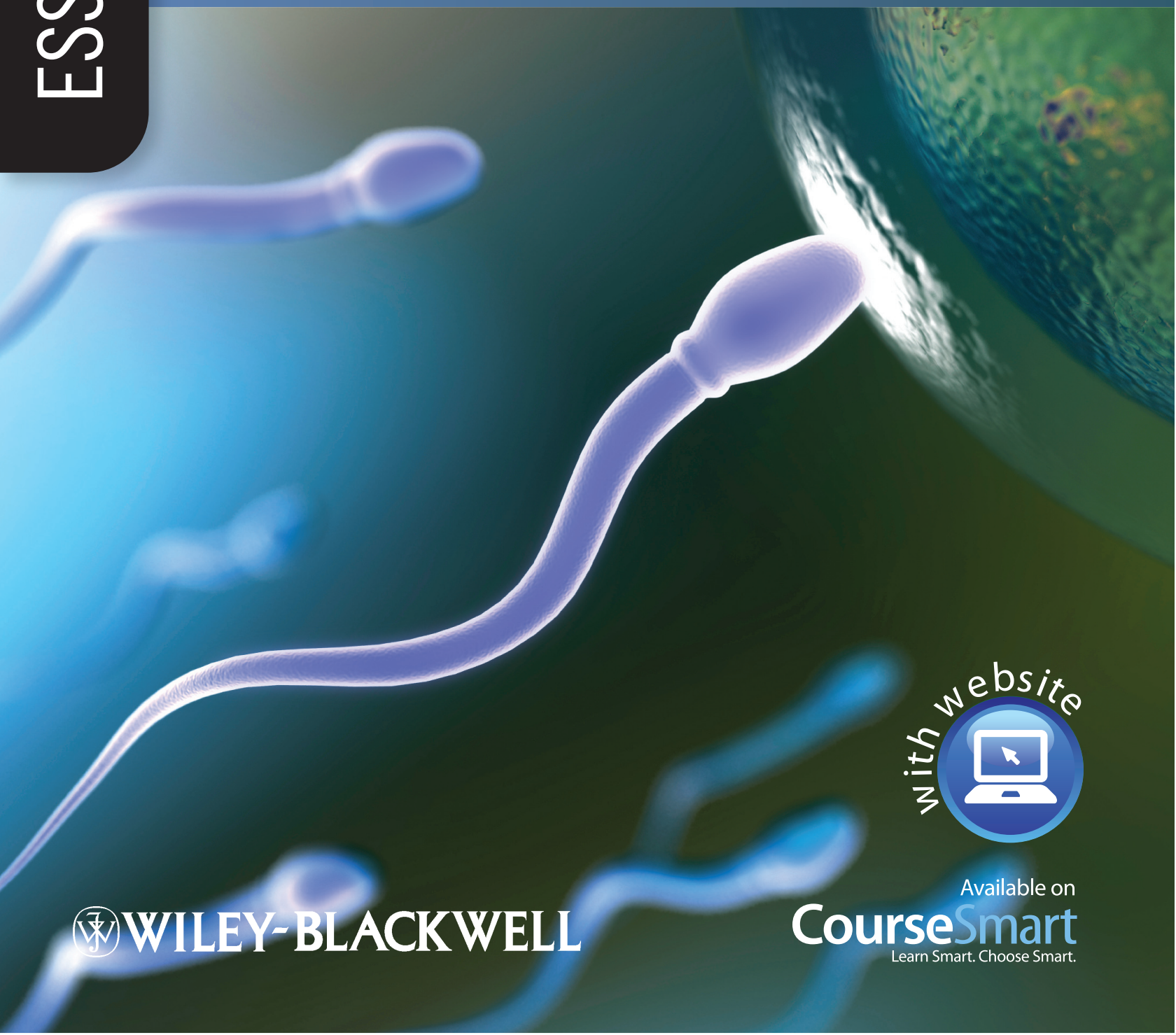
ESSENTIALS

ESSENTIAL REPRODUCTION

MARTIN H. JOHNSON

7TH EDITION

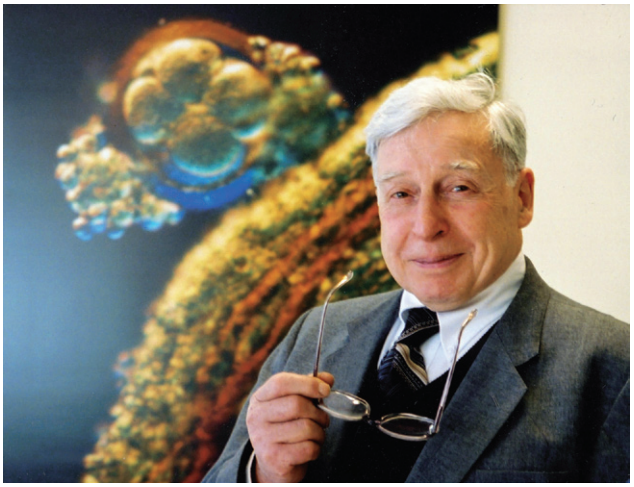
with Wiley E-Text
Powered by VitalSource®



with website

WILEY-BLACKWELL

Essential Reproduction



To Professor Sir Bob Edwards
Nobel Laureate in Physiology or Medicine 2010
who first stimulated my interest
in the science of reproduction

Essential Reproduction

Martin H. Johnson
MA, PhD, FRCOG, FSB, FMedSci
Professor of Reproductive Sciences
Department of Physiology, Development and Neuroscience
University of Cambridge
Fellow of Christ's College, Cambridge
Cambridge, UK;
Honorary Academic Fellow of St Paul's College
Sydney, NSW, Australia

Seventh edition

WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

This edition first published 2013 © 2013 by Martin H. Johnson

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing program has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

Registered office: John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell

Library of Congress Cataloging-in-Publication Data
Johnson, M. H.
Essential reproduction / Martin H. Johnson. – 7th ed.
p. ; cm.
Rev. ed. of: Johnson & Everitt's essential reproduction / Martin H. Johnson.
6th ed. 2007.
Includes bibliographical references and index.
ISBN 978-1-4443-3575-0 (pbk. : alk. paper)
I. Johnson, M. H. Johnson & Everitt's essential reproduction. II. Title.
[DNLM: 1. Reproductive Physiological Phenomena. 2. Mammals–physiology. WQ 205]
573.6'19–dc23

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Cover image: iStock © Mark Evans
Cover design by Fortiori Designs
Inside part page image: iStock © Natalia Lukiyanova

Set in 10/12 Adobe Garamond Pro by Toppan Best-set Premedia Limited

1 2013

Contents

A companion website

Your textbook is also accompanied by a FREE companion website that contains:
- Figures from the book in PowerPoint format

Log on to www.essentialreproduction.com to find out more.

