Environmental Toxins in Perinatal and Early Life Development and the Link to Cancer and Metabolic Diseases Later in Life

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Educational Objectives

- To understand the concept of developmental origins of health and disease.

- To learn about the pathophysiologic processes in humans caused by chemical contaminants associated with unconventional shale gas operations ("fracking").

- To understand the role of toxins in carcinogenesis.

- To understand how chronic metabolic diseases result from epigenetic and physiologic changes that occur due to early exposure to chemical toxins.
The Barker Hypothesis: Early 1990s:
- Poor maternal nutritional environment resulted in intrauterine growth retardation (IGR) and the delivery of low birth weight infants.

This was linked to chronic diseases developing in these individuals later on in life, including:

- coronary heart disease
- diabetes (Type II) (non-insulin dependent)
- hypertension
- stroke
Today, much epidemiological and experimental evidence exists which supports an expansion of these theories, called the: “Developmental Origins of Health and Disease”.

The expanded theory includes developmental susceptibility throughout all the stages of growth and development from prenatal to childhood and adolescence, and not only to poor nutritional issues, but also to intrauterine and childhood exposures to environmental toxic substances, such as chemicals called endocrine disrupting chemicals (EDCs), carcinogens, mutagens, immunosuppressors and many more.
Irrefutable evidence of exposure to environmental chemicals comes from the finding of more than 100 or even 200 chemical toxins in umbilical cord blood of newborn infants in studies by the Environmental Working Group in 2005 and 2011, and by many other studies.

Similar research provides evidence of toxins in meconium and amniotic fluid.
Body Burden of Chemical Contaminants in Humans and Animals Today

- Humans, animals and the ecosystem in which we live today, are continually exposed to toxins in air, water, food, personal care products and household products.

- Exposure begins during prenatal development

- Many of the chemicals have long half-lives, and are poorly metabolized and excreted, so they are **persistent and accumulative** in our bodies.

- Therefore, they are already present in maternal tissues.

- Many toxins are able to cross the placental barrier, where they expose the developing fetus during one of the most sensitive periods of development.
The Potential Effects of Complex Mixtures of Toxins

- As part of a complex mixture of chemical contaminants, these toxins may cause more tissue damage than they would during isolated exposures because they act additively or synergistically potentiating the actions of the other toxins present.

- The complex mixture of toxins may include new toxins to which the mother is currently being exposed, such as fracking-related chemicals, as well as other contaminants which are already stored as part of her existing “body burden of chemicals”.

- Furthermore, “legacy chemicals” which have been banned since the 1970’s (such as PCBs, dioxans, POPs and pesticides) are still present in the ecosystem and will continue to contribute to the mother’s current daily overall exposure to the complex mixture of toxins, in the air she breathes, the water she drinks, and the food she consumes.
Unconventional Shale Gas Toxins: Adding Insult to Injury

- There are many “unknowns” about long-term health effects caused by recently introduced fracking toxins.

- But much is already known about the long-term health hazards of many historical environmental toxins, linked to irreversible chronic diseases (such as obesity, diabetes and cancer) among many generations of the American population, and many subpopulations.

- After decades of experience with endocrine disrupting chemicals (EDCs) and known carcinogens, it is reasonable to predict what diseases may result from further environmental insults from fracking–related toxins.
Endocrine Disruptors Associated With Unconventional Shale Gas Operations: Arsenic-1

- Arsenic - affects all 5 steroid receptors:
  - Glucocorticoid receptor
  - Mineralocorticoid receptor
  - Progesterone receptor
  - Androgen receptor
  - Estrogen receptor

also effects: - Retinoic acid receptor
and: - Thyroid hormone receptor

(Has significant effects on these at very low doses.)
Endocrine Disruptors Associated With Unconventional Shale Gas Operations: Arsenic-2

- It is likely that a common metabolic pathway is central to the effects on all 5 steroid receptors. But not well understood at this time.

