

# Special susceptibility of children

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## References:

Handbook of Pediatric Environmental Health, 2<sup>nd</sup>  
Edition, R. Etzel and S. Balk, eds. American Academy  
of Pediatrics, Nov 2003, pages 9-24

Env Hlth Perspectives special issue – [Critical windows](#)

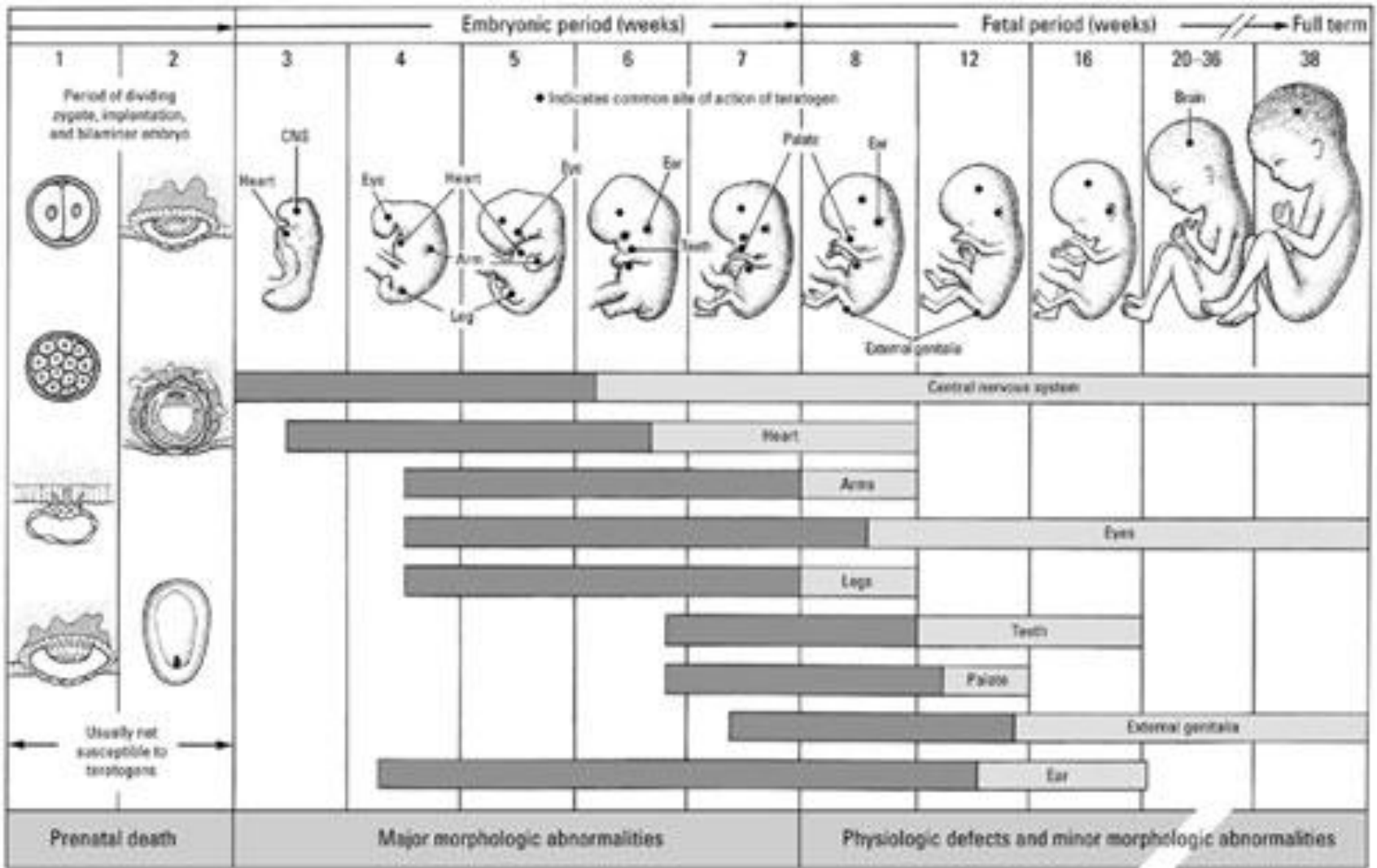
# Topics for discussion

- ◆ The six developmental stages
- ◆ Critical windows of vulnerability
- ◆ The human environment
  - Physical
  - Biological
  - Social