Preface

There have been many advances in our understanding of the reproductive processes in humans since the sixth edition. Much of this progress has been due to the continuing application to reproductive studies of the expanding range and sensitivity of the techniques of molecular biology, which now allow much more sophisticated descriptions and manipulations of reproductive activities. Advances have also come from the development of live imaging techniques of greater utility. These include imaging of reproductive organs and also of brain function *in situ*, as well as less invasive long-term imaging of the behaviours of cells and embryos in culture. The advances in medical research on reproduction have been truly spectacular – which, in many parts of this edition, renders potentially dangerous extrapolations from other mammals to humans less necessary.

Major health and social issues continue to place reproduction at the centre of scientific, clinical, political and ethical discourse. The threat posed by the continuing growth in world population to the planet's resources and to our fragile climate presents a major challenge. The tragic and unnecessary high maternal mortality rates throughout much of the world are an indictment of our best efforts and intentions to 'do better' – as expressed in the WHO Millennium Aims. At least some progress is being made in managing the effects of infection with human immunodeficiency virus through the cheaper provision of generic drugs. However, it is unclear that transmission rates are coming down, a testament to the importance of understanding sexual behaviours and addressing the impact of gender inequalities. These issues are made more pressing by the rise in genitourinary infections that are resistant to antibiotics with their implications for individual fecundity. Continuing clinical developments in the field of assisted conception have expanded opportunities for the alleviation or circumvention of subfertility, genetic disability and, through stem cells, degenerative disease, but have also ignited new (and old) controversies. The explosion of obesity and the realization that both child and adult health and well-being are affected enduringly by life *in utero* have focused work on pregnancy, the placenta and the neonatal period of care. Finally, we are at last beginning to understand more fully how genetic expression during development interacts with environmental factors to influence complex behavioural phenotypes that include psychiatric disease and antisocial behaviour. It is clear from all these examples that reproduction reaches into all parts of our lives! Science thus forms just part of this book – albeit at its core. One might have hoped that the advances in scientific knowledge and understanding would helpfully inform prevailing socio-legal discussions, attitudes and values. Sadly, since the last edition, for much of the world, the enlightenment viewpoint based on a cool appraisal of evidence has been crushed in a miasma of antiscience rhetoric: whether against climate change, evolution, women's progress, or rights for sexual minorities.

On a more positive note, I am very happy to formally record here my delight that the Nobel Foundation at last decided to award the 2010 Nobel Prize for Physiology or Medicine to the dedicatee of this book, Professor Sir Bob Edwards. This belated award, followed by a Knighthood in 2011, recognized Bob's unique role in the development of research on human reproduction. Although his award cited his work on IVF, it explicitly recognized the wider role Bob has played in reproductive science, medicine and ethics, together with his pioneering role in communicating science to the public. Sadly, Bob's ill-health prevented him from receiving the prize in person. I was honoured that Bob and his wife and long-term scientific collaborator, Ruth, who received the prize on Bob's behalf, both invited me to open the Nobel Symposium dedicated to his work. A flavour of his achievements can be gained from the published paper based on that lecture, which is freely available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3171154/?tool=pubmed

Finally, for this edition, the book has been totally restructured as well as updated. This restructuring hopefully gives better balance to the contents and a stronger narrative thread to the text. To aid this, in many places, more detailed information on deeper, comparative or applied aspects of some topics has been transferred to boxes, table and figures. In addition, requests for more specific references have hopefully been met with longer reading lists divided into general and specific references. As before, many helpful comments, corrections and letters of advice have been received from readers, students and teachers all over the world. As always, in this seventh edition, now in its 33rd year, I have tried to provide for students of reproduction a compact and comprehensive text that carves through the micro-detail of the subject to bring out its theoretical cores, but illustrates it with experiment, information and context.

M.H.J.
Cambridge
2012

How to use this book

This book represents an integrated approach to the study of reproduction. There can be few subjects that so obviously demand such an approach. During my teaching of reproduction at Cambridge University, the need for a book of this kind was clear to me and my colleagues. I know this volume goes some way towards filling this need because of the many appreciative comments I receive from colleagues at scientific meetings as well as from the Cambridge students.

I have written the book about human reproduction in a comparative context for medical, veterinary and science students at all professional levels. Throughout, I have attempted to draw out the general, fundamental points common to reproductive events in all or most species. However, a great range of variation in the *details* of reproduction is observed amongst different species and, in some respects, very *fundamental* differences are also observed. Where the details differ, I have attempted to indicate this in the numerous tables and figures, rather than clutter the general emphasis and narrative of the text. Where the fundamentals differ, an explicit discussion is given in the text. These fundamental differences should not be ignored. For example, preclinical medical students may consider the control of luteal life in the pig, of parturition in the sheep or of ovarian cyclicity in the rat to be irrelevant to their future interests. However, as a result of extrapolation between species, in the past the human has been treated as a pig, a sheep and a rat (with much discomfort and detriment). If, on finishing this book, the student appreciates the dangers of uncritical extrapolations between species, I will have achieved a major aim.

Science is uncertain and provisional, and this provisionality has been illustrated in several places in this book. I have not tried to give a simple story where a simple story does not exist. Uncertainty can be hard to handle, especially in medicine, but it is a reality that is as important as those informational facts that we think we have certain knowledge of – indeed, knowing the boundary between the certain and the uncertain is perhaps the most important knowledge of all. For you students, this uncertainty also provides future research opportunities!

Confinements of space have unfortunately necessitated the omission of the subject of embryonic development from the text. To give only passing reference to this fascinating subject would be an injustice; to treat it fully would require a text of similar length to the present one. I recommend that the interested student seeks this information elsewhere.

