The Ratio of Males to Females 1 in Humans Is Not 1.0

- The presence of heteromorphic sex chromosomes in one sex of a species but not the other provides a potential mechanism for producing equal proportions of male and female offspring.
- This potential depends on the segregation of the X and Y chromosomes during meiosis, such that half of the gametes of the heterogametic sex receive one of the chromosomes and half receive the other one.
- As we learned in the previous section, small pseudoautosomal regions of pairing homology do exist at both ends of the human X and Y chromosomes, suggesting that the X and Y chromosomes do synapse and then segregate into different gametes.
- Provided that both types of gametes are equally successful in fertilization and that the two sexes are equally viable during fetal and embryonic development, a 1:1 ratio of male and female offspring should result.

- The secondary sex ratio reflects the proportion of each sex that is born.
- The secondary sex ratio is much easier to determine but has the disadvantage of not accounting for any disproportionate embryonic or fetal mortality.
- When the secondary sex ratio in the human population was determined in 1969 by using worldwide census data, it was found not to equal 1.0.
- For example, in the Caucasian population in the United States, the secondary ratio was a little less than 1.06, indicating that about 106 males were born for each 100 females.
Despite these ratios, it is possible that the primary sex ratio is 1.0 and is later altered between conception and birth.

- For the secondary ratio to exceed 1.0, then, prenatal female mortality would have to be greater than prenatal male mortality.
- However, this hypothesis has been examined and shown to be false.
- In fact, just the opposite occurs.
- The sex of approximately 6000 embryos and fetuses recovered from miscarriages and abortions was determined, and fetal mortality was actually higher in males.
- On the basis of the data derived from that study, the primary sex ratio in U.S. Caucasians was estimated to be 1.079.
- It is now believed that the figure is much higher—between 1.20 and 1.60, suggesting that many more males than females are conceived in the human population.

It is not clear why such a radical departure from the expected primary sex ratio of 1.0 occurs.

To come up with a suitable explanation, researchers must examine the assumptions on which the theoretical ratio is based:

- 1. Because of segregation, males produce equal numbers of X- and Y-bearing sperm.
- 2. Each type of sperm has equivalent viability and motility in the female reproductive tract.
- 3. The egg surface is equally receptive to both X- and Y-bearing sperm.

No direct experimental evidence contradicts any of these assumptions; however, the human Y chromosome is smaller than the X chromosome and therefore of less mass.

Dosage Compensation Prevents Excessive Expression of X-Linked Genes in Mammals

- The presence of two X chromosomes in normal human females and only one X in normal human males is unique compared with the equal numbers of autosomes present in the cells of both sexes.
- On theoretical grounds alone, it is possible to speculate that this disparity should create a "genetic dosage" difference between males and females, with attendant problems, for all X—linked genes.
- There is the potential for females to produce twice as much of each product of all X-linked genes.
- The additional X chromosomes in both males and females exhibiting the various syndromes discussed earlier in this chapter are thought to compound this dosage problem.
- Embryonic development depends on proper timing and precisely regulated levels of gene expression.
- Otherwise, disease phenotypes or embryonic lethality can occur.
Barr Bodies

- Murray L. Barr and Ewart G. Bertram’s experiments with female cats, as well as Keith Moore and Barr’s subsequent study in humans, demonstrate a genetic mechanism in mammals that compensates for X chromosome dosage disparities.

- In humans, this body can be easily demonstrated in female cells derived from the buccal mucosa (cheek cells) or in fibroblasts (undifferentiated connective tissue cells), but not in similar male cells.

- This highly condensed structure, about 1 um in diameter, lies against the nuclear envelope of interphase cells.

• Current experimental evidence demonstrates that this body, called a sex chromatin body, or simply a Barr body, is an inactivated X chromosome.

• Susumu Ohno was the first to suggest that the Barr body arises from one of the two X chromosomes.

• This hypothesis is attractive because it provides a possible mechanism for dosage compensation.

