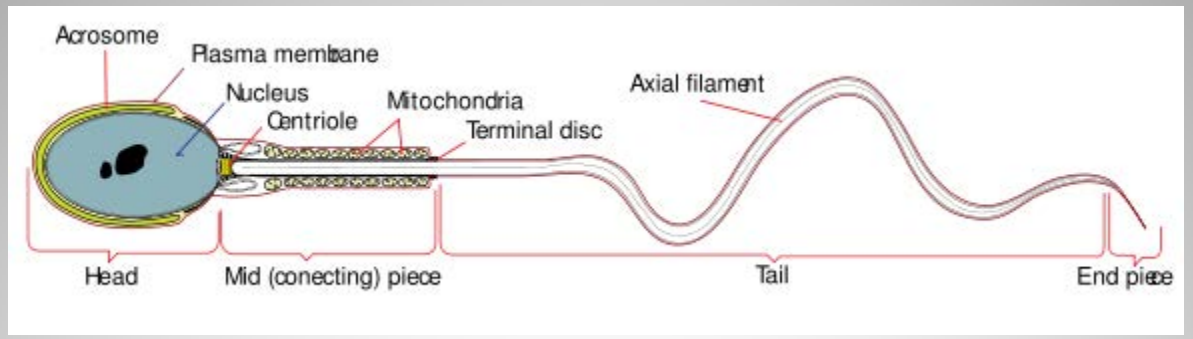
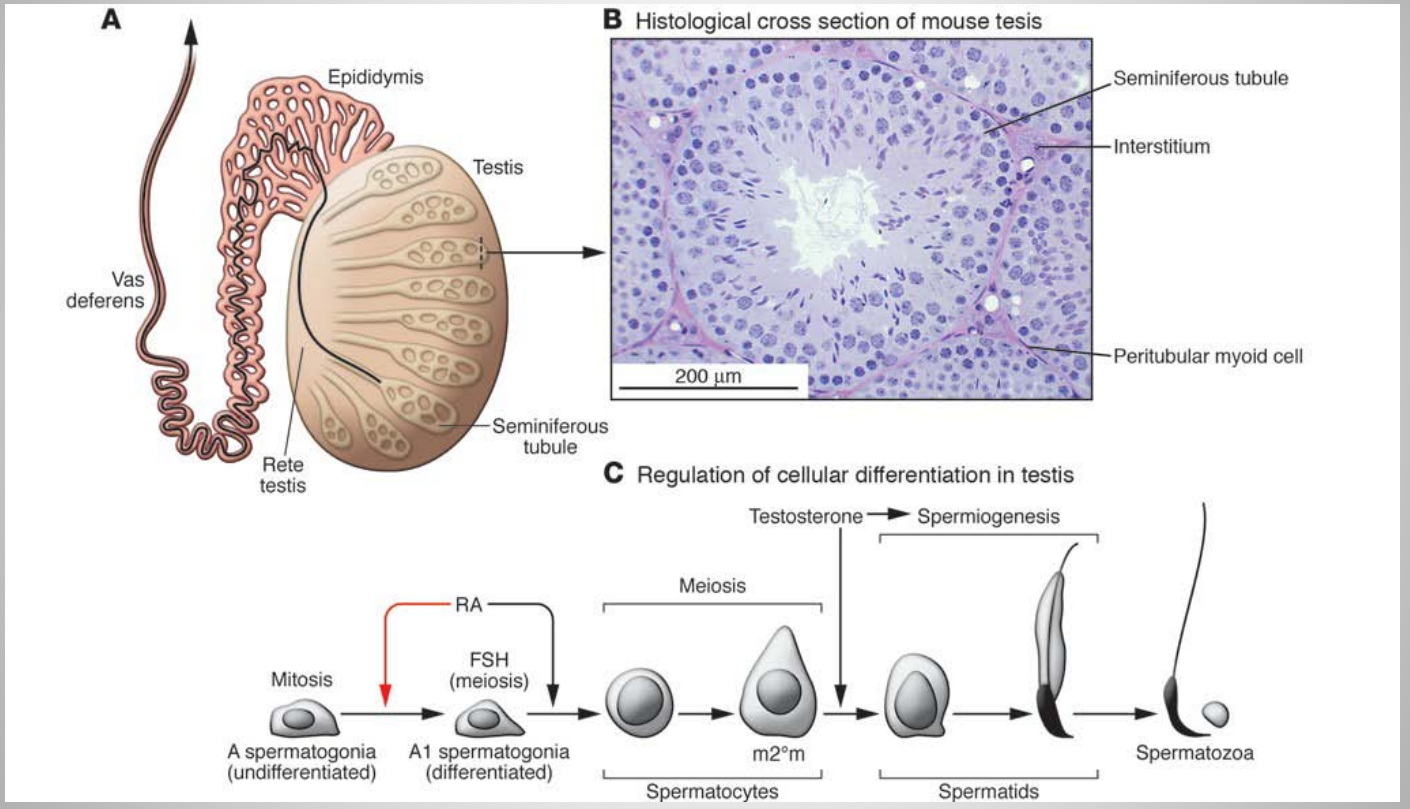