I suggest that you first read through each chapter with only passing reference to tables, boxes and figures. In this way, I hope that you will grasp the essential fundamentals of the subject under discussion. Then re-read the chapter, referring extensively to the tables and figures and their legends, in which much detailed or comparative information is located. Finally, because my approach to reproduction is an integrated one, the book needs to be taken as a whole, as it is more than the sum of its constituent chapters.

Acknowledgements

I owe particular thanks to many people for help at many stages of the preparation of this edition: to present and former students for their interest, stimulation and responsiveness; to my colleagues at Wiley-Blackwell for their help and advice; to the AudioVisual Media team in the Anatomy School at Cambridge for advice and help with photographic illustrations; to the Histology section of the Department of Physiology, Development and Neuroscience, Cambridge for making available slides for photography; to Professor Peter Braude, Professor Graham Burton, Professor Tomas Hökfelt, J. Moeselaar, Dr Tony Plant, Dr J.M. Tanner and Dr Pauline Yahr for allowing me to use their original photographs and data; and to my many colleagues who read and criticized my drafts and encouraged me in the preparation of this edition.

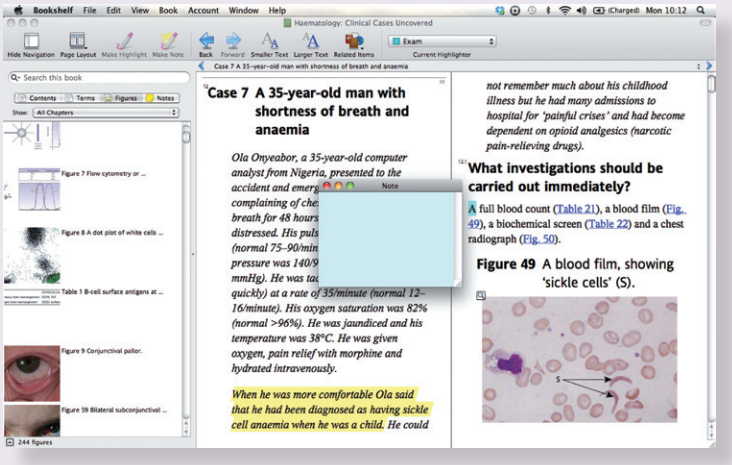
Features of your textbook

Welcome to the new edition of *Essential Reproduction*. Over the next few pages you will be shown how to make the most of the learning features included in the textbook.

The Anytime, Anywhere Textbook

For the first time, your textbook comes with free access to a **Wiley E-Text: Powered by VitalSource** – a digital, interactive version of this textbook which you own as soon as you download it.

Your **Wiley E-Text: Powered by VitalSource** allows you to:
Search: Save time by finding terms and topics instantly in your book, your notes, even your whole library (once you've downloaded more textbooks)
Note and Highlight: Colour code, highlight and make digital notes right in the text so you can find them quickly and easily
Organize: Keep books, notes and class materials organized in folders inside the application
Share: Exchange notes and highlights with friends, classmates and study groups
Upgrade: Your textbook can be transferred when you need to change or upgrade computers
Link: Link directly from the page of your interactive textbook to all of the material contained on the companion website



Wiley E-Text
Powered by VitalSource®

To access your Wiley E-Text: Powered by VitalSource:

- Find the redemption code on the inside front cover of this book and carefully scratch away the top coating of the label.
- Visit **www.vitalsource.com/software/bookshelf/downloads** to download the Bookshelf application.
- If you have purchased this title as an e-book, access to your **Wiley E-Text: Powered by VitalSource** is available with proof of purchase within 90 days. Visit **http://support.wiley.com** to request a redemption code via the 'Live Chat' or 'Ask A Question' tabs.
- Open the Bookshelf application on your computer and register for an account.
- Follow the registration process and enter your redemption code to download your digital book.
- For full access instructions, visit: **www.essentialreproduction.com**.

CourseSmart gives you instant access (via computer or mobile device) to this Wiley-Blackwell eTextbook and its extra electronic functionality, at 40% off the recommended retail print price. See all the benefits at **www.coursesmart.com/students**.

Instructors . . . receive your own digital desk copies! ▶
It also offers instructors an immediate, efficient, and environmentally-friendly way to review this textbook for your course.

For more information visit **www.coursesmart.com/instructors**. With CourseSmart, you can create lecture notes quickly with copy and paste, and share pages and notes with your students. Access your Wiley CourseSmart digital textbook from your computer or mobile device instantly for evaluation, class preparation, and as a teaching tool in the classroom.

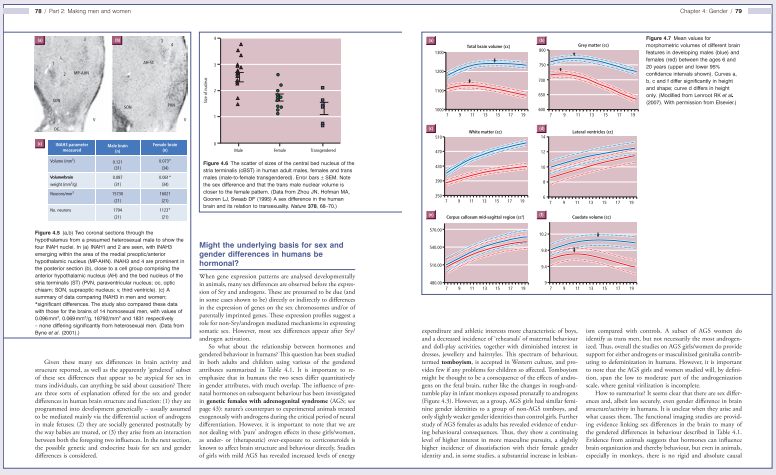
Simply sign in at **http://instructors.coursesmart.com/bookshelf** to download your Bookshelf and get started. To request your desk copy, hit 'Request Online Copy' on your search results or book product page.

A companion website

Your textbook is also accompanied by a FREE companion website that contains:
- Figures from the book in PowerPoint format

Log on to www.essentialreproduction.com to find out more.

