An Introduction to Children’s Environmental Health: Why Kids? Why Environment?

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No disclosures

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Pediatric Environmental Health Specialty Units

Western States PEHSU
http://coeh.berkeley.edu/ucpehsu/
1-866-827-3478

National PEHSU System
www.pehsu.net 888-347-2632
Breathing rates calculated from inhalation rates (m$^3$/kg-day) and body weights reported in Layton (1993); original data from NFCS (1977-78).
Parental Concern vs. Pediatrician Advice

Stickler GB, Simmons PS., Clin Pediatr 1995
Case

- Female infant
- breastfed with formula supplement
- normal 1 month checkup (mother notes acrocyanosis at 2 weeks)
- At 2 months pharmacist comments on cyanotic color
• Given progressively more formula made with well water
• At 2 months develops vomiting and severe diarrhea
• Rushed to physician - cyanosis doesn’t respond to oxygen / full arrest
• Chocolate-brown blood
• Well water 150mg/L nitrates
Nitrates

• Preventable cause of methemoglobinemia in infants
• Over 2,000 cases reported with case fatality rate of 10%
• EPA drinking water standards nitrates $< 10\text{mg/L (10ppm)}$
• 4.5 million people served > EPA standard
  • 65,000 infants
  • 117,000 children via public systems
Infant Under 4 Months

Hemoglobin F dominant – more readily oxidized

Methemoglobin reductase activity low

↑ Gastric pH
(↑ bacteria that convert nitrate to nitrites)

Single food source

High fluid intake
EXPOSURES DURING DEVELOPMENTAL PERIODS AND AT DOSES NOT ASSOCIATED WITH ADULT TOXICITY MAY RESULT IN IMPACTS UNEXPECTED BY ADULT EXPOSURE
Transient Hypertonia in an Infant

✓ 7lbs. 14 oz. term female, jaundice peak bili 12.6
✓ NI. PE at 12 weeks except lower extremity hypertonicity
✓ Pediatric consult at 16 weeks - upper and lower extremity hypertonicity, ankle clonus with Dx of cerebral palsy
✓ Physical therapy begun
✓ No environmental hx was taken

Wagner SL, Orwick DL., Pediatrics 1994
Transient Hypertonia in an Infant

- Diazinon 1% sprayed by **unlicensed** pesticide applicator
- Levels still high six months after spraying
- Serum cholinesterase normal
- Urine metabolites high
  - similar to post-shift urine of applicators
- Six weeks after removal from house muscle tone returned to normal
A window of vulnerability is a time during which the fetus, infant, or child is especially susceptible to particular environmental chemical exposures, general environmental deprivation, suboptimal nutrition, or psychosocial stress.
Chlorpyrifos Impacts Neurodevelopment

- Detected in >64% of maternal and newborn blood samples
  - Follow up at 3 yrs. for 189 children
- Highly exposed
  - Delays in psychomotor and mental developmental indexes (Bayley)
    - PDI delays 5 times as great (MDI 2.4 times)
- Symptoms ADHD and PDD significantly more likely (child behavior checklist)
- Declines in working memory and full scale IQ at age 7

Rauh et al. Pediatrics 2006
Rauh et al., EHP 2011
Chlorpyrifos has Measurable Impact on Brain Structure (non-occupational)

Brain anomalies in children exposed prenatally to a common organophosphate pesticide, Rauh et al., PNAS 2012 (copyrighted)
Regional enlargements of the cerebral surface (primarily underlying white matter)

- Posterior middle temporal, inferior postcentral gyri bilaterally
  - Attention and receptive language
- Superior frontal gyrus, superior temporal gyrus, cuneus, and precuneus
  - Social cognition
- Gyrus rectus (related orbitofrontal regions)
  - Reward, emotion, and inhibitory control
- L superior frontal gyrus (dorsal and mesial surfaces)
  - Executive function
Time Lines of Developmental Processes in Humans

<table>
<thead>
<tr>
<th>Prenatal Period (Months)</th>
<th>Postnatal Period (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>Birth 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

- **Cell Proliferation**
  - Radial glia, neurons
  - Glia

- **Migration of Neurons**
  - Brain, spinal cord
  - Ext. granular layer cerebellum

