The case for puberty as the canary in the coal mine

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On behalf of the BCERC and BCERP
CCTST Grand Rounds
A canary in the coal mine…

“Early coal mines did not feature ventilation systems, so miners would routinely bring a caged canary into new coal seams. Canaries are especially sensitive to methane and carbon monoxide, which made them ideal for detecting any dangerous gas build-ups. As long as the canary in a coal mine kept singing, the miners knew their air supply was safe.”
The case for puberty as the canary in the coal mine: Basic premises

- Age of pubertal onset (in girls) is decreasing
- Puberty is a time of biologic change; the timing of puberty may serve as a sensitive indicator of environmental influences (the canary)
- Natural selection favors earlier reproductive development
The case for puberty as the canary in the coal mine

Puberty is a time of biologic change; the timing of puberty may serve as sensitive indicator of environmental influences.
Contemporary studies of the onset of puberty in girls

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Age B2</th>
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<tbody>
<tr>
<td>Reynolds &amp; Wines</td>
<td>1948</td>
<td>10.8</td>
</tr>
<tr>
<td>Marshall &amp; Tanner</td>
<td>1969</td>
<td>11.2</td>
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<td>Harlan (NHES)</td>
<td>1980</td>
<td>12.8</td>
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<tr>
<td>Herman-Giddens (PROS)</td>
<td>1997</td>
<td>8.9/10.0</td>
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<tr>
<td>Sun (NHANES III)</td>
<td>2002</td>
<td>9.5/10.4</td>
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<tr>
<td>Biro (NGHS)</td>
<td>2006</td>
<td>9.8/10.4</td>
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<tr>
<td>Aksglaede (Copenhagen)</td>
<td>2009</td>
<td>9.96 (10.88)</td>
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Breast development by age
Cincinnati BCERC compared to PROS

![Graph showing breast development by age]

- Percent with breast development
- Age in years

Legend:
- BCERC AA
- PROS AA
- BCERC Wh
- PROS Wh
Correlation of age at onset of puberty to age at menarche

These data suggest onset of puberty and age of menarche are, increasingly, independent events.
Sequence of pubertal events - girls

Data from NHLBI Growth & Health Study; Biro 2006
FFMI and FMI, by BMI group at age 9, and by age, NGHS girls
Sequence of pubertal events - boys

- **Height velocity**
- **Increase in testicular vol**
- **Pubic hair stage 2**
- **Completion of pubic hair 5**
- **Peak height velocity**
- **Sperm in urine**
- **Strength spurt**

Data multiple sources: Biro 1995; Neu 2001; Karpati 2002; Dore 2005
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- Puberty is a time of biologic change; the timing of puberty may serve as sensitive indicator of environmental influences

  - Bogalusa Heart Study: trends in menarcheal age between 1973 and 1994; menarcheal age decreased 9.5 months among black and 2 months among white girls- same environment, suggesting interaction between genes and environment (Freedman 2002)

  - Several studies report lead exposure with delay of breast development and menarche (Selevan 2003; Wu 2003)
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- Natural selection favors earlier reproductive development
  - Probability of mortality greater than zero
  - Early development increases total reproductive output through shorter generation times
Factors impacting onset of puberty

- 4-5 year variability in onset of puberty
- Genetic factors account for 30-70% of variability
  - Twin studies (MZ vs DZ, raised together or apart)
  - Sisters higher correlation than mother/daughter
  - Polygenetic factors (similar to height, weight)
  - Polymorphisms E receptor; CYP17, CYP3, CYP3A4
- Behavioral/ environmental factors
  - Health, public health issues
  - Nutrition/ overnutrition
  - (Lack of) physical activity
  - Environmental exposures
Factors impacting onset of puberty

- Single most important environmental factor is nutritional (up to 25% of variance)
- Interaction between genetics and environment
  - Studies have shown an interaction between BMI and race on age of onset of puberty
  - Gene expression favors conservation of energy; storage of excess energy as fat
    - Maladaptive in rapidly changing environment that maximizes opportunities for energy intake, minimizes expenditure (genetic homology past 10,000 yrs)
Obesity trends among US adults


(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

Source: CDC Behavioral Risk Factor Surveillance System.
Trends in overweight for girls (BMI > 95%tile), by age and year

NHANES I ’71-74; NHANES II ’76-80; NHANES III ’88-94; NHANES ’99-00; NHANES ’03-6; NHANES ’07-08
And don’t forget the boys: the testicular dysgenesis syndrome

- Four conditions: hypospadias, cryptorchidism, reduced semen quality, testicular cancer
- Similar trends in incidence and prevalence noted in 1990’s with hypothesis of underlying environmental causes; in 2001 Skakkebaek proposed “testicular dysgenesis syndrome”
  - Testicular dysgenesis syndrome: in utero exposure leading to abnormal Sertoli cell dysfunction and decreased Leydig cell function
  - More recently, association of prenatal phthalate exposure and reduced anogenital distance
The testicular dysgenesis syndrome

- Increased incidence hypospadias (x4 in Netherlands; x2 in US) with increased proportion of severe cases
- TDS associated with some cases hypospadias and impaired spermatogenesis
- Decline in sperm motility and concentration; incr levels of EDCs with herbicide and pesticide levels
- Increased risk cryptorchidism in sons of female gardeners
- Increased incidence of testicular cancer; higher levels of organochlorines in mothers of men with testicular cancer
Mean sperm density by year and geographic area

Sperm density by year and geographic area:
- Europe
- North America
- Other

Adapted from Swan, 2000.
The canary in the coal mine

- The age of breast development is declining
- BMI and prevalence of obesity are increasing
- Prevalence of components of the testicular dysgenesis syndrome is increasing
- Exposure to several potential Endocrine Disrupting Chemicals (EDCs) are ubiquitous
  - Phthalates are associated with central adiposity, precocious thelarche
Many thanks to our all of our colleagues, advocacy community, families!

Drawn by two study participants when in second grade.