Paternal Involvement in Pregnancy Outcome: It's more than just DNA'

Stuart B. Moss
Reproductive Sciences Branch
NICHD
July 16, 2012

Sperm Formation



(Hogarth and Griswold 2010 JCI 120:956-962)

What does the Sperm Provide to the Next Generation (and ones after that)?

- Genetic information
  - A haploid amount of DNA
- Non-genetic information
  - Epigenome – regulates gene transcription/protein translation
    - DNA methylation
    - histone modification
    - Non-coding microRNAs
  - Epigenome, leading to transgenerational inheritance

Sperm Nuclear Integrity

- Semen parameters include sperm count, motility and morphology
  - But these don't necessarily assess the quality of the sperm, particularly sperm nuclear integrity
- DNA integrity
  - Mutations, e.g., base substitutions
  - Chromosomal alterations, e.g., aneuploidy, DNA strand breaks
- Chromatin integrity
  - Amount of DNA compaction and the proteins associated with the DNA
- Damaged sperm can result in infertility, miscarriage, pre-term labor, birth defects

Reactive Oxygen Species and Oxidative Stress

- ROS – byproducts of oxygen metabolism
  - Involved in etiology of various conditions from neurogenerative disorders to male infertility
    - Affects sperm motility
  - Numerous sources
    - Chemical, e.g., drugs, toxins
    - Physical, e.g., radiation
    - Biological, e.g., hyperglycemia, infections
  - Anti-oxidants in the diet may reduce sperm damage

Stressors on Sperm DNA Integrity: Environmental Factors

Compounds	Sperm Quality	Species	Mechanism
Irradiation	Aneuploidy	Mice	
	Abnormal chromatin structure	Mice	
	DNA strand breaks	Mice	
	Mutations	Mice	
Chemotherapeutic agents	Aneuploidy	Human	
	Abnormal chromatin structure	Human	
	DNA strand breaks	Human	
	Lower protamination	Human	
Estradiol/genistein	DNA strand breaks	Human	Oxidative stress
PCBs/p,p'-DDE	Abnormal chromatin structure	Human	
	DNA strand breaks	Human	
Phthalates	DNA single strand breaks	Human	Oxidative metabolites
Lead	Abnormal chromatin structure	Human	Oxidative stress
	Lower protamination	Human	
Cadmium	DNA fragmentation	Rat	
Air pollution	Mutations	Mice	
	Abnormal chromatin structure	Human	
Heat	Abnormal chromatin structure	Mice	

(Delbes et al. 2010 Mol Human Reprod 16:14-22)

Stressors on Sperm DNA Integrity: Paternal Age

- More acceptable to delay fatherhood
  - See an increase in mutations and DNA fragmentation index as males age
- ~20 autosomal dominant disorders associated with paternal age, e.g., Apert syndrome
  - Disorders are overwhelmingly single base substitutions (not deletions, translocations)
    - More cell divisions during spermatogenesis than oogenesis
    - Decreased efficiency of DNA repair as males ages (?)

