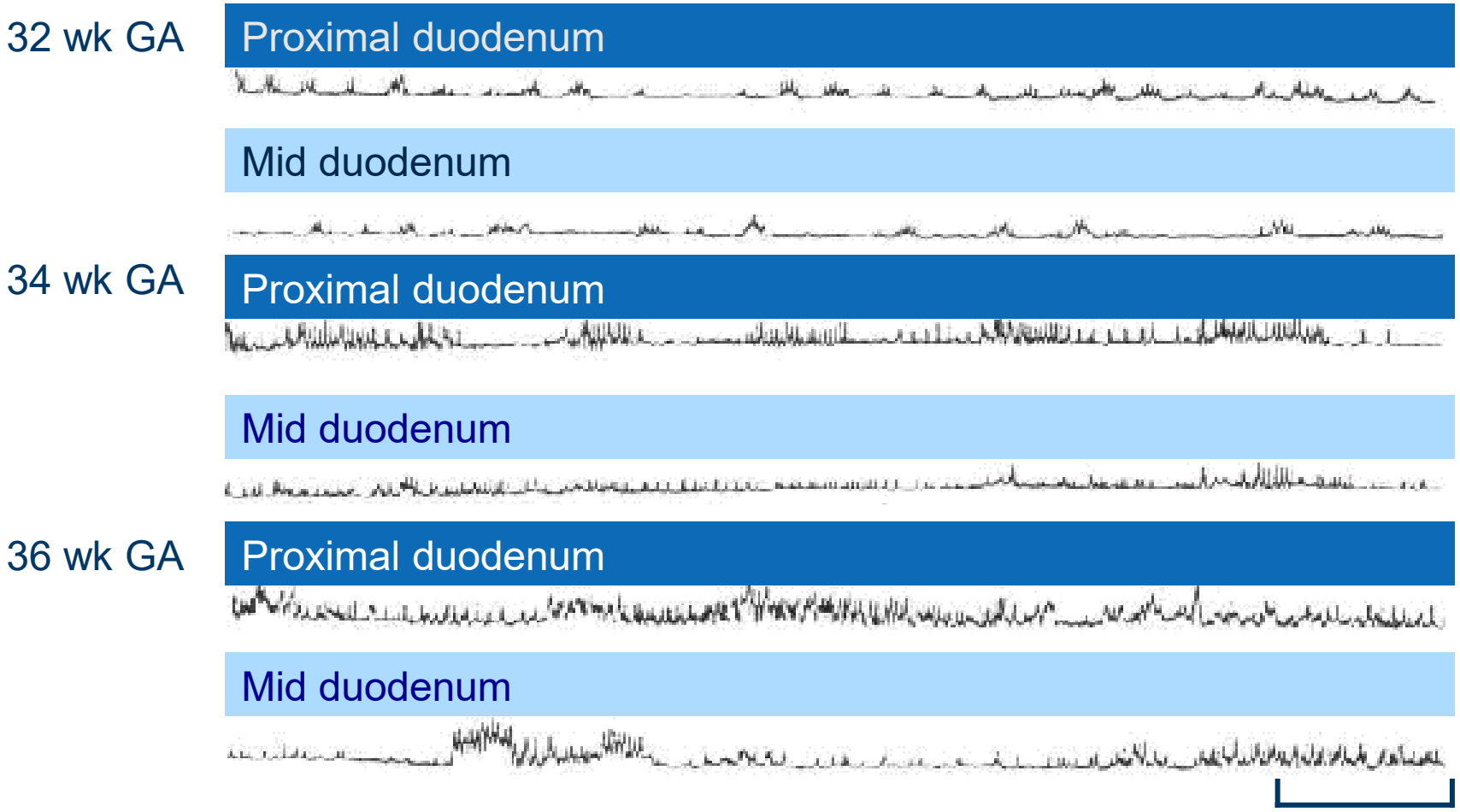

aq, aqueous solution; bm, breast milk; fm, formula; ss, semi-solid meal; sol, solid meal

Bonner et al. *Biopharm Drug Dispos* 2015;36:245

# Intestines

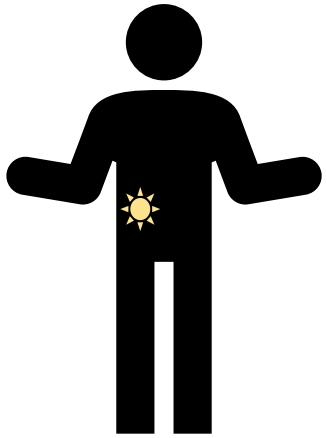


# Infant intestinal motility changes with gestational age




Berseth *J Pediatr* 1989;115:646

# Scintigraphic studies show slower smaller intestinal transport in preterm infants



**Oral → Cecal transit time**

**Adult 2.8 +/- 1.5 hours**

**Preterm* 3.1 (1.3–6.1) hours**

*Gestational age: 28.9 (26–33) weeks

Read *Gut* 1986

Bodé *JPGN* 2004

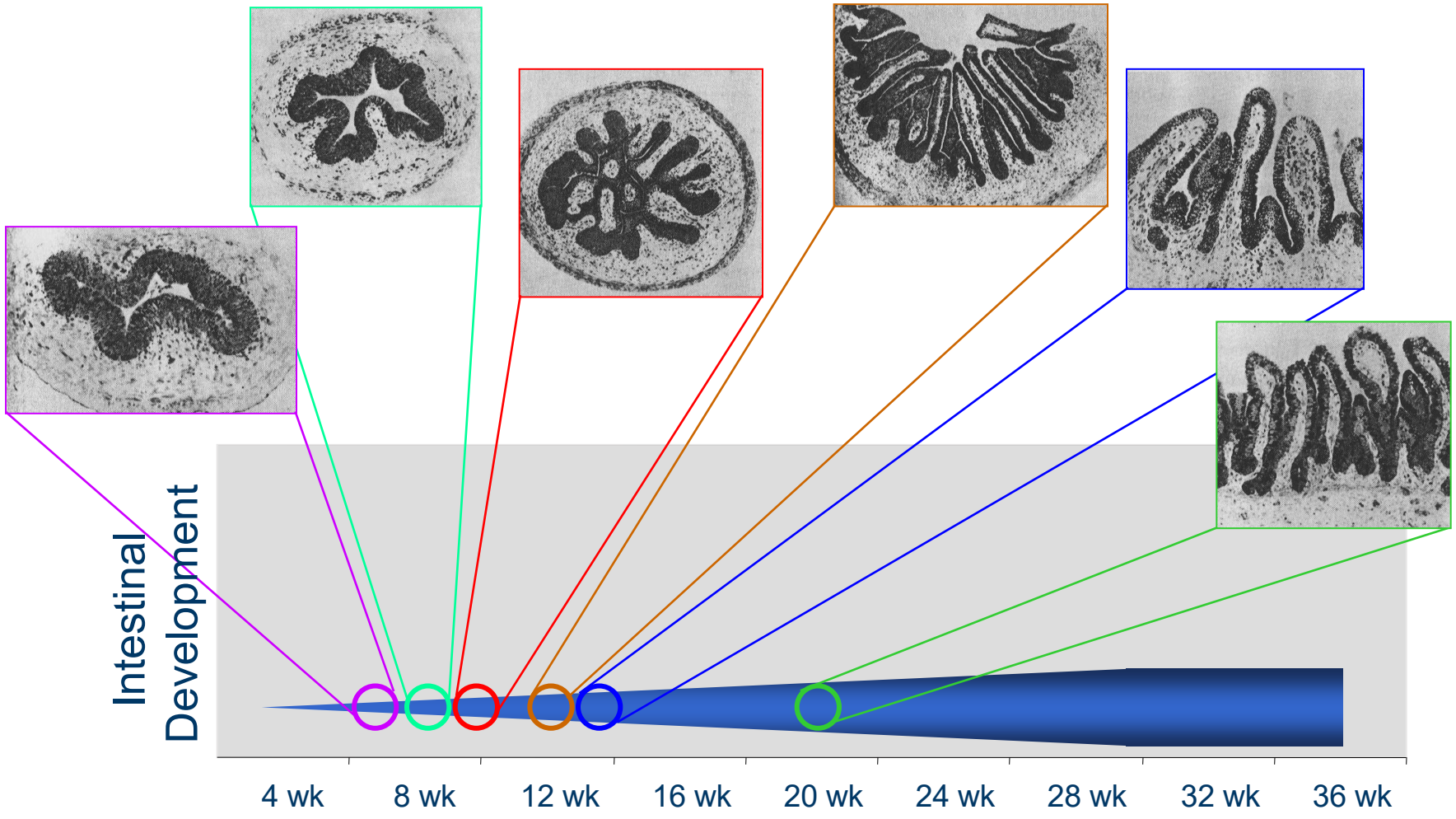
# Slower GI tract transit increases $T_{max}$ in infants for single dose cisapride

| | Postconceptional Age | | |
|---|---|---|---|
| | 28-36 wks. (n = 17) | 36-42 wks. (n = 13) | 42-54 wks. (n = 5) |
| $C_{max}$ (ng/ml) | 30.0 ± 17.5 | 23.3 ± 11.7 | 44.5 ± 19.5 |
| **$T_{max}$ (hr)*** | **5.0 ± 2.6** | **4.3 ± 3.3** | **2.2 ± 1.1** |
| $T_{1/2}$ (hr) | 11.6 ±3.0 | 11.5 ± 3.0 | 4.8 ± 3.0 |
| AUC (ng/ml*hr | 568 ± 257 | 362 ± 198 | 364 ± 249 |
| $VD_{ss}/F$ (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 |

***Adults 1.8 hr**

Kearns et al. *Clin Pharmacol Ther* 2001;69:31

# Absorptive surface area and efficacy of intestines changes with fetal development




Grand et al. *Gastroenterology* 1976;70:790
Siebert. *Am J Dis Child* 1980;134(6):593

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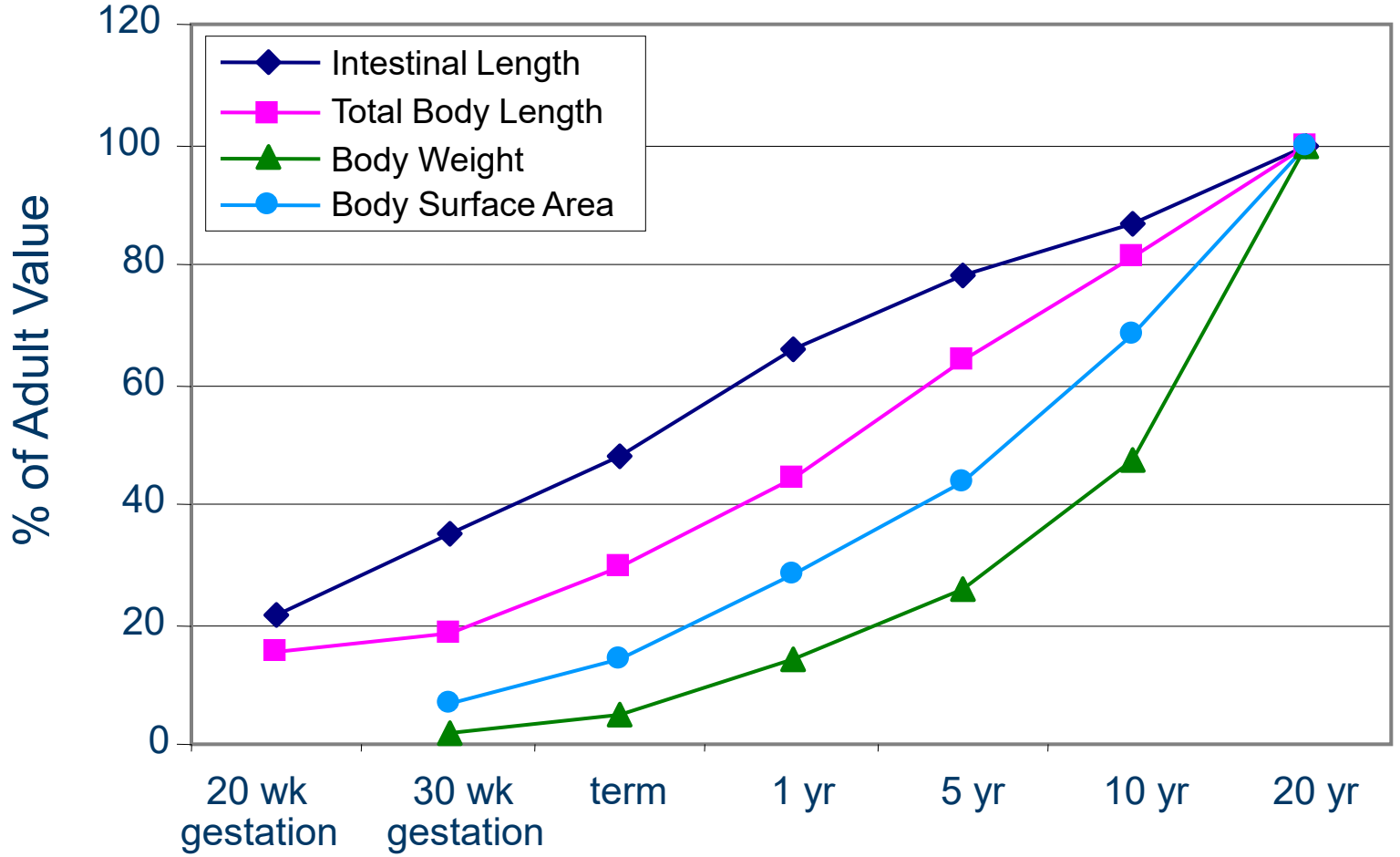
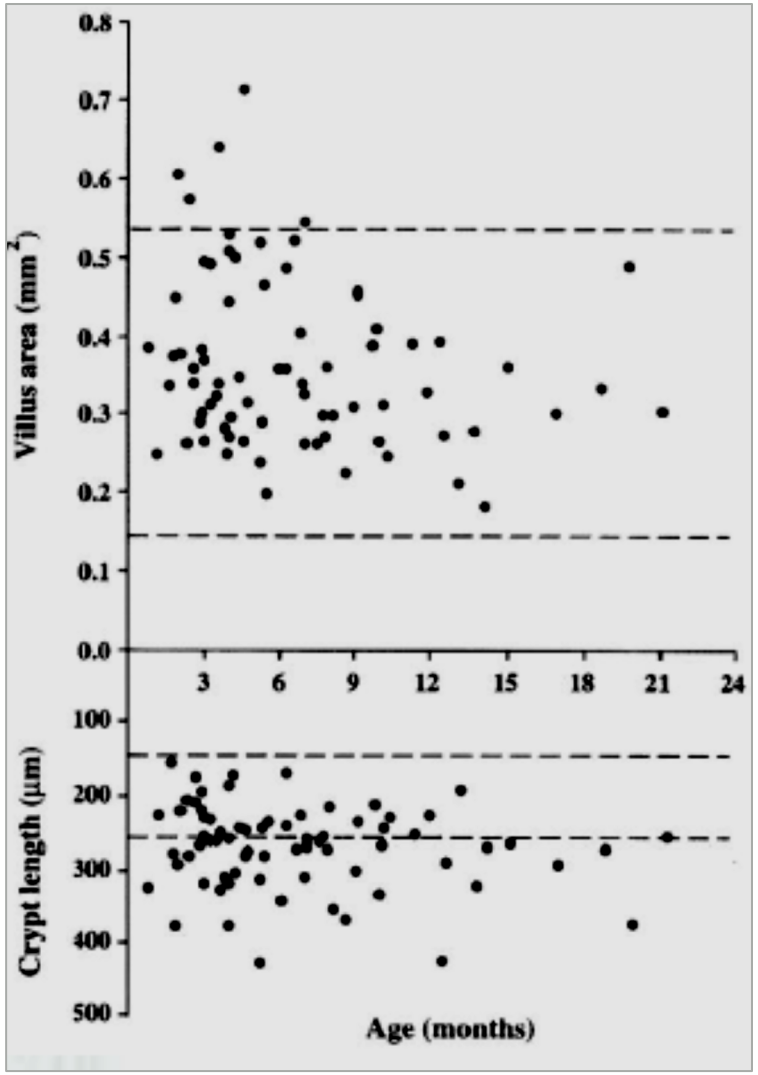
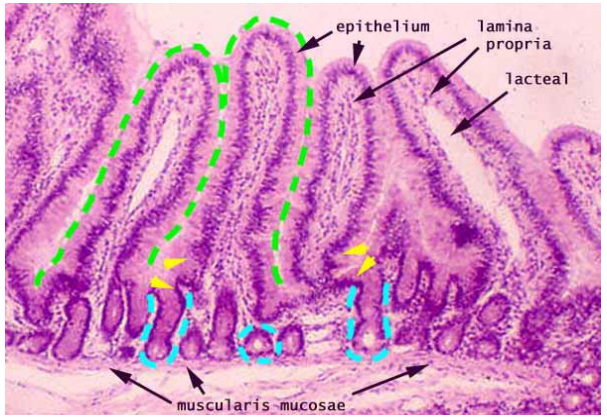
# Intestinal surface area increases quicker than other anthropomorphic measures