Features contained within your textbook



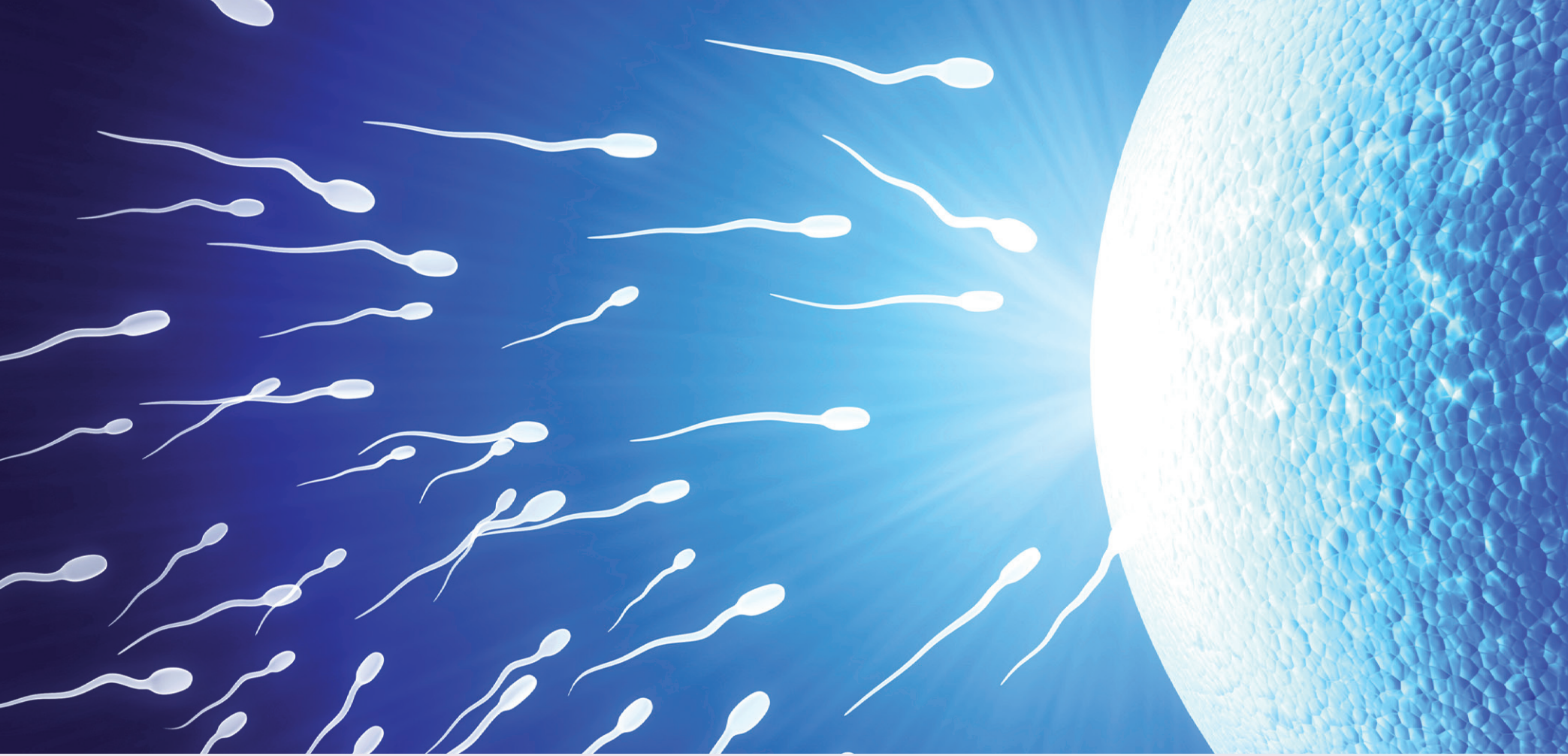
◀ Your textbook is full of useful photographs, illustrations and tables. The Desktop Edition version of your textbook will allow you to copy and paste any photograph or illustration into assignments, presentations and your own notes.

Every chapter ends with a Key learning points box which can be used for both study and revision purposes. ▶

Key learning points

- Sexuality involves the erotic and may be classified by the stimulus of erotic arousal. This system of classification is unsatisfactorily rigid. Many people find a range of stimuli arousing and the range may change with time.
- A sexual stereotype is the constellation of attributes and behaviours associated with people whose erotic arousal is classified according to a particular type of stimulus.
- The sexual identity of a person describes their inner state of feeling as a sexual being.
- Asexual people are not aroused erotically.
- Genes, brain structure, hormones and social learning have all been implicated in the development of sexuality, but there is no clear evidence directly linking any one element causally to a particular sexual identity.
- Hormones can act to influence sexual behaviour.

We hope you enjoy using your new textbook. Good luck with your studies!



Part 1
Introduction

CHAPTER 1

What is reproduction?

Essential Reproduction, Seventh Edition. Martin H. Johnson.

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' for their 'fitness' to live and to reproduce by disease resistance and by successful competition for resources and mates. 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 4, 5, 19 and 22). 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**; in relation to time – the **reproductive life cycle**; and in relation to both physical organization – the **reproductive body** – and functional organization – the **reproductive messengers**.