# The six stages of development

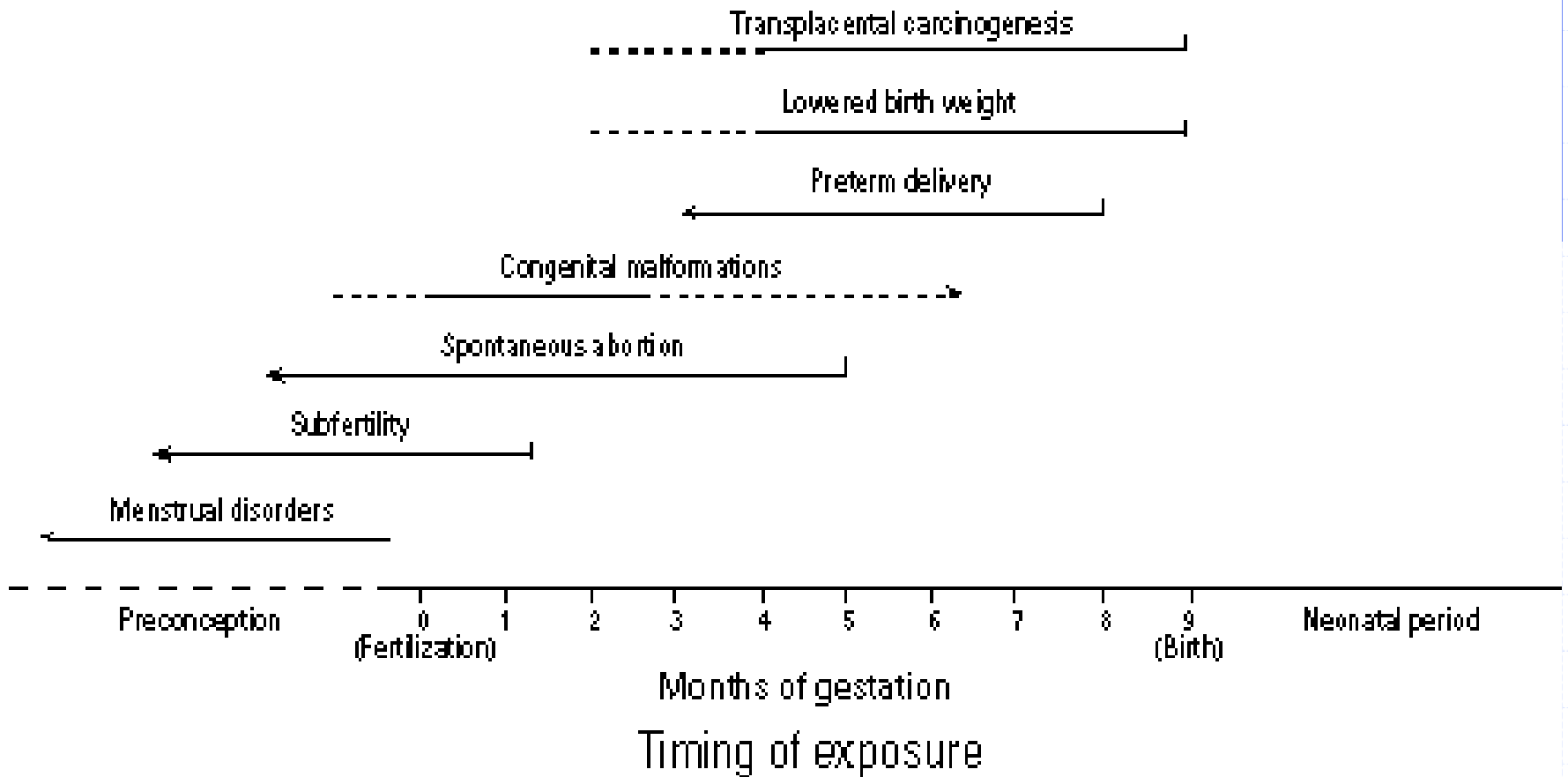
- ◆ Fetus (conception to delivery)
- ◆ Newborn (birth to 2-months)
- ◆ Infant/toddler (2-months to 2-yrs)
- ◆ Pre-school aged (2-yrs to 6-yrs)
- ◆ School-aged (6-yrs to 12-yrs)
- ◆ Adolescent (12-yrs to 18 yrs)

