Webinars
Series of scientific webinars that provide a forum for discourse on scientific issues.
Live and On-Demand
Case Conferences
Journal Clubs
Grand Rounds
CE Available

Online Courses
Evidence-based online courses on a variety of children's environmental health topics.
Interactive and Self-Paced
CE Available

Resource Catalog
Fact sheets, journal publications, reports, and other resources for parents, community members, patients and healthcare professionals
Topics included: Air Quality, Pesticides, Natural Disasters, BPA, Mold, Lead, Mercury
The Role of Early Life Exposures in Late Life Neurodegenerative Disorders

Samuel M. Goldman, MD, MPH
University of California-San Francisco
Division of Occupational & Environmental Medicine and Department of Neurology
Co-Director PEHSU Region 9
<table>
<thead>
<tr>
<th>Collaborators</th>
<th>Kaiser Permanente DOR</th>
<th>Capital Univ Med Sci</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stephen Van Den Eeden</td>
<td>Piu Chan</td>
</tr>
<tr>
<td></td>
<td>Kathleen Albers</td>
<td>Kitty Gu</td>
</tr>
<tr>
<td></td>
<td>Amethyst Leimpeter</td>
<td>Favaloro University</td>
</tr>
<tr>
<td>NIEHS</td>
<td>Freya Kamel</td>
<td>Anabel Chade</td>
</tr>
<tr>
<td></td>
<td>David Umbach</td>
<td>Buddhist Tzu Chi Hospital</td>
</tr>
<tr>
<td></td>
<td>Marie Richards</td>
<td>Raymond Lo</td>
</tr>
<tr>
<td></td>
<td>Dale Sandler</td>
<td>Shiga University</td>
</tr>
<tr>
<td>Stanford University</td>
<td>Lorene Nelson</td>
<td>Robert Abbott</td>
</tr>
<tr>
<td></td>
<td>James Tetrud</td>
<td>VA Pacific Islands Healthcare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G. Webster Ross</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DZNE</td>
</tr>
<tr>
<td>NCI</td>
<td>Aaron Blair</td>
<td>Sarah Jewell</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dino DiMonte</td>
</tr>
<tr>
<td>Columbia University</td>
<td>Andrew Singleton</td>
<td>Toronto Western Hospital</td>
</tr>
<tr>
<td></td>
<td>Ruth Ottman</td>
<td>Connie Marras</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anthony Lang</td>
</tr>
</tbody>
</table>

Research Funders:  Michael J. Fox Foundation; NIEHS; NINDS; NIOSH; Department of Defense; UCSF Academic Senate; Parkinson’s Foundation
Outline

• Neurodegenerative diseases overview
• Neurodegenerative disease & environment
• Vulnerabilities of the young brain
• Early Life Risk Factors for Neurodegenerative Disease
  • Metals
  • Infection
  • Pesticides
  • Air Pollution
Background & Epidemiology

Neurodegenerative Diseases
“Primary” Neurodegenerative Disorders: Clinical Classification

- Primary dementing disorders (may manifest parkinsonism)
  - Alzheimer Disease (AD)
  - Frontotemporal dementias (FTD, FTLD)
  - Dementia with Lewy Bodies (DLB)

- Primary parkinsonian disorders (may manifest dementia)
  - Parkinson Disease (PD)
  - Atypical parkinsonisms: Multiple System Atrophy (MSA); Progressive Supranuclear Palsy (PSP); Corticobasal Ganglionic Degeneration (CBD)

- Choreiform disorders (may manifest dementia & parkinsonism)
  - Huntington’s Disease
  - Spinocerebellar ataxias

- Neuromuscular disorders
  - Amyotrophic Lateral Sclerosis (ALS)
  - primary lateral sclerosis, spinal/bulbar muscular atrophy

- Others
  - Chronic traumatic encephalopathy (CTE)
  - Guamanian PD-ALS-dementia
Neurodegenerative Disorders
Histopathological Classification (often overlapping)

- β-amyloidoses:
  - Alzheimer disease (AD)
  - Dementia with Lewy bodies (DLB)

- Tauopathies:
  - Alzheimer disease (AD)
  - Progressive supranuclear palsy (PSP)
  - Chronic traumatic encephalopathy (CTE)