- While researchers actively pursue answers to explain the deleterious effects of toxins associated with the fracking process, there are lessons to be learned from past exposures, that may expedite our understanding of future health threats from new, often chronic, low dose daily exposures.
Endocrine Disruptors Associated With Unconventional Shale Gas Operations: BTEX

- Women of child-bearing age (18-42), employed at the US Air Force were studied in 2002 to see if fuels and solvents such as benzene, toluene, ethylbenzene and xylenes to which they were exposed from jet fuel, JP-8, could have adverse reproductive effects.

- Pharmacokinetic modeling revealed that women metabolize 23 -26% more benzene than men, under same exposure conditions.

- They studied endocrine endpoints at 4 times during the ovulatory cycle, using urinary levels and breath levels for the selected endocrine markers: pre-ovulatory LH (luteinizing hormone), follicular Pd3G (pregnanediol 3 glucuronide), midluteal Pd3G and midluteal E\textsubscript{1}3G (estrone 3-glucuronide).

- Findings: Exposure to these hydrocarbons had lowered the pre-ovulatory LH levels in this exposed population, signifying that chronic exposure to these hydrocarbons could compromise reproduction.

Fracking-related EDCs from Water Samples from Colorado River Near High Density Fracking Operations

- Linked with estrogenic activity:
  Bisphenol A

- Linked with anti-estrogenic activity
  2-ethyl-1-hexanol
  Ethylene glycol

- Linked with anti-androgen activity
  Ethylene glycol
  n,n dimethylformamide
  cumene

Alarming Trends in Obesity, Diabetes and Metabolic Syndrome

- One of the most alarming trends in metabolic disease today is the obesity epidemic, and the rising incidence and prevalence of diabetes Type 2, and their comorbidities which include hypertension, hypertriglyceridemia and heart disease.

- These diseases are now common among children and adolescents, as well as adults. Even young infants are beginning to demonstrate evidence of obesity.

- Much speculation concerns the underlying cause of the rapidly expanding obesity problem, which is widespread throughout the US population (and in other developed nations).
The Effect of Prenatal Exposure to EDCs on Lipid Metabolism

- Various pharmaceutical agents and environmental chemicals can influence the process of adipocyte differentiation and lipid storage.

- Among the environmental chemicals, several endocrine disruptors, the obesogens, feature prominently as likely culprits.

- These endocrine disruptors (EDCs) have been deposited in our environment for decades and are now an integral part of our lives. They interfere with hormonal processes that regulate lipid homeostasis, by disturbing gene expression and signaling pathways.
The Effect of Prenatal Exposure to EDCs on Lipid Metabolism

- Obesogens are believed to be one of several factors which can provide epigenetic influences over gene expression.

- Thus they can influence the differentiation of multipotent mesenchymal stem cells into preadipocytes rather than osteoblasts. In that way they can promote the production of increased numbers of fat cells (*adipose hyperplasia*).

- They can also influence lipid storage resulting in enlargement of individual fat cells. (*adipose hypertrophy*)

- They can also influence the hormones that control hunger and satiety.
Differentiation of Multipotent Stem Cells

![Diagram showing the differentiation of multipotent stem cells into osteoblasts and adipocytes](http://www.hindawi.com/journals/ppar/2009/421376/fig1/)

Osteogenesis  Adipogenesis

Factors governing normal adipogenesis and osteogenesis from multipotent mesenchymal stem cells

Multipotent mesenchymal stem cells (MSC) can differentiate into a number of cell types, including adipocytes and osteoblasts.

The transcriptional coactivator Taz negatively regulates adipogenesis and promotes osteogenesis through suppression of PPARγ and activation of RUNX-2, while overexpression of PPARγ can reduce bone formation and promote adipogenesis.

(see diagram shown in previous slide)

Source: http://www.hindawi.com/journals/ppar/2009/421376/fig1/
The Gestational Environment

- **Second Trimester**

  - The embryo becomes a fetus by the end of the 8th week (embryonic age) and 10th week (gestational age).