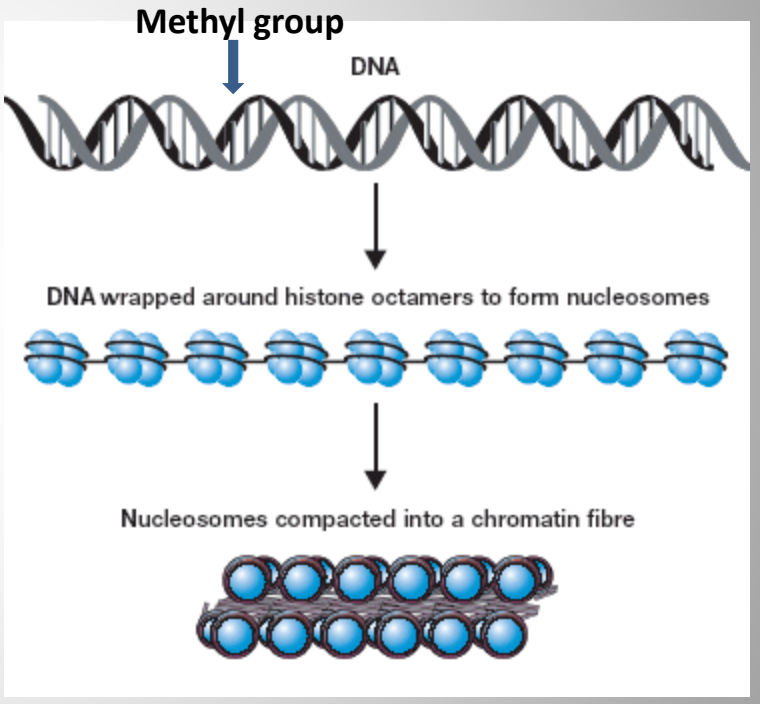
- Correlations with offspring being more susceptible to e.g., autism and schizophrenia

Stressors of the Sperm DNA Integrity: Lifestyle

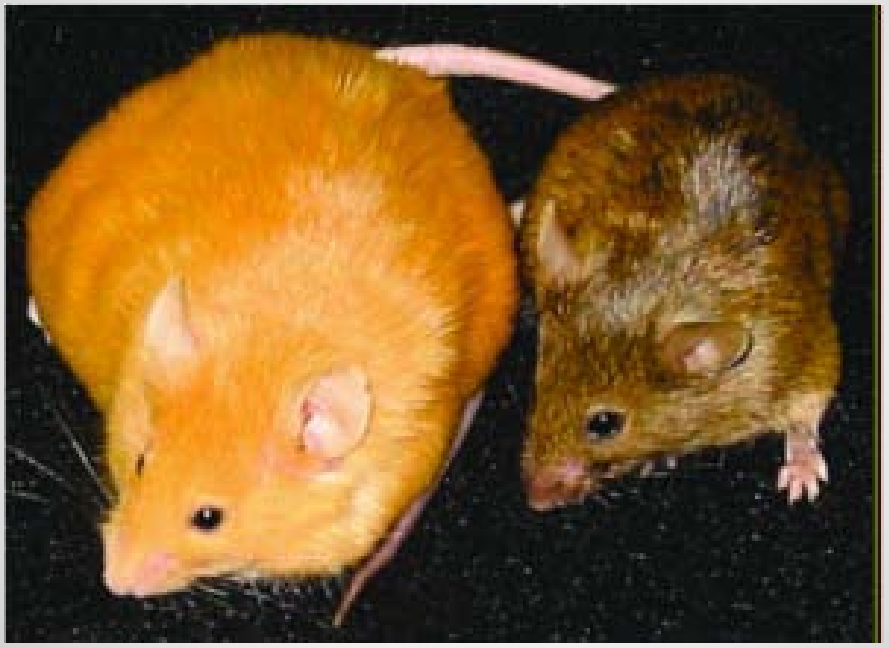
- Diet
  - Obesity
    - Reduce sperm concentration and motility
      - See an increase in ROS and sperm DNA damage
    - Bariatic surgery and restoration of fertility (?)
- Lack of exercise

Epigenetics

- Heritable modifications in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence
  - Cytosine methylation
    - Decrease gene expression
    - Imprinted genes
  - Histone modifications
    - Increase/decrease gene expression
  - microRNAs
    - Regulate protein translation