- α-synucleinopathies:
  - Parkinson disease (PD)
  - Dementia with Lewy bodies (DLB)
  - Multiple system atrophy (MSA)

- TDP-43:
  - Amyotrophic lateral sclerosis (ALS)
  - Frontotemporal lobar degeneration (FTLD)
Challenges in Studying Neurodegenerative Diseases

- Few or no diagnostic tests
- Clinically heterogeneous
- Pathologically heterogeneous
- Etiologically heterogeneous
- Diseases of aging: long pre-clinical period
  - Exposures may occur decades before symptoms
  - Competitive mortality
The Shaking Palsy

Parkinson Disease
Parkinson Disease: parkinsonism

Clinical Syndrome:
Bradykinesia, resting tremor, rigidity, postural reflex impairment

Neural substrate: Nigrostriatal system, disrupted dopaminergic transmission
Parkinson Disease: Overview

- Most common cause of parkinsonism
- Described fully in 1817 by James Parkinson
- Affects ~ 1 million in U.S.; 50,000-70,000 new cases annually
- ~ 2% prevalence > 65 years of age
- Cause unknown > 90%

PD Pathology: Loss of Pigmented Dopaminergic Neurons in the *Substantia nigra pars compacta*

But….PD is a systemic disease

- Synuclein pathology in myenteric plexus
- Synuclein pathology in olfactory bulb

Lewy bodies in a neuron from the substantia nigra in PD
PD Incidence *may be increasing over time*

Parkinson’s disease incidence in Olmstead County, MN 1976-2005

**RR per decade**
Men: 1.24 (95%CI 1.08-1.43)
Women: 1.09 (95%CI 0.87-1.38)

*Savica et al, JAMA Neurol, 2016*
Alzheimer Disease
Alzheimer’s Disease: Overview

- Most common neurodegenerative disease
- 60-80% of dementias
- Other common dementias: vascular, DLB, FTLD, PD, CTE
- > 5 million Americans
- 6% > age 60, 30% > 85
- Pathology
  - Aggregated $\beta$-amyloid plaques
  - Phosphorylated neurofibrillary tau tangles
  - Others common: synuclein, TDP-43
Alzheimer’s Trends: increasing prevalence, decreasing incidence

Change in causes of death 2000-2015

Alzheimer’s Association Report, Alzheimer & Dementia, 2018

Figure 1. Crude Dementia Incidence in the Einstein Aging Study Cohort as a Function of Date of Birth and Age

Derby et al, JAMA Neurol, 2017
Amyotrophic Lateral Sclerosis
Amyotrophic Lateral Sclerosis (ALS)

- 90% of degenerative motor neuron diseases
- First described by Charcot in 1869
- Clinical Features
  - Degeneration of upper & lower motor neurons
  - Spasticity & muscle atrophy
  - Survival ~3 years
- Incidence 1-2/100,000 p-y
- Median age at onset 65-70
- Men at ~40% higher risk
- Pathologically heterogeneous
  - TDP-43 (usually sporadic)
  - SOD1 (usually familial)
  - C9orf72 (usually familial)

ALS Incidence May Be Increasing

Figure 2. Age-standardized incidence of amyotrophic lateral sclerosis (to the Swedish population in 1991, 1 per 100,000 person-years) by sex and calendar period in Sweden, January 1, 1991, through December 31, 2005.

Fang et al, 2009, Arch Neurol
Environment is a major determinant of neurodegenerative disease risk
Environment & Parkinson Disease
“…paralysis agitans is not a family disease”
Charcot, 1877

“Many patients with the disease have a strong family history…”
Gowers, 1888
Name This Disease
Twins: Nature's Controlled Study

Tanner, Goldman, et al, JAMA 1999

- Identical twins share 100% of genes
- Fraternal twins share ~ 50% of genes

Hypothesis:
If PD is primarily a genetic disorder, MZ concordance should be >> DZ concordance.