- **Subplate Neurons**

- **Synapse Formation**
  - Mz sp hp rf visual cortex association cortex

- **Myelination**

**Key:**
- Mz – marginal zone; sp – subplate; hp – hippocampus; rf – reticular formation
Specific processes disrupted by neurodevelopmental toxicants

<table>
<thead>
<tr>
<th>Process</th>
<th>Toxicants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation</td>
<td>Radiation, ethanol, mercury, cholinesterase inhibitors</td>
</tr>
<tr>
<td>Migration</td>
<td>Radiation, mercury, ethanol</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Ethanol, nicotine, mercury, lead</td>
</tr>
<tr>
<td>Synaptogenesis</td>
<td>Radiation, ethanol, lead, triethyl tin, parathion, PCBs</td>
</tr>
<tr>
<td>Gliogenesis &amp; Myelinization</td>
<td>Thyroid, ethanol, lead</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Ethanol, lead, mercury</td>
</tr>
<tr>
<td>Signaling</td>
<td>Ethanol, cholinesterase inhibitors, mercury, lead, PCBs</td>
</tr>
</tbody>
</table>
What do parents do at work?

✓ A day laborer goes to the ER for a work related injury.
✓ Working on demolishing a firing range - lead level is 74 mcg/dl after 3 days on this job.
✓ Four other workers tested between 57 and 98 (all worked less than 2 ½ weeks).
✓ None had previously worked with lead.

Hipkins KL, Materna BL, Payne SF, Kirsch LC., Clin Pediatri 2004
Occupational/Take Home Exposures

✔ 9 children of three workers tested between 13 and 34 mcg/dl. (highest 18 month old)

✔ Wife of one with symptoms and Pb level of 36 mcg/dl.

✔ Workers may bring home hazards on clothing, shoes, and body.

✔ In 2001-2002 year, 22% of California childhood lead poisoning cases had potential contribution from occupational sources.
The ecological health framework extends to the sub-cellular level.
Not all of the factors that are important for health occur within the individual’s genetic and biological makeup. Your interaction with your family, social support, and community can also impact your health.
Ecological Health Framework

- Individual
- Relationships
- Family
- Community
- Society
- Ecosystem

Timing of exposures
Effects of multilevel variables over lifespan
Recent historic/evolutionary time

Time Dimension

Individual
Organ system
Cell
Organelle
Cell signaling
Developmental origins of health and adult disease (DOHAD)

- Under-nutrition *in utero and infancy* resulted in changes in organ structure, function, and metabolism that were permanent
  - *adult lipid profiles linked to high cholesterol and hypertension*
  - *Impaired glucose regulation (insulin resistance)*
  - *Metabolic syndrome*
Morris Water Maze

- Test of memory and spatial learning (adults)
- LG babies do better
  - Non-LG babies raised by LG mom’s do better
- Adults born to mothers with prenatal stress but same postnatal environment do worse

It is a combination of genetics and pre/postnatal environment that determines function into adulthood
Genetics = Gene + Expression
Demethylation of GR exon 1
Deacetylation of histones around GR
Permanent increase in GR expression in hippocampus
Increased NGF1-A activity in hippocampus
Increased serotonin tone
Less methylation GAD1
Mother high licker groomer
Pup
Adult high hippocampal GR levels
High licker groomer behavior
Exploratory, less fearful and stress reactive more cognitively intact in old age.

Champagne and Meany, Behavioral Neuroscience 2007
Champagne et al., Journal Neuroscience 2008
Zhang et al, Journal Neuroscience Sept. 2010
Prenatal Stress – Effects in Adult Female Offspring

• Exposures
  – Relationship hardship (eg. Divorce)
  – Death/severe illness of someone close
  – Severe financial, car accident, refugee

• Impacts
  – Altered HPA axis response (Trier Social Stress and ACTH stimulation)
  – Bias to Th2, IL-4, IFN –gamma, IL6, IL10 production

Entringer et al Dev Psychobiol 2008
Entringer et al Hormones and Behavior, 2009
Allostasis – active process for adaptation (brain – body)

Limbic Plasticity effected by
- Parental resources
- Education
- Exposures/nurturance

Costs: metabolic, cardiovascular, immune, behavioral dysregulation

Adapted from McEwen and Gianaros, 2010
Lead/Stress Act by Similar Mechanisms

- Effects additive

- Learning and memory in hippocampus dependant on activation of NMDA glutamate receptors