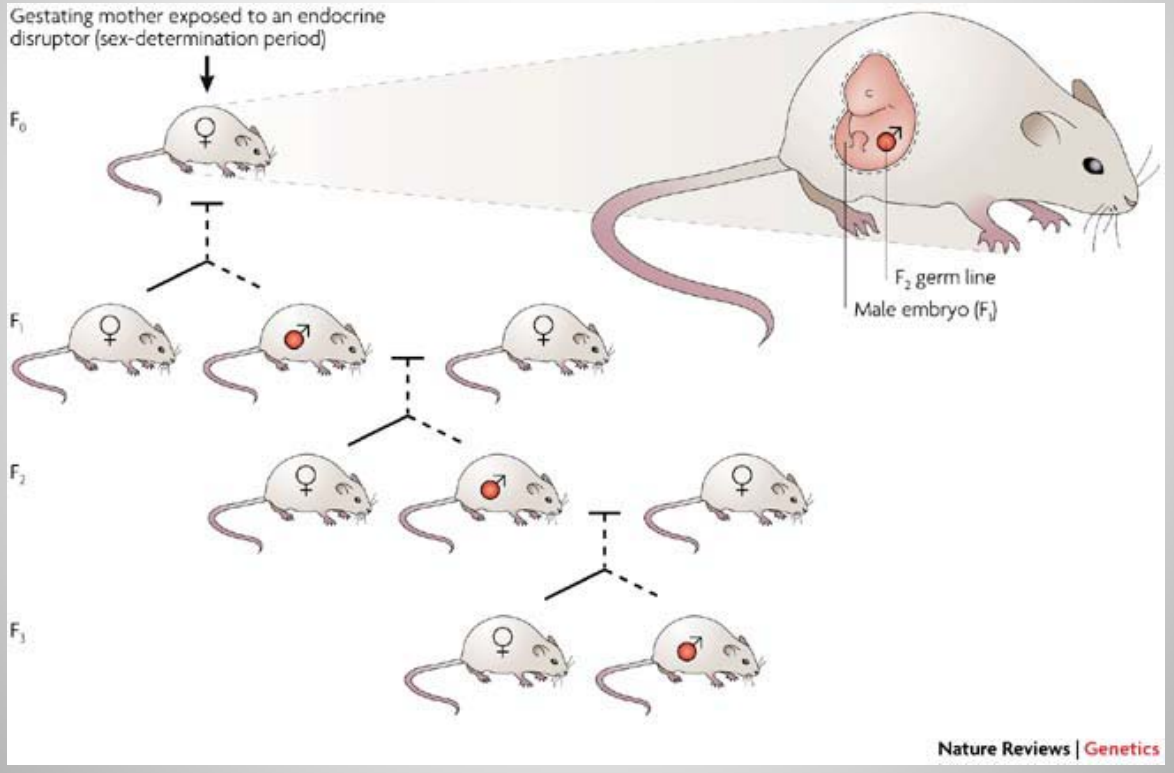
Epigenetics: A picture is worth a 1000 words…



(From Waterland and Jirtle)

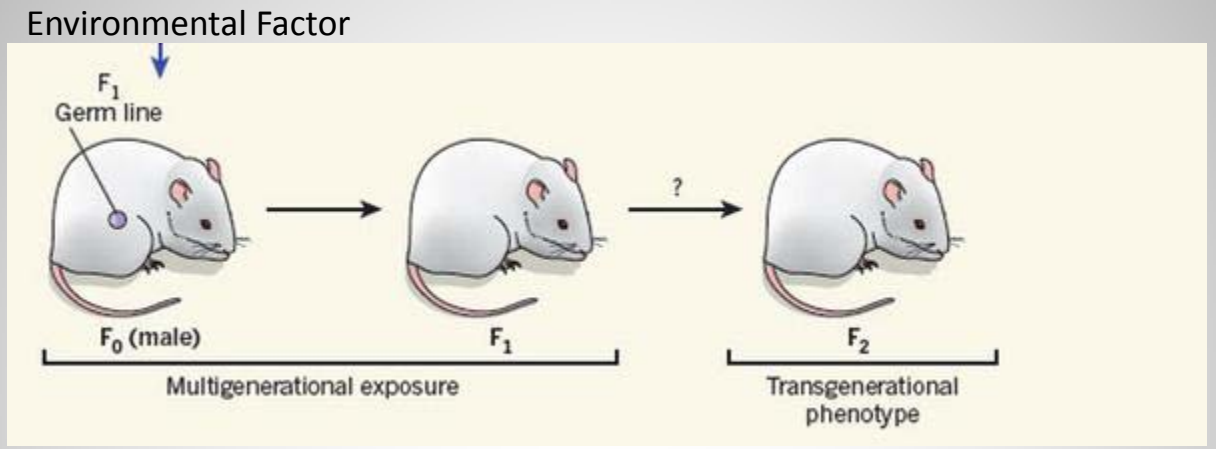
Epigenetic Transmission Can Be Transgenerationally Inherited