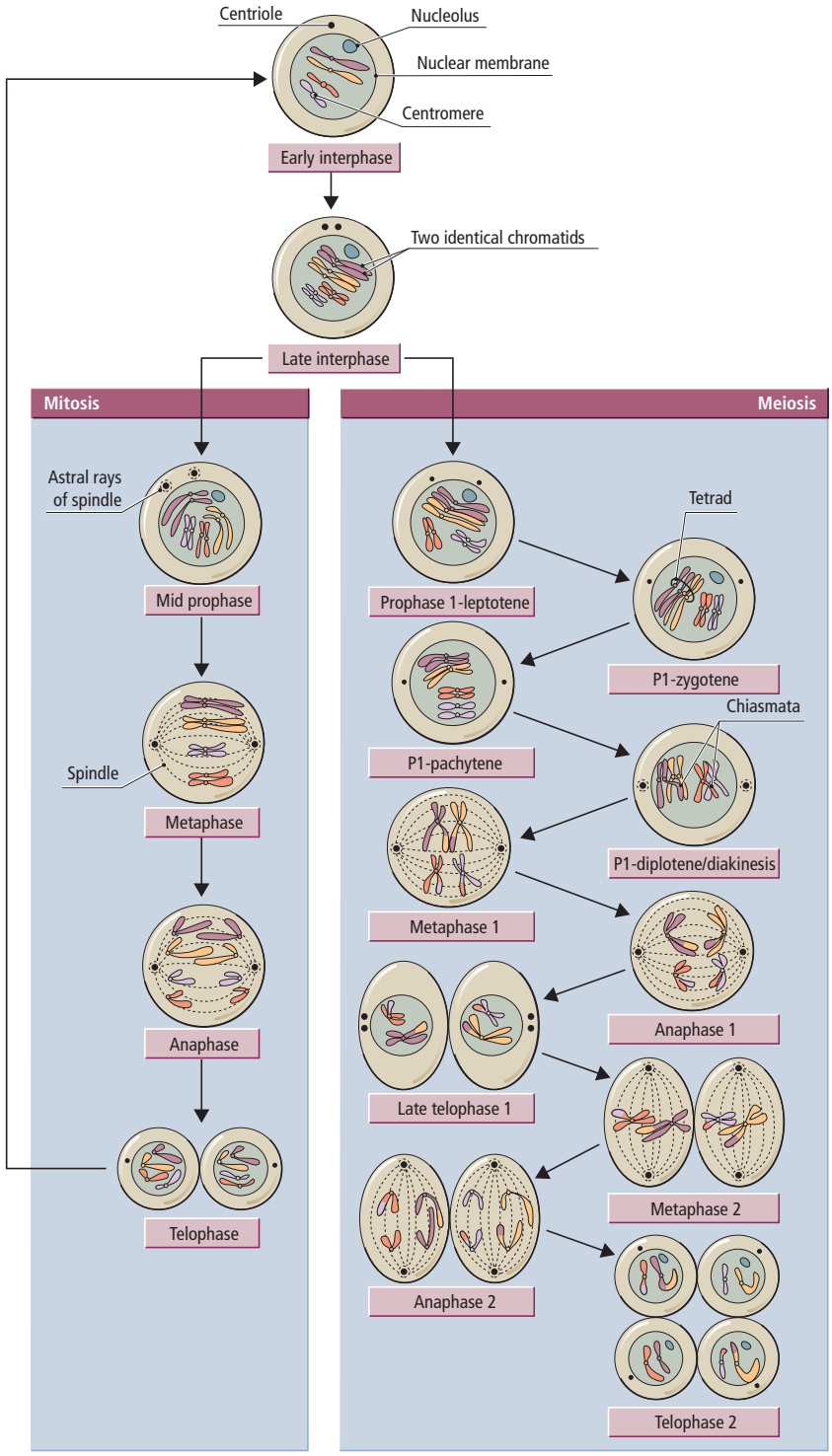
Reproductive strategies

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 by setting aside a special population of **egg cells** that can

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.

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 has 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 yield 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.


Centriole
Nucleolus
Nuclear membrane
Centromere
Early interphase
Two identical chromatids
Late interphase
Mitosis
Meiosis
Astral rays of spindle
Mid prophase
Spindle
Metaphase
Anaphase
Telophase
Prophase 1-leptotene
Tetrad
P1-zygotene
P1-pachytene
Chiasmata
P1-diplotene/diakinesis
Metaphase 1
Anaphase 1
Late telophase 1
Metaphase 2
Anaphase 2
Telophase 2

differentiate into embryos 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, such that it undergoes the early processes of development and may even implant in the uterus, these parthenogenetic embryos 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 equal portions: half carried in a **male gamete**, the **spermatozoon** (see Chapter 6), and half in a **female gamete**, the **oocyte** (see Chapter 8). These gametes come together at **fertilization** (see Chapter 11) 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 2 and 3, 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 5.

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 embryos developing from them, and so large numbers are produced to increase the chances of some surviving.

Mammals, in contrast, **fertilize internally** (see Chapter 10). 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 eggs does conserve energy resources, because it happens before egg 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 embryos. 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).

Viviparity also reduces the evolutionary pressure to develop as rapidly as possible 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 to 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,

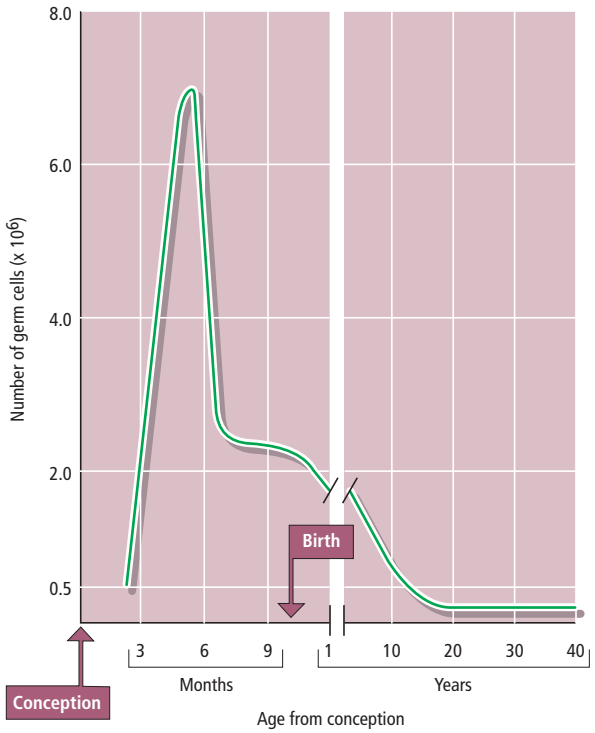


Figure 1.2 Numbers of ovarian germ cells during the life of a human female from conception. Note the steady rise early in fetal life followed by a precipitous decline prior to birth and shortly afterwards. (Drawn from original data from T. Baker.)

