CHAPTER 1 What is reproduction?

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The ability to reproduce is a defining feature of all living organisms. Through reproduction, we pass our genes to a new generation. Each new generation in turn reproduces or dies out. The survivors are 'selected', by disease resistance and by successful competition for resources and mates, for their 'fitness' to live and to reproduce. In this way, the gene pool of surviving species is constantly adapting to the prevailing environment to provide the best available 'fit'. Thus, reproduction has been central to our **evolution** as the species *Homo sapiens*.

However, humans transmit more than simply their genes across generations. Humans have evolved high levels of sociability through which **cultures** are formed. Cultural practices are also transmitted across generations, and reproduction itself lies at the very heart of many of our cultural practices and taboos (see Chapters 5, 6, 20 and 23). Human society, by influencing socially and/or medically who survives to reproduce and with whom, is itself now part of the 'selection' process. This pivotal position of reproduction in our culture makes it a sensitive subject for study. Indeed, scientific enquiry into human reproduction was relatively late to the modern research scene and even today can provoke hostility, embarrassment or distress.

In this opening chapter, human reproduction is introduced and contextualized: in relation to other species – **reproductive strategies**, and in relation to time – the **reproductive life cycle**.

Reproductive strategies

Most organisms reproduce **asexually** (or **vegetatively**). For example, many unicellular organisms reproduce themselves **mitotically**, just like the individual cells of our body (Figure 1.1). Mitotic divisions generate two offspring that are genetically identical to each other and to their single parent. Among multicellular organisms, some shed cells or even body parts from which another genetically identical individual can be generated – a process called **regeneration**. Others, including some complex vertebrates such as lizards, reproduce themselves

Figure 1.1 Mitosis and meiosis in human cells. Each human cell contains 23 pairs of homologous chromosomes, making 46 chromosomes in total. Each set of 23 chromosomes is called a **haploid** set. When a cell has two complete sets, it is described as being **diploid**. In this figure, we show at the top a single schematized human cell with just two of the 23 homologous pairs of chromosomes illustrated, each being individually colour-coded. Between divisions, the cell is in **interphase**, during which it grows and duplicates both its **centriole** and the DNA in each of its chromosomes. As a result of the DNA replication, each chromosome consists of two identical **chromatids** joined at the **centromere**. Interphase chromosomes are not readily visible, being long, thin and decondensed (but are shown in this figure in a more condensed form for simplicity of representation).

Lower left panel: In **mitotic prophase**, the two chromatids become distinctly visible under the light microscope as each shortens and thickens by a spiralling contraction; at the end of prophase the **nucleoli and nuclear membrane** break down. In **mitotic metaphase**, microtubules form a **mitotic spindle** between the two centrioles and the chromosomes lie on its **equator**. In **mitotic anaphase**, the centromere of each chromosome splits and the two chromatids in each chromosome migrate to opposite poles of the spindle (**karyokinesis**). During **mitotic telophase** division of the cytoplasm into two daughters (known as **cytokinesis**) along with breakdown of the spindle and the reformation of nuclear membranes and nucleoli occurs, as does the decondensation of chromosomes so that they are no longer visible under the light microscope. Two genetically identical daughter cells now exist where one existed before. Mitosis is a non-sexual or vegetative form of reproduction. by setting aside a special population of **egg cells** that can differentiate into conceptuses in the absence of a fertilizing spermatozoon. This type of asexual reproduction is called **parthenogenesis**, and generates a completely new organism with the same gene complement as its parent.

Mammals reproduce sexually

Parthenogenesis is simply not an option available to mammals. Thus, although it is possible to activate a mammalian egg (including a human egg) in the complete absence of a spermatozoon,