Maternal impact on adult-onset disease in offspring is often due to fetal exposure



(Jirtle and Skinner 2007 Nature Reviews Genetics 8, 253-262)

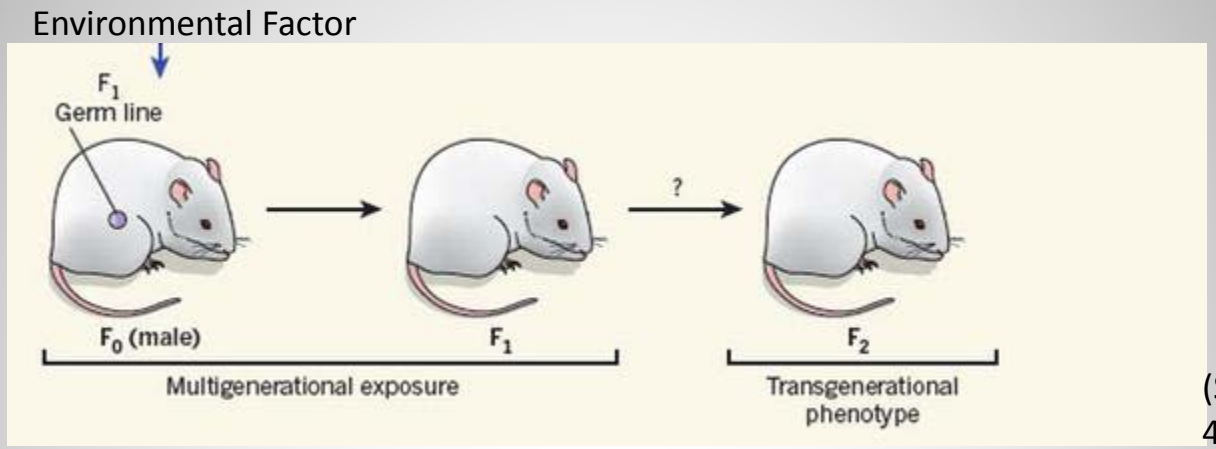
Multi-generation Inheritance of Disease in the Male



Skinner 2010 Nature 467:922-923

- Feed male rats a HFD (Ng et al. 2010 Nature 467:963-966)
  - Animals become obese and exhibit resistance to insulin (expected)
    - Female offspring do not show altered body weight/fat but…
    - Unexpectedly show a diabetes-like condition of impaired glucose tolerance and insulin secretion
  - Gene expression profile of pancreatic islet cells is abnormal
    - Genes show altered DNA methylation which could alter their expression
  - Altered sperm integrity promotes an adult-onset disease in daughter

Multi- and Transgeneration Inheritance of Sub-Fertility in the Male



(Skinner 2010 Nature 467:922-923)

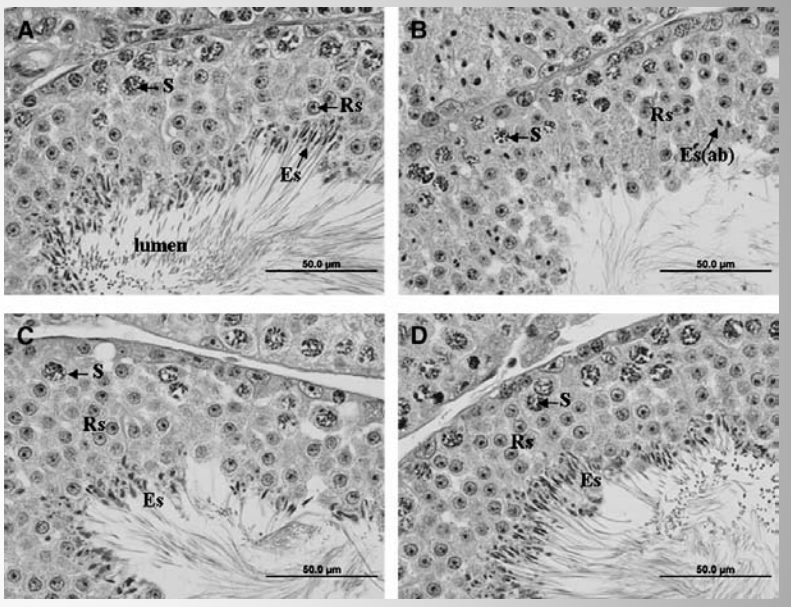
- Feed male mice a HFD (Fullston et al. 2012 Human Reprod 27:1391-1400)
  - Animals become obese
    - Paternal initiation of subfertility in both male and female offspring of F1 and F2 generations (w/o obesity)
    - Maternal initiation of subfertility in male offspring only of F1 and F2 generations (w/ obesity) – can't separate the 2 phenotypes
  - Hypothesis: Obesity in the founder male alters the epigenome of sperm
    - Leads to developmental programming of subfertility in subsequent generations