- Stress or an environmental chemical (lead) impact same mechanism

- Both lead and stress impact HPA axis

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Guilarte Ann Neurology 2003
Neal Neurotoxicology 2011
Environmental enrichment enhances memory and learning /plasticity

- Early lead exposure results in decrease in learning, memory, NMDA r activity \( (BDNF) \)
- Enriched environment reduces leads cognitive impacts and normalizes NMDA r activity \( (BDNF) \)

Environmental enrichment effective in ameliorating neuro-cognitive effects

Social environment

- **Lead** – association cognitive deficit <10mcg/dl only in “less advantaged”, >10mcg/dl → effect attenuated for “advantaged”*

- **PCBs** – (prenatal) negative effect only in “less optimal” parenting and home characteristics. Breastfeeding protective of attention at school age.

- **ETS** – greatest cognitive effect in those with “unmet basic needs in the areas of food, housing, and clothing”

References:

Weiss and Bellinger, 2006
Rauh et al., Neurotox Teratol, 2004
Vreugdenhil et al. EHP 2002
Bellinger, Neurotox Teratol, 1988*, Miranda et al. 2008**
Jacobson and Jacobson, 2003
Oral Succimer for Lead Chelation Does Not Lead to Better Neuropsychological Outcomes (children with 20 – 45 mcg/dl)
Risk Factors for Asthma

Age, Sex, Race
Genes
SES, Stress
Neighborhood
Tobacco smoke
Obesity
Infections
Outdoor Pollution
Indoor Pollution
Ozone - postnatal exposure (+/-HDMA)

- Results permanently alters bronchioles (monkeys)
  - Fewer branches
  - Longer
  - Smaller diameter
  - Altered muscle bundle orientation
  - Change in innervation

Plopper et al. 2007
Community/Home Violence Link to Decrease in Lung Function

- Girls with home conflict (highest tertile) had >5% decrease in FEV$_1$ and FVC (smaller decrease in boys)
- Boys with exposure to community violence (highest tertile) had >5% decrease in FEV$_1$ and FVC
  - Independent of SES, SHS, birth wt., respiratory illness history

Suglia et al 2007 Psychosomatic Med
Asthma – neurobiology underlying stress vulnerability

• Early life adversity (chronic stress) linked to:
  – Disturbed regulation of endocrine and autonomic processes
    • HPA axis; sympathetic adrenal medullary system
      – May permanently program for exaggerated stress response
    • Alterations in Th1/Th2 balance
    • Alterations in inflammatory cytokines, IgE
Air Pollution + Exposure to Violence (EOV) Synergistic Effects

• Birth cohort N=417
• \( \text{NO}_2 \) measured
• Lifetime exposure to violence surveyed
  – Association between air pollution and asthma only in those with above median ETV
  – For lifetime residents (most accurate exposure)
    asthma OR 2.4 (1.48-3.88) for higher air pollution + ETV

Clougherty et al EHP 2007: Shankardas et al PNAS 2009
Shankardass, et.al. J Epidemiol Community Health 2011
Days exceeding CA standards for Ozone (1 hr) and PM10 (24 hr) (South Coast air basin Data California Air resources Board)

A portion of adult lung function is set by infancy

Up to 14% of adult lung function predicted by lung function at 2-3 mos
Stern 2007

Quartiles infant Vmax at functional residual capacity

FEV₁

FEF₂₅-₇₅

Quartiles infant Vmax
△ High
Medium-high
Low-medium
Low

FEV₁/FVC ratio

Predicted FEV₁/L

Predicted FEF₂₅-₇₅ (L/s)

Predicted FEF₂₅-₇₅ (L/s)
Resources

- Western States PEHSU website (wspehsu.ucsf.edu)
  - Story of Health e-book (SOH). (https://wspehsu.ucsf.edu/for-clinical-professionals/training/a-story-of-health-a-multi-media-ebook/) Using the setting of a family reunion as a backdrop, SOH explores how various environments influence our health across the lifespan. Over 5,000 physicians, nurses, and health educators have already received CE credits from the CDC for completing chapters.

- Pediatric Environmental Health Toolkit is a combination of easy-to-use reference guides for health providers and user friendly health education materials on preventing exposures to toxic chemicals and other substances that affect infant and child health. The new mobile device ready version to be posted soon. Online intro for CE at: https://www.atsdr.cdc.gov/emes/health_professionals/pediatrics.html

Coming soon!