• If one of the two X chromosomes is inactive in the cells of females, the dosage of genetic information that can be expressed in males and females will be equivalent.

• Convincing, though indirect, evidence for this hypothesis comes from the study of the sex-chromosome.

• Regardless of how many X chromosomes a somatic cell possesses, all but one of them appear to be inactivated and can be seen as Barr bodies.

• For example, no Barr body is seen in the somatic cells of Turner 45,X females; one is seen in Klinefelter 47,XXY males; two in 47,XXX females; three in 48,XXXX females; and so on (Figure 7-9).

• Therefore, the number of Barr bodies follows an N - 1 rule, where N is the total number of X chromosomes present.
• For example, because one of the two X chromosomes is inactivated in normal human females, why then is the Turner 45,X individual not entirely normal?
• Why aren’t females with the tri-plo-X and tetra-X karyotypes (47,XXX and 48,XXXX) completely unaffected by the additional X chromosomes?
• Furthermore, in Klinefelter syndrome (47,XXY), X chromosome inactivation effectively renders the person 46,XY.
• Why aren’t these males unaffected by the extra X chromosome in their nuclei?

• One possible explanation is that chromosome inactivation does not normally occur in the very early stages of development of those cells destined to form gonadal tissues.
• Another possible explanation is that not all of each X chromosome forming a Barr body is inactivated.
• Recent studies have indeed demonstrated that as many as 15 percent of the human X-chromosomal genes actually escape inactivation.
• Clearly then, not every gene on the X requires inactivation.
• In either case, excessive expression of certain X-linked genes might still occur at critical times during development despite apparent inactivation of superfluous X chromosomes.
The Lyon Hypothesis

- In mammalian females, one X chromosome is of maternal origin, and the other is of paternal origin.
- Which one is inactivated?
- Is the inactivation random?
- Is the same chromosome inactive in all somatic cells?
- The inactivation of X chromosomes occurs randomly in somatic cells at a point early in embryonic development, most likely sometime during the blastocyst stage of development.
- Once inactivation has occurred, all descendant cells have the same X chromosome inactivated as their initial progenitor cell.

- This explanation, which has come to be called the Lyon hypothesis, was initially based on observations of female mice heterozygous for X-linked coat color genes.
- The pigmentation of these heterozygous females was mottled, with large patches expressing the color allele on one X and other patches expressing the allele on the other X.
- This is the phenotypic pattern that would be expected if different X chromosomes were inactive in adjacent patches of cells.
- Similar mosaic patterns occur in the black and yellow-orange patches of female tortoiseshell and calico cats.
- Such X-linked coat color patterns do not occur in male cats because all their cells contain the single maternal X chromosome and are therefore hemizygous for only one X-linked coat color allele.
The most direct evidence in support of the Lyon hypothesis comes from studies of gene expression in clones of human controlled by an X-linked gene.

Fibroblasts have been taken from females heterozygous for different allelic forms of GGPD and studied.

The Lyon hypothesis predicts that if inactivation of an X chromosome occurs randomly early in development, and thereafter all progeny cells have the same X chromosome inactivated as their progenitor, such a female should show two types of clones, each containing only one electrophoretic form of GGPD, in approximately equal proportions.

In 1963, Ronald Davidson and colleagues performed an experiment involving 14 clones from a single heterozygous female.

Seven showed only one form of the enzyme, and 7 showed only the other form.

Most important was the finding that none of the 14 clones showed both forms of the enzyme.

Studies of GGPD mutants thus provide strong support for the random permanent inactivation of either the maternal or paternal X chromosome.

The Lyon hypothesis is generally accepted as valid; in fact, the inactivation of an X chromosome into a Barr body is sometimes referred to as lyonization.

One extension of the hypothesis is that mammalian females are mosaics for all heterozygous X-linked alleles - some areas of the body express only the maternally derived alleles, and others express only the paternally derived alleles.