Lower right panel: Meiosis involves two sequential divisions. The first meiotic prophase (prophase 1) is lengthy and can be divided into several sequential steps: (1) leptotene chromosomes are long and thin; (2) during zygotene, homologous pairs of chromosomes from each haploid set come to lie side by side along parts of their length; (3) in pachytene, chromosomes start to thicken and shorten and become more closely associated in pairs along their entire length at which time synapsis, crossing over and chromatid exchange take place and nucleoli disappear; (4) in diplotene and diakinesis, chromosomes shorten further and show evidence of being closely linked to their homologue at the chiasmata where crossing over and the reciprocal exchange of DNA sequences have occurred, giving a looped or cross-shaped appearance. In meiotic metaphase 1, the nuclear membrane breaks down, and homologous pairs of chromosomes align on the equator of the spindle. In meiotic anaphase 1, homologous chromosomes move in opposite directions. In meiotic telophase 1, cytokinesis occurs; the nuclear membrane may re-form temporarily, although this does not always happen, yielding two daughter cells each with half the number of chromosomes (only one member of each homologous pair), but each chromosome consisting of two genetically unique chromatids (because of the crossing-over at chiasmata). In the second meiotic division, these chromatids then separate much as in mitosis, to vield a total of four haploid offspring from the original cell, each containing only one complete set of chromosomes. Due to chromatid exchange and the random segregation of homologous chromosomes, each haploid cell is genetically unique. At fertilization, two haploid cells will come together to yield a new diploid zygote.



such that it undergoes the early processes of development and may even implant in the uterus, these parthenogenetic conceptuses always fail and die eventually (see page 10 for an explanation as to why this is). Reproduction in mammals is invariably **sexual**. Sex is defined formally in biology as a process whereby a genetically novel individual is formed as a result of the mixing of genes from two individuals. So, the essential feature of mammalian sexual reproduction is that each new individual receives its chromosomes in two roughly equal portions: half carried in a male gamete, the spermatozoon (see Chapter 7), and half in a female gamete, the oocyte (see Chapter 9). These gametes come together at fertilization (see Chapter 12) to form the genetically novel zygote. In order to reproduce subsequently, the individual formed from that zygote must transmit only half its own chromosomes to the new zygotes of the next generation. In sexually reproducing species, therefore, a special population of germ cells is set aside. These cells undergo the division process of meiosis, during which the chromosomal content of the germ cells is reduced by half and the genetic composition of each chromosome is modified as a result of the exchange of pieces of homologous chromosomes (Figure 1.1). The increased genetic diversity that is generated within a sexually reproducing population offers a richer and more varied source of material on which natural selection can operate. The population therefore shows greater resilience in the face of environmental challenge. In Chapters 3 and 4, we examine how the two sexes are formed and matured.

Both natural and sexual selection operate in mammals

Asexually reproducing organisms do not need to find a sexual partner. Whether or not they reproduce depends entirely on their survival - natural selection operates simply at this level. Sexual reproduction introduces a complication since it involves two individuals. These have to come together and synchronize their egg and sperm production and shedding: spatial and temporal coordination is highly desirable to optimize fertility. The conjunction of two sexes also provides opportunities for mate selection. For successful reproduction, the survival of offspring to sexual maturity is critical and so it is advantageous to share your genes with a mate who has the genes most likely to achieve this success. It is not therefore surprising that mechanisms for recognizing 'fitness' in a sexual partner have evolved, a process called sexual selection. However, there is a cost to sexual selection: it involves considerable energy expenditure in locating, attracting and keeping a sexual partner, and also can expose both partners to increased risk of death - from sexual competitors or predators preying on the sexually occupied! So there is an evolutionary trade-off between the pros of sexual selection and the cons of performing it. How sexual selection operates in humans, and the cultural rituals around it, are discussed further in Chapter 6.

Fertilization in mammals is internal

The fertilization of oocytes is achieved in most aquatic and amphibious vertebrates by discharging large numbers of oocytes and spermatozoa into the water – **spawning**. This process of **external fertilization** provides opportunities for the easy predation of eggs and the conceptuses developing from them, and so large numbers are produced to increase the chances of some surviving.



Figure 1.2 Numbers of ovarian germ cells during the life of a human female from conception. Note the steady rise early in fetal life followed by a precipitous decline prior to birth and shortly afterwards. (Source: Drawn from original data from T. Baker.)

Mammals, in contrast, **fertilize internally** (see Chapter 11). This reproductive strategy **reduces the numbers of eggs shed**, in humans to only one or two at a time, thereby reducing the energy resources invested in egg production. In fact, in an evolutionary hangover, considerable egg wastage still occurs in mammals. Thus, a woman acquires all her eggs when she is herself a fetus, with numbers peaking at around 7 million at 6 months of her fetal life. Thereafter, most eggs die in the ovary during fetal, neonatal and pubertal life (Figure 1.2). Nonetheless, this programmed loss of follicles does conserve energy resources, because it happens before follicle growth has occurred.

