Update 11.5

• Katsuhiko Hayashi et al. (2011, 2012) at Kyoto University have turned mouse male ES and iPS cells into sperm and female cells into eggs. The resulting gametes were capable of fertilization and resulted in normal mouse pups.
• Such research may lead to treatments for human infertility.
• Because ES cells as well as iPS cells lend themselves to genetic transformation, combining these methods would amount to germ line gene therapy for humans.
• While correction of known genetic defects is a defensible goal, no attempts should not be made in humans to raise novel genotypes (“designer babies”).

Seminar on stem cells (BIO 137): Wed 2-4 pm, beginning after Spring Break (www.bio.utexas.edu/courses/kalthoff/bio137). You are welcome to just sit in.
Haruko Obokata et al. (2014a,b) have recently reported that external stimuli, such as low pH, can induce differentiated cells from newborn mice to stimulus-triggered acquisition of pluripotency (STAP).

STAP is reminiscent of phenocopying, the mimicking of mutant phenotypes by stressful environmental factors, such as heat, at the time when critical genes are expressed.

However, several other investigators have been unable to reproduce the results of Obokata et al. An investigation by her home institution (RIKEN) is pending.

Phenocopies, and possibly STAP, are reminders that gene expression depends on the folding of polypeptides into a biologically active conformations, a process that may be disturbed by extreme values of environmental parameters.
Nature and Nurture

- It’s Nature and Nurture, not Nature versus Nurture
- Neuronal Connections Change During Learning
- Animals are Genetically Prepared to Learn
- Some Behaviors Depend on Epigenetic Changes that Are Both Heritable and Reversible
- Birds and Apes Have (Some) Culture
- Traits May Vary Discontinuously or Continuously
- The Heritability of a Discontinuously Variable Trait Can Be Estimated by its Concordance Ratio
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NMDA receptors as coincidence detectors in memory formation.

Memories are formed by the strengthening of synapses between neurons that are excited simultaneously. The presynaptic neuron (top) then releases the neurotransmitter glutamate (purple), which binds to the NMDA receptor (blue) of the postsynaptic neuron (bottom). If the latter is stimulated independently it ejects magnesium (orange triangles) from the NMDA receptors. As a result, the NMDA receptors allow calcium ions (red dots) to enter the cytoplasm. Ca^{2+} ions activate regulatory proteins, which cause a signaling cascade that will eventually strengthen the synapse.

*From J. Tsien, Sci. Amer. April 2000, p. 67*
Figure 13.1: The sea slug *Aplysia* has a simple nervous system with large neurons that can be individually penetrated by electrodes.
**Habituation:** In *Aplysia*, touching the skin repeatedly without other negative experiences weakens the gill withdrawal reflex: With time, the sensory neuron releases less neurotransmitter and forms fewer presynaptic terminals. *From Goldsmith and Zimmermann (2001)*
Figure 13.2: Sensitization. The gill withdrawal reflex of *Aplysia* intensifies if touching of the siphon is accompanied by an electric shock to the tail skin.

Stimulated by a facilitating interneuron, the sensory neuron forms more presynaptic terminals and releases more neurotransmitter.

*After Goldsmith and Zimmermann (2001)*
Serotonin released by the facilitating interneuron binds to a receptor on the sensory neuron. This activates the formation of cyclic AMP. cAMP activates a kinase that blocks $K^+$ channels. As a result, $Na^+$ and $Ca^{++}$ channels stay open longer when an action potential arrives. With more $Ca^{++}$ admitted, more neurotransmitter is released from the sensory nerve terminal.

*After Goldsmith and Zimmermann (2001)*
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Figure 13.4: Behavioral Imprinting.

Young geese imprinted on ethologist Konrad Lorenz, who happened to be nearby when the geese were hatching. Since then, they followed him around as they normally would do with a parent.
Young geese imprinted on ethologist Konrad Lorenz. Because he happened to be nearby when the geese were hatching, he became “mother goose” to them.
a, b: Prairie voles (a) are social and monogamous, liking to 'huddle' with their mate, whereas meadow voles (b) are solitary and polygamous.

c, d: Partner preference test. After mating with a female, a male prairie vole (c) tended to spend significantly more time in contact with his mate (filled columns) than with a strange female (open columns) ($P < 0.05$), whereas meadow voles (d) did not form partner preferences and spent little time huddling with either female.

e, f: Autoradiograms of the forebrain showing expression of the gene for the vasopressin 1a receptor ($V1aR$) in the ventral pallidum (VP). $V1aR$ expression is stronger in prairie vole VP.