Weaver et al. *Gut* 1991;32:1321

# Intestinal villi change in size and characteristics with age



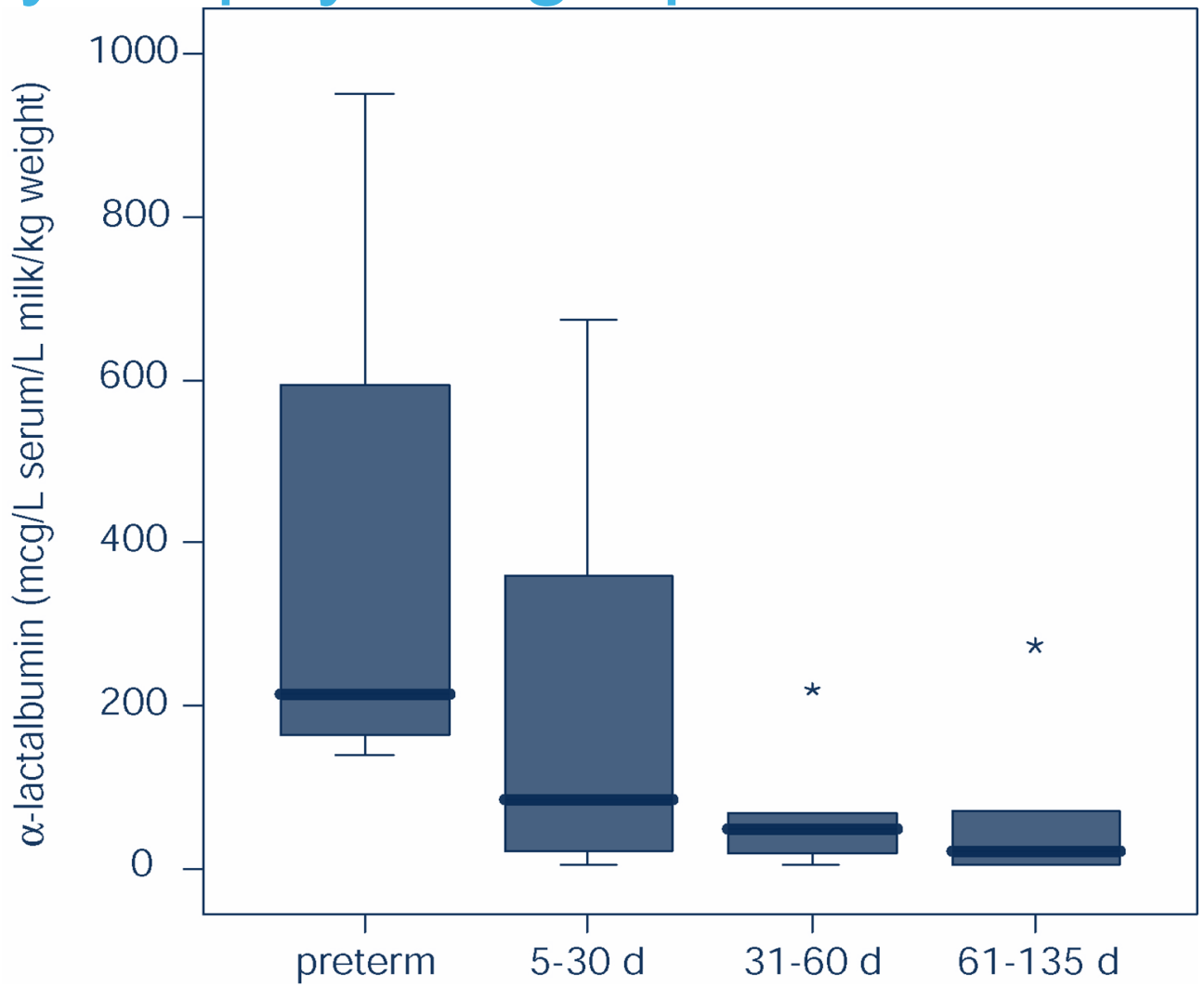







Vyhlidal et al. Clin Transl Sci 2021;14:729
Cummins et al. *JPGN* 2008;47:153
Thompson et al. *JPGN* 1998;26:506
Stenling et al. *Ultrastruct Pathol* 1984;6:131
Walker-Smith *J. Arch Dis Child* 1972;47:80

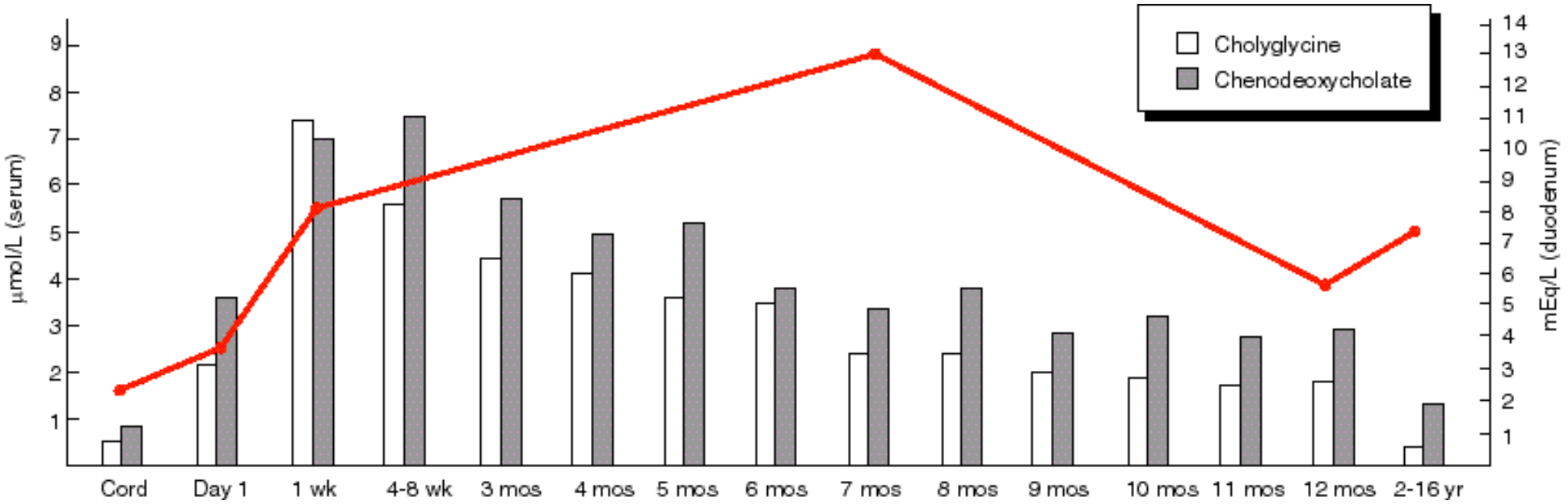
# Infant macromolecular absorption is high in infancy for physiologic protection




Jakobsson et al. *Gut* 1986;27:1029

# Intestinal fat absorption is immature and limits absorption of fat soluble vitamins

## Bile Acids





Poley et al. *J Lab Clin Med* 1964;63:838
Suchy et al. *Gastroenterology* 1981;80:1037

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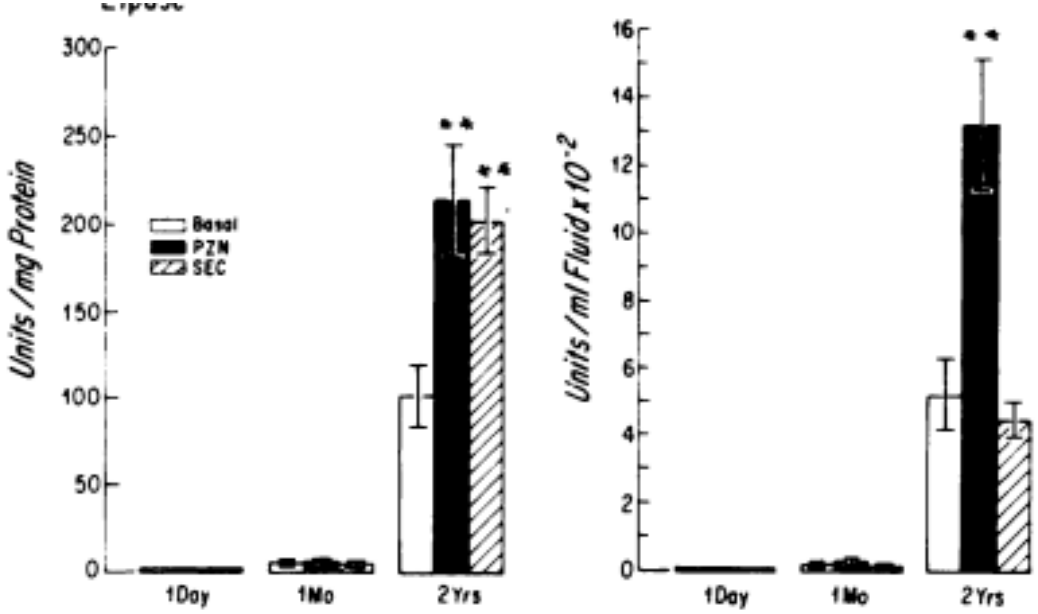
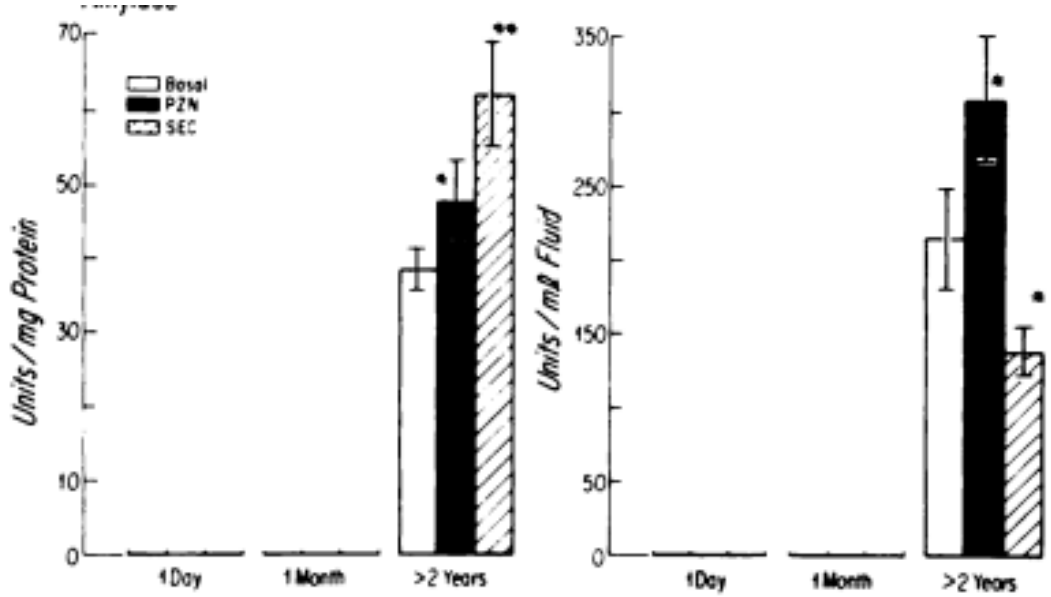
# Infant pancreatic enzyme production is a small fraction of “adult” levels

Lipase



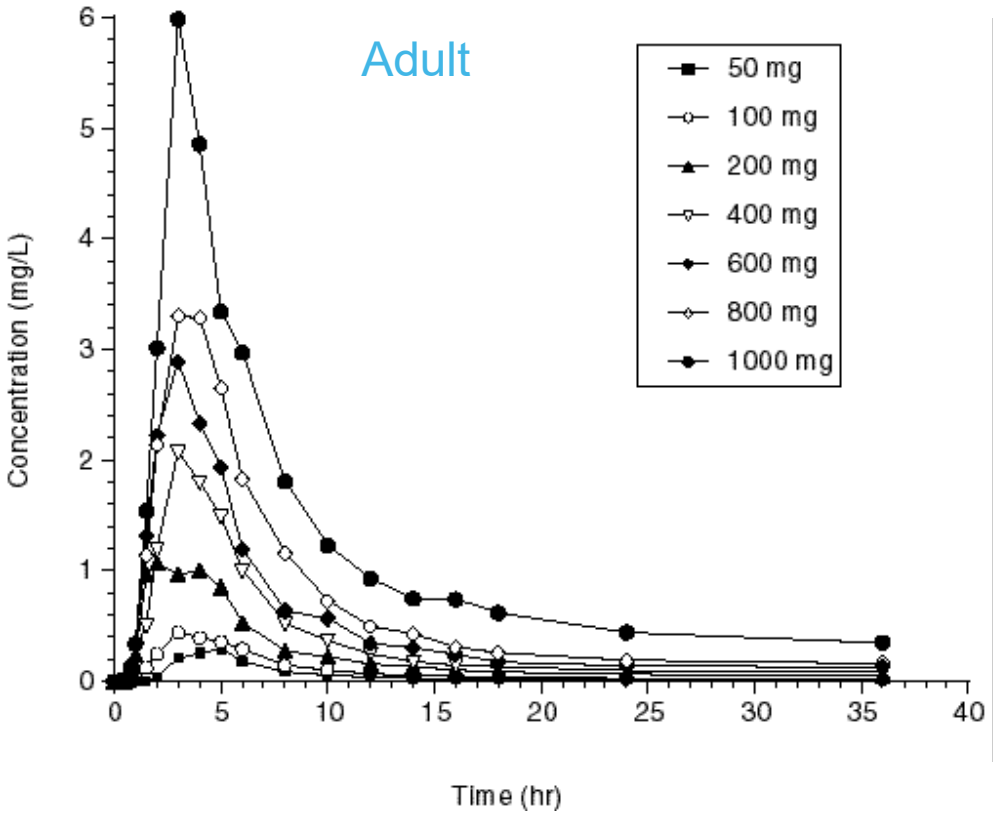

Amylase

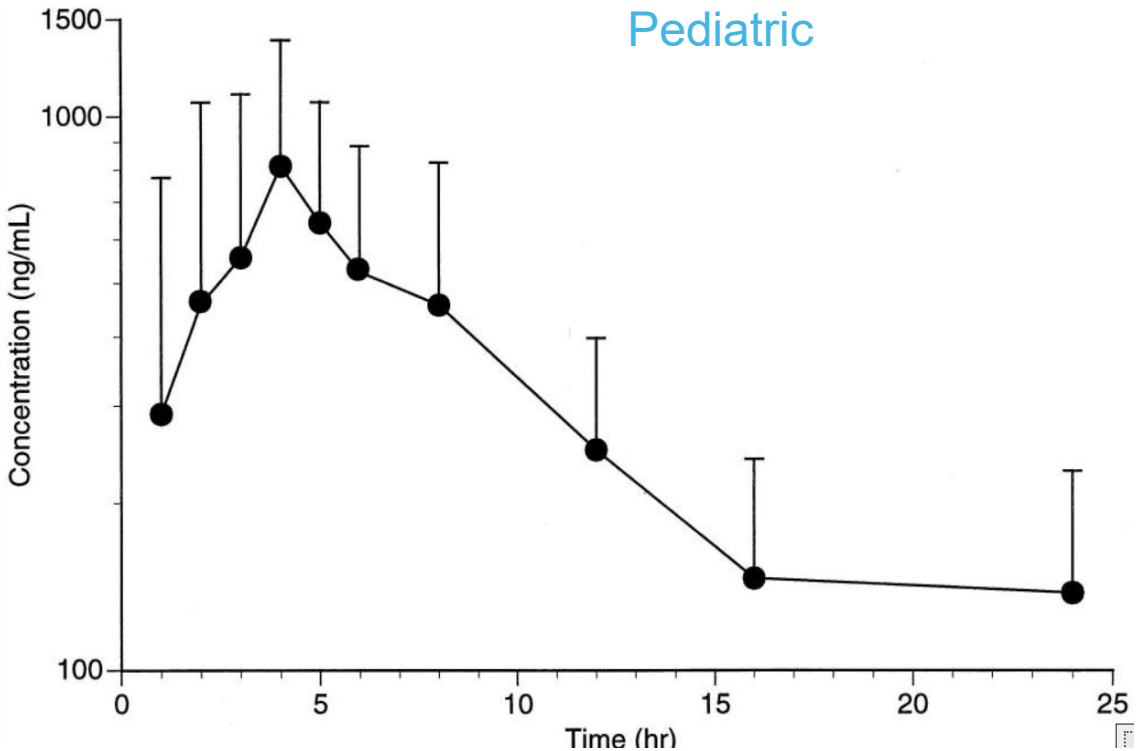



Lebenthal E, Lee PC. Pediatrics 1980

# Lipophilic drugs may demonstrate capacity limited absorption in pediatric patients

## Pleconaril




Abdel-Rahman et al. *J Clin Pharmacol* 1999;39:613
Kearns et al. *Clin Pharmacol Ther* 1999;65:140