Oviparity versus viviparity

Most reptiles and birds, like all mammals, also fertilize internally, but they then lay eggs that contain the developing conceptuses. These eggs, like those shed by externally fertilizing species, must be relatively large, because they have to carry sufficient energy resources to complete the development of young to the point at which they are capable of feeding. In contrast, all mammals are **viviparous**, producing smaller eggs that develop *in vivo* and giving birth to live young, except for the **oviparous** monotremes – the platypus and echidnas. Mammals have evolved not just **fewer eggs**, but also much **smaller eggs** (Figure 1.3).



Figure 1.3 Cartoon to show differences between mammalian and frog eggs. From bottom up: frog and mouse; the relative sizes of each egg (diameters); the numbers recoverable from each at a single ovulation; the transition achieved in the first 24 hours after fertilization. Note that human eggs are of very similar size to mouse and elephant eggs, despite giving rise to very different-sized animals; all three are much smaller than frog eggs. This is because frog eggs must carry with them most of what they need to transform into swimming tadpoles that can then feed themselves, something that they do very rapidly! Mammalian eggs in contrast gain their nutrients for growth from the mother: largely through the placenta (see Chapters 14 and 15).

Viviparity also reduces the evolutionary pressure to develop as rapidly as possible, so as to gain the sensory awareness and movement capability helpful for escaping predation. So, in general, mammalian zygotes **develop more slowly** – perhaps most dramatically observed in the mammalian zygote taking 24 hours to divide to just two cells by which time a frog zygote has developed into a swimming tadpole!

A further consequence of viviparous reproduction is that the early growth of the next generation must be nourished within the female genital tract, which is accordingly adapted anatomically and functionally to support this growth. Thus, the **female tract has evolved a dual role** in mammals: it transports spermatozoa to the site of fertilization, and then nourishes the developing conceptus. This dual role imposes complex functional changes on the tract, in which the female genital tract cycles between a preovulatory phase suitable for transmitting sperm to the site of fertilization, and a postovulatory phase in which nurturing of the conceptus predominates, the subject of Chapters 10 and 11. Corresponding changes have evolved in the developing conceptus to optimize its nutrition. These include the development of **specialized membrane systems** and **placentae** for tapping into maternal nutrition in the uterus. These maternal–embryonic interactions are described in Chapters 14 and 15.

Viviparity involves relatively prolonged periods of **gestation or pregnancy**, which make major demands on the **pregnant** female, whose metabolism and physiology are modified to meet the needs of the developing **conceptus**, **embryo** and **fetus** (see Chapter 15). Pregnancy can often go wrong – a considerable selective cost to the species (see Chapters 16 and 17). Indeed, a major source of evolutionary selective pressure comes at around **parturition** or **birthing** (see Chapter 18).

Parental care

The universal feature unique to all mammals, and through which they are named, is the production of milk from 'mammae' or **nipples** to nurture the neonate (see Chapter 19). **Milk production** is just one aspect of the extended period of **parental care** shown by mammals – a further energy investment in just a few young (see Chapter 20). This parental care takes different forms depending on the relative maturity of the young at birth and the social organization of the species. In mammals that move around in herds, such as sheep and cattle, the young have evolved to be able to walk soon after birth. Where animals are territorial and have dens or nests, the young may be born naked and immature. Parental care is evident in all cases and takes different forms. In higher primates, like ourselves, the young are born very immature and depend for many years on parental and social support, a subject considered in Chapter 20.

Reproduction strategies: summary

Mammals have evolved a high-investment, low-volume reproductive strategy. Our reproduction involves sex, the selection of sexual partners, internal fertilization, viviparity and extended parental care. Mammalian eggs and conceptuses are smaller, fewer in number and develop more slowly than those of non-mammals, and have evolved specialized membrane systems for tapping into maternal nutrition. There is heavy parental investment in the relatively few offspring. Whilst these features characterize all eutherian and marsupial mammals, including humans, there is rich variety within the order Mammalia. Thus, rodents (such as mice and rats) go for higher volume and faster production of young than do ungulates (such as cattle and sheep). We have already alluded to the wide range of maturity at birth with its consequences for parental care patterns. It is important to keep in mind these variations in the details of reproductive strategy among different mammals, because animal models of reproduction are often used as surrogates for human reproductive enquiries. Even among

higher primates there are important reproductive differences. Extrapolation of data and ideas across species can be helpful, but must be undertaken cautiously, and in this book we will be alert throughout to the dangers.