An especially interesting example involves red-green color blindness, an X-linked recessive disorder.

In humans, hemizygous males are fully color-blind in all retinal cells.

However, heterozygous females display mosaic retinas, with patches of defective color perception and surrounding areas with normal color perception.
The Mechanism of Inactivation

• The least understood aspect of the Lyon hypothesis is the mechanism of X chromosome inactivation.
• Somehow, either DNA, the attached histone proteins, or both DNA and histone proteins, are chemically modified, silencing most genes that are part of that chromosome.
• Once silenced, a memory is created that keeps the same homolog inactivated following chromosome replications and cell divisions.
• Such a process, whereby expression of genes on one homolog, but not the other, is affected, is referred to as imprinting.
• This term also applies to a number of other examples in which genetic information is modified and gene expression is repressed.
• Collectively, such events are part of the growing field of epigenetics.

A Question of Gender

• In medieval Europe, prospective parents would place a hammer under the bed to help them conceive a boy, or a pair of scissors to conceive a girl.
• Other practices were based on the ancient belief that semen from the right testicle created male offspring and that from the left testicle created females.
• As late as the eighteenth century, European men might tie off or remove their left testicle to increase the chances of getting a male heir.
• In some cultures, efforts to control the sex of offspring has had a darker outcome- female infanticide.
• In ancient Greece, the murder of female infants was so common that the male to female ratio in some areas approached 4:1.
• In some parts of rural India, hundreds of families admitted to female infanticide as late as the 1990s.
• In 1997, the World Health Organization reported population data showing that about 50 million women were “missing” in China, likely because of selective abortion of female fetuses and institutionalized neglect of female children.
• In recent times, sex-specific abortion has replaced much of the traditional female infanticide.
• For a fee, some companies offer amniocentesis and ultrasound tests for prenatal sex determination.
• Studies in India estimate that hundreds of thousands of fetuses are aborted each year because they are female.
• As a result of sex-selective abortion, the female to male ratio in India was 927:1000 in 1991.
• In some northern states, the ratio was as low as 600:1000.

• In Western industrial countries, new genetics and reproductive technologies offer parents ways to select their children’s gender prior to implantation of the embryo in the uterus - called pre-implantation gender selection (PGS).
• Following in vitro fertilization, embryos are biopsied and assessed for gender.
• Only sex-selected embryos are then implanted.
• The simplest method involves separating X and Y chromosome bearing spermatozoa based on their DNA content.
• Because of the difference in size of the X and Y chromosomes, X-bearing sperm contain 2.8 to 3.0 percent more DNA than Y-bearing sperm.
• Sperm samples are treated with a fluorescent DNA stain, then passed through a laser beam in a Fluorescence-Activated Cell Sorter machine that separates the sperm into two fractions based on the intensity of their DNA-fluorescence.
• The sorted sperm are then used for standard intrauterine insemination.

• The emerging PGS methods raise a number of legal and ethical issues.
• Some people feel that prospective parents have the legal right to use sex-selection techniques as part of their fundamental procreative liberty.
• Proponents state that PGS will reduce the suffering of many families.
• The majority of people who under- take PGS, however, do so for nonmedical reasons—to “balance” their families.
• A possible argument in favor of this use is that the ability to intentionally select the sex of an offspring may reduce overpopulation and economic burdens for families who would repeatedly reproduce to get the desired gender.
• By the same token, PGS may reduce the number of abortions.
• It is also possible that PGS may increase the happiness of both parents and children, as the children would be more “wanted.”

• On the other hand, some argue that PGS serves neither the individual nor the common good.
• They argue that PGS is inherently sexist, having its basis in the idea that one sex is superior to the other, and leads to an increase in linking a child’s worth to gender.
• Other critics fear that social approval of PGS will open the door to other genetic manipulations of children’s characteristics.
• It is difficult to predict the full effects that PGS will bring to the world.