  - Fetal mesenchymal stem cells (MSC) are "multipotent" and can divide into adipocytes and osteoblasts, during this phase.

  - Various factors influence the "commitment" of the MSC into a preadipocyte, thus programming the stem cell for later differentiation into fat cells.
Pre-programming of Adipocyte

- **Obesogens** are thought to pre-program the adipocytes of the fetus, such that he/she is destined to become obese and/or diabetic later in life.

- Of course other pathways contribute to the early programming of adipocytes, including glucocorticosteroids (maternal stress), nutrient abundance during fetal development, and also intrauterine growth restriction, followed by a “catch up” period post-natally.
The Gestational Environment

- **Third Trimester**
  - Adipose depots are first observed in the third trimester.
## Windows of Vulnerability: Critical Periods of Development During Gestation

<table>
<thead>
<tr>
<th>Main Embryonic Period (in weeks)</th>
<th>Fetal Period (in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3</strong></td>
<td><strong>4</strong> <strong>5</strong> <strong>6</strong> <strong>7</strong> <strong>8</strong> <strong>9</strong> <strong>16</strong> <strong>32</strong> <strong>38</strong></td>
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<td>Period of dividing zygote, implantation, and bilaminar embryo</td>
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<tr>
<td>Embryonic disc</td>
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<tr>
<td>Morula</td>
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<td>Amnion</td>
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<td>Blastocyst</td>
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<td>Not susceptible to teratogenesis</td>
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<td>Death of embryo and spontaneous abortion common</td>
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</tbody>
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### Neural tube defects (NTDs)

- TA, ASD, and VSD
- Amelia/Meromelia
- Amelia/Meromelia
- Cleft lip
- Low-set malformed ears and deafness
- Microphthalmia, cataracts, glaucoma
- Enamel hypoplasia and staining

### Mental retardation

- Heart
- Upper limb
- Lower limb
- Upper lip
- Ears
- Eyes
- Teeth
- Cleft palate
- Palate
- Masculinization of female genitalia
- External genitalia
- Functional defects and minor anomalies

### CNS

- Common site(s) of action of teratogens
- Less sensitive period
- Highly sensitive period

TA — Truncus arteriosus; ASD — Atrial septal defect; VSD — Ventricular septal defect
Prepubescence and Adolescence: Other Critical Windows of Vulnerability

- In prepuberty and adolescence, the ovaries and the testes are developing and primordial stem cells are at risk if exposed to chemical contaminants and radioactive materials.
Part 2: Ionizing Radiation: Known Carcinogen

Penetrating Distances

- Alpha
- Beta
- Gamma and X-rays
- Neutron

Paper Plastic Lead Concrete
What is radon and its progeny?

- A radioactive gas:
  - colorless
  - odorless
  - invisible
  - imperceptible

- Ubiquitous: in soil, rock, and in ground water everywhere

- Half-life 3.8 days

- Decay pathway to other radioactive substances. ("progeny", "daughters")

- Alpha decay particles emitted by invisible radon gas in the small gold tube cause radioluminescence of zinc sulfide phosphor:

Radon and its Progeny Emit Alpha Radiation

- Alpha particles are a highly ionizing form of radiation and when inhaled or ingested can cause considerable biologic damage.

- Otherwise, it does not pass through the skin, or cause burns on the skin.

- Radon and its progeny have short half lives, so they emit alpha particles very actively. The delicate lining of the lungs gets bombarded with the rapid emission of alpha particles, which leads to tissue inflammation and damage.

- Tissue damage can lead to DNA damage.
What is the main source of radon?

- **Radon**: a radioactive, indirect breakdown product from the decay of uranium and thorium.