# Intestinal mucosa contributes to metabolism before drugs reach systemic circulation

- Digestive Enzymes
- Nutrient Transporters
- DMEs and Transporters

http://www.gastrohep.org

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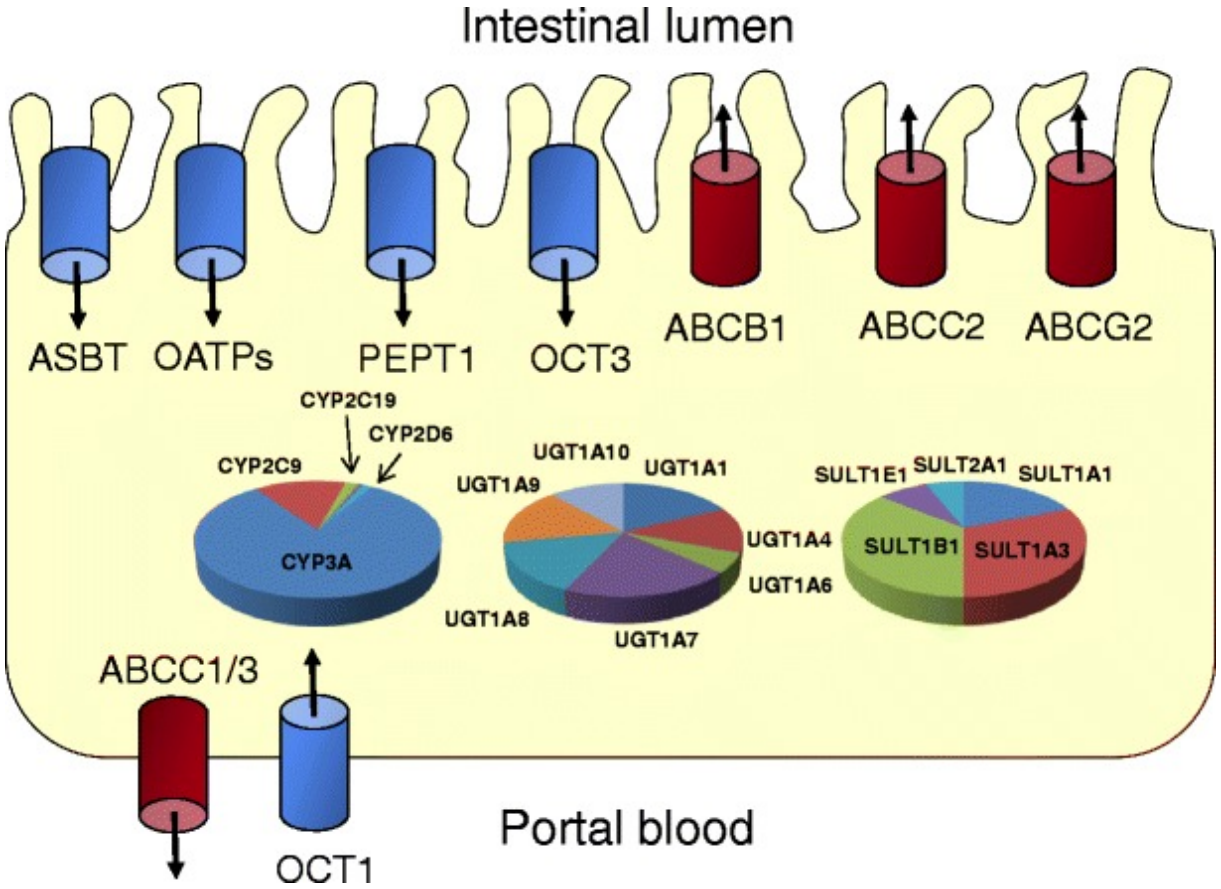
# The intestinal epithelium contains different drug metabolizing enzymes and transporters




Oswald et al. *AAPS J* 2013;15:1128
Giacomini *et al*. 2010 Paine *et al*. 2006 Riches *et al*. 2009 and Harbourt *et al*. 2012

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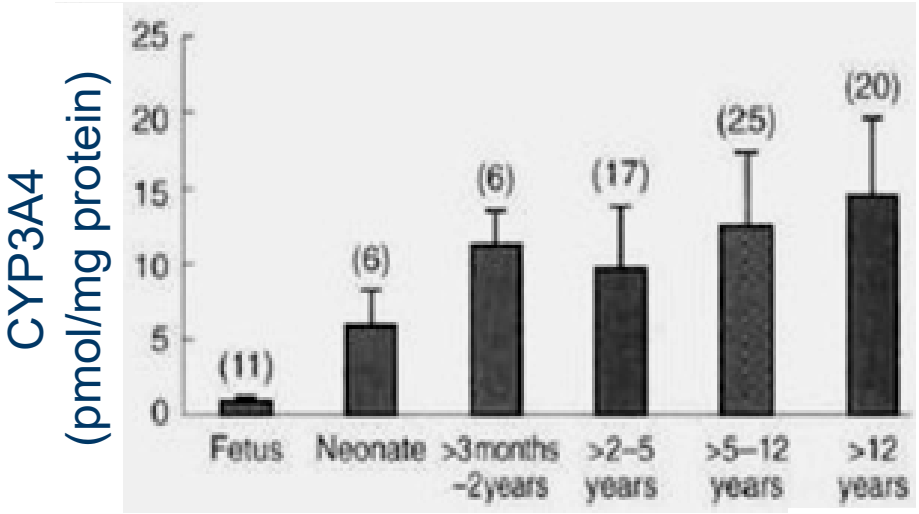
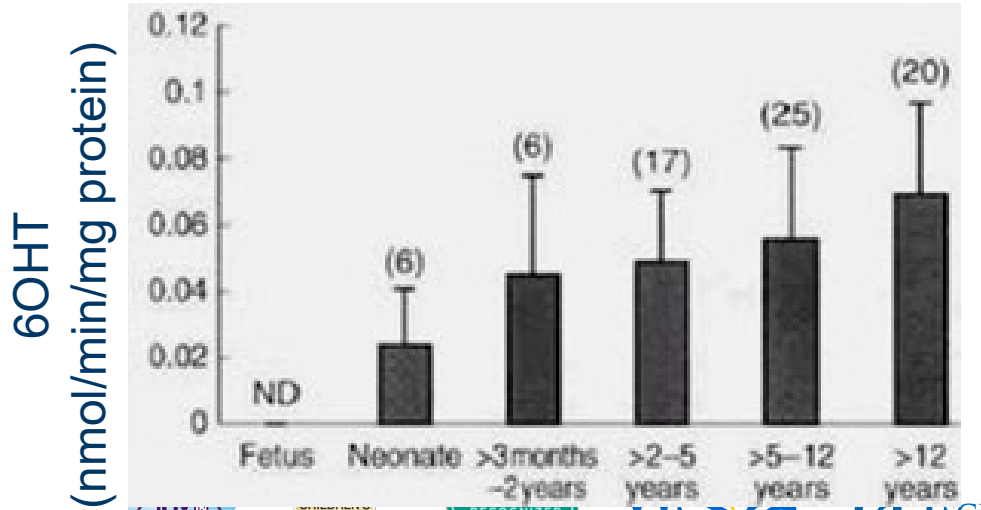
# Intestinal expression of DMEs increases with age




Johnson et al. *Br J Clin Pharmacol* 2001;51:451

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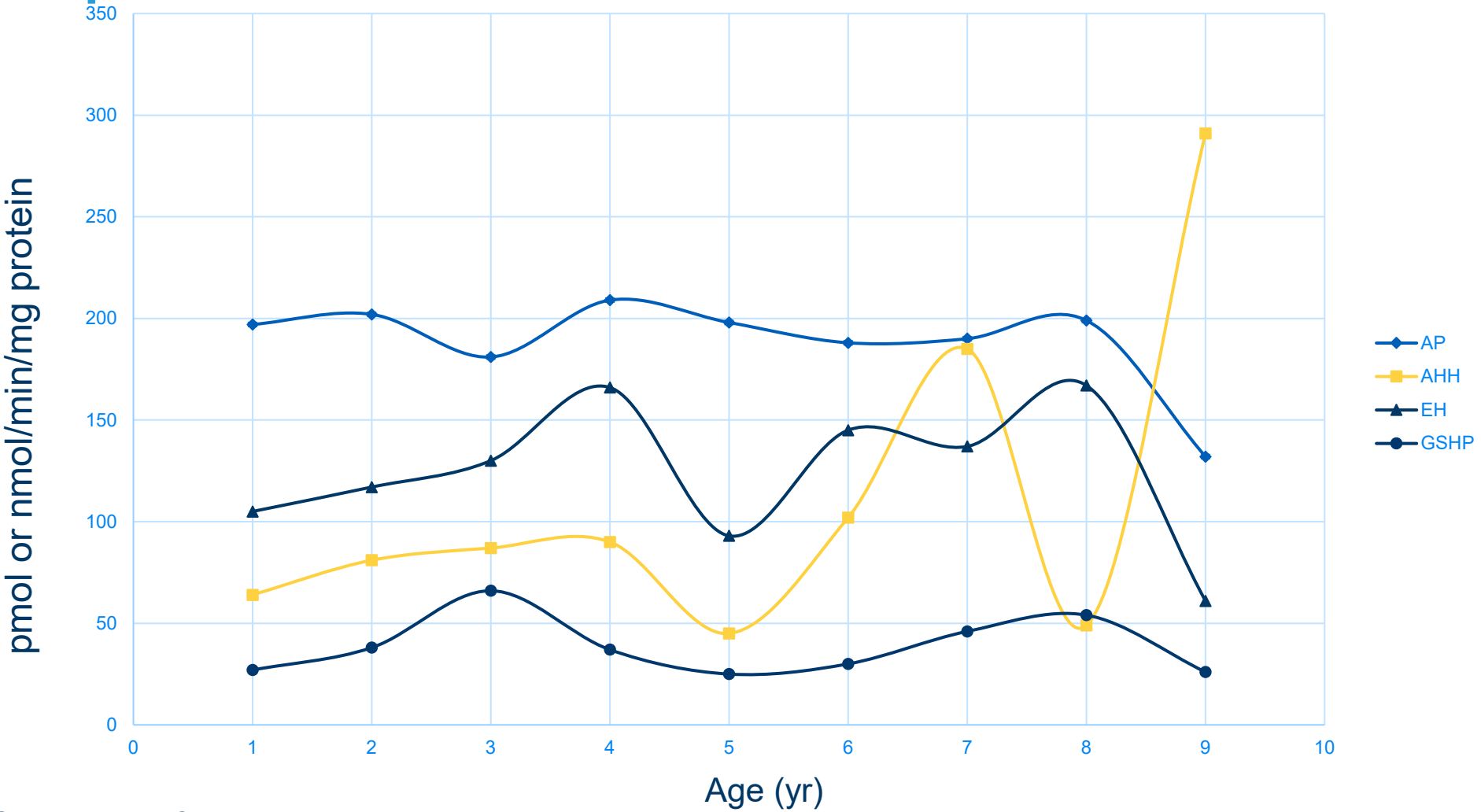
# Enzyme activity in pediatric intestinal biopsies