Having identified the reproductive pattern that characterizes mammals, we will now look in a little more detail at time and the reproductive life cycles.

Reproductive life cycles

We have seen that reproduction is central to our lives as mammals. Whether and with whom we mingle our gametes is deeply significant biologically and culturally. At the most reductionist level, each of us can be viewed as a vehicle for our gametes and the chromosomes they transmit to the next generation. It is this distinction between the **germ cells** and the **soma** (or body in which they develop) that is considered here.

The somatic and social life cycles

We are born physically and sexually immature. We then spend the first decade of our life growing and maturing physically and establishing an individual identity. Shortly thereafter, at adolescence, we mature sexually at **puberty** (see Chapter 4). By the early- to mid-teens, we achieve the capacity to produce fertile eggs or sperm (see Chapters 7-12) and, in women, to carry a pregnancy (see Chapters 13-18). This reproductive capacity, or fecundity, then characterizes much of our adult life. However, there are distinct differences between men and women in their life-time fecundity patterns. Male fecundity, once achieved, persists throughout life, albeit slowly tapering downwards with increasing age. Female fecundity, in contrast, is 'time limited', declining steeply from about 35 years until ending by the **menopause** at around age 50 years (Figure 1.4). This reduction in female fecundity is due to the **loss of guality** eggs (see Chapters 9, 22 and 23), and has been described as a 'public health problem' in Western societies in which many women are delaying having families until well into their 30s. Many do so in the erroneous belief that modern medicine can treat any infertility that emerges should they leave reproduction until later (see Chapter 23). The social life cycle has shifted to later in life, while the somatic life cycle remains as it always has, the ageing process proceeding apace.

The generative life cycle

The **somatic life cycle** is about the physical transmission of the germ cells across generations, and so we now turn to the germ cells themselves and to the concept of the **generative life cycle** (Figure 1.5). The essential element that sets apart the germ cells from the somatic cells is their potential to give rise to the many tissues of the next generation: their so-called **pluripotency**. Thus, as the **somatic conceptus** develops and grows in size and cell number, so also its complexity increases as muscle, gut, nerve, blood and other types of somatic cell develop. Each cell is specialized for a particular function so that together cells make an effective soma for maximizing the chance of survival



Figure 1.4 Female fecundity is 'time limited'. Rates of fertility (red range) and childlessness (blue bars) by age of woman. The fertility rate data were collected from populations of married women who reported that no efforts were made to limit their fertility. These data approximate to a measure of fecundity by age in humans. Note the steep decline from 35 years. (The range reflects the different circumstances of the populations, drawn from different parts of the world.) The histograms show the proportions of women remaining childless after first marriage at the ages indicated despite continuing attempts to deliver a child. Note again the sharp rise above 35 years, implying a fall in fecundity from this time onwards until the menopause at around age 50 years.

and reproductive success. The latter success depends, however, on the subpopulation of persisting **pluripotent cells** within the soma that form the **germ cell lineage**.

What exactly does pluripotent mean? The very early conceptus consists entirely of pluripotent **stem cells** capable of giving rise to a whole organism (Figure 1.5). As somatic cells of different types develop within the embryo, a subpopulation of more pluripotent stem cells can always be detected – diminishing proportionately in number to the developing soma, but traceable throughout until they enter the rudimentary **ovary** or **testis** as the **primordial germ cells** (Figure 1.5; see Chapter 3). These cells will go on to form the oocytes and spermatozoa, one of each of which then combine to provide a new conceptus of pluripotent stem cells, and so the cycle continues through another turn of the generational wheel. In their nature, cycles lack beginnings and ends – unless of course broken by a failure to reproduce.