# Critical windows of vulnerability, fetus



**Figure 3.** Schematic illustration of the sensitive or critical periods in human development. Dark gray denotes highly sensitive periods; light gray indicates stages that are less sensitive to teratogens. Reprinted with permission of W.B. Saunders Co. [(3); first published in 1973].

# Critical windows, fetus, reproductive



**Figure 4.** Reproductive outcomes associated with timing of maternal exposure. Solid lines indicate the most probable timing of exposure for a particular outcome; dotted lines indicate less probable but still possible timing of exposure. Arrows suggest that a defined cutoff point for exposure to a specific outcome is not known. Reprinted with permission of Lippincott, Williams and Wilkins (4).

# Examples

## ◆ Trans-placental exposures

- Thalidomide and limb development
- Fetal alcohol syndrome (retarded brain development)
- Diethylstilbestrol (DES) (effect on daughters)

## ◆ Post-natal

- Lead (developmental disorders)

# The physical environment

## ◆ Location (macro environment)

- School, home, daycare, outdoors
- Environmental chemical sources

## ◆ Micro environment

- Room, carpet, kitchen, outdoors, crib, school, sporting events, air pollution, pesticides, etc

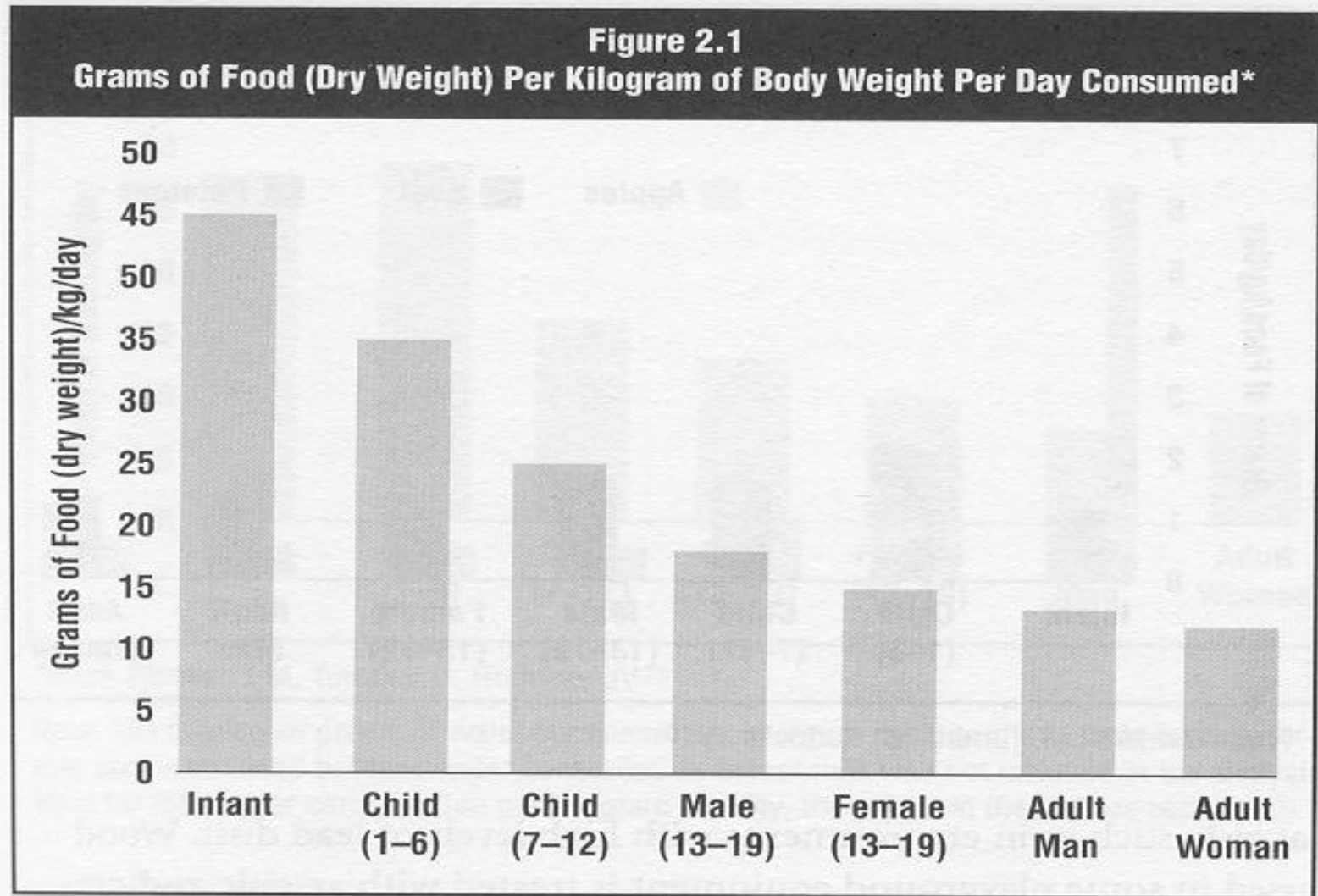
# Children are not small adults

- ◆ Breathing zones lower to floor
  - Hg vapor example
- ◆ Oxygen consumption/respiration
  - Minute ventilation 400 mL/min (newborn) vs 150 mL/min (adult)
  - Newborn's dose of toxicant higher than adult