Stahlberg et al. *Gut* 1988;29:1058

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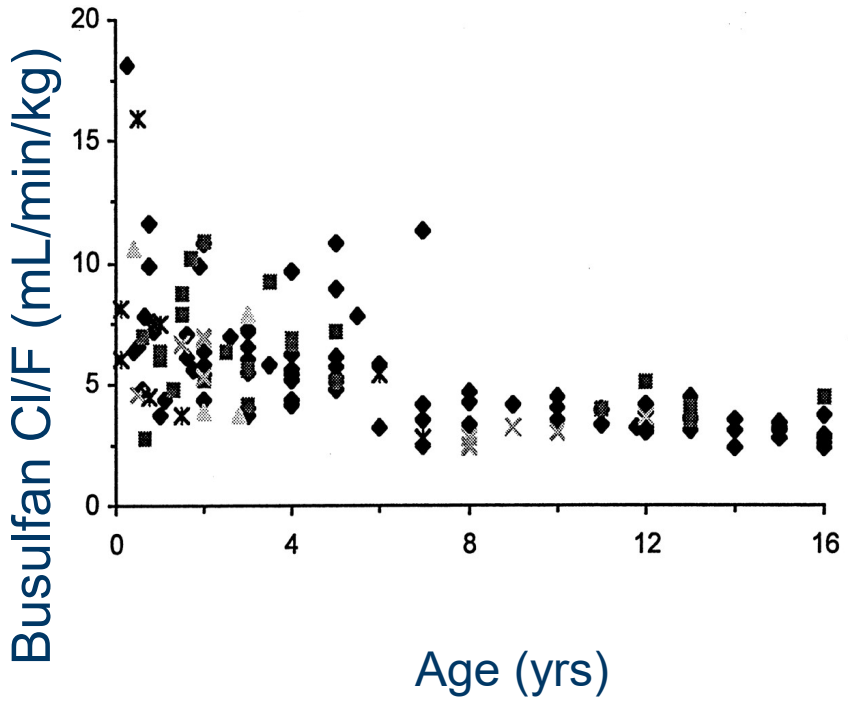
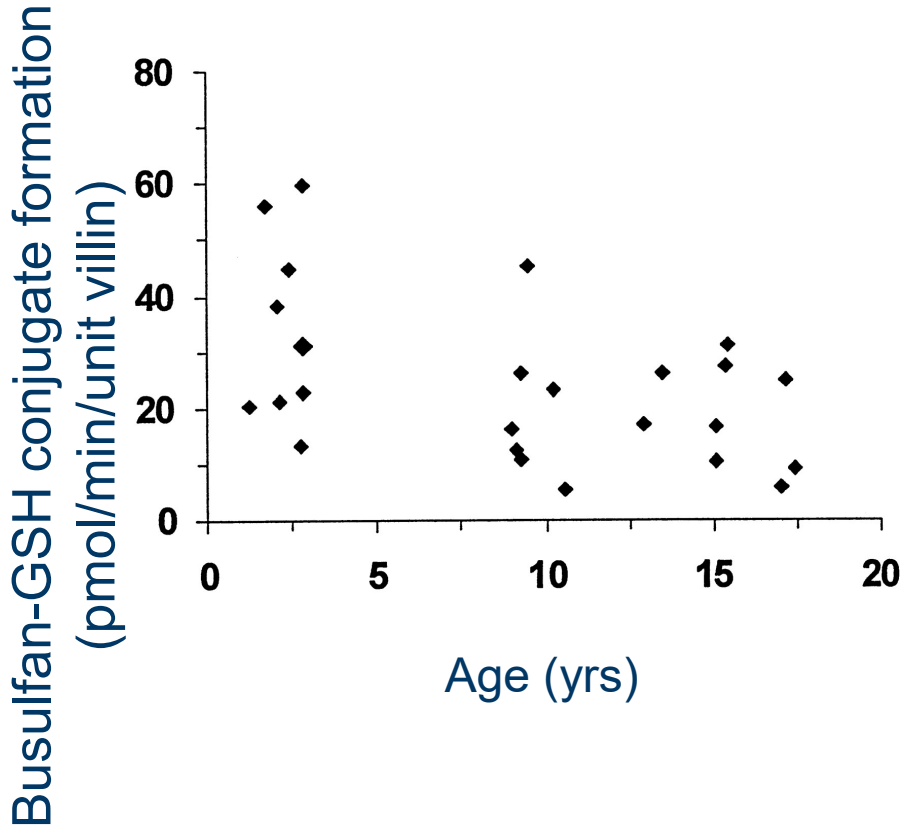
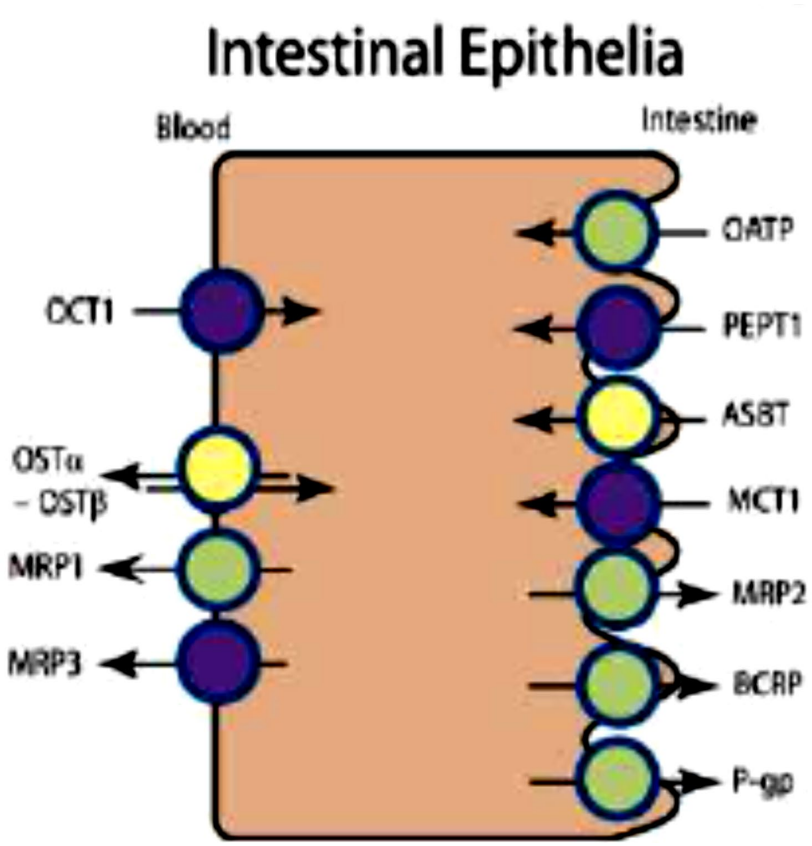
# Glut-S-Transferase activity wanes with age



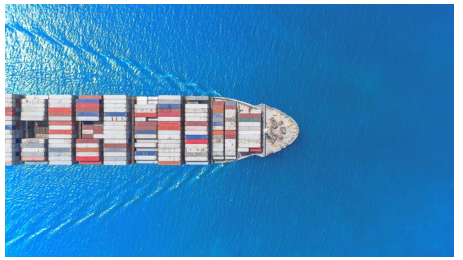



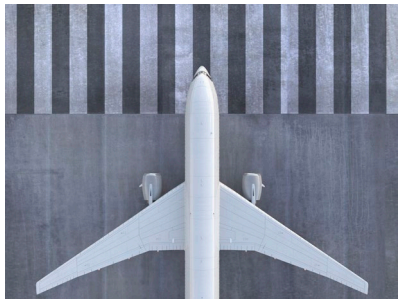

Gibbs et al. *Drug Metab Dispos* 1999;12:1466

# Intestinal transporters show no single developmental pattern

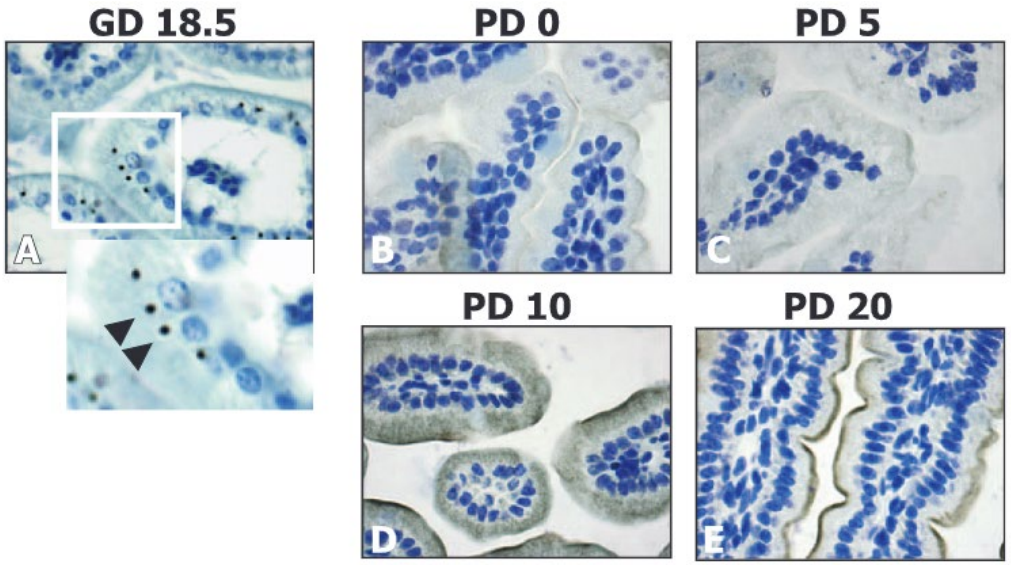


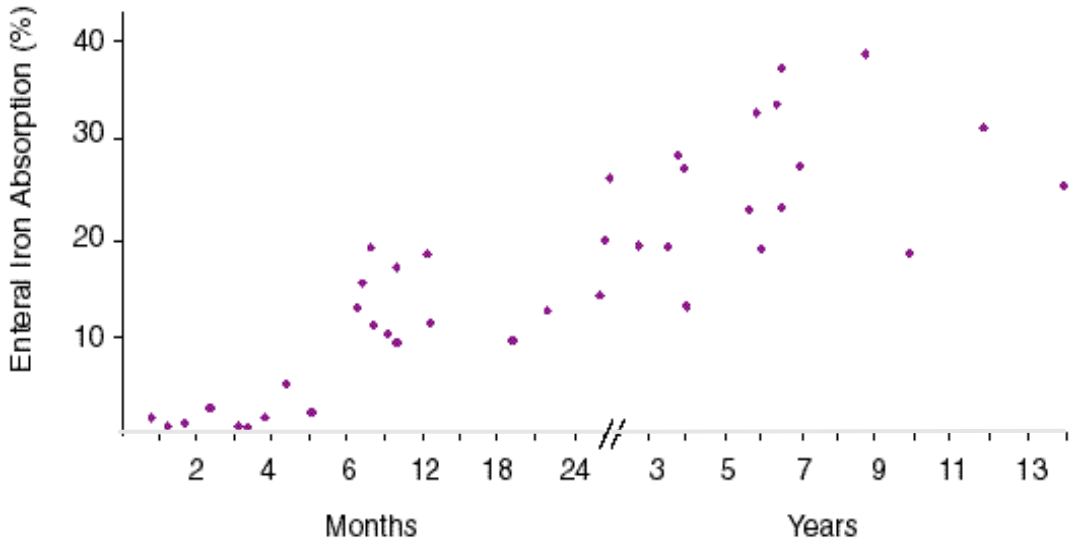

Brouwer et al. *Clin Pharmacol Ther* 2015;98:266





# Efficacy of iron transport via DMT1 increases with age




Gladtke & Heimann. Basic and Therapeutic Aspects of Perinatal Pharmacology 1975
Lopez et al. *Biochem and Cell bio* 2006

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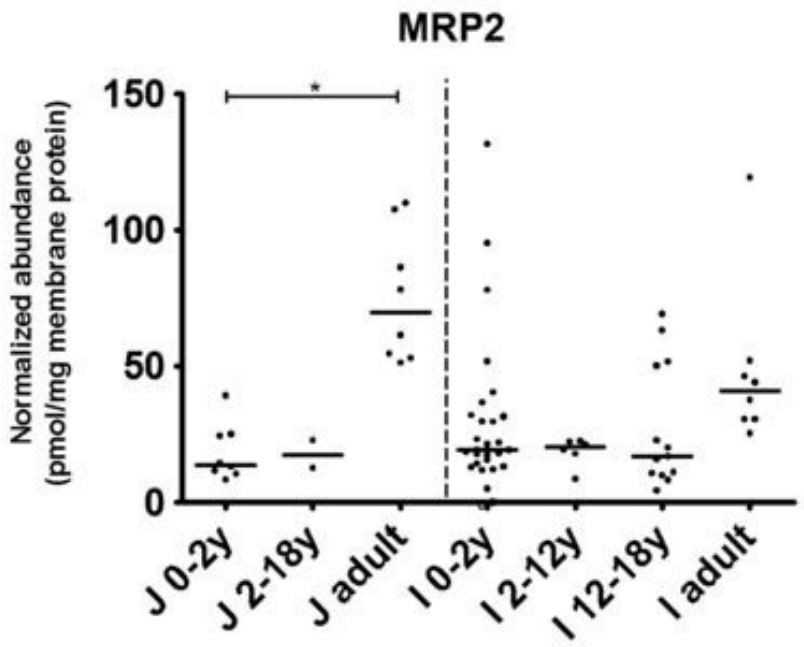
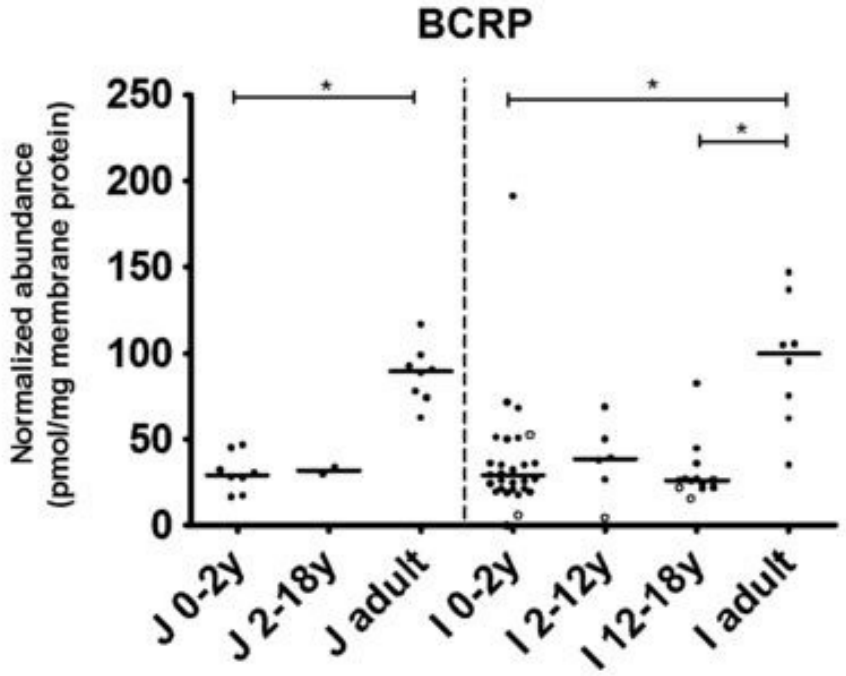
# MRP2 and BCRP show increased protein expression with age




