Endocrine Disruption and Immune Dysfunction

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EDCs and DIT
Dose sensitivity
Persistence
Spectrum of effects
Latency

The majority of risk factors we discuss in this book are...... EDCs.
Outline

1. Endocrine disrupting chemicals (EDCs) as a priority health threat for non-communicable diseases (chronic diseases and conditions)
2. The role of EDCs in developmental immunotoxicity (DIT) and immune dysfunction
3. Misregulated inflammation as the foundation bloc that connects EDCs to networks of chronic diseases
4. Inadequacy of current safety testing to protect us from environmentally-induced chronic diseases.
The Landscape of Endocrine Disrupting Chemicals (EDCs)

Endocrine disruptors are chemicals that may interfere with the body’s endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. – (NIEHS, Dec. 2013)

Approximately 1,000 potential EDCs have been identified. - (The Endocrine Disruption Exchange [TEDX], Dec. 2013)

They can be found among: household products, personal care products, food, flame retardants, pesticides, plastic and rubber products, antimicrobials, metal mixtures, industrial additives, solvents, metabolites of other chemicals, and biogenic compounds. – (TEDX, Dec., 2013)

EDCs are active at very low doses (non-monotonic dose-response curves).

EDC-linked dysfunction has been reported for virtually every organ and tissue of the body.
The 65 yr. old F2 woman could experience an adult-onset chronic disease or condition linked to an EDC exposure of germ cells from 100 years earlier.

Adapted from Dietert, Transgenerational Epigenetics of EDCs, in press
1,000 EDCs across different chemical categories

Multiple Pathways and Forms of Endocrine Disruption

Can these be simplified?

(Misregulated Inflammation)

A Myriad of Disparate Tissue-Related Chronic Diseases and Conditions
NIH Examination of the Inflammation-Chronic Disease Link

NIH STEP Forum
STEP - Inflammation: The Root and Route of Chronic Diseases?
(HHS Only)
Tuesday, November 15, 2011
Jerry Phelps, Rodney Dietert, Charles Serhan and David Mosser
441 views (276 live, 165 VOD)

NIEHS Partnership for Environmental Public Health
PEPH Webinar - Connecting Environmental Exposures to Chronic Inflammation and Diseases
February 28th, 2012 – 12:00 to 1:30 p.m. ET
Webinar Summary (337KB)
NIEHS Calendar
Non-Communicable Diseases (*i.e.*, Chronic Diseases) are the Number One Health Threat and Most Likely Adverse Outcomes Following EDC Exposure

- The Number #1 Cause of Mortality Worldwide (63%)*
- Most Chronic Diseases are Increasing in Prevalence
- They Dramatically Impact Quality of Life
- Estimated to Cost 48% of Global GDPs by 2030*
- 45.3% of all US adults age 65 and above have two or more chronic diseases: a 20% increase from the previous decade.*

*Joint 2011 report: Harvard School of Public Health and World Economic Forum and NCHS Data Brief Number 100, July 2012
Chronic diseases are highly interconnected; Depression, CVD, tissue-specific cancer, sleep disorders, metabolic disease and sensory loss, are common to immune dysfunction-driven disease patterns.

Approximately one quarter of children in certain developed countries have immune-based chronic diseases. Dietert and Zelikoff, 2009 Curr Pediatr. Rev.
<table>
<thead>
<tr>
<th>TYPE 1 DIABETES</th>
<th>CELIAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
<td>Osteoporosis (&amp; fractures)</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>COPD (men)</td>
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<tr>
<td><strong>Endometrial cancer (women)</strong></td>
<td><strong>Specific G.I. tract cancer</strong></td>
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<tr>
<td>Depression and anxiety</td>
<td>Depression (women)</td>
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<tr>
<td>Hearing loss</td>
<td>Hearing loss</td>
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<tr>
<td>Eating disorders</td>
<td>Eating disorders (women)</td>
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<tr>
<td><strong>Cardiovascular disease</strong></td>
<td><strong>Cardiovascular disease</strong></td>
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<tr>
<td>Hypertension</td>
<td>Sarcoidosis</td>
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<tr>
<td>Osteopenia</td>
<td>Restless leg syndrome</td>
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<tr>
<td>Addison’s disease</td>
<td>Liver Cirrhosis</td>
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<tr>
<td>Vitelligo</td>
<td>Recurrent Miscarriage (women)</td>
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</table>
EDCs and Critical Windows of Immune Vulnerability
(Interference in real-time maturation and/or epigenetically-programmed later-life malfunction)