# Quality and quantity of food

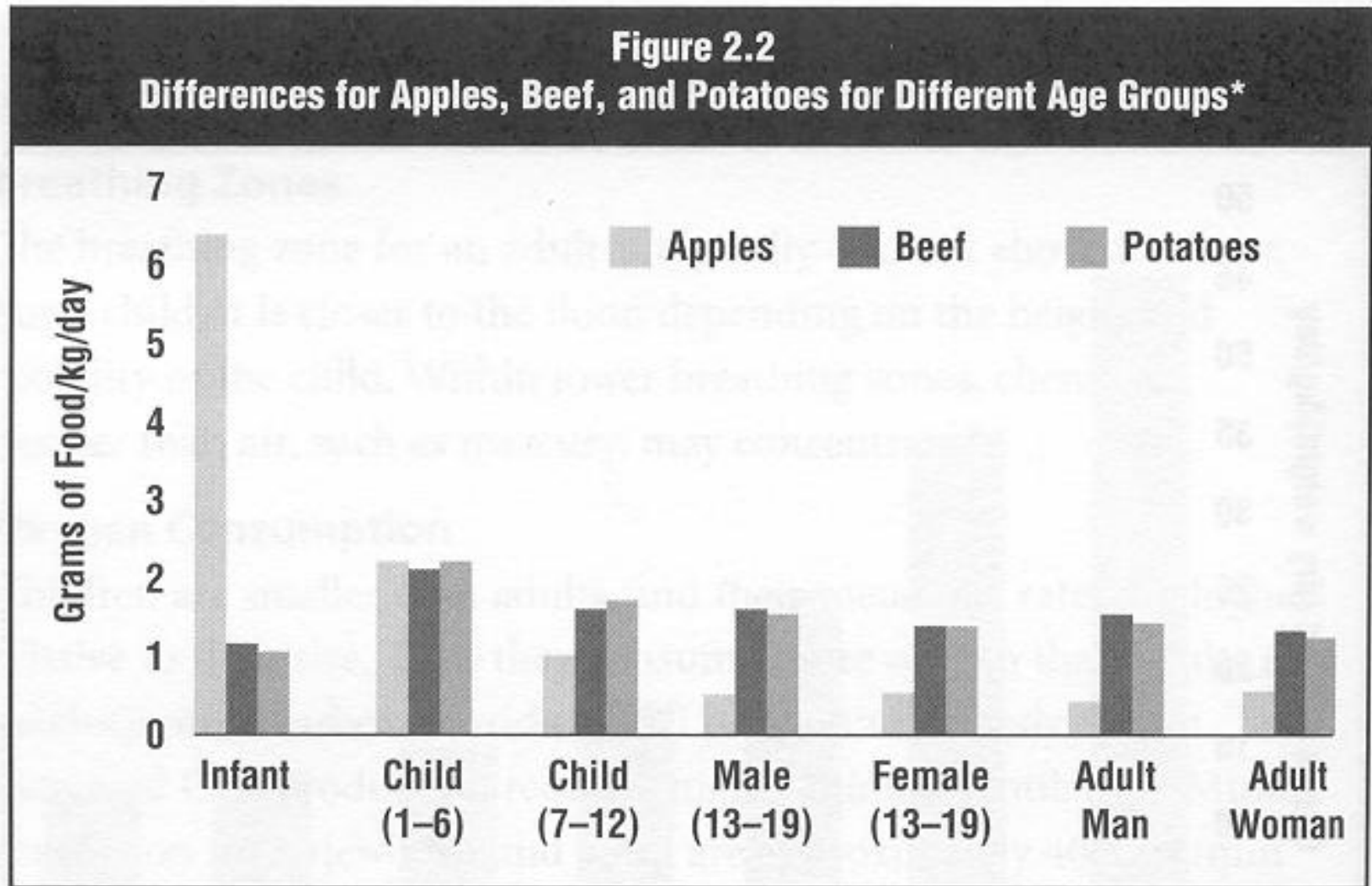
- ◆ Children eat more per capita than adults
  - Contamination of foods more of a problem
  - See next slide
- ◆ Children eat different kinds of foods
  - Young primarily breast milk, with lots of fruits and veggies

