Sexual Differentiation of the Nervous System

To what extent are the behavioral differences that we recognize as male and female imposed by the environment or by our genes?

Why should we care?

*Testosterone Rules.* Discover 1997, March 45-50

Nature versus Nurture?

There are two fundamentally different explanations for how gender develops.

Many psychologists believe that gender is the result of environmental influences, particularly the way we are treated by our parents, guardians, friends and relatives. According to Dr John Money we are *psychosexually neutral at birth*, and our gender is a consequence of the nurture we receive as children.

A less popular view is that gender is the result of nature, particularly the effects of hormones on the developing brain.

Pope Benedict XVI has responded firmly to the first challenge of his papacy by condemning a Spanish government bill allowing marriage between homosexuals.

The bill would make Spain the first European country to allow homosexual people to marry and adopt children. Belgium and the Netherlands only allow same-sex marriages.
“Face it, we all do it - we all believe in stereotypes about minorities. These stereotypes are typically pejorative and false, but every now and then they have a core of truth. I know, because I belong to a minority that lives up to its reputation. I have a genetic abnormality generally considered to be associated with high rates of certain socially abhorrent behaviors: I am male.”

Robert Sapolsky, 1997

Testosterone Rules. Discover 1997, March 45-50

Homicide victimization by gender, 1976-2000
Rate per 100,000 population

Males were 3.2 times more likely than females to be murdered.

Males were 10 times more likely than females to commit murder.

70% of homicides are committed by males between the ages of 17 and 34.

www.ojp.usdoj.gov/bjs/homicide/gender.htm
Reserved reading:

Chapter 57, “Sexual differentiation of the nervous system.”
From - Principles of Neural Science.

“Testosterone Rules” by Robert Sapolsky,
Discover, March, 1997
The developing gonads are embryologically bipotential, becoming testes if the TDF gene is present and ovaries if it is not.

The secretions of the fetal testes in turn determine subsequent events in the sexual differentiation of the male. Removal of the gonadal tissue from early fetal rabbits, results in development as females. Thus, the female phenotype can “partially” develop in the absence of any gonadal tissue.

The fetal testes secrete two major hormones: 1) testosterone, a steroid secreted by Leydig cells, which masculinizes the sex organs, mammary gland rudiments, and nervous system, and 2) Mullerian duct-inhibiting substance, a glycoprotein secreted by Sertoli cells, which causes resorption of the tissues that would otherwise become the oviducts, uterus, cervix, and vagina. The absence of these two hormones, or of receptors for them, results in female development.

Testosterone is the prohormone for dihydrotestosterone and estradiol
Tissues that are equivalent for the two sexes in the undifferentiated state become different organs by the time of birth.
Effects of testosterone on male humans:
- body hair
- baldness
- voice
- skin, acne
- protein formation and muscle development
- bone growth and calcium retention
- basal metabolism
- red blood cells

Effects of estrogens on female humans:
- breasts
- skeleton growth and proportions
- basal metabolism
- fat deposition
- hair distribution
- skin
**Activational and organizational effects of hormones**

Hormones have two fundamentally different effects on sexual behaviour:

- **Organizational** effects refer to the effects of hormones during the *early development* of an animal.

- **Activational** effects refer to the effects of hormones in the *adult* organism.

Exposure to hormones during a **critical period** of development changes the way in which the organism reacts to hormones in *adulthood*. This does not mean that early exposure to hormones has a permanent effect on behaviour. Instead it suggests that exposure to hormones in infancy affects how the adult reacts to hormones.

In adults, circulating steroid hormones primarily *activate* sexual responses.

![Graph](image)

Estrogen induces sexual receptivity in ovariectomized female rats in a dose-dependent manner. After eight daily subcutaneous injections of estradiol benzoate, receptivity was measured by the lordosis quotient (number of lordotic responses of the subject divided by the number of mounts, multiplied by 100).
During a critical period at the time of birth, (perinatal period) exposure to steroid hormones has an **organizational effect**.
During the critical period, actions of hormones are organizational and permanent.
Data from rats.

Table 57-2 Consequences of Hormonal Manipulation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age when treated</th>
<th>LH secretion pattern</th>
<th>Sexual behavioral responsiveness</th>
<th>Number of spine synapses in MPOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Controls</td>
<td>—</td>
<td>Cyclic</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Postnatal day 4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Acyclic</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Testosterone</td>
<td>Postnatal day 16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cyclic</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>Males</td>
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<tr>
<td>Controls</td>
<td>—</td>
<td>Acyclic</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Castration</td>
<td>Postnatal day 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cyclic</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Castration</td>
<td>Postnatal day 7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Acyclic</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Abbreviations: LH = Luteinizing hormone; MPOA = medial preoptic area.
<sup>a</sup>During the critical period of sexual differentiation.
<sup>b</sup>After the critical period of sexual differentiation.

Exposure to steroid hormones during the critical period result in strong sex differences in the nonreproductive behavioral repertoires of prepubertal juveniles.

Female rhesus monkeys exposed to androgen during the critical period show more rough-and-tumble play, more aggressive encounters with normal males, and less maternal imitative behaviors than normal females.

Also, animals exposed to androgen during the critical period spend more time playing with others who are similarly exposed, regardless of their genetic sex.

Human data from girls with congenital adrenal hyperplasia.

*European Journal of Endocrinology (2008) 155 S115-S121*
Perinatal hormones also determine the degree to which sex-linked behaviors are expressed by normal males and females.

Female mice that develop between two male fetuses (2M females) have a higher concentration of testosterone.

Although 2M females reproduce normally, they are more aggressive, display erratic estrus cycles, begin to mate later, and cease to bear young earlier than 0M females.

The dosage of testosterone required to induce aggression in adult neonatally castrated males that develop between two male siblings is lower than that required for similarly castrated males that develop between two females. (vom Saal and Bronson 1980 Science 208:597)

In humans there is considerable variation in the amounts of testosterone and estrogen to which a developing fetus is exposed.

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Testosterone is the prohormone for dihydrotestosterone and estradiol
Estradiol is the masculinizing hormone for many sexually dimorphic brain characteristics.