Sex:
--- understanding its biological significance
--- appreciating how genetics was used to understand how it is determined.

**ESD**: environmental sex determination

**GSD**: genotypic sex determination

GSD via a Maternal Effect system:
(For a blowfly)

<table>
<thead>
<tr>
<th>Genotype of mother</th>
<th>Phenotype of the progeny</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-producing</td>
<td></td>
</tr>
<tr>
<td>Female-producing</td>
<td></td>
</tr>
</tbody>
</table>

- Male-producing mothers: \( f/f \) X males \( f/f \)
  - \( f/f \) sons
  - 1:1 sex ratio
- Female-producing mothers: \( F/f \) X males \( f/f \)
  - \( F/f \) & \( f/f \) daughters

A potential problem with many GSD systems (including our own):

<table>
<thead>
<tr>
<th>Fruit flies:</th>
<th>Honeybees:</th>
</tr>
</thead>
<tbody>
<tr>
<td>XX AA male</td>
<td>AA A male</td>
</tr>
<tr>
<td>XY AA female</td>
<td>female male</td>
</tr>
</tbody>
</table>

- Males are monosomic for 1/5 of their genome
- Females are monosomic haploid for entire genome

- Potentially genetically unbalanced

XX XY

How eliminate the anticipated X-linked gene expression difference between the sexes?

= X-chromosome dosage compensation

1. Increase X-linked gene expression 2x in males
   - Fruit flies (“the fly”)
2. Decrease X-linked gene expression in females by 1/2
   - 2a: reduce each X by 50%
   - The worm
   - 2b: inactivate one X
   - Us mammals
Recall that Muller observed X-linked gene dose effect within a sex but not between the sexes.

\[ w^a/w^a > (\text{darker, more "wildtype"}) w^a/Df(w) \]
\[ \text{or } w^a/w^a \]

\[ w^a/Y < (\text{lighter, less "wildtype"}) w^a/Y; Dp(w^a)/+ \]

**YET:**

\[ w^a/w^a = (\text{same color as}) w^a/Y \]

"Leaky" (hypomorphic) mutant alleles twice as leaky in males vs. females. It must follow that:

\[ w^a/Y; Dp(w^a)/+ > (\text{darker, more "wildtype"}) w^a/w^a \]

Infer: wildtype alleles twice as active in males vs. females to achieve balance.

**wildtype (normal) X-linked alleles work twice as hard in males as they do in females**

\[ XX \times Y \Rightarrow X\text{-chromosome dosage compensation} \]

Are the male genes working twice as hard, or instead are the female genes working half as hard? (is the glass half full or half empty)

Can actually answer the question.

But first:

Are the alleles on both the female’s X chromosomes even working? **YES**

Muller knew: white gene functioning is “cell autonomous”:

- **a cell’s phenotype reflects its genotype with respect to the particular gene**
- **w*/w- eye is solid red, not mosaic red and white**
- **alleles on both X’s must be active**

Gynandromorph:

- **w*/w- Male**
- **w*/w- Female**

- **X chromosome**

2800 genes

**Average transcription rates (per unit DNA):**

- Female X = female autosomes = male autosomes < male X

**transcription rate for Male X-linked genes are turned UP relative to autosomal or female X-linked genes**

**Giant Polytene Salivary-Gland Chromosomes**

measure rate of RNA precursor incorporation into "nascent" transcripts (during interphase)

...average transcription rates (per unit DNA)

- **Male X-linked genes are turned UP**
- **female X-linked genes turned DOWN?**

**Are male X-linked genes turned UP or are female X-linked genes turned DOWN?**

Female: XX

Male: XY

\[ \text{no X hyperactivation} \]

X hyperactivation

need only for 

**Normal gene function:**

Phenotypic consequences of loss by mutation:

- needed (only) for hyper male (X:A=0.5)-specific lethal
- needed (only) to prevent hyper female (X:A=1)-specific lethal

That is how the relevant genes are recognized

\[ \text{MSLs encode protein complex on male X} \]
How do we mammals dosage compensate?

First clue:  
“sex chromatin”

Barr Body rule:  

<table>
<thead>
<tr>
<th>#BB</th>
<th>#X-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Barr Body</td>
<td>One Barr Body</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X0 AA</th>
<th>XXY AA</th>
<th>XXXX AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner females</td>
<td>No Barr Body</td>
<td>(mentally retarded) females Three Barr Bodies</td>
</tr>
<tr>
<td>Kleinfelter males</td>
<td>One Barr Body</td>
<td></td>
</tr>
</tbody>
</table>

Odd behavior of an X-linked mammalian gene:

<table>
<thead>
<tr>
<th>G6PD+</th>
<th>G6PD-</th>
<th>heterozygote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual blood cells are</td>
<td>phenotypically either</td>
<td>only one or the other X-linked allele seems to be active in any given blood cell</td>
</tr>
</tbody>
</table>

not what we saw with the eye of the w+/w- fly

Geneticist Mary Lyon:

#BarrBodies = #X-1

mosaic expression of G6PD+ (on X)

mosaic c- expression when c- on X

(translocation of autosomal coat color gene c to X)

Hypothesis:  
(1) Barr Body = inactivated X chromosome

(2) Dosage compensation by inactivation of all but one X chromosome

X chromosome inactivation:

<table>
<thead>
<tr>
<th>X maternal</th>
<th>X paternal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) initiated very early in development</td>
<td>at ~500 cell stage in humans</td>
</tr>
<tr>
<td>(2) generally random in embryo proper</td>
<td>(paternal = maternal) (often paternal in extra-embryonic)</td>
</tr>
<tr>
<td>(3) once initiated, stably inherited</td>
<td>an epigenetic phenomenon</td>
</tr>
<tr>
<td>(4) reactivation of inactivated X occurs in germ cells during oogenesis</td>
<td></td>
</tr>
</tbody>
</table>

Striking human example of X inactivation in action:

Anhidrotic Ectodermal Dysplasia (EDA):  

hemizygous males (EDA/Y) & homozygous females (EDA/EDA)  

no sweat glands (incl. breasts)  
missing & abnormal teeth/hair  

cell autonomous trait

EDA+/EDA- PHENOTYPIC MOSAICS

Identical twins:  

Patchiness signifies little skin cell mixing during development

For X-linked genes:

If a/a mammals are functional mosaics of a+ & a- cells  

...are all non-functional X-linked alleles (a) semi-dominant?  

don'tance depends on how phenotype is operationally defined

NO  

Need to know for gene a: how is a phenotype related to a+ gene expression?

(1) perhaps not cell autonomous  
(and 50% a+ function is sufficient for normal phenotype)  
consider hemophilias

(2) perhaps cell autonomous, but deleterious early  
--- abnormal cells selected against  
they may be outcompeted by normal cells

Most animals compensate well for cells lost during development
Mapping the source of the inactivation bias defined Xce

\[ X_{1\text{mat}}X_{2\text{pat}} \quad 50:50 \quad \text{mat vs. pat active} \]
\[ X_{2\text{mat}}X_{1\text{pat}} \quad 50:50 \quad \text{mat vs. pat active} \]
\[ X_{1\text{mat}}X_{1\text{pat}} \quad 65:35 \quad \text{mat (1) vs. pat (2) active} \]
\[ X_{2\text{mat}}X_{2\text{pat}} \quad 35:65 \quad \text{mat (2) vs. pat (1) active} \]

Among the genetic pathways that control development, those controlling sexual development are perhaps the best understood. Among the genetic pathways that control development, those controlling sexual development are perhaps the best understood.