# Quantity of food consumed



\*From Plunkett LM, Turnbull D, Rodricks JV.<sup>10</sup>

# Differences in foods consumed



\*From Plunkett LM, Turnbull D, Rodricks JV.<sup>10</sup>

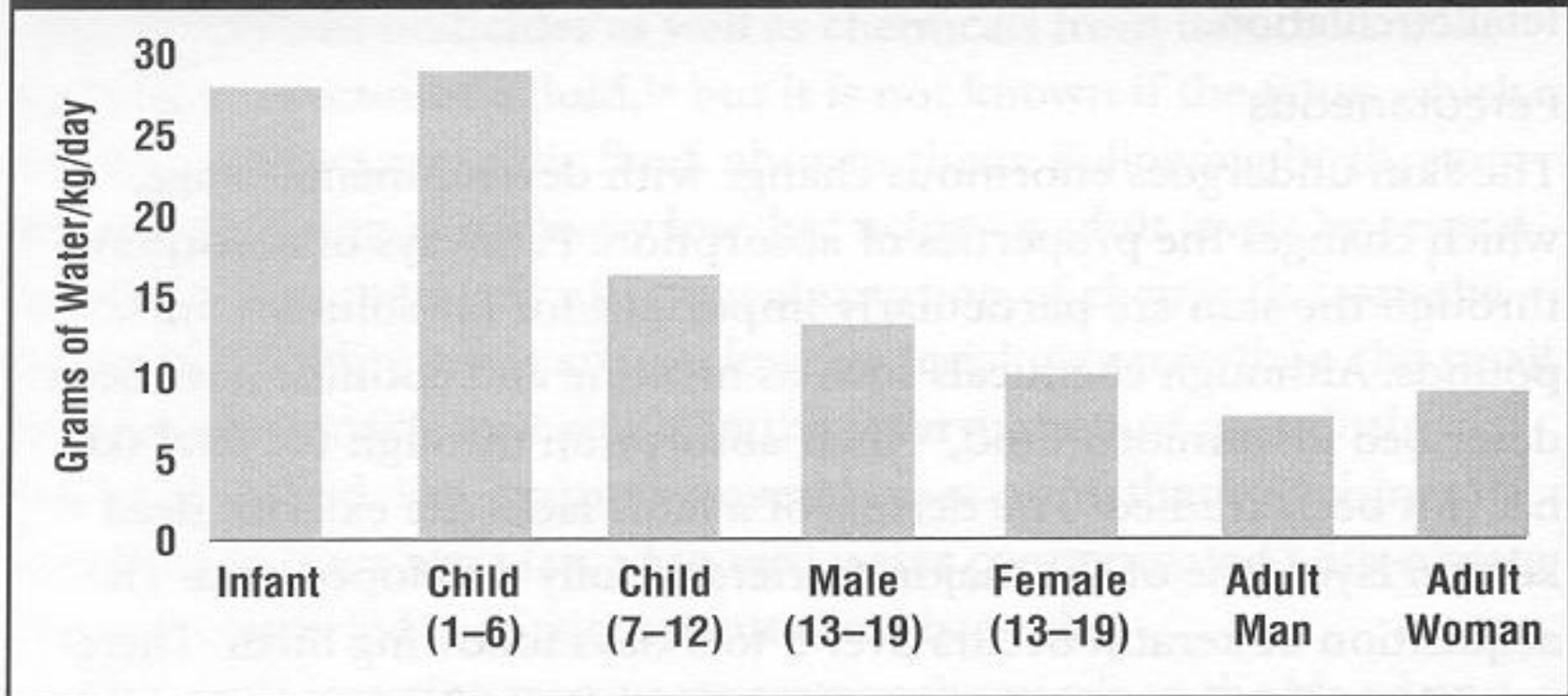
# Differences in fluid intake

- ◆ Newborn consumes 5 oz fluid/kg (equivalent to 30 12 oz cans of soda for adult)
- ◆ If breast milk, 100% of fluid from mom
- ◆ If formula, 100% fluid from local water supply
- ◆ Contamination – provides more dose to child than adult who gets fluids from many sources

# Water consumption over time

**Figure 2.3**

**Differences in Water Consumption for Different Age Groups\***



\*From Plunkett LM, Turnbull D, Rodricks JV.<sup>10</sup>

Note: The citation of grams of water consumed per kilogram per day in this table is considerably underestimated because water consumed as breast milk was not included in the analysis. Thus for total water consumption per kilogram per day, the values in the text are accurate.

# Behavior and development

- ◆ Infant/pre-school – intense mouthing
  - Vulnerability to lead dust, pesticides
- ◆ Pre-school, school – playground equipment
  - CCA/Pentachlorophenol/creosote/lead
- ◆ Adolescents – exploratory
  - Contaminated drums, items from nearby waste area