- Uranium and thorium are part of the earth’s bedrock:
  - have been there since the earth was created
  - have very slow half-lives (billions of years)
  - decay to **radium** which decays to **radon**

- So, radon is found in rocks and soil, and in ground water.
Decay Chain of Radioactive Materials

- **Uranium-238 Decay Chain**

  ![Uranium-238 Decay Chain Diagram](http://www.epa.gov/rpdweb00/understand/chain.html)

  Source: [http://www.epa.gov/rpdweb00/understand/chain.html](http://www.epa.gov/rpdweb00/understand/chain.html)
Comparison Maps of Location of Marcellus Shale Distribution and High Density Radon Potential

- Marcellus Shale distribution in New York, Pennsylvania, Ohio and West Virginia
- Geologic Radon Potential in New York, Pennsylvania, Ohio and West Virginia
How radon enters a house:

- Radon in soil
- Radon in well water
- Radon in groundwater
- Cracks
- Windows
- Sump
- Drain
- Water table
- Bedrock
- Fractured bedrock
Radon is a component of natural gas

- radon is “delivered” to our homes along with natural gas for appliances that use natural gas:
  - gas stoves
  - gas heaters
  - gas fireplaces

- Also emanates from:
  - exhaust fans in:
    - clothes dryers
    - kitchen
    - bathroom

- Builders materials - dry wall
  - granite
Most Common Route of Exposure: Inhalation of Radon and its Progeny

- Radon progeny are solid and electrically charged.

- Therefore, they adhere to dust particles and can then be inhaled.

- They then drop down into the deep lung tissue where alpha radiation can cause lung damage.
Inhalation of Radon and its Progeny can cause Lung Cancer which can rapidly metastasize via lymphatics.

Source: http://activerain.com/blogsview/1881853/-radon-gas-what-s-okay-
The Synergistic Effects of Radon, its Progeny, and Tobacco Smoke:

- Cigarette smoking is the leading cause of lung cancer deaths per year (approximately 90% of all lung cancer deaths, more than 160,000 people each year).

- Radon and its progeny are the second leading cause of lung cancer deaths per year (about 10% = 15,000-22,000).

- Radon is the leading cause of lung cancer deaths among non-smokers (about 2,300 deaths per year).
More on the synergistic effects of Radon, its Progeny and Tobacco Smoke

- If someone is exposed to radon AND is also a cigarette smoker, the risk is almost **10 times higher**.

- Secondary smokers (passive smokers) are also at greater risk.
Tobacco in many cigarettes contains polonium 210 and lead 210 and emits alpha radiation!

- The tobacco plants take up radioactive material from soil and fertilizer, through its root system into and onto its leaves.
The main health threat from exposure to radon and its progeny: Lung Cancer

- The most common cancer in men and women.
- Approx 50% of patients die within 1 year after diagnosis.
- The 5 year survival rate is the lowest among all cancers. (16% 5 year survival rate)


How Carcinogenesis is related to radiation exposure:
(How cancers develop)

- Alpha particles cause DNA damage

- If natural DNA repair mechanisms are ineffective, a mutation that has occurred, will be allowed to remain within a viable cell.

- Subsequent cell proliferation will multiply the mutation in the cell line.

- Inborn processes such as tumor suppressor genes and tumor promoter genes regulate whether a cell with damaged DNA can survive and proliferate, or if it will be removed by apoptosis (programmed cell death).

- Proliferation of mutated cells leads to tumor growth
Carcinogenesis, continued: (How cancers develop)

- Mutagens are chemicals that can cause actual mutations in the cellular DNA.

- But, no single mutation leads to tumor development.

- Additional “hits” to the genes are needed for carcinogenesis to proceed, and occur throughout the life of the individual.

- Other chemicals, called carcinogens, may not necessarily cause actual mutations, but they work to support the progression of the carcinogenic process.

- Other factors also involved: epigenetics, individual resiliency, immune status, other mutations

- Long latency period between exposure and tumor development (could be decades)
Children: The Most Vulnerable Population

- Greater exposure to inhalational agents, because:
  - faster respiratory rate per kilogram of body weight than adults
  - may not yet have well enough developed immune systems
  - they are closer to the floor (where radon progeny particles settle).
  - have many more years of future life within which a cancer with a long latency period can allow for the cancer to develop.

- If an individual has been exposed to mutagens or carcinogens during fetal development, he has received his first "hit" during a period of greatest developmental vulnerability.
EPA Estimates for Deaths due to Radon
(from “A Citizen’s Guide to Radon”)

- **RADON**: 21,000 deaths per year
- Drunk Driving: 17,400
- Falls in the Home: 8,000
- Drownings: 3,900
- Home Fires: 2,800
“Do-it-yourself” Radon Gas Test Kits available from many stores and on-line (see example below)
Testing for radon in your home: Many commercial services available

- Contact your local Chamber of Commerce for recommendations of local contractors.
New York State Department of Health: Bureau for Environmental Radiation

- Center for Environmental Health
  Bureau of Environmental Radiation Protection
  Empire State Plaza-Corning Tower, Room 1201
  Albany, New York 12237 (518) 402-7556

- radon@health.state.ny.us
Radon Mitigation

- EPA standard: radon levels must be between 2 - 4 pCi/Liter in indoor air

Some approaches to mitigation:
- Mechanical ventilation systems
- Different approaches are used based on foundation type:
  - basement
  - crawl space
  - slab on grade
Summary:
Increased delivery of natural gas to New York State homes, is a serious public health concern, because it will:

- Increase levels of indoor radon and its progeny above background levels.
- Increase exposure of NYS residents to radon and its progeny.
- Increase risk of lung cancer among NYS residents.
- Increase risk of eventual cancer among vulnerable populations, including:
  - children
  - elderly people and patients with immunosuppressed health status
  - people with existing chronic pulmonary diseases
  - people with other chemical exposures such as arsenic, asbestos, direct tobacco smoke, and environmental tobacco smoke (second-hand smoke).
References for Environmental Chemical Toxins Discussion (Part 1)


http:www.ncbi.nlm.nih.gov/pmc/articles/PMC3706252/

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2235215/
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   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713042/


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   http://dx.doi.org/10.1155/2013/640673

   http://www.nature.com/jio/journal/v28/n10/full/0802753a.html


References for Radon Discussion:

1. Why is radon the public health risk that it is? (EPA)
   [http://www.epa.gov/radon/aboutus.html](http://www.epa.gov/radon/aboutus.html)

2. "The Health Effects of Exposure to Indoor Radon", in, the Biological Effects of Ionizing Radiation (BEIR) VI Report; The National Academy of Sciences; 1998

3. Measured Basement Screening Radon Levels by County - October 2012 (NYS Department of Health)
   [http://www.health.ny.gov/environmental/radiological/radon/county.htm](http://www.health.ny.gov/environmental/radiological/radon/county.htm)

4. "Map of Radon Zones in New York Based on EPA Data":
   [http://www.city-data.com/radon-zones/New-York/New-York.html](http://www.city-data.com/radon-zones/New-York/New-York.html). The red areas are the areas of higher radon levels. Thirty four counties are listed as "Zone 1" having higher levels of background radon. These include Albany, Rensselaer, Schoharie, Greene, Columbia, Putnam, Ulster, Broome, Orange, Delaware, Duchess, Cattaraugus, Cayuga, Chautauqua, Chemung, Chenango, Cortland, Erie, Madison, Livingston, Onondaga, Ontario, Otsego, Seneca, Steuben, Sullivan, Tioga, Tompkins, Washington Wyoming, Yates.

   **This map is very good, and it is followed by 52 more pages which list the percent of homes with picoCurie/L measurements above 4, for each of the NYS counties and the townships within them**
References for Radon Discussion, continued:


7. Lung Cancer Fact Sheet; American Lung Association

8. Radon and Cancer Fact Sheet; National Cancer Institute
   http://www.cancer.gov/cancertopics/factsheet/Risk/radon#ques4

9. Lung Cancer Statistics; CDC (page last updated, October 23, 2013)

    http://www.epa.gov/radon/pubs/citguide.html

    http://download.journals.elsevierhealth.com/pdfs/journals/1054-139X/PIIS1054139X13000888.pdf
Thank you!