Kiss et al *Drug Metab and Dispo* 2021

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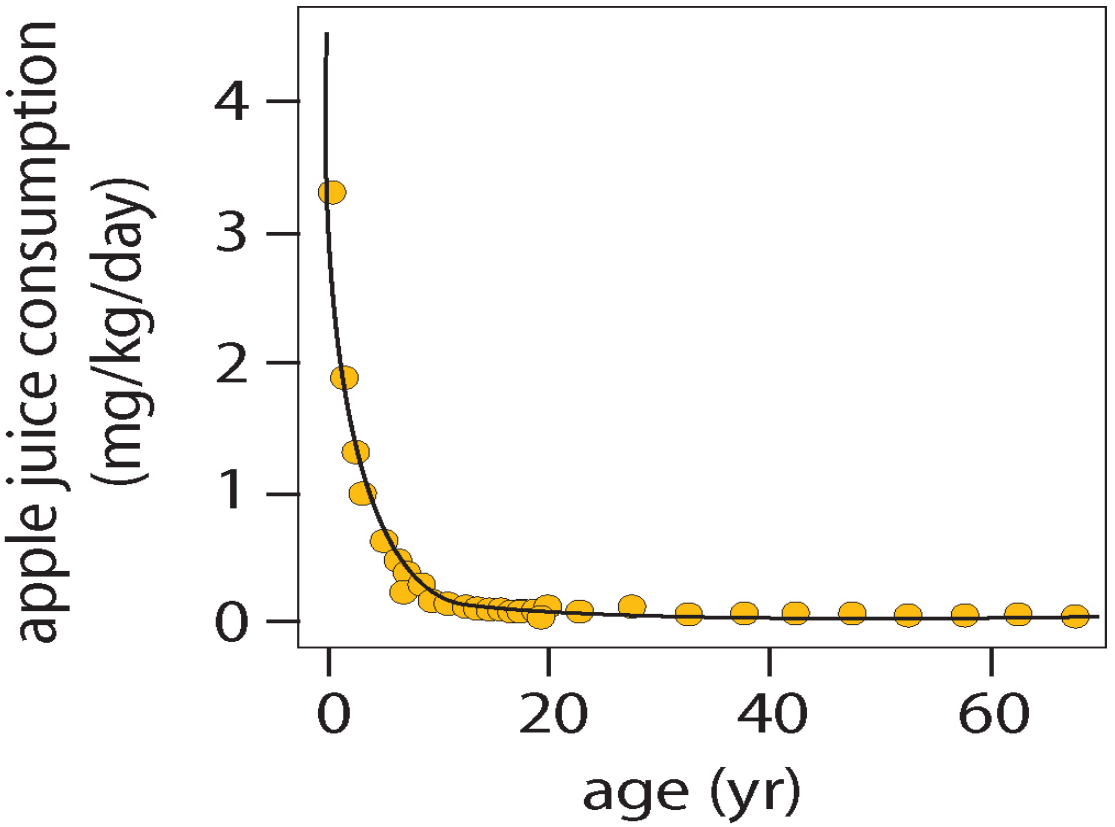
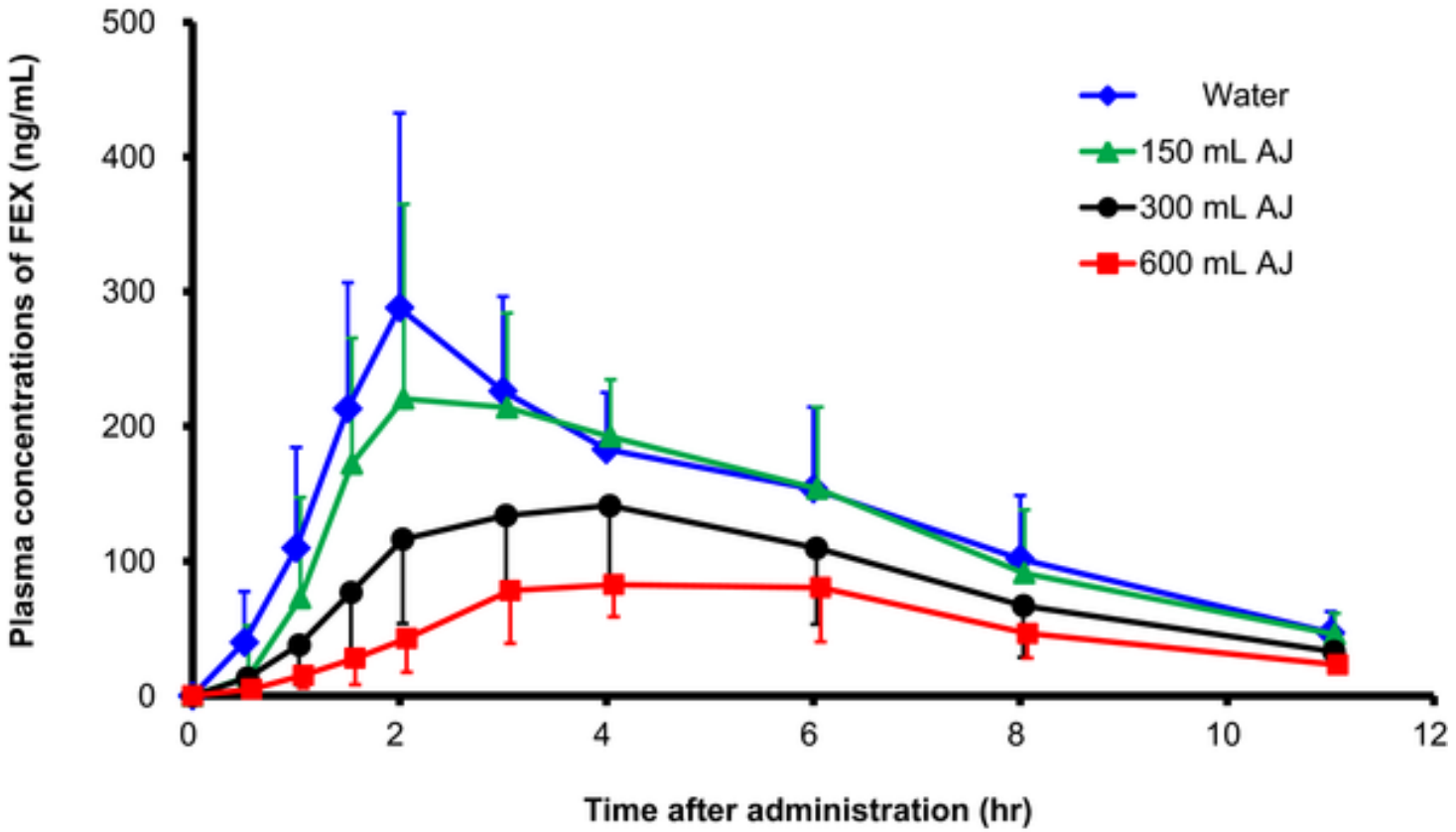
# Age-appropriate diets may contain components that alter exposure




Murdoch et al. *Risk Anal* 1992;12:569

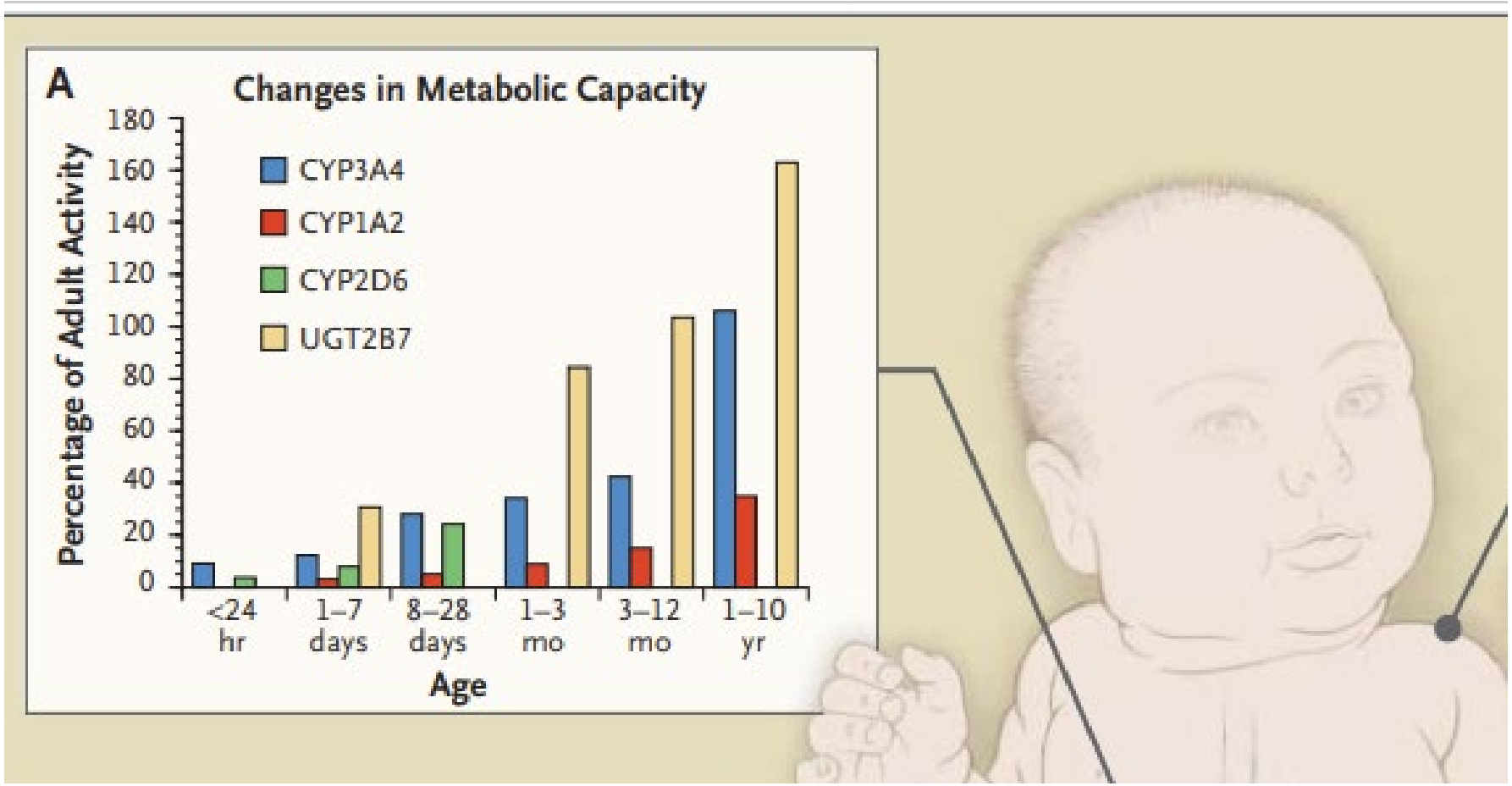
# Apple juice competes with fexofenadine for OATP transport




Luo et al. *Clin Transl Sci* 2016;9(4):201

# Liver

# Hepatic DMEs increase with age generally, but at different rates to adult levels




*Wood et al NEJM 2003*

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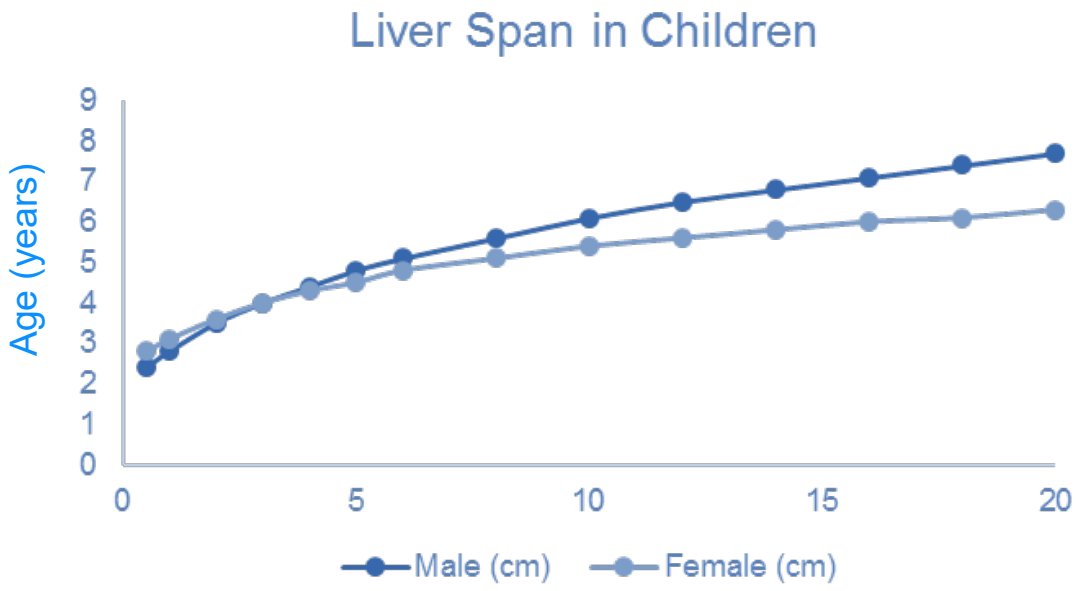
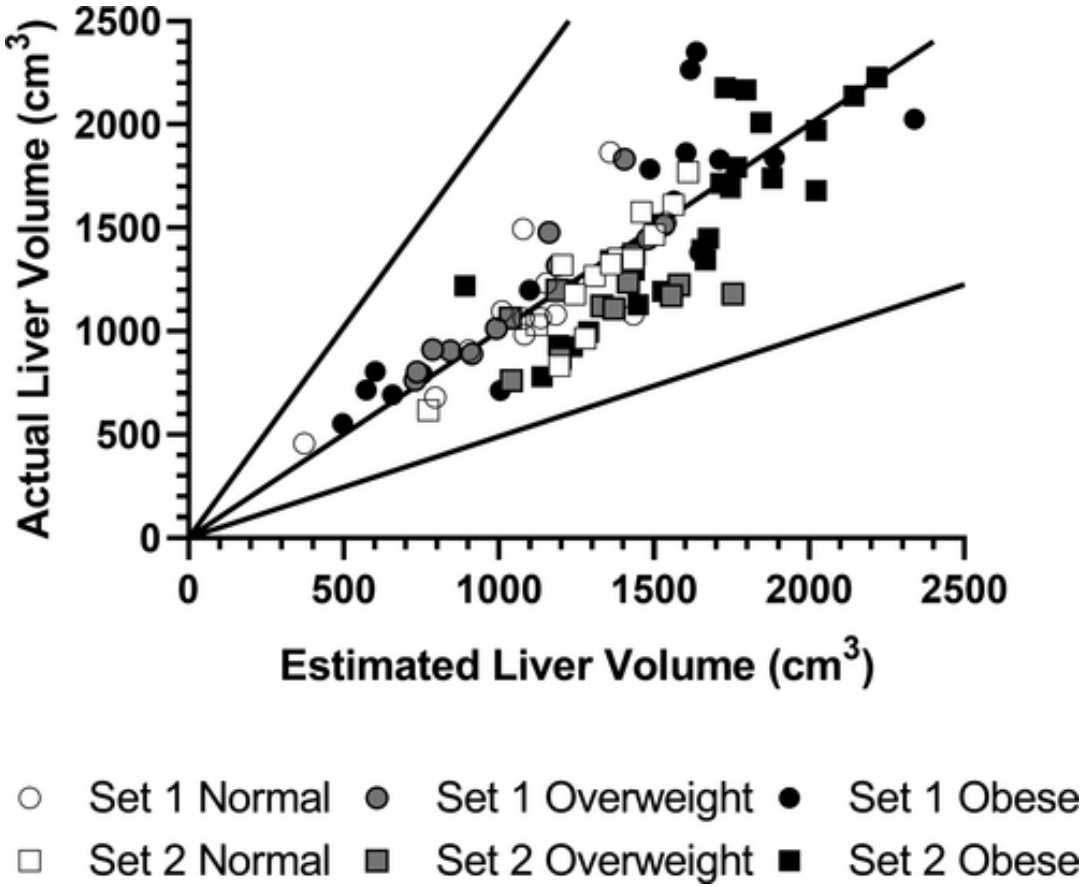
# Liver size increases with age and varies with sex and body habitus




Hosey-Cojocari et al. *Clin Transl Sci* 2021;14(5):2008
Dhirngra et al. *Indian Pediatr* 2010;47:487