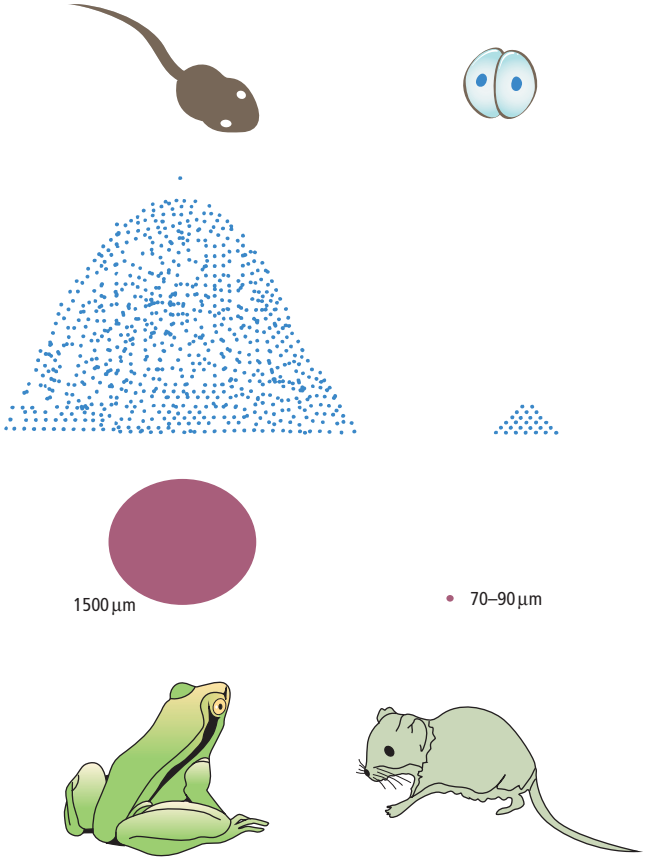


Figure 1.3 Cartoon to show differences between mammalian and frog eggs. From bottom up: frog and mouse; the relative sizes of each egg; the numbers recoverable from each at a single ovulation; the transition achieved in the first 24 hours after fertilization. Note that human eggs are of very similar 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 13 and 14).

the **female tract has evolved a dual role** in mammals: it transports spermatozoa to the site of fertilization, and then nourishes the developing embryo. This dual role imposes complex functional changes on the tract, the subject of Chapters 9 and 10. Corresponding changes have evolved in the developing embryo 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 12 and 13.

Viviparity involves relatively prolonged periods of **gestation**, which make major demands on the **pregnant** female, whose metabolism and physiology are modified to meet the needs of the developing **embryo** and **fetus** (see Chapter 14). Pregnancy can often go wrong – a considerable selective cost to the species (see Chapters 15 and 16). Indeed, a major source of evolutionary selective pressure comes at around **parturition** or **birthing** (see Chapter 17).

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 18). **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 19). 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 19.

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 embryos are smaller, fewer and develop more slowly than those of non-mammals, and have 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 this book 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 the reproductive cycle and body.

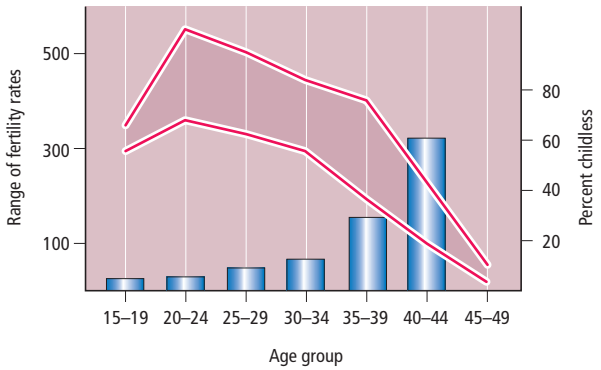


Figure 1.4 Female fecundity is 'time limited'. Rates of fertility (red range) and childlessness (blue bars) by age of woman. The fertility rate data were collected from populations of married women who reported that no efforts were made to limit reproduction. These data approximate to a measure of fecundity 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.

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 life cycle

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 3). By the early- to mid-teens, we achieve the capacity to produce fertile eggs or sperm (see Chapters 6–11) and, in women, to carry a pregnancy (see Chapters 12–17). 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 at the **menopause** at around age 50 years (Figure 1.4). This reduction in female fecundity is due to the **loss of quality eggs** (see Chapters 8 and 21), 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 hope that modern medicine can treat any infertility that emerges should they leave reproduction until later (Figure 1.4; see Chapter 21). 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 embryo** 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 reproductive success. That 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 embryo consists entirely of pluripotent **stem cells** capable of giving rise to a whole organism (Figure 1.5). As somatic cells of different

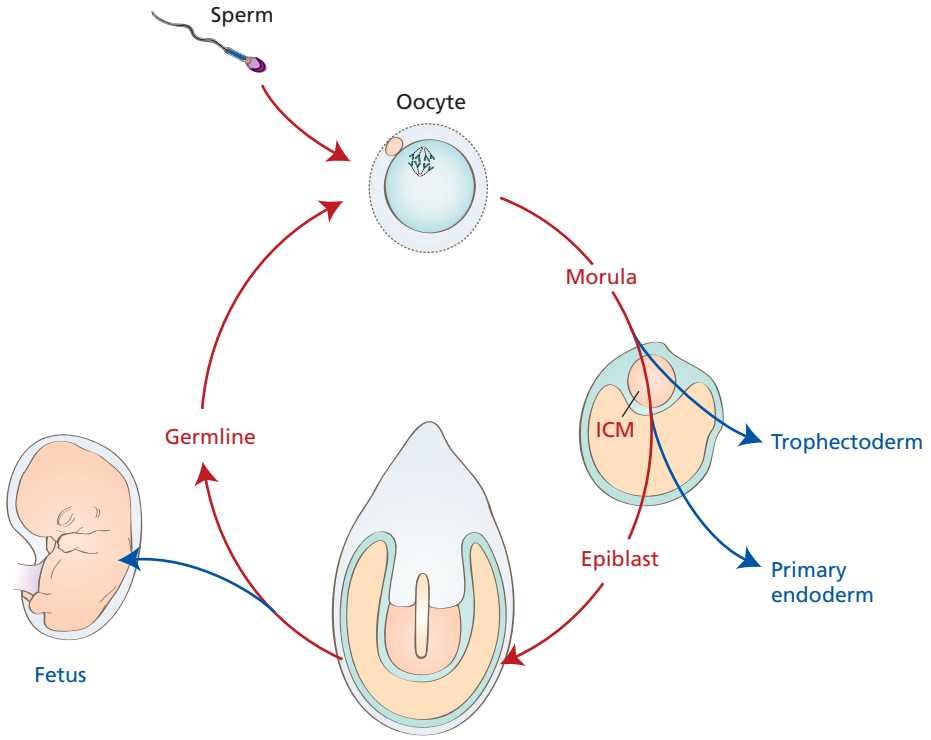


Figure 1.5 The generative life cycle is shown in red and indicates the pluripotent lineage, whereas the somatic life cycle is in blue and concerns the physical transmission of the germ cells across generations. (Adapted from an original idea by Monk (1981) *Differentiation* **19**, 71–76.)