Stressors of the Epigenome

- Environmental toxicants
- Diet and metabolism
  - Diabetes
  - Obesity
- Stress

Poor Gamete Quality Can be Reversed: Effect of Diet

- In humans, DHA is the main HUFA in sperm
- D6D – enzyme involved in HUFA synthesis
  - KO mouse males are infertile due to arrest in spermatogenesis
  - Abnormal elongation of spermatid head
- Dietary DHA, and to a lesser extent AA, restores spermatogenesis and fertility



(Roqueta-Rivera et al. 2009 J. Lipid Res 51:360-367)

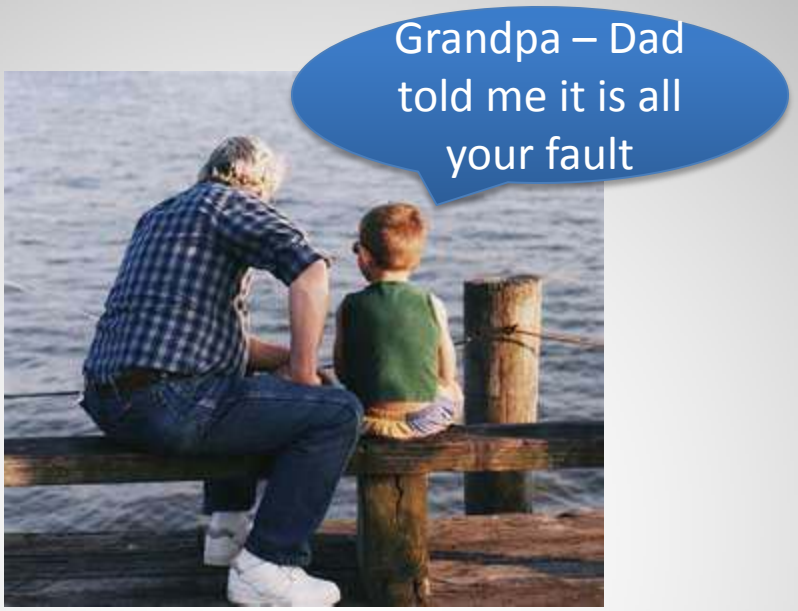
What the RSB/NICHD funds

- PA-11-326: Gamete Quality in Natural and Assisted Reproduction (R01)
  - 'Good gametes'
  - Co-participants include Office of Dietary Supplements and the NIEHS
- Starting to see grant proposals on epimutations
  - Types and relationship to genetic alteration?
  - Mechanisms underlying their generation?
  - Can epimutations be fixed?
    - Mutations in imprinted genes arising from ART (deWaal et al., 2012 PNAS 109:4163-4168)

Paternal Involvement in Pregnancy Outcomes: A Basic Science Perspective

- Gamete quality is critical
  - Integrity can be negatively influenced by e.g., environmental exposures, lifestyle decisions
    - Both DNA and epigenome can be affected
- Detrimental effects can be reversed, e.g., by diet
- Health Disparities
  - Individuals of a lower SES – may have a greater exposure to environmental toxicants, better chance of having a poorer diet leading to e.g., obesity/diabetes, a more stressful life
- Transgenerational effects leading to a variety of adult-onset diseases

decisions by fathers can affect not only their children, but their grandchildren (and beyond ?)



Thank you

Questions?