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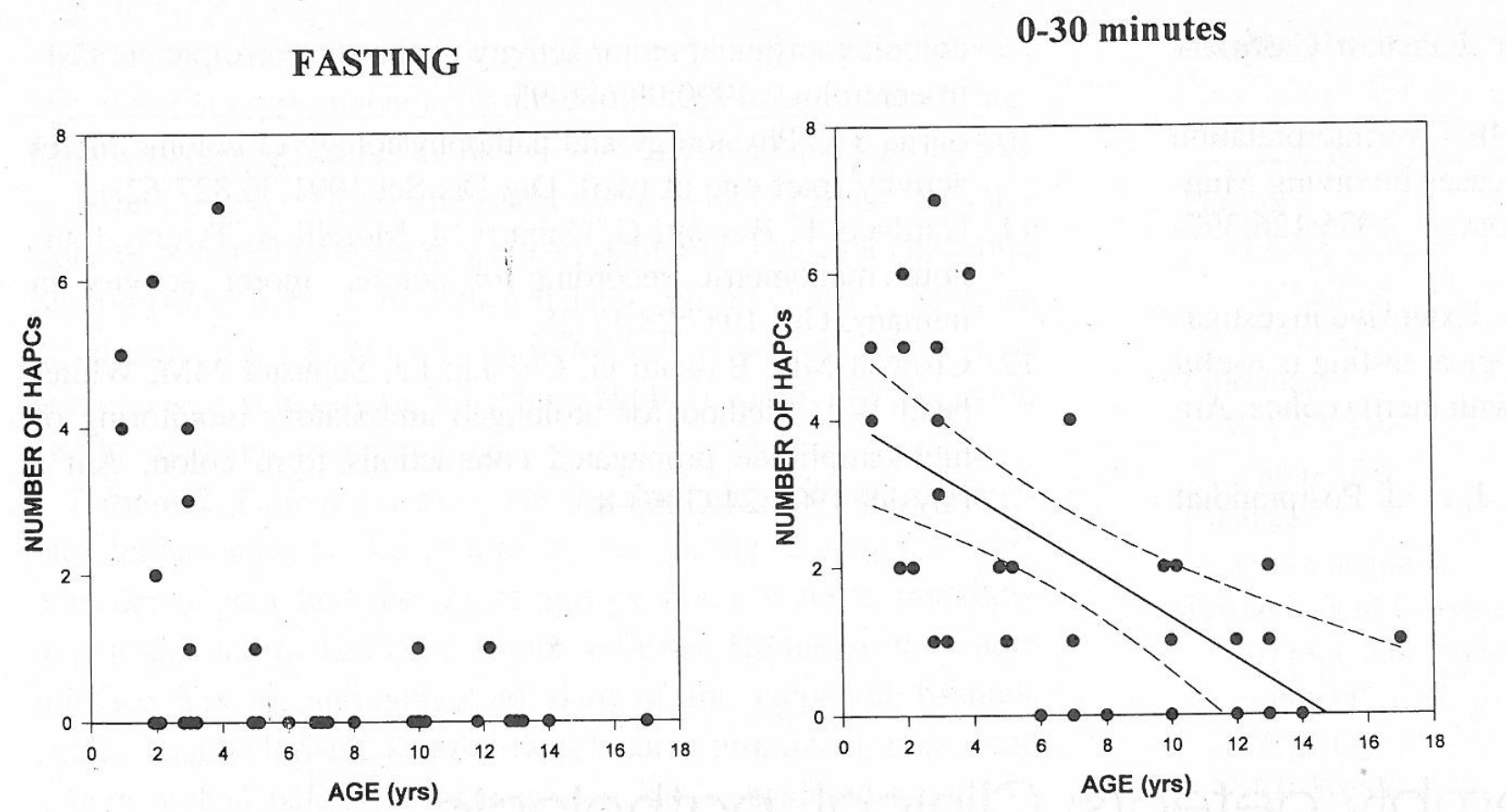
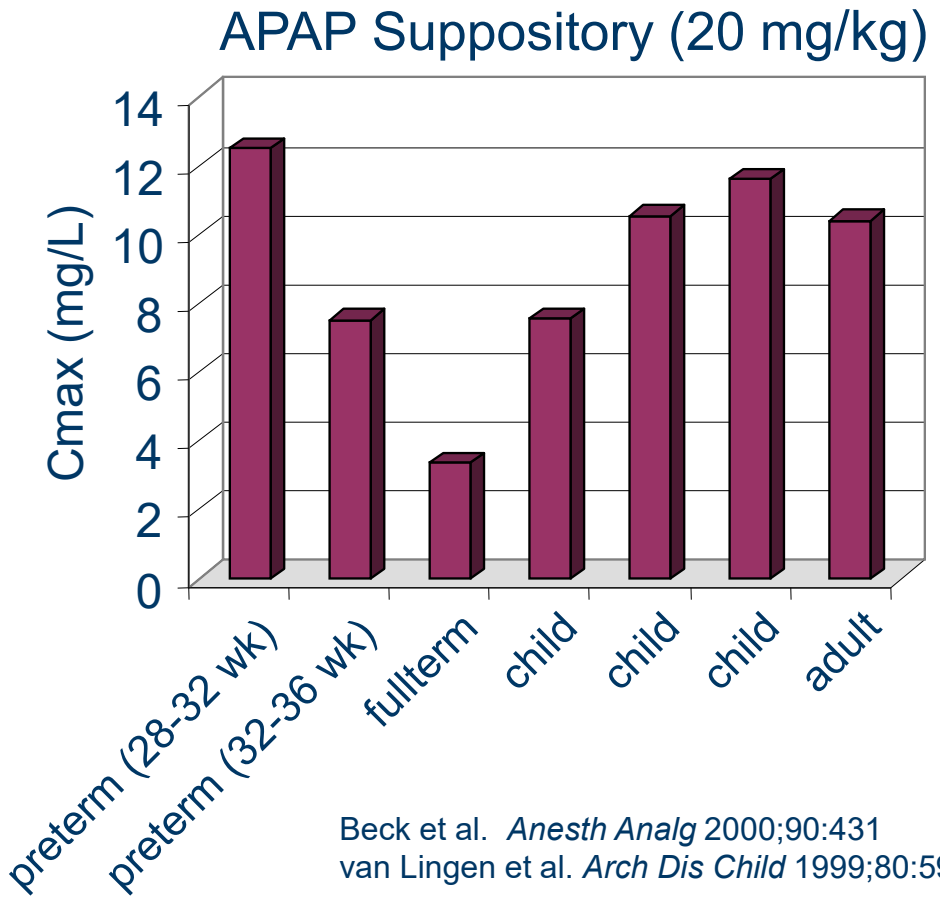
# Colon

# Colonic high amplitude propagated contractions (HAPCs) decrease in frequency with age

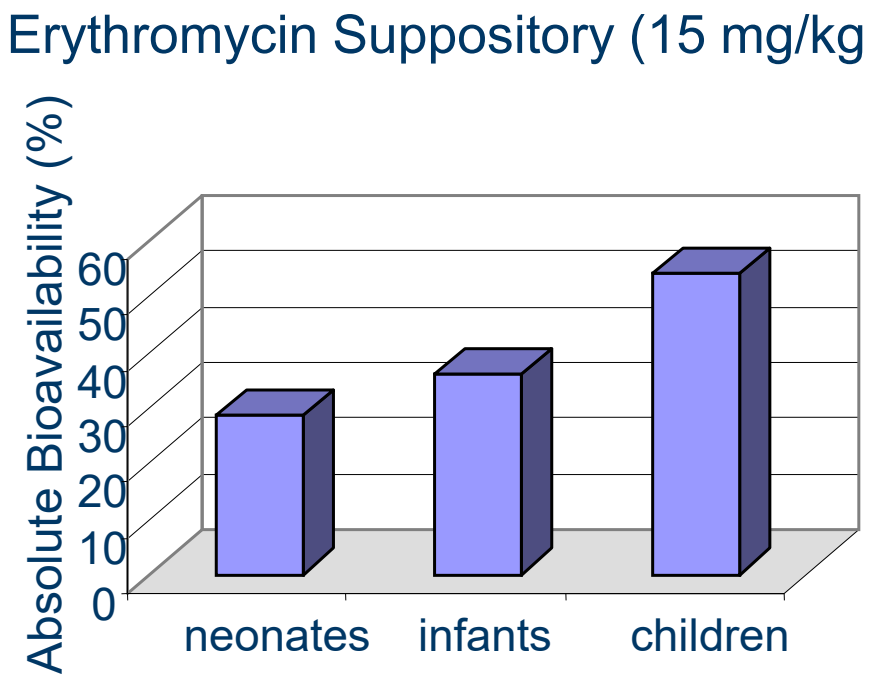



Di Lorenzo et al. *J Pediatr* 1995; 127(4):593

# Suppository bioavailability is affected by developmental age




Beck et al. *Anesth Analg* 2000;90:431
van Lingen et al. *Arch Dis Child* 1999;80:59




Stratchunsky et al. *Eur J Drug Metab Pharmacokinet* 1991;3:321
van Lingen et al. *Clin Pharmacol Ther* 1999;66:509
Coulthard et al. *J Pediatr Child Health* 1998;34:425

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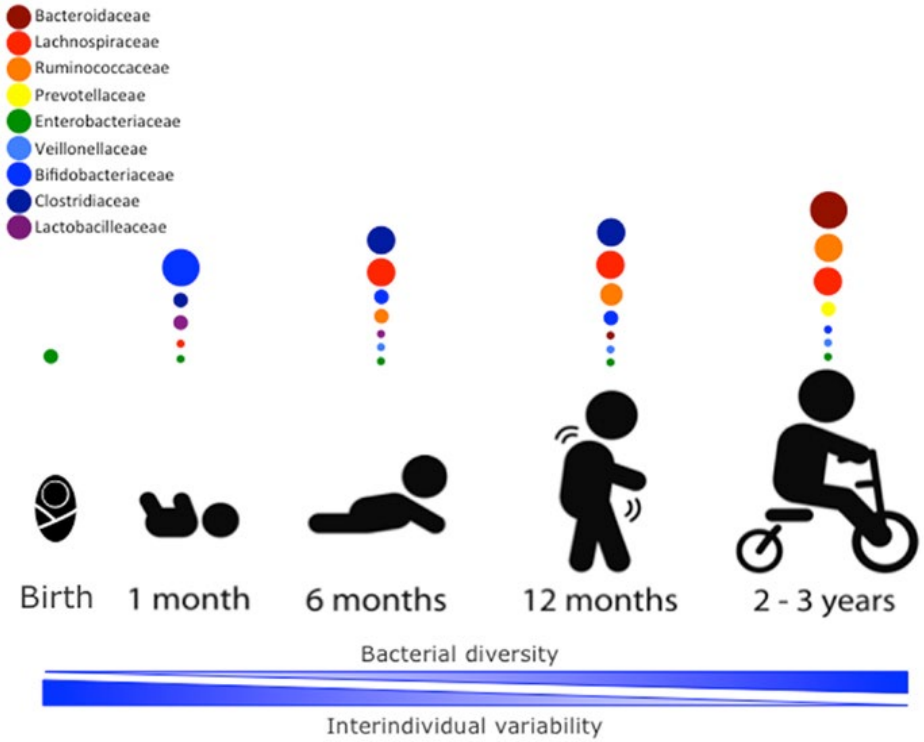
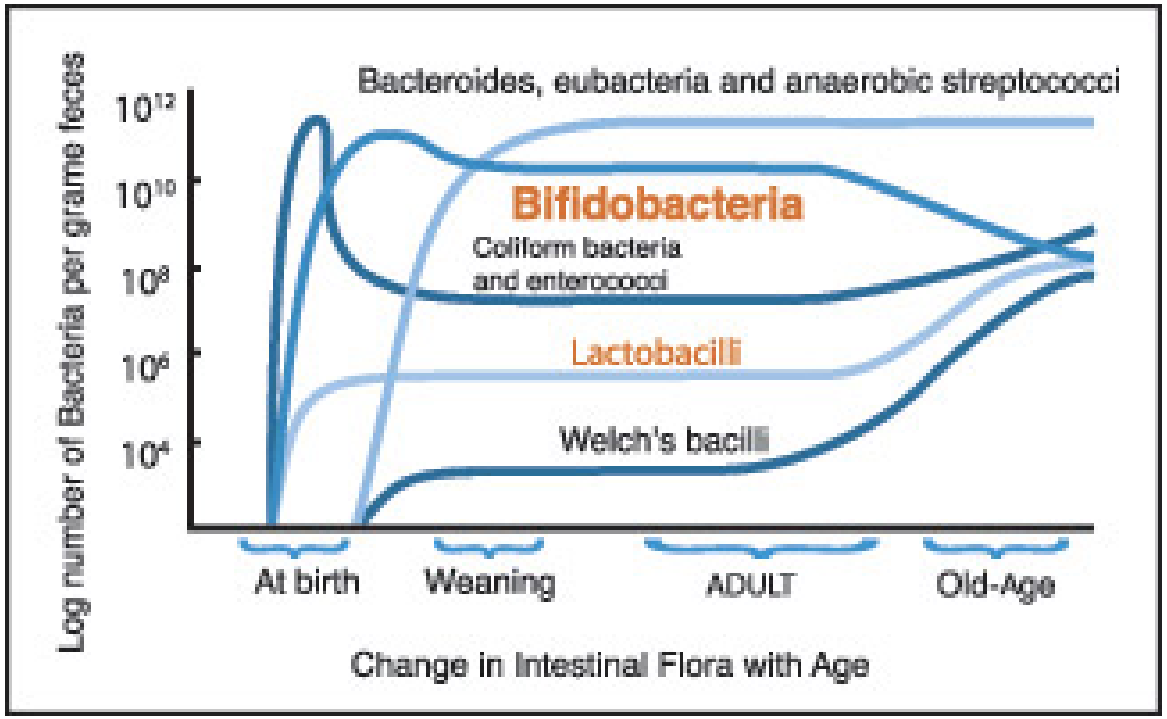
# Microbiome: Drug-Bug Interactions

# Bacterial diversity changes drastically with age and development including early childhood




Saad et al. *Gut Pathogens* 2012;4:16
Arrieta et al. *Front Immunol* 2014; http://dx.doi.org/10.3389/fimmu.2014.00427

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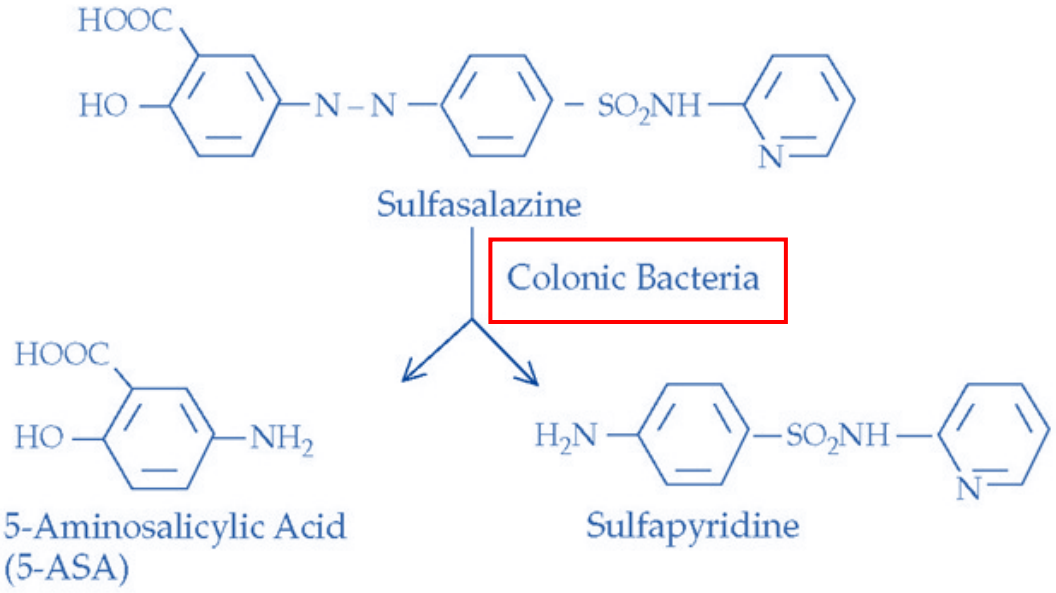
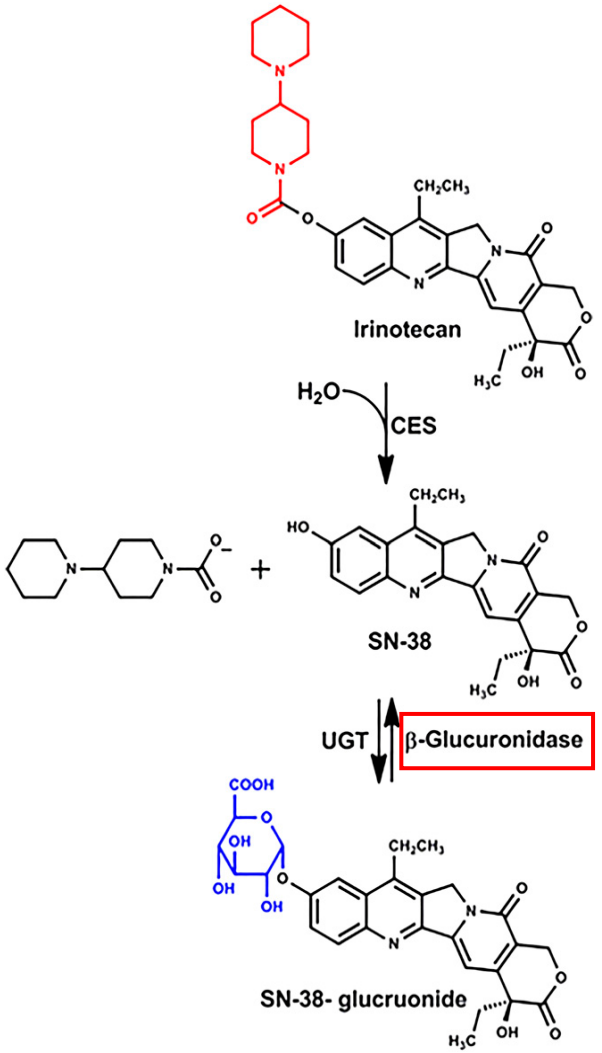
# Intestinal bacteria can alter duration or efficacy of action of medications