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 2). These cells will go on to form the oocytes and spermatozoa, one of each of which then combine to provide a new embryo 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 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 21 and 22). 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 20 000 and 25 000 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

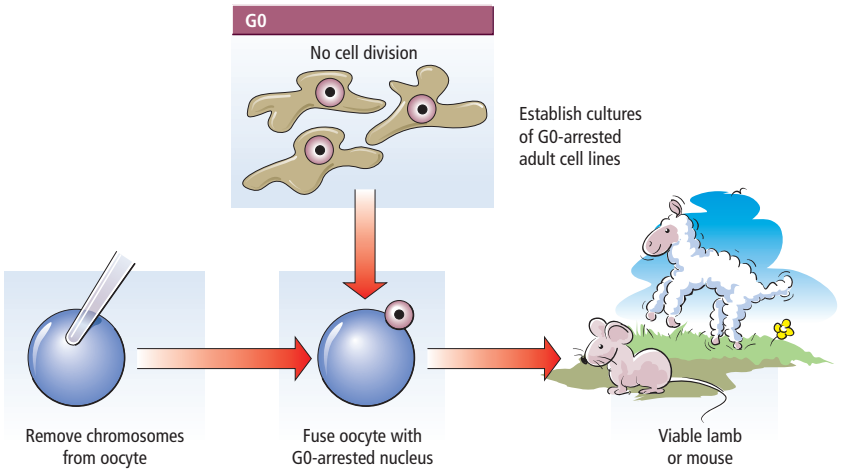


Figure 1.6 Schematic summary of the procedure for somatic cell nuclear transfer (SCNT) in sheep or mice. A differentiated cell is cultured and its division cycle arrested by removal of nutrients (G0 stage). A **karyoplast** (the nucleus with a small amount of cytoplasm and cell membrane surrounding it) 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.

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: changes 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 embryo 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 21 and 22).

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).

Having considered the different generative cycles that make up the reproductive life cycles, we now introduce the reproductive body.

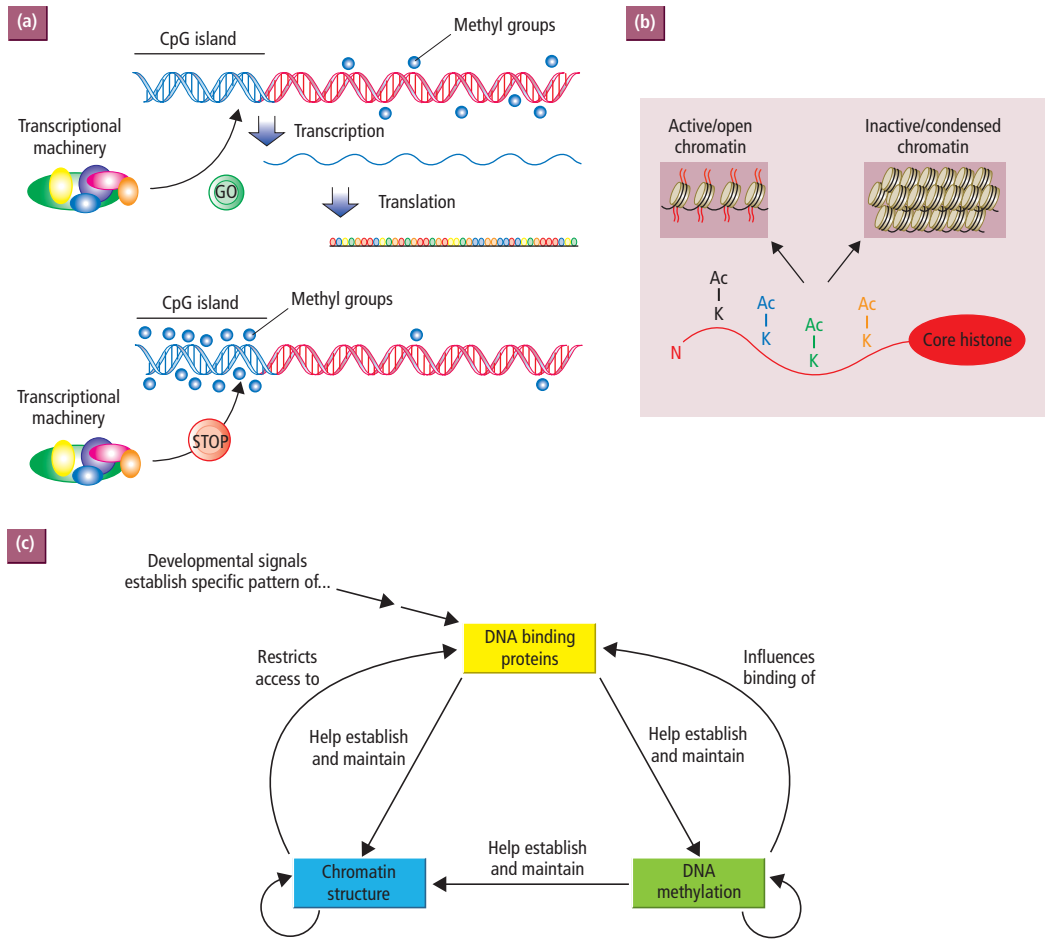


Figure 1.7 Summary of mechanisms available for genetic imprinting. Two sorts of epigenetic modification can leave an imprint. (a) The direct methylation of some, but not all, cytosines (see CpG island in lower part of panel) within the DNA sequence itself. This methylation then blocks access to transcriptional machinery – lower part of (a). Once initiated, this methylation pattern can be copied at each round of DNA replication as long as the maintenance methylase is present, and it is thus heritable through many mitoses. (b) A second sort of epigenetic modification is seen in the histone isotypes present in the chromatin surrounding the promoter region of the genes, as well as in their post-translational modification (me = methylation; Ac = acetylation). Depending on the chromatin structure, the DNA can be organized in a 'loose' or open state, and so is accessible to the transcriptional machinery and available for expression, or packed tightly and repressed. See also Box 6.3 for discussion of this type of modification during chromatin reorganization during spermatogenesis. (c) Quite complex interactions may occur during development between these two types of epigenetic modification and associated transcriptional proteins. However, these are early days in the science of epigenesis and much remains to be understood (see Chapters 15 and 19 for further discussion of the importance of epigenetic imprinting in health and disease).