Results:
Similar concordance in MZ & DZ twin pairs
Heritability ≤ age 50 ~100%
Heritability > age 50 only 7%

Conclusion:
Environment is a major contributor to the cause of typical PD
Toxicants Associated with PD Risk: Mechanistic & Structural Similarity

**Rotenone**

**TCE**

**PERC**

**CYP2E1**

**Tryptamine**

**TaClo***

**Paraquat**

**MPP**

*1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline*
PD Environmental Associations

Increased Risk

Lifestyle
- Head trauma
- Diet (dairy products, animal fats)

Environmental exposures
- MPTP
- Pesticides (paraquat, rotenone, others)
- Industrial agents (PCBs)
- Solvents (TCE, PERC)
- Metals (lead, iron)

Rural residence
- Drinking well water

Occupations: health care, teaching, woodworking/carpentry, legal work, religious work, farming

Reduced Risk

Cigarette smoking and tobacco use

Coffee and tea drinking

Diet
- “Mediterranean” diet
- polyunsaturated fats
- uricogenic diet

High physical activity

Medications
- Calcium-channel blockers
- Statins

"From Goldman & Tanner, in Parkinson’s Disease & Movement Disorders, Jankovic & Tolosa eds, 2015."
AD heritability estimated at ~50%: APOE4

Scheltens et al., Lancet, 2015
Alzheimer Disease: Risk Factors

**Increased Risk**

**Lifestyle**
- Head trauma
- Diet (animal fats)
- **Smoking**

**Environmental exposures**
- **Air pollution**
- Pesticides
- Metals (lead, aluminum, copper…)
- Solvents

**Comorbidities**
- Cardiovascular disease
- Hypertension
- Diabetes
- Obesity

**Reduced Risk**

**Cognitive Reserve**
- **Education**
- IQ
- Intellectual engagement

**Diet**
- “Mediterranean” diet
- polyunsaturated fats

**Physical activity**

**Medications**
- Statins
Environment &

Amyotrophic Lateral Sclerosis
90% of ALS is sporadic. Gene mutations identified in 75% of familial ALS, but only 10% of sporadic.

*Fig. 1* Approximate frequency of gene mutations in familial ALS (other known affected family members) and apparently sporadic ALS (no other known family members). Sporadic ALS represents approximately 90%, and familial ALS 10% of patients.

*Morgan et al, Br Med Bull, 2016*
ALS Risk Factor Associations

- Pesticides
- Lead exposure
- Military service
- Smoking
- Electromagnetic field exposure
Life Course Mechanisms

Vulnerability of the young brain
Differences in BBB and blood-CSF barrier
BBB is established very early in development but penetration likely higher in infants < 4 months
Membrane influx & efflux pumps vary substantially over development

Ghersi-Egea et al, Pharm Res, 2018
Xenobiotic sensitivity: mechanisms

- Larger exposures
  - Large surface area:volume ratio; high respiratory rate
  - Slower hepatic metabolism of xenobiotics
  - Reduced cellular extrusion of xenobiotics

- Immunologic priming
  - Microglial sensitization
  - Microbiota development

- Genomic priming
  - Epigenomic modification

Fig. 1. One-year-old female genetically identical viable yellow agouti mice (A^vy). Maternal dietary supplementation with methyl donors such as folic acid, choline, and betaine [34] or the phytoestrogen, genistein [32], shifts the coat color of the offspring from yellow to brown, and reduces the incidence of obesity, diabetes, and cancer.

Dolinoy et al, Reprod Toxicol, 2007
The Evidence: Early Life Risk Factors for Neurodegenerative Disease
• Prior concordance estimates based on incomplete data (many still living)
• National Death Index: 95% of all twins now deceased (2016)

Still find only minor genetic liability in typical onset PD
• But, very high concordance in DZ twins (13%)—3x higher than other 1st-degree relatives: shared early environment!
AD in Swedish Twins: High DZ Concordance
Gatz et al, Arch Gen Psychiatry, 2006

- 1083 same sex MZ pairs
  - Intrapair concordance 41%
- 1688 same sex DZ pairs
  - Intrapair concordance 32% overall, 41% in women

<table>
<thead>
<tr>
<th></th>
<th>Shared Genetics</th>
<th>Shared Environment</th>
<th>Non-shared Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.59</td>
<td>0.21</td>
<td>0.20</td>
</tr>
<tr>
<td>Women</td>
<td>0.37</td>
<td>0.53</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Evolution of PD Pathology: Decades in the Making

Peripheral pathology may precede CNS pathology by decades

Synuclein pathology in myenteric plexus

Braak et al, J Neurol, 2002
Alzheimer pathology begins early

Braak & Braak, Neurobiol Aging, 1997

~20% < age 30 have neurofibrillary pathology
Early Life Risk for Neurodegeneration

Metals
• **Iron dysregulation in PD & AD**
  - PD: increased free, non-ferritin iron in substantia nigra
  - AD: iron associated with amyloid plaques, and tau aggregation, increased APP expression

• **Oxidative stress: Fenton reaction**
  \[
  \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^-
  \]

• **Human sources**
  - Dietary: infant formula, fortified foods, water, nutritional supplements
  - Inhaled: pollution, occupational

MRI of iron in PD brain
*Ward et al, Lancet Neurol, 2014*
Neonatal Iron: Mouse Model
Kaur et al, Neurobiol Aging, 2007

- Administered doses equivalent to iron-fortified infant formula
- Daily from 10-17 days post-partum (~first human year of life)
- Sacrificed at 2, 12, 16, or 24 months
- Half of each group received MPTP injection prior to sacrifice

Results:
- Infant dietary iron decreased SN DA only in aged
- Increased sensitivity to MPTP beginning in late adulthood
Lead

- Extensive literature on cognitive and other developmental impairments associated with any level of lead exposure
  - Lower IQ associated with increased risk of AD

- Suggestive human epidemiologic evidence of association of bone lead (tibial, t\(_{1/2}\) 10-30 years) with AD & PD

- Stronger evidence in ALS

- Proposed mechanisms
  - Epigenetic modification
  - Oxidative stress
  - Protein aggregation
Neonatal Lead & Alzheimer pathology

- Lead exposure during first year of life increased cortical p-tau & Aβ in aged (23-yrs) monkey

Bihaqi et al, Neurotoxicol, 2013

Wu et al, J Neurosci, 2008
Lead & Neurodegeneration: Epigenetics

- Mice fed 200 ppm Pb days 1-20
- Cortical APP at various times

- Adult lead exposure did not increase APP expression
- Strongly suggests an epigenetic effect

- Maternal bone Pb inversely associated with cord blood DNA methylation
- Reduced DNA methylation associated with increased gene transcription

Basha et al, J Neurosci, 2005

Pilsner et al, EHP, 2009
Early Life Risk for Neurodegeneration

Infection & Microglial Priming
Infection & Neurodegeneration

**PD**
- encephalitis lethargica epidemic
- gut microbial differences
- perinatal/childhood infection studies very limited:
  - croup/diphtheria (Martyn & Osmond 1995)
  - decreased risk with several childhood infections (Sasco & Paffenberger 1985)
  - spring birth (Mattock 1988; Torrey 2000)

**AD**
- Periodontitis associations
- Increasingly compelling autopsy data

### AD Autopsy Associations

<table>
<thead>
<tr>
<th>Organism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Maheshwari &amp; Eslick, J Alz Dis, 2015</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Porphyromonas gingivalis</td>
<td></td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td></td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Licastro et al, Immun Ageing, 2014</td>
</tr>
<tr>
<td><em>Herpes simplex I</em></td>
<td></td>
</tr>
<tr>
<td>Epstein Barr</td>
<td>Mastroeni et al, Neurobiol Aging, 2018</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
</tr>
<tr>
<td>HHV-6A</td>
<td>Redhead et al, Neuron, 2018</td>
</tr>
<tr>
<td>HHV-7</td>
<td></td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>Pisa et al, J Alz Dis, 2015</td>
</tr>
</tbody>
</table>
Infection & Neurodegeneration

- Redhead et al, Neuron, 2018
  - Common viral species frequently detected in normal, aging brain
  - Increased HHV-6A and HHV-7 in brains of subjects with (AD)
  - Findings replicated in two additional, independent cohorts
  - Viral regulation of APP processing genes

- $\alpha$-synuclein has anti-microbial properties (Tomlinson et al, J Neural Transm, 2017)

- $\text{A}\beta$ has anti-microbial properties (Kumar et al, Sci Transl Med, 2016)
  - Ab expression protects against fungal & bacterial infections in mouse, nematode, cell culture
  - Ab fibrils colocalize to reduce pathogen adhesion

- LRRK2 & ApoE are modulators of immune function
Microglial Priming: the lipopolysaccharide model  

- LPS = bacterial endotoxin
- outer membrane of Gram – bacteria
- Rapidly immunogenic (nanomolar)

a) A single \textit{peripheral} injection
- Immediate microglial activation
- Delayed loss of dopaminergic neurons
  - Specific for substantia nigra
  - Gradual, progressive loss: 23% at 7 months, 43% at 10 months

b) \textit{In utero} model
- Single maternal injection gestation day 10
- Reduced SN dopaminergic neurons in pups, rate of loss unchanged
- But! \textit{Adult} exposure to a sub-toxic dose of rotenone caused degeneration in the LPS-exposed rats
LPS or saline administered to mice on day 5

Low dose rotenone or saline days 70-84

LPS-primed neonates exhibited markedly increased adult sensitivity to a sub-toxic dose of rotenone
Early Life Risk for Neurodegeneration

Pesticides
Pesticides & Neurodegeneration

- PD epidemiology consistent:
  - Rotenone: mitochondrial poison
  - Paraquat: redox cycling
  - Organochlorines: protein aggregation
  - Others: Organophosphates, pyrethroids....

- AD, ALS epidemiology smaller, less consistent

Proposed Mechanisms
- Excitotoxicity
- Mitochondrial damage
- Oxidative stress
- Protein aggregation
- Epigenetic modification

Gene x Pesticide interactions likely important

Van der Mark et al, EHP, 2012
Early Life Pesticide Exposures & Developmental Effects

- Increasing evidence of neurodevelopmental effects of intrauterine and early life pesticide exposures.
  - Autism, developmental delay, lower IQ
  - Organophosphates, carbamates, pyrethroids, fumigants neonicotinoids

**CHAMACOS study** (Gunier et al, EHP, 2017)
- Salinas Valley, California
- Pesticide application data mapped to mother’s residence during pregnancy
- Lower IQ at age 7

<table>
<thead>
<tr>
<th>Neurotoxic Pesticides</th>
<th>β</th>
<th>(95% CI)</th>
<th>β</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full-Scale IQ (n = 255)</td>
<td>Verbal Comprehension (n = 283)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPs</td>
<td>-2.1</td>
<td>(-3.8, -0.3)</td>
<td>-2.5</td>
<td>(-4.1, -1.0)</td>
</tr>
<tr>
<td>Acephate</td>
<td>-2.3</td>
<td>(-3.9, -0.6)**</td>
<td>-2.7</td>
<td>(-4.3, -1.2)**</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td>-1.4</td>
<td>(-3.0, 0.2)</td>
<td>-2.2</td>
<td>(-3.7, -0.7)**</td>
</tr>
<tr>
<td>Diazinon</td>
<td>-1.7</td>
<td>(-3.4, 0.1)</td>
<td>-1.6</td>
<td>(-3.2, -0.1)*</td>
</tr>
<tr>
<td>Malathion</td>
<td>-0.8</td>
<td>(-2.5, 0.8)</td>
<td>-1.3</td>
<td>(-2.8, 0.2)</td>
</tr>
<tr>
<td>Oxydemeton–methyl</td>
<td>-2.3</td>
<td>(-4.0, -0.7)**</td>
<td>-2.8</td>
<td>(-4.3, -1.3)**</td>
</tr>
<tr>
<td>OPs toxicity weighted</td>
<td>-2.2</td>
<td>(-3.9, -0.5)**</td>
<td>-2.9</td>
<td>(-4.4, -1.3)**</td>
</tr>
<tr>
<td>Carbamates</td>
<td>-1.2</td>
<td>(-2.8, 0.4)</td>
<td>-2.4</td>
<td>(-3.9, -1.0)**</td>
</tr>
<tr>
<td>Carbamates toxicity weighted</td>
<td>-1.3</td>
<td>(-2.9, 0.3)**</td>
<td>-2.5</td>
<td>(-4.0, -1.0)**</td>
</tr>
<tr>
<td>Carbamates and OPs toxicity weighted</td>
<td>-2.1</td>
<td>(-3.7, -0.4)*</td>
<td>-2.9</td>
<td>(-4.5, -1.4)**</td>
</tr>
<tr>
<td>Neonicotinoids</td>
<td>-1.7</td>
<td>(-3.3, 0.0)*</td>
<td>-1.9</td>
<td>(-3.5, -0.3)*</td>
</tr>
<tr>
<td>Pyrethroids</td>
<td>-2</td>
<td>(-3.7, -0.3)*</td>
<td>-1.8</td>
<td>(-3.4, -0.3)*</td>
</tr>
<tr>
<td>Mn-fungicides</td>
<td>-2</td>
<td>(-3.7, -0.2)</td>
<td>-2.1</td>
<td>(-3.7, -0.6)**</td>
</tr>
<tr>
<td>Rank index of 5 neurotoxic groups</td>
<td>-2</td>
<td>(-3.7, -0.4)*</td>
<td>-2.4</td>
<td>(-4.0, -0.9)**</td>
</tr>
</tbody>
</table>
Pesticides & Alzheimer’s Disease