The concept of this **cycle of pluripotentiality** is central to the generative cycle. Indeed, we can envisage the **somatic cells** – nerve, muscle, skin, gut, etc. – that make up most of our bodies, as being mere vehicles for transmission of our germ cells. So, what is it about this subset of pluripotential cells that makes them so special? After all, every cell in the body – whether a somatic or germ cell – has the same chromosomal and genetic composition (give or take a few atypical cells) and, moreover, all these genes are functionally competent. We know this because you can take a nucleus from an adult somatic cell and inject it into an enucleated oocyte, where it can then direct the formation of a new individual. This process of **somatic cell nuclear transfer (SCNT)** is also known as **'reproductive**



Figure 1.5 The generative life cycle is shown in red and indicates the pluripotent lineage, whereas the somatic life cycle is in blue and ensures the survival and physical transmission of the germ cells across generations. (Source: Adapted from an original idea by Monk (1981) *Differentiation* **19**, 71–76.)



Figure 1.6 Schematic summary of the procedure for somatic cell nuclear transfer (SCNT) in sheep or mice. A differentiated cell is cultured and its division cycle arrested by removal of nutrients (G0 stage). A **karyoplast** (the nucleus with a small amount of cytoplasm and cell membrane surrounding it) is then prepared from the quiescent cell. It is placed next to an unfertilized oocyte from which its own genetic material has been removed by suction. A fusogenic signal is then given. The nucleus and enucleated oocyte fuse and initiate cleavage. The cleaving conceptus is placed into the mouse or ewe uterus and a viable offspring may result. Source: Stewart C. (1997) *Nature*, 385, 769. Adapted with permission from *Nature*.

cloning', and gave rise to the famous sheep, Dolly, who shared all her nuclear genes and chromosomes with the donor (Figure 1.6). Reproductive cloning has now been achieved in many species, including cattle, pigs, goats, cats, dogs, mice and monkeys, so there is every reason to believe it would work in humans too (see Chapters 22 and 23). It essentially defies nature by providing an asexual route to mammalian reproduction. However, it leaves us with a problem. Given that all cells have an identical genetic make-up, how do cells from the pluripotent lineage differ from somatic cells? The answer lies not in genes but in **epigenesis**.

The epigenetic cycle

It is estimated that humans have between 20000 and 25000 genes. Our genes, through their code of DNA triplets, encode proteins and it is proteins that largely make us who we are – **genotype encodes phenotype**. However, only a restricted subset of genes is expressed in any one cell, and that subset is characteristic for each cell type at particular times in its life cycle. Thus, muscle, nerve, skin and gut cells each express

different combinations of genes. When these expressing gene sets are studied at the molecular level, they are found, as expected, to be identical in their gene sequences (or genetic codes) to the same genes in different, non-expressing tissues. However, they do differ in three ways:

- 1. They differ in the pattern of chemical modification to certain cytosine bases in the DNA, lacking methyl groups that are present on non-expressing genes: differences in the **DNA methylation patterns** (Figure 1.7a).
- **2.** They are wrapped up in a distinctive subset of associated proteins called histones that give the chromatin a distinctive looser **euchromatin structure**.





3. These histones themselves show characteristic patterns of post-translational modification by acetylation, methylation, etc. (Figure 1.7b).

These three processes are each the result of **epigenetic influences** (from *epi* = outside of the genes), which are so called because they do not affect the genetic code itself (which would be a genetic change), but only the gene organization in ways that affect the **capacity of those genes to be expressed** (Figure 1.7c).

When the cells of the developing early conceptus are examined, the genes in all of its cells are shown to undergo a profound series of changes in their patterns of epigenetic modification. However, those cells that form part of the pluripotent germ cell lineage are characterized by quite distinctive epigenetic patterns from those in non-pluripotent somatic cells. It is clear that this distinctive epigenetic pattern underlies their pluripotency. How this distinctive **cycle of epigenetic patterning** is controlled is the subject of intense study. Understanding 'how' could have profound practical consequences. Thus, these pluripotent cells can now be isolated and persuaded to grow indefinitely *in vitro* as **embryonic stem cells (ESCs)**. ESCs, given their pluripotency, have medical promise as sources of repair for damaged tissues (see Chapters 22 and 23).