The reproductive body

At the core of sexual reproduction lies the creation and fusion of the two types of gamete: the female **oocyte** and the male **spermatozoon**. Their production occurs in distinctive female and male **gonads**: the **ovary** and **testis**. Thus, the human male (Figure 1.8) develops obvious **external genitalia** and a system of internal ducts and glands that conveys the spermatozoa in **seminal fluid** from the testis to the **penis** and thence reproductively to the **vagina** (see Chapters 7 and 10). The female (Figure 1.8) develops less prominent external genitalia (see Chapters 9 and 10), but has an internal system of ducts that accommodate the erect penis and its ejaculated spermatozoa and transport some of them through the **cervix** and **uterus** to the **oviduct** (or **fallopian tube**). The oviduct is the site of fertilization, but the fertilized oocyte must then pass back to the uterus to **implant** and **gestate** until delivery through the cervix and vagina (see Chapters 11–17). After birth, the woman's breasts have developed to provide milk for the neonate, whereas the man's breasts remain vestigial (see Chapter

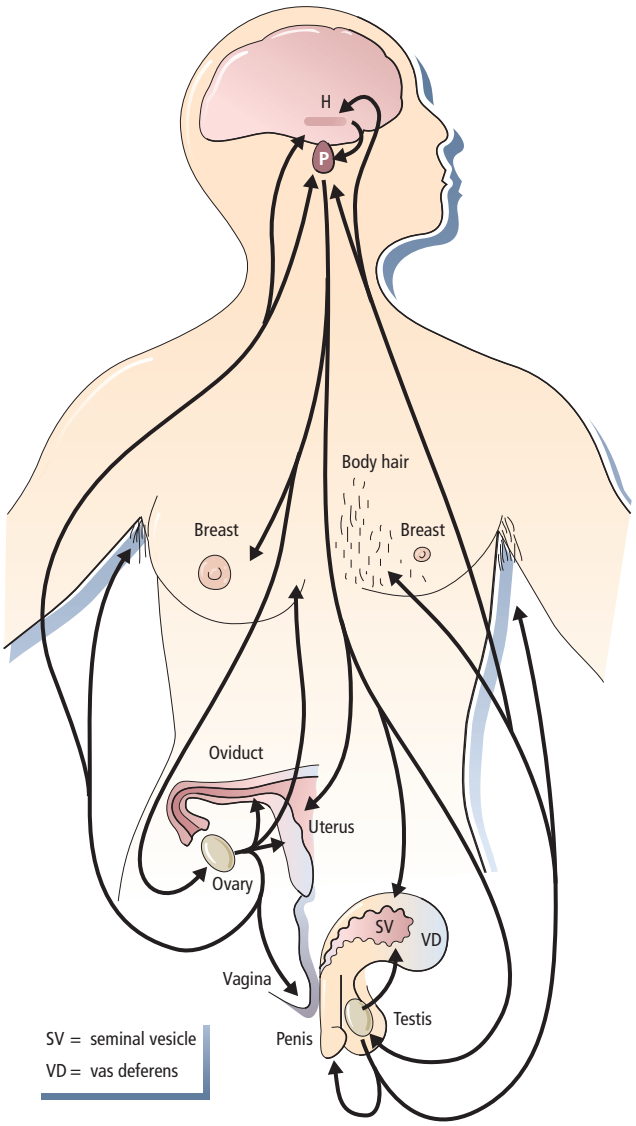


Figure 1.8 A schematic view of the main anatomical structures associated with the reproductive system. The hypothalamic region (H) sits at the base of the brain and is connected to the pituitary gland (P). The pituitary gland communicates hormonally with a range of reproductive organs and tissues including the breasts (see Chapter 18), the uterus and cervix (see Chapters 9 and 17), and the gonads: testis and ovary (see Chapters 3, 7 and 9). The gonads themselves in turn communicate hormonally with the pituitary and the brain (see Chapters 7 and 9 for details). The gonads also influence hormonally multiple sites in the internal and external genitalia (see Chapters 2, 3, 7, 9 and 12).

18). Thus, the basic anatomical differences between men and women are rooted in their different reproductive roles.

In addition to the production of different gametes, each gonad also has a distinctive pattern of hormone production, notably of the **sex steroid hormones**. The sex steroids play key roles in both the development (see Chapter 2) and the functioning of the two sexes (Figure 1.8). Thus, they are critically involved in the acquisition of sexual maturity at **puberty** (see Chapter 3). They orchestrate the cyclic changes in fecundity in females (see Chapter 9), and the seasonal changes in fecundity in many male and female mammals (see Chapters 7 and 9). They play key roles in pregnancy and parturition, and in preparing for maternal lactation and parental care (see Chapters 16–19). They can also influence the behaviour of males and females: in many species to ensure that mating will only occur between different sexes at times of maximum fecundity (see Chapters 4 and 5).

However, the sex steroids do not act alone but in conjunction with a range of other hormones as well as with the nervous system. Key hormones amongst these are the **gonadotrophins and prolactin**, large proteinaceous hormones produced by the **pituitary gland**, and some smaller hormones produced by the **hypothalamus – oxytocin, gonadotrophin releasing hormone (GnRH)**, and **prolactin inhibitory factor (PIF)**. Before these various hormones and their actions are introduced, we first explore some key anatomical features of those parts of the nervous system of reproductive interest.

The brain, hypothalamus and pituitary

In higher primates the central nervous system (CNS), and particularly the **neocortex**, plays an important role in reproduction. It does so largely via a much older part of the brain called the **hypothalamus**, which mