THE ENVIRONMENT and CHILDRENS HEALTH : THE ROLE OF RESEARCH IN UNDERSTANDING AND PREVENTING RISK

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CRITICAL RESEARCH ISSUES in ENVIRONMENTAL HEALTH

- UNDERSTANDING EARLY EXPOSURES – LATE OUTCOMES
- UNDERSTANDING VARIABILITY IN DOSE
- UNDERSTANDING EFFECTS OF MIXTURES [SIMILAR and DIFFERENT STRESSORS]
- UNDERSTANDING ROLE OF DIET IN TOXIC RESPONSES
- UNDERSTANDING OTHER SOURCES OF VARIABILITY IN RESPONSE
TYPES OF RESEARCH

- BASIC RESEARCH
- EPIDEMIOLOGY
  - SURVEILLANCE AND VIGILANCE
  - OBSERVATIONAL RESEARCH
  - INTERVENTION RESEARCH
- TOXICOLOGY
  - CHEMICAL TESTING
  - CHEMICAL ANALYSIS
  - MECHANISTIC TOXICOLOGY
THE ROLE OF BASIC RESEARCH in ENVIRONMENTAL HEALTH

- WHAT ARE THE IMPLICATIONS OF NEW RESEARCH FOR CHILDREN’S ENVIRONMENTAL HEALTH?
  - CAN BASIC RESEARCH CHANGE THE PARADIGMS?

- HOW CAN RESEARCH CONTRIBUTE TO IMPROVING CHILDREN’S HEALTH?
  - CAN BASIC RESEARCH CONTRIBUTE TO EPIDEMIOLOGY?
GENETICS and ENVIRONMENT

OLD CONCEPT: DISEASES ARE EITHER GENETIC OR ACQUIRED

NEW CONCEPT: GENETICS & ENVIRONMENT INTERACT IN HEALTH AND DISEASE

- GENES RESPOND TO ENVIRONMENT
- ENVIRONMENT AFFECTS GENES
- GENES INFLUENCE RANGE OF INDIVIDUAL RESPONSE
- ENVIRONMENT INFLUENCES EXPRESSION OF GENES
GENE: ENVIRONMENT INTERACTIONS

- Genes or environmental exposures separately can cause disease
  - Genetic defect (BrCa 1,2) causes breast cancer
  - Exposure to estradiol causes breast cancer
- Genes and exposures are necessary for response
  - Asthma? Autoimmune diseases?
- Genes modulate environmental exposures
  - GST polymorphisms regulate activation/deactivation of solvents that cause cardiac malformations
- Genes modulate response to environmental exposures
  - Paraoxonase polymorphisms determine neurotoxic responses to chlorpyrifos
- Environmental exposures modulate genetic disease
  - Lead exposure exacerbates clinical severity of acute intermittent porphyria
APPLICATION OF NEW
GENE:ENVIRONMENT CONCEPTS TO
EPIDEMIOLOGY

BIOMARKERS – OPENING THE
"BLACK BOX" OF EPIDEMIOLOGY

DEFINITION

MEASURABLE SIGNALS IN BIOLOGICAL
COMPARTMENTS

TYPES OF BIOMARKERS

SUSCEPTIBILITY
EXPOSURE
OUTCOME
BIOMARKERS – from toxicology to epidemiology

RISK FACTORS ➔ HOST ➔ OUTCOMES
BIOMARKERS and TOXICOLOGY: BIOMARKERS FOR EXPOSURE TO BUTADIENE – Albertini et al 2003

Fig. 1. Partial metabolic scheme for 1,3-butadiene (BD).
ENVIRONMENTAL ETIOLOGIES OF DEVELOPMENTAL DYSFUNCTION

- OLD CONCEPT: ONLY MATERNAL EXPOSURES CAN CONTRIBUTE TO PRENATAL IMPACTS
- NEW CONCEPT: BOTH PATERNAL AND MATERNAL EXPOSURES CAN AFFECT FETAL DEVELOPMENT AND CHILDREN’S HEALTH
ROLE OF PATERNAL FACTORS IN FETAL DEVELOPMENT – GENOMIC IMPRINTING

- GENOMIC IMPRINTING – DIFFERENTIAL IMPORTANCE OF PARENT OF ORIGIN FOR EXPRESSION OF SPECIFIC GENES
  - MATERNAL, PATERNAL IMPRINTS CONTRIBUTE DIFFERENTIALLY TO DEVELOPMENT
- MOST IMPRINTED GENES REGULATE INTRAUTERINE DEVELOPMENT
  - PLACENTAL/FETAL GROWTH AND NUTRITION
- ENVIRONMENT CAN AFFECT GENOMIC IMPRINTS
  - ADVERSE EFFECTS OF ASSISTED REPRO TECHNOLOGIES, MAMMALIAN CLONING
RISKS OF LEAD EXPOSURE TO PERINATAL DEVELOPMENT

OLD CONCEPT: MOTHER’S BLOOD LEAD IS TRANSFERRED TO FETUS, SO RISKS RELATE TO HER CURRENT LEAD EXPOSURE

NEW CONCEPT: MOTHER’S BONE LEAD IS TRANSFERRED TO FETUS, SO RISKS RELATE TO HER PAST HISTORY OF LEAD EXPOSURE
Mobilization of bone lead during pregnancy (Gulson et al 1999)
ENVIRONMENTAL HEALTH RISKS AND DEVELOPMENT

OLD CONCEPT – PRE/POST TRANSITION HEALTH RISKS ARE DIFFERENT, AND RESULT IN DIFFERENT PATTERNS OF DISEASE

NEW CONCEPT – COMPLEX HEALTH RISKS OCCUR AT ALL STAGES OF DEVELOPMENT, AND MAY INTERACT
THE OLD MODEL

- PRE-TRANSITION HEALTH RISKS – INFECTIOUS DISEASE, ACUTE EXPOSURES, PERINATAL MORTALITY OF MOTHERS AND INFANTS
- POST-TRANSITION HEALTH RISKS – CHRONIC DISEASE, CHRONIC EXPOSURES, DISEASES OF OLDER AGE
THE NEW MODEL

● CHRONIC EXPOSURES INTERACT WITH INFECTIOUS DISEASE TO INCREASE RISKS OF BOTH ACUTE DISEASE (INFECTION) AND CHRONIC DISEASE (POST INFECTION SEQUELAE)
  ○ EXAMPLE: MERCURY, GOLD MINING, INFECTIOUS DISEASE, AUTOIMMUNE DISEASE
CO-LOCALIZAÇÃO de MALARIA e GARIMPAGEM – WHO/OMS
ECOLOGIA e DOENÇAS INFECCIOSAS

MEIO AMBIENTE

VETORES

HOSPEDEIROS
 Numeros
 Imunidade

PARASITAS
GARIMPAGEM – Rio Crepuri, PARA, BRAZIL
O MERCURIO e MALARIA em ratinhos

INFECÇÃO PARA SPOROZOITÉS (P yoelli)
- INCREMENTO DO PARASITEMIA

ESTAGIO SANGUE INFECÇÃO
- NAO EFEITOS DO PARASITEMIA

ESTAGIO FIGATO INFECÇÃO (in vitro)
- INIBIÇÃO de SINAIS IFN-\(\gamma\), IL-1\(\beta\), IL-6, TNF-\(\alpha\)
- DOWNREGULATION de EXPRESSION de iNOS

IMUNIZÃO e IMUNIDADE EXPERIMENTAL
- INIBIÇÃO TOTAL DE AQUISIÇÃO DE IMUNIDADE
MERCURY & MALARIA – EPI DATA

- MERCURY INCREASES LIKELIHOOD OF MALARIA INFECTIONS
- MERCURY APPEARS TO INHIBIT ACQUIRED IMMUNITY TO MALARIA
- MERCURY EXPOSURES INCREASE PREVALENCE OF ELEVATED ANA, ANoA [autoantibodies]; INTERACTIONS WITH MALARIA
Antinuclear (ANA) e antinucleolar (ANoA) autoanticorpos em seros de pessoas em Amazonia.
CAN MERCURY INCREASE RISKS of POST-INFECTION DISEASE?

- POST-INFECTION AUTOIMMUNE DISEASE
- MIOCARDITIS CHAGASTICA
- SYSTEMIC LUPUS ERYTHEMATOSIS
CARDIOMIOPATOLOGIA em RATINHOS PRETREATED COM MERCURIO (Nyland et al 2003)
## EFFECTS OF PRENATAL MeHg EXPOSURE ON IMMUNE FUNCTION at ADULTHOOD – MICE EXPERIMENTS

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age [Days]</th>
<th>N/gp</th>
<th>Treatment</th>
<th>IL-4</th>
<th>IL-10</th>
<th>IFN-g</th>
<th>IL-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/M</td>
<td>60</td>
<td>10</td>
<td>dH₂O</td>
<td>&lt; LOD</td>
<td>37±18</td>
<td>313±100*</td>
<td>1809±90**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HgCl₂</td>
<td>&lt; LOD</td>
<td>&lt; LOD</td>
<td>&lt; LOD ▼</td>
<td>37±22</td>
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<tr>
<td>Lymph Nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▼</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dH₂O</td>
<td>757±49</td>
<td>376±43*</td>
<td>5045±1045</td>
<td>2730±77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HgCl₂</td>
<td>617±91</td>
<td>191±15</td>
<td>3728±909</td>
<td>2637±99</td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dH₂O</td>
<td>2869±279*</td>
<td>831±63*</td>
<td>3963±155**</td>
<td>&lt; LOD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HgCl₂</td>
<td>1213±165</td>
<td>^ 327±91</td>
<td>285±45</td>
<td>21±8</td>
</tr>
</tbody>
</table>

The table above shows the effects of prenatal MeHg exposure on immune function at adulthood in mice through experiments. The table includes cytokine levels (IL-4, IL-10, IFN-g, and IL-2) measured in pg/ml for different treatments (dH₂O and HgCl₂) and tissues (Lymph Nodes, Spleen, and Thymus). The data indicates significant changes in cytokine levels, particularly in the Thymus, with MeHg exposure leading to decreased IL-4 and increased IFN-g levels.
CONCLUSIONS [from a basic research perspective]

- BASIC RESEARCH CAN IDENTIFY NEW CONCEPTS FOR THE ROLE OF ENVIRONMENT IN CHILDREN’S HEALTH
- BASIC RESEARCH CAN PREDICT NEW OUTCOMES RELATED TO ENVIRONMENTAL EXPOSURES
- BASIC RESEARCH CAN PROVIDE TOOLS FOR CLINICAL/EPIDEMIOLOGICAL STUDIES
PERSPECTIVES ON INTERNATIONAL RESEARCH COLLABORATION

- RESEARCH CAPACITY IS A PRECIOUS INTERNATIONAL RESOURCE
- INTERNATIONAL RESEARCH COLLABORATIONS ACROSS DISCIPLINES NEED ENHANCEMENT
- RESULTS FROM BASIC RESEARCH NEED TO BE TRANSLATED INTO APPLIED RESEARCH AND PUBLIC HEALTH POLICY
- EPIDEMIOLOGICAL OBSERVATIONS (EXPOSURES, OUTCOMES) SHOULD MORE RAPIDLY STIMULATE BASIC RESEARCH
CAN WE SHARE RESEARCH FINDINGS INTERNATIONALLY?

- YES
  - INTERNATIONAL STUDIES OF LEAD, MERCURY

- NO
  - PESTICIDE EXPOSURES AMONG SPECIFIC GROUPS – PERI-OCCUPATIONAL EXPOSURES, CHILD LABOR IN AGRICULTURE, MIXTURES
  - DIETARY DIFFERENCES – FISH CONSUMPTION PATTERNS
TORREON MEXICO – LEAD SMELTER
CARTARET USA – LEAD SMELTER