

Report 12: Early Life Exposures (periconceptual through adolescence) leading to Later Life Impacts (child to old age) – Prevention and Interventions

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Brief History: Why now? Several factors lead to timeliness of this topic such as: Emerging human data indicating its validity; basic science mechanisms such as epigenetics and stem cell biology, implying biological plausibility; broaden definition of environment (nutrition, stressors); recognition of critical windows of hypersensitivity during development; the recognition of susceptible responders (prior exposures leading to susceptible individual, 2 hit theory); rising incidence of diseases that have been related to childhood exposures; concept that early interventions are more effective at repair, normalization of development and/or compensation; the start of the NCS as a vehicle for such needed longitudinal studies; data on changing male reproductive function and increase in prostate cancer; data suggesting adolescent exposure leading to increase in breast cancer; cutting edge technology enabling asking these questions; technology to deal with complex systems; increasing public awareness and hence pressure to address these questions; indicators that show that US children's health falling behind that of other nations.

Discussion Highlights:

- Need computational models for complex systems.
- Various stressors/exposures – must first understand basic biology to understand impact/reaction of system to stressor
- Need to develop model systems – molecular, cellular, animal, etc. Dependent on the question being addressed.
- Must consider child-mother-father as a unit
- Biomarkers are needed of both recent and distant exposures/impacts
- Getting away from toxics: How do exposures change pathway of development (low level exposures/subtle changes in outcome)
- Need to understand what this system (early response to environment leading to change in adult) is for evolutionarily, why has it evolved?
- What biological samples do we need to store for future/collaborative/ongoing studies? What cell types? Organ tissues? Epigenetics has focused on lymphocytes, are there other potential tissues/cells? Target tissue may be impossible to access, need to identify surrogate tissues.
- Need to include genetic information into data analysis/research design.

- For biomarkers of effect, need to know mechanism to validate biomarker. Other biomarkers may be independent of mechanism and are validated in other ways, such as biomarker of exposures or biomarker of cell growth.
- Concerns were raised about disease specific research. Should we have a disease focus?
- Multi-hit hypotheses require longitudinal studies.
- Need to study the populations of progenitors and stem cells in tissues – reduction of these populations by early exposure may lead to life long impact.
- Windows of susceptibility maybe windows of opportunity (windows where intervention more effective at repair, undoing, compensation)
- Combinations of nutrients and stressors
- Is there transgenerational passage? No compelling evidence yet as requires 3rd generation (great grand kids of exposed parent). However, folate supplementation in animals results in changes in 7th generation (increased of in utero abortions)
- Balance measures of outcomes or changes with exposure assessment and exposure endpoints – what is the exposome?
- Need to define critical period of susceptibility to what type of exposure. Model of 3D space with life span, exposure/environment, gene. (See diagram). Identify critical windows for big outcomes associated with common exposures.
- Research problem is overwhelming. Need for groups of researchers informing each other and the model. How can multiple inputs be put into a common understanding?

Recommendations:

- Need exposure platforms and better methods to measure and define a complex “exposome”
- Need platforms for epigenetics
 - Measure these changes broadly
- Need better informatics for both epigenetics and exposome
- Need critical stage specific biomarkers
- More strategy around integrating studies at molecular, animal, individual and epidemiology levels. Level of complexity of issue and longitudinal nature requires structure beyond programs & centers.

- NIEHS needs to create a research strategy like the NIH Roadmap concept – integrated R01’s around a common question, integrated intramural research programs
- This problem requires interdisciplinary/multidisciplinary research
- Could NIEHS convene a “like” researchers network? Working models include:
 - CGH Atlas for mutations associated with cancer
 - Children’s Environmental Health Centers with yearly exchange of information meetings
 - Children’s Oncology Group
 - NICHD Neonatal Research Network
 - NICHD Maternal-Fetal Medicine Research Network
- Establish cores within centers to facilitate interaction and efficiency
- Increase communication of resources (cores & services) and research results to “outsiders” of individual institutions.
- Facilitate integration of research via cores, network meetings, interinstitutional program projects, etc.

Discussion Participants:

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