- **Conception**
  - Prenatal
    - TCDD (Dioxin)
      - Thymocyte maturation
    - Pb (Lead)
      - T helper and dendritic cell maturation

- **Birth**
  - TCDD (Dioxin)
    - Thymocyte apoptosis
    - Altered regulatory populations
  - Pb (Lead)
    - T helper imbalance
    - Allergy; Allergic inflammation
  - Bisphenol A (BPA)
    - Mucosal immune-gut microbiome
      - Leaky gut inflammation
  - Polychlorinated biphenyls (PCBs)
    - T cell and innate immune maturation
      - Allergic sensitization; Skewed adaptive responses

- **2 yrs**
  - Postnatal
<table>
<thead>
<tr>
<th>Organ or tissue</th>
<th>Population(s)</th>
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<tbody>
<tr>
<td>Liver</td>
<td>Kupffer cells</td>
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<tr>
<td>Lung</td>
<td>Alveolar macrophages</td>
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<tr>
<td>Brain</td>
<td>Microglia</td>
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<td>Astrocytes</td>
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<td>Fat</td>
<td>Preadipocytes</td>
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<tr>
<td>Gut</td>
<td>Intestinal macrophages</td>
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<tr>
<td>Kidney</td>
<td>Mesangial phagocytes</td>
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<td>Cardiovascular</td>
<td>Monocytes</td>
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<td></td>
<td>Perivascular macrophages</td>
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<tr>
<td>Reproductive organs</td>
<td>Testicular macrophages</td>
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<td>Uterine macrophages</td>
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<tr>
<td>Placenta</td>
<td>Placental macrophages (Hofbauer cells)</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoclasts</td>
</tr>
</tbody>
</table>

* These residents affect tissue homeostasis, dysfunction, and pathology
Most EDCs Produce Problematic Unresolved Inflammation

- BPA
  - Bronchial and other tissue inflammation
  - Asthma, Atherosclerosis, Prostate enlargement, cancer

- Pb
  - Testicular, brain and other macrophage-driven inflammation
  - Male infertility, Neurobehavioral alterations, Cardiovascular disease
  - Prostastis, Reduced sperm production

- Vinclozolin
  - Prostate inflammation

- Cadmium
  - Misregulation of proinflammatory cytokines
  - Testicular autoimmunity, Atherosclerosis

- Acetaldehyde
  - Airway inflammation
  - Asthma and exacerbation of asthma

- Coplanar
  - Proinflammatory cytokine production
  - Atherosclerosis

- PCBs

- Arsenic
  - Proinflammatory cytokine production
  - Cardiovascular disease
  - Lipid peroxidation
The Predominate Gene Network Changes for BPA and Phthalate Exposure Involve Inflammation

A recent study of genes altered by both BPA and Phthalates found that 5 of the top 10 gene networks are involved with inflammation.

Inadequate Safety Testing of Chemicals and Drugs

Based on current causes of global mortality, the top priority for regulated safety testing of chemicals and drugs should be to reduce the risk of NCDs (Chronic Diseases). But it is not! In fact, required safety testing has little relevance to risk of chronic disease.

**Question Posed to FDA Drug Safety Evaluators:**
(at a May 2011 internal seminar)

What safety data do you require for new drugs that are relevant for the risk of childhood immune dysfunction-based diseases such as

…..Childhood asthma?

…..Type 1 diabetes?
Conclusions

• EDCs are a serious threat to health and wellbeing.
• The predominate outcomes of EDC exposure are: NCDs (aka Chronic Diseases and Conditions).
• Chronic Diseases are highly interrelated via comorbidities.
• Misregulated inflammation linked with immune dysfunction is required to produce and/or maintain chronic diseases.
• The developing immune system is a primary target for immune dysfunction-driven chronic diseases.
• Current required safety testing is inadequate to protect against developmental immunotoxicity (DIT) and risk of chronic diseases.