Within the developing embryo, these pluripotent stem cells give rise to the germ cells, and as they do so, most of their epigenetic marks are erased – the **epigenetic slate is wiped clean in the germ cells**. Then, during the packaging of the chromosomes in eggs or spermatozoa for transmission to the zygote, new epigenetic marks are placed on the genes. Curiously, the sex of the environment in which the chromosomes are packaged influences whether and how some 100–200 genes are marked. These marks then affect the gene's ability to become transcriptionally active subsequently in the conceptus. This process is called **parental** imprinting, because it leaves a sex-specific imprint on the genes, which is 'remembered' as having been paternally or maternally derived. These maternal and paternal imprinting processes mean that, although the oocyte and the spermatozoon each contribute one complete set of chromosomes and genes to the conceptus, each set is not on its own fully competent to direct a complete programme of development. Only when a set of genes from an oocyte is combined with a set of genes from a spermatozoon is a fully functional genetic blueprint achieved. A parthenogenetically activated oocyte lacks access to some crucial genetic information, which, although present in its chromosomes, cannot be accessed because of the maternal imprinting to which it was subjected during oogenesis. In the normal zygote, this information would be provided by genes on the paternally-derived set of chromosomes. It is parental imprinting that compels us to reproduce sexually and means that parthenogenesis is not possible in mammals (see also page 6).

Conclusions

This introductory chapter sets the scene and context for all that follows. It does so by setting out some of the key distinguishing features of reproduction in mammals and, in particular, humans. In the rest of this book, we will use human examples wherever possible. However, the advances of molecular genetics have emphasized our close evolutionary relationships to the whole living world and so, despite the clear evidence of the many idiosyncratic features of human reproduction, there are many useful reproductive lessons for us to learn from other species. These are lessons on which we will draw – but cautiously. Having considered the different generative cycles that make up the reproductive life cycles, we now introduce the reproductive body.

Key learning points

- Mammals reproduce sexually through the union of a haploid egg with a haploid spermatozoon.
- Sexual selection operates in mammals and is culturally influenced in humans.
- The mammalian female reproductive tract has a dual role.
- Fertilization is internal and involves spermatozoal transport and fewer eggs being shed.
- Development is viviparous and involves smaller eggs and conceptuses.
- Early development is slower and involves attachment to the mother's uterus that leads ultimately to placental formation.
- Birth marks the beginning of the period of parental care of neonates through milk production: the unique feature of all mammals.
- Overall, mammals have a high-investment, low-volume reproductive strategy.
- The somatic reproductive life cycle involves growth, sexual maturation at puberty, a period of fecundity and then reproductive decline.
- Reproductive decline in women is more marked than in men, occurring earlier, being steeper and resulting in complete loss of fecundity by the menopause.
- The generative life cycle involves the setting aside within the embryo of a population of pluripotent germ cells that develop into the gametes in the ovary and testis.
- The epigenetic life cycle describes the corresponding changes in chromatin and DNA modification that underlie pluripotency.
- Parental imprinting describes the epigenetic marks that identify some genes as being derived from the mother and some from the father, and which also ensure that those genes are not expressed in somatic cells.

Clinical vignette

Why is imprinting important?

A 3-year-old girl who was born by normal delivery at full term was noted to be significantly behind her peers in terms of language development. Her growth was reduced compared to her birth-weight and, at 3 years of age, she was not yet walking confidently. After careful assessment by a paediatrician, global developmental delay was diagnosed. She underwent a series of genetic and functional tests. These revealed a diagnosis of Angelman's syndrome. With specialist therapy, she made some progress in her motor development, but her parents were informed that she would always have severe learning difficulties. Her parents were considering a future pregnancy, but were unclear regarding the risks of a second child being similarly affected.

Angelman's syndrome is a disorder of epigenetic imprinting. The epigenome is a series of modifications to the structure of DNA that determine how it can be transcribed. The gene responsible for Angelman's syndrome is always expressed from the paternal allele, as the maternal allele carries a methyl group at a location that blocks expression. If a mutation is present in the paternal copy of the gene, a normal maternal allele cannot compensate. In this case, the chances of recurrence in a future pregnancy are 50%, because the father is assumed to have one normal copy and one mutated copy of the gene in question. Not only the sequences of genes, but also their expression patterns are vital in determining disease risk.

FURTHER READING

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