- Limited human data on early life pesticide exposures & AD
- Richardson et al, JAMA Neurol, 2014
- DDT & it’s primary metabolite DDE
- DDE highly persistent (t₁/₂ ~10 years)

OR for highest tertile of serum DDE = 4.2 (2.5-5.8)

Figure 1. Serum Levels of Dichlorodiphenyldichloroethylene (DDE)

DDT & DDE increase levels of amyloid precursor protein in culture
Early Life Pesticide Exposures & PD
An Animal Model (Cory-Slecta et al, EHP, 2005)

- Maneb (Mn-carbamate fungicide) & paraquat
- Dosed with saline, Maneb, PQ or both
  - Ages 5-19 days and/or 7 months
- Additive effect on SN DA neurons
- Increased susceptibility to adult toxicity
Early Life Risk for Neurodegeneration

Air Pollution
Air Pollution & Neurodegeneration

- Increasingly compelling link with AD, dementia, cognitive decline
- Proposed mechanisms related to PM$_{2.5}$, ozone, NO$_x$, ultrafine (< 100nm)
  - Inflammation/microglial activation
  - Oxidative stress
  - Protein aggregation
  - Epigenetic modification
  - BBB breakdown
- Peripheral effects leading to CNS effects
- Direct effects (e.g. ultrafine transport through olfactory bulb)
Autopsy series around Mexico City
- 203 consecutive autopsies
  - sudden death w/o direct injury to brain, no prior CNS illness
  - Aged 11 months-40 years

\[ \text{Aβ in 38yo} \]
Early Life Air Pollution: ultrafine “nano” particles

Maher et al, PNAS, 2016

- Autopsy series in Manchester, England and Mexico City
- Magnetite nanoparticles likely derived from traffic-related combustion
- Direct cortical access through olfactory bulb
- Highly redox-active particles
- Previously found in association with plaques & tangles

Scanning electron micrograph of magnetite particles extracted from frontal cortex
Neurodegeneration Models: Early Hits & Multiple Hits

Cory-Slecta et al, EHP, 2005
Summary

- Very limited human epidemiologic data on early life risk factors for late life neurodegenerative diseases

But....
- Extensive and growing understanding of disease mechanisms
- Better animal and cellular models
- Emerging “in silico” tools

Consistent findings
- Early insults prime the system
- Later life & multiple hits accelerate disease processes
- Genes & environment converge on common pathways:
  - Inflammation
  - Mitochondria
  - Protein aggregation & impaired clearance

Neurodegenerative diseases evolve over decades: opportunities for prevention
Webinars:
Series of scientific webinars that provide a forum for discourse on scientific issues.
- Live and On-Demand
- Case Conferences
- Journal Clubs
- Grand Rounds
- CE Available

Online Courses:
Evidence-based online courses on a variety of children's environmental health topics.
- Interactive and Self-Paced
- CE Available

Resource Catalog:
Fact sheets, journal publications, reports, and other resources for parents, community members, patients and healthcare professionals
- Topics included: Air Quality, Pesticides, Natural Disasters, BPA, Mold, Lead, Mercury

www.pehsu.net/nationalclassroom.html