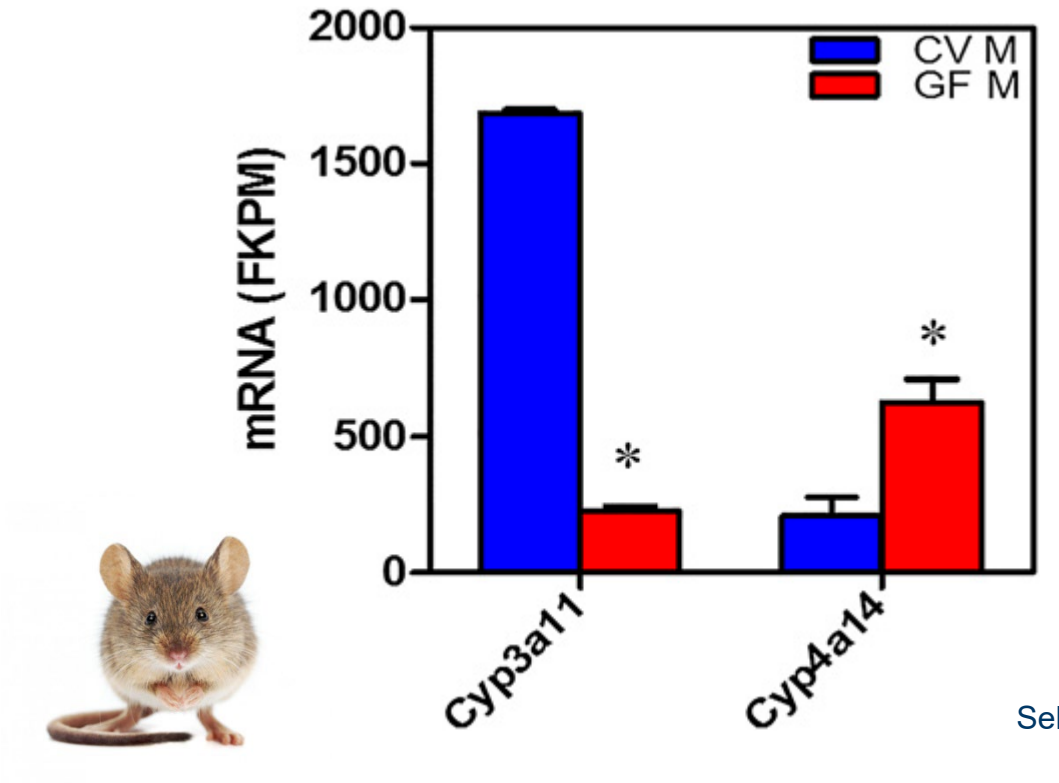



Irinotecan

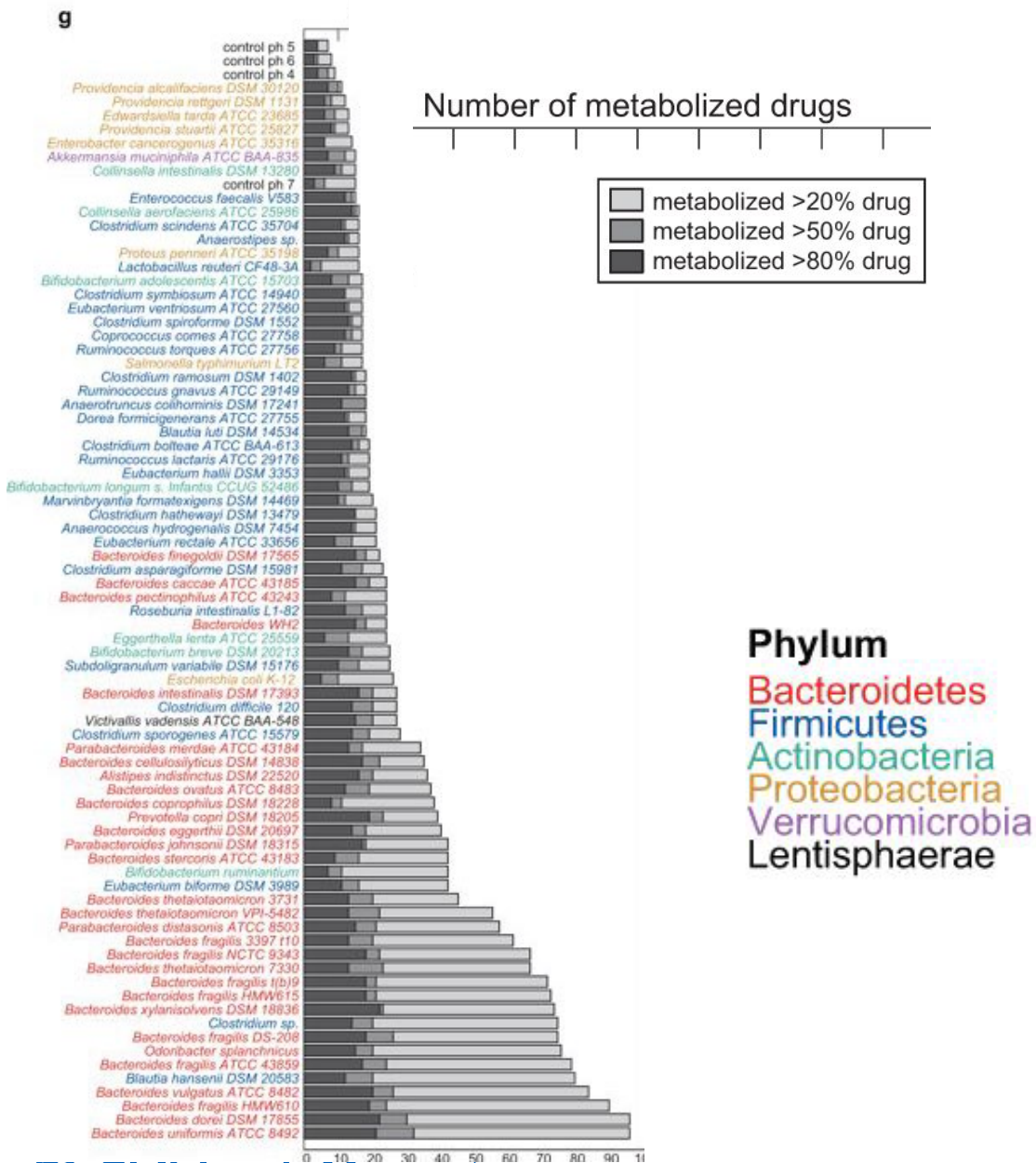


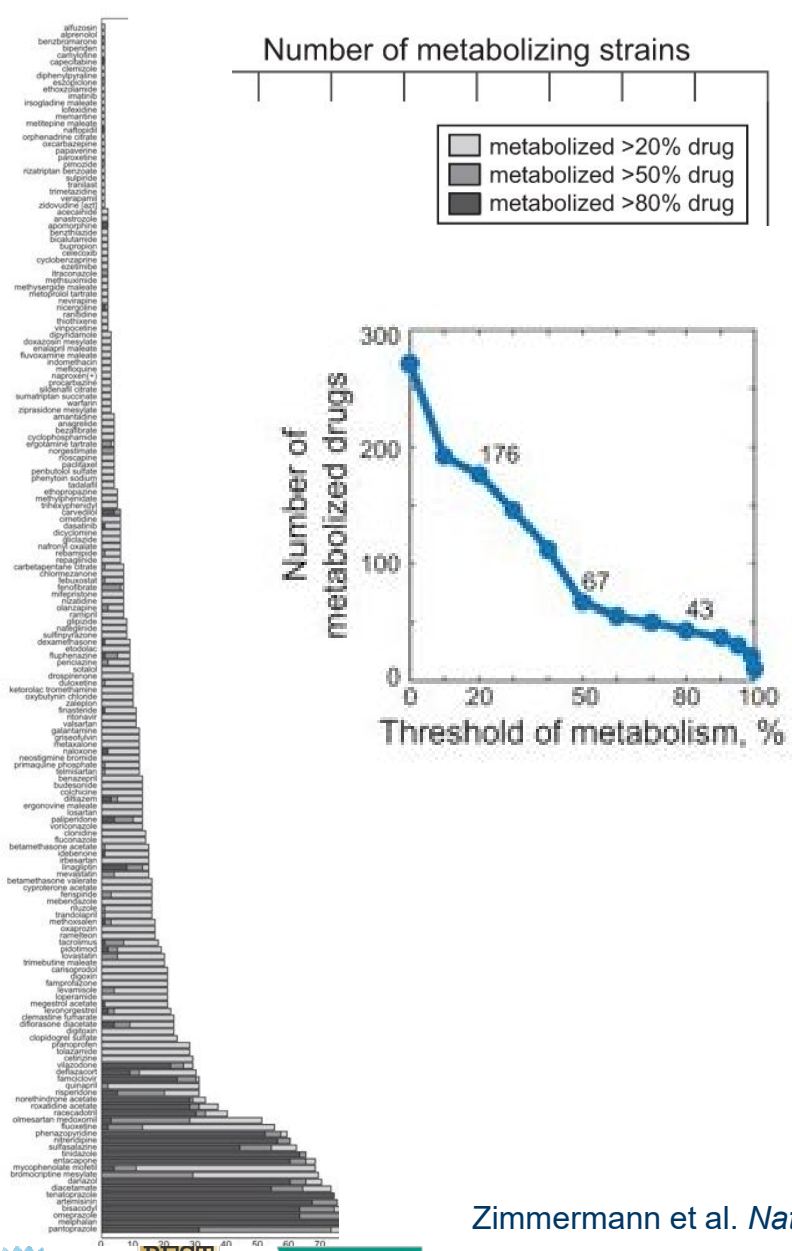

Klaassen & Cui. *Drug Metab Dispos* 2015;43:1505
Tsunoda *Clin Pharmacokinet* 2021

# Intestinal microbiota affects host drug metabolism




Selwyn et al. *Drug Metab Dispos* 2015;43:1505




Zimmermann et al. *Nature* 2019;570:462-7

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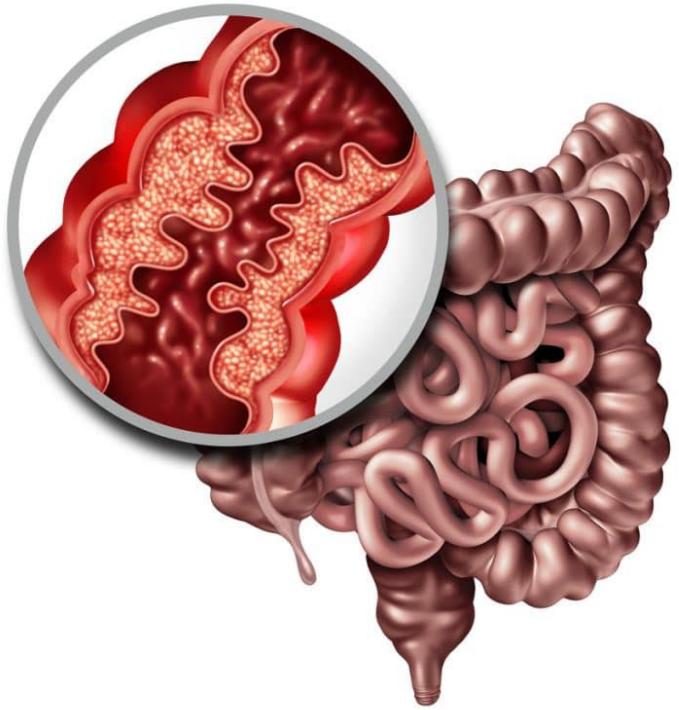
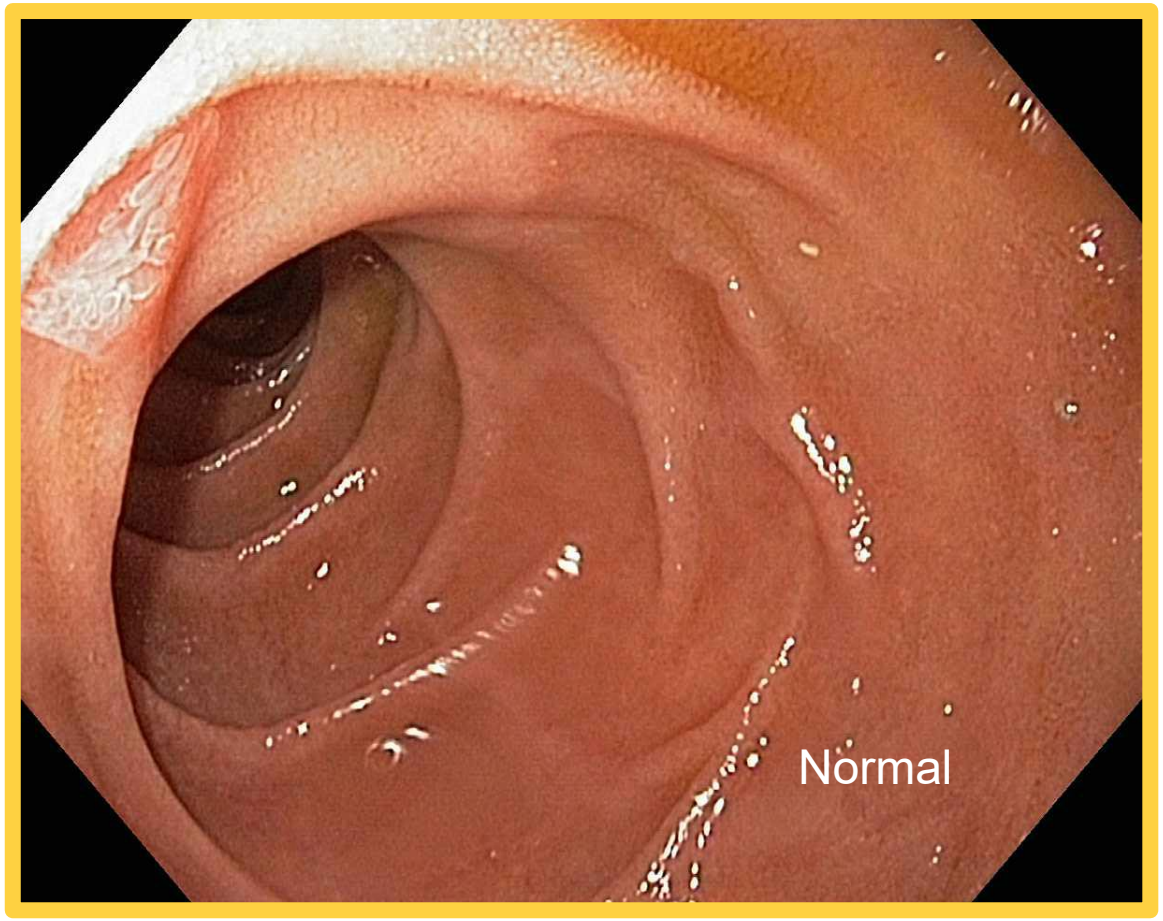
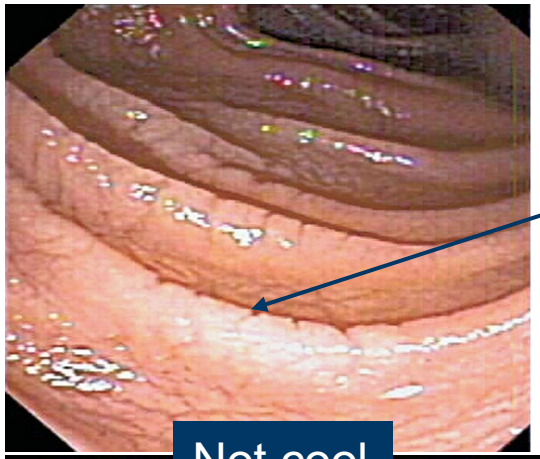
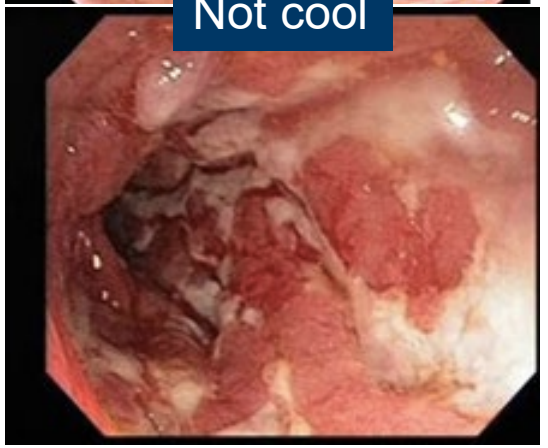
# Impact of Disease