**Table 2** Differences in children and adults.

## Differences in children and adults

	Infants	Children	Teens	Adults	Reference
Surface area: body mass ratio (m <sup>2</sup> /kg)	<u>Newborn</u> 0.067	<u>Young child</u> 0.047	<u>Older child</u> 0.033	<u>Adult</u> 0.025	(35)
Respiratory ventilation rates	<u>Infant</u>			<u>Adult</u>	(35)
Respiratory volume (mL/kg/breath)	10			10	
Alveolar surface area (m <sup>2</sup> )	3			75	
Respiration rate (breaths/min)	40			15	
Respiratory minute Ventilation rate <sup>a</sup>	133			2	
Drinking water (tap)	<u>&lt; 1 year</u>	<u>1–10 years</u>	<u>11–19 years</u>	<u>20–64 years</u>	(36)
Mean intake (mL/kg/day)	43.5	35.5	18.2	19.9	
Fruit consumption (g/kg/day)	<u>&lt; 1 year</u>	<u>3–5 years</u>	<u>12–19 years</u>	<u>40–69 years</u>	(37)
Citrus fruits	1.9	2.6	1.1	0.9	
Other fruits (including apples)	12.9	5.8	1.1	1.3	
Apples	5.0	3.0	0.4	0.4	
Soil ingestion (mg/day)		500			(38)
Pica child					
Outdoor		<u>Child age 2.5 years</u> 50		<u>Adult</u> 20 <sup>b</sup>	
Indoor		60		0.4	
Differences in GI absorption of lead	<u>Age 0–2 years</u> 42–53%	<u>Age 2–6 years</u> 30–40%	<u>Age 6–7 years</u> 18–24%	<u>Adult</u> 7–15%	(39)

<sup>a</sup>mL/kg body weight/m<sup>2</sup> lung surface area/min. <sup>b</sup>Gardening for adults.

# The biological environment

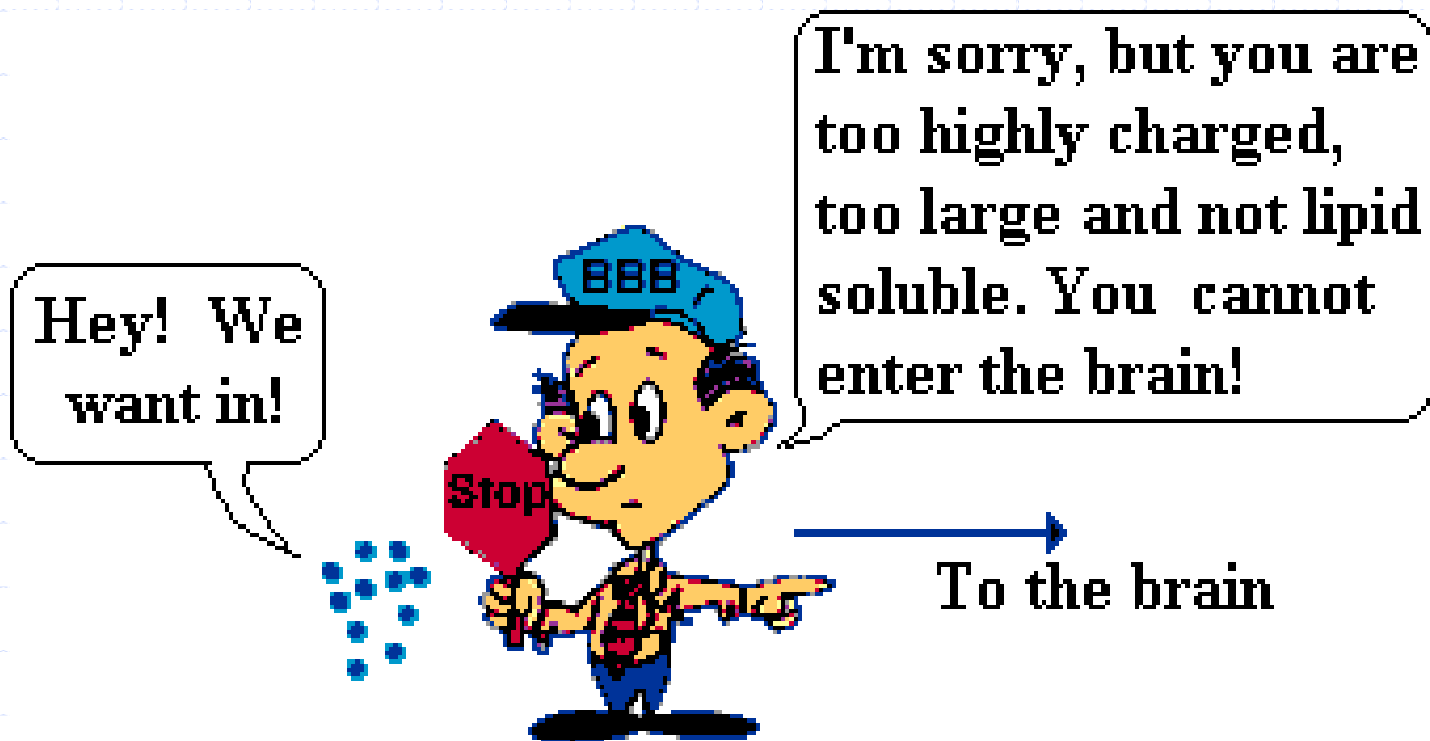
- ◆ All vary by developmental state
  - Absorption
  - Distribution
  - Metabolism
  - Target organ susceptibility
- ◆ All impact potential toxicity in child