Experiment: Injection of cloned $V1aR$ gene into VP made meadow vole males more social and monogamous.
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The mothering style of rats is inherited by biological as well as adopted daughters. Underlying mechanisms include demethylation of the glucocorticoid receptor (GR) gene and acetylation of surrounding histones. These changes are passed on during cell division and by maternal programming.

From Sapolsky (2004)
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Figure 13.7: Culture in non-human primates. Macaques on the Japanese island of Koshima wash potatoes before eating them, a cultural trait started by a female around 1950. From Nature 399: 635
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Discontinuously Variable Traits

A trait is called discontinuously variable, or qualitative, if an individual either shows the trait or does not. Such traits are often, but not always, controlled by single (or “Mendelian”) genes.

Human examples: blood groups, albinism, cystic fibrosis, sickle cell anemia, epilepsy, hemophilia
The ABO locus on the human chromosome 9 exists in 3 alleles, \( A \), \( B \), and \( O \). It controls the presence, on red blood cells, of antigens \( A \) (genotypes \( AA \) or \( AO \)), \( B \) (genotypes \( BB \) or \( BO \)), both (genotype \( AB \)), or none (genotype \( OO \)). Expression of these antigens is co-dominant. The H antigen is also present in small amounts on A and B cells, so that no blood group forms antibodies to it.

*From Sutton (1988), p. 423*

**Table 18-1  Antigens and Antibodies Associated with the ABO Blood Groups**

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Red Cell Antigens</th>
<th>Plasma Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>( A )</td>
<td>anti-( B )</td>
</tr>
<tr>
<td>B</td>
<td>( B )</td>
<td>anti-( A )</td>
</tr>
<tr>
<td>AB</td>
<td>( A, B )</td>
<td>none</td>
</tr>
<tr>
<td>O</td>
<td>( H )</td>
<td>anti-( A ), anti-( B )</td>
</tr>
</tbody>
</table>
Albinism is caused by complete lack of pigment in skin, hair, and retina. Typically, it is a recessive autosomal disorder, caused by mutations in the gene for tyrosinase, an enzyme involved in the synthesis of the black pigment melanin.
Albinism, a Recessive Autosomal Disorder

Two alleles for albinism ($A, a$) segregate during gamete formation. The phenotype shows up in 25% of the offspring of a heterozygous pair, even though both parents are phenotypically normal.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 $AA$</td>
<td>3/4 normal</td>
</tr>
<tr>
<td>2 $Aa$</td>
<td></td>
</tr>
<tr>
<td>1 $aa$</td>
<td>1/4 albino</td>
</tr>
</tbody>
</table>

Continuously Variable Traits

A trait is called continuously variable, or quantitative, if an individual may express the trait anywhere within a wide range. Such traits are controlled by multiple genes and environmental factors, each of which makes a small contribution.

Human examples: height, weight, systolic blood pressure, skin pigmentation, IQ
Figure 13.8: Stature (height) as a continuously variable trait. Data in increments of 1 inch recorded for Englishmen called up for military service in 1939. Vertical solid line indicates mean, vertical broken lines indicate standard deviation. Broken curve shows normal distribution fitted to the mean and standard deviation of the actual data. *From Sutton* (1988)
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Any two individuals showing the same version of a discontinuously variable trait are said to be concordant for this trait.

The concordance rate is defined for a sample of analyzed pairs (siblings, parent-child, etc.) in which at least one partner shows a (relatively rare) trait.

\[
\text{Number of concordant pairs} = \text{Concordance rate} \times \text{Number of analyzed pairs}
\]
Monozygotic (“identical”) twins develop from one fertilized egg, or zygote, which subsequently splits into two embryos. Dizygotic (“fraternal”) twins result from two eggs fertilized independently during the same ovulatory cycle. *From Cummings (2006)*
Table 13.1: Monozygotic and Dizygotic Twins

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic Twins</th>
<th>Dizygotic Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>derived from one fertilized egg, or zygote</td>
<td>derived from two independently fertilized eggs</td>
</tr>
<tr>
<td><strong>Synonym</strong></td>
<td>identical twins</td>
<td>fraternal twins</td>
</tr>
<tr>
<td><strong>Shared Genetic Information</strong></td>
<td>100 %</td>
<td>~50 %</td>
</tr>
<tr>
<td><strong>Boy/Girl Pairs</strong></td>
<td>none</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>3.5 - 5 per 1,000 live births</td>
<td>2 - 50 per 1,000 live births</td>
</tr>
</tbody>
</table>
The heritability of discontinuously variable traits can be estimated by calculating the concordance ratio from the concordance rates for monozygotic twins (MZT) and for dizygotic twins (DZT).