# Intestinal inflammation disrupts mucosal integrity, enzyme production, and more




- Exudate (Pus)
- Erythema
- Edema
- Erosion
- Deep ulcerations
- Narrowed lumen

http://www.gastrolab.net/ya431x.jpg

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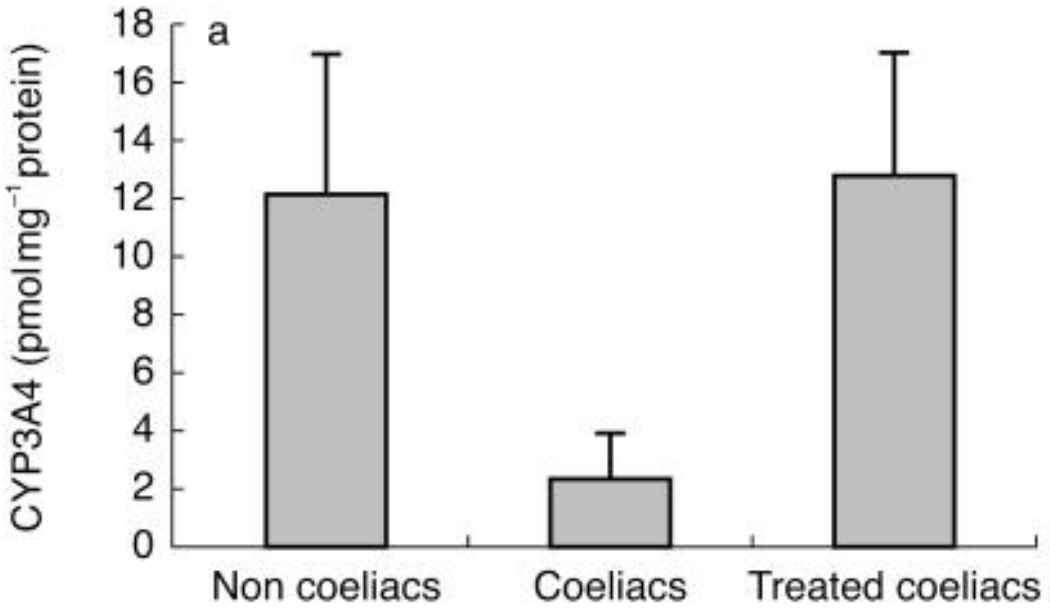
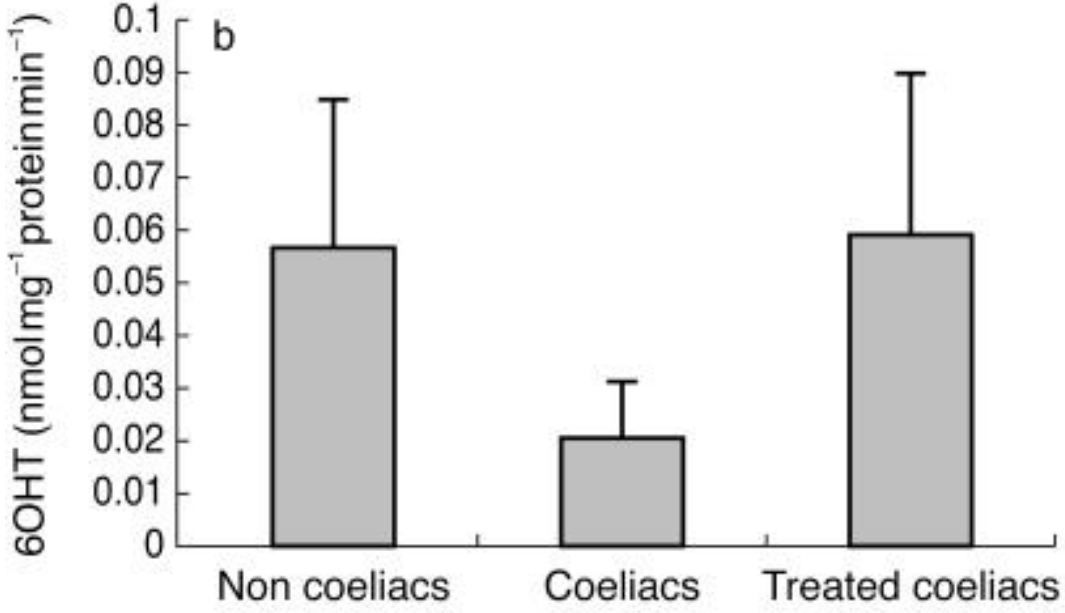
# Intestinal inflammation from celiac disease decreases CYP3A4 and 6OHT protein expression but is recoverable with treatment




Johnson et al. *Br J Clin Pharmacol* 2001;51:451

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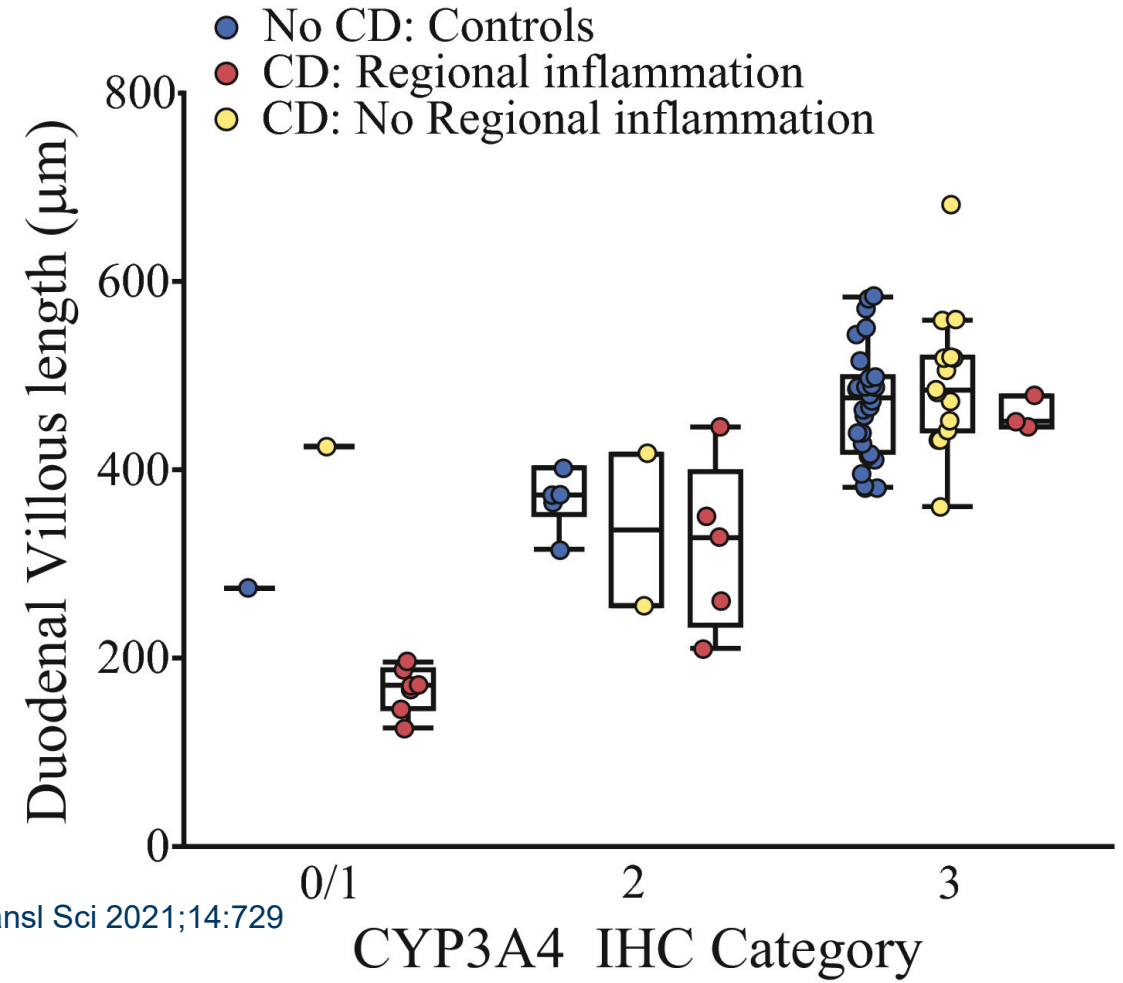
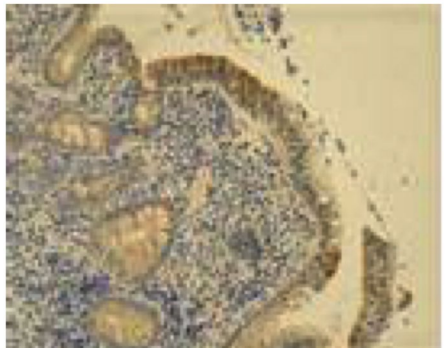
# Villous length (as a measure of intestinal inflammation) predicts CYP3A4 expression duodenal villi

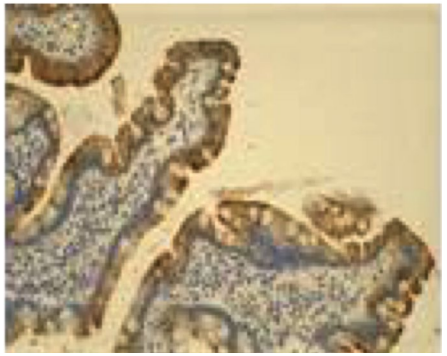



Vyhlidal et al. Clin Transl Sci 2021;14:729

Grade 0/1



Grade 2



Grade 3

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# Take Home Messages

## Vast differences in GI physiology in infant vs. adult

- Delayed gastric emptying, small stomach volume, more alkaline stomach pH, shorter GI track, slower upper track transit time, faster colonic transit time, absorptive capacity differences, etc

## Differences accentuated in pre-term infants

- Not all 1 week old babies are the same

## Intestinal CYPs & transporters are affected by age

- Not just liver!

## Different parts of GI track mature at different rates, making age of “adult GI maturity” difficult to pin-point

- E.g., safe to swallow pills 6-7yrs

## For precision medicine, consider organ physiology & disease effect

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**GI Physicians**
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Laurie McCann
Alex Biller
Halee Patel
Katy Clarkston
Julie Bass
Jordan Sevart
Everyone who collects biopsies

**Biostatistics**
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**CMRI CRIB**

**IBD/EoE Support**
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Susie Vega
Kristen Mace
Amy Harris
Jamie Coillot
Suzanne Brewer
Kass Erazo
Katie Barr
Joy Leon
Shiela Wiebe

# Thank You


NASPGHAN Foundation

GRIP Study Participants

**Support in hospital and out**
Kevin/John/Sam
Williamses/Chevaliers/Shavers
Corinth Elementary School
Little Owly's Daycare
JCPRD
Miras
Soccer Carpool

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# Thank you

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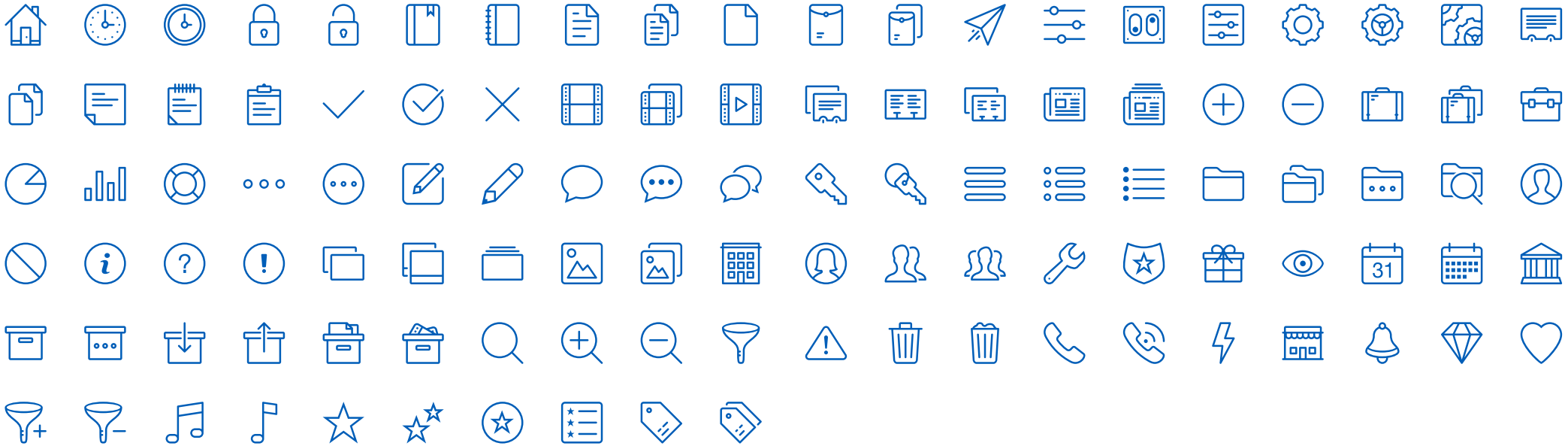

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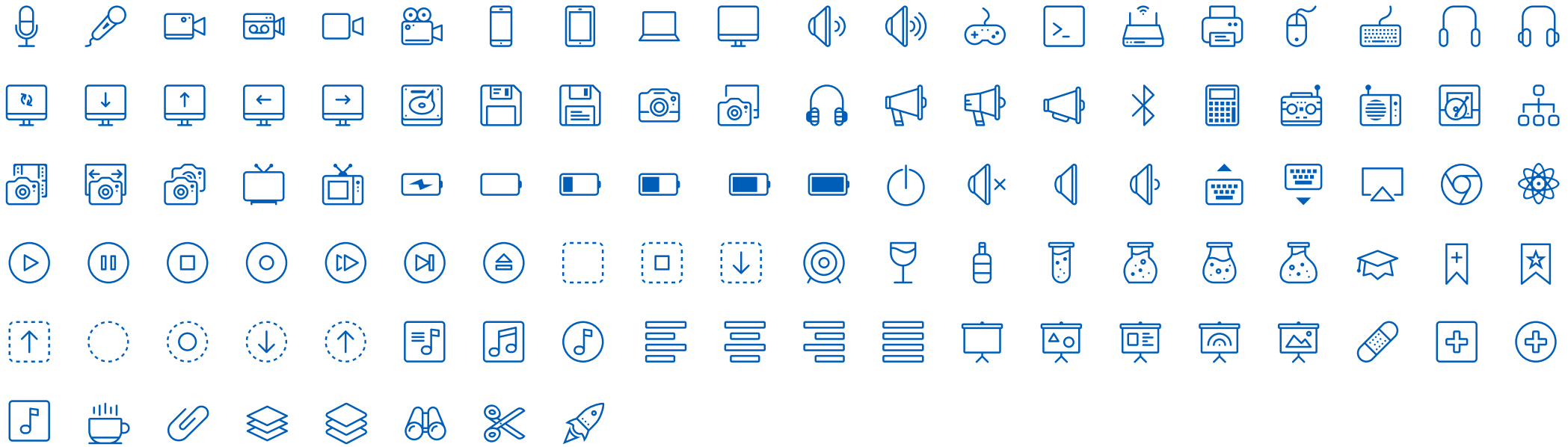

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