# Transplacental absorption

- ◆ Examples: CO, Ca, Pb, PAHs from ETS, MeHg, ethanol, lipophilic compounds
- ◆ CO has higher affinity for fetal Hb, thus smoking pregnant lady delivers higher dose of COHb to her fetus
- ◆ Case of pica behavior in pregnant lady resulted in high bone lead in infant.

# The blood brain barrier

- ◆ Ehrlich, 1885 - injected dyes did not stain the brain and spinal cord like rest of tissues
- ◆ Blood-brain barrier "porous" in children placing them at special risk for neurotoxic effects



# Percutaneous absorption

- ◆ Favors lipid solubles
- ◆ No protective keratin layer in fetus
- ◆ Keratin in dermis develops over first two weeks of life
- ◆ Skin of newborn extremely permeable
  - Hypothyroidism from Betadine scrubs
  - Neurotoxicity from hexachlorophene
  - Hyperbilirubinemia from phenolic hospital disinfectants

# Respiratory absorption

## ◆ Respiratory

- Some evidence of absorption by fetus
- Lung development through proliferation of pulmonary alveoli and capillaries until 5-8 yrs
- Alveolar expansion continues to adulthood
- Respiratory rates higher as discussed

# Gastrointestinal absorption

- ◆ Stomach acid very low in newborn
  - Higher pH causes alternations in GI absorption
  - Higher pH favors bacterial overgrowth
- ◆ Examples:
  - Consumption of nitrates in Iowa farm drinking water resulted in methemoglobinemia
  - Newborn absorbs 50% of Pb, adults, 10%

# Distribution

- ◆ Distribution depends on changing body composition
  - Methyl mercury and the blood-brain barrier
  - Pb accumulation in infant brain and bones



# Metabolism

- ◆ Metabolism varies with development and genetic susceptibility
  - CYP450 enzymes have different activity at different ages
    - ◆ Theophylline, caffeine, ethanol
- ◆ May be protective or harmful
  - Acetaminophen metabolism in infants not developed, do not produce liver toxicity as compared to adults

# Target organ susceptibility

- ◆ Differentiation – cell-specific function
  - Triggers are hormonal – environmental estrogens may present reproductive risks
  - Scrotal cancer in teens, due to rapidly developing DNA and shorter time for DNA repair
- ◆ Migration from site of formation
  - Low doses of Pb may affect dendric trimming of synapses to lower numbers to adult levels.
  - Child's brain is 4/5<sup>th</sup> adult size by 2-yrs.
    - ◆ Pb and Hg impact the brain of the infant
  - ETS – reduces lung function development

# Regulatory environment

- ◆ Regulations based on 70 kg male
- ◆ Do not account for
  - Developmental characteristics
  - Physical environment
  - Biological environment
- ◆ 1996 Federal directive to agencies
  - Take children's special susceptibilities into account

# Advocacy

- ◆ Parents and pediatric providers must advocate for children's health when dealing with environmental exposures
- ◆ Toxicologists and regulators must take into account the special susceptibilities of children in designing tox studies as well as establishing regulations

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