Concordance rate (MZT)
------------------------ = Concordance ratio

Concordance rate (DZT)
<table>
<thead>
<tr>
<th>Trait</th>
<th>MZ Conc. Rate (%)</th>
<th>DZ Conc. Rate (%)</th>
<th>Concordance Ratio</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>72</td>
<td>15</td>
<td>4.8</td>
<td>Cummings</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>16</td>
<td>3.6</td>
<td>Sutton</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>56</td>
<td>22</td>
<td>2.6</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>19</td>
<td>3.1</td>
<td>S</td>
</tr>
<tr>
<td>Measles</td>
<td></td>
<td></td>
<td>1.0</td>
<td>KK notes</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>89</td>
<td>7</td>
<td>12.7</td>
<td>C</td>
</tr>
<tr>
<td>Diabetes</td>
<td>65</td>
<td>18</td>
<td>3.6</td>
<td>C</td>
</tr>
<tr>
<td>Cleft lip</td>
<td>42</td>
<td>5</td>
<td>8.4</td>
<td>C</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>25</td>
<td>6</td>
<td>4.5</td>
<td>S</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>88</td>
<td>31</td>
<td>2.83</td>
<td>S</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>26</td>
<td>13</td>
<td>2.0</td>
<td>S</td>
</tr>
<tr>
<td>Eye color</td>
<td>99</td>
<td>28</td>
<td>4.5</td>
<td>C</td>
</tr>
<tr>
<td>Handedness (left or right)</td>
<td>79</td>
<td>77</td>
<td>1.0</td>
<td>C</td>
</tr>
<tr>
<td>Male homosexuality</td>
<td>52</td>
<td>22</td>
<td>2.4</td>
<td>Bailey &amp;</td>
</tr>
<tr>
<td>Female homosexuality</td>
<td>50</td>
<td>25</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>
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Garcia effect.

Top: A rat who received a shock remembers the looks of the food eaten at the time of the pain.

Bottom: A rat who received X-rays to feel nauseous later remembers the smell of the food eaten before the nausea.
Figure S13.a: Learning whom to mob. Many birds chase away predators by sounding alarm calls and mobbing.

A. Blackbird on left mobs a stuffed owl seen through the screening of its cage. Blackbird on right hears the ruckus but initially stays calm because he sees only a harmless honeycreeper.

B,C. Later, blackbird on right starts mobbing the honeycreeper as if he were a bird of prey.

C,D. Blackbird on left, hearing the noise from the blackbird on the right, learns to mob a honeycreeper as well.

From Goldsmith and Zimmermann (2001)
Threshold model to explain the discontinuous variation of some multifactorial traits, such as schizophrenia or homosexuality. Several genes and environmental factors seem to have small additive effects, but the trait tends to vary in an all-or-nothing fashion rather than gradually.
Drug use and other addictive behaviors activate dopaminergic pathways in the brain, thus “highjacking” parts of the normal reward circuits that regulate hunger, thirst, and sex drive as well as needs for sharing and community.
Drug Effects Coverage on Dopaminergic Pathways

Marihuana: THC binds to endogenous receptors
Opiates: Bind to endorphine receptors
Nicotine: Binds to Acetylcholine receptor
Alcohol: Other brain regions
Cocaine: Reuptake pumps for DA, other neurotransmitters
Amphetamine etc.: Force DA release from storage

Dopaminergic Neurons:
- Ventral Tegmental Area (VTA)
  - GABA Interneurons
  - Various brain regions

Dopamine (DA):
- Mesolimbic Pathway
  - Nucleus Accumbens (NAC): part of Ventral Striatum
- Mesocortical Pathway
  - Frontal Cortex
- Nigrostriatal Pathway
  - Dorsal Striatum

Inhibitory enzyme
Hemophilia A (OMIM 306700) is a recessive X-linked trait caused by lack of blood clotting factor VIII. Queen Victoria of England carried the disease into the royal families of Russia and Spain. From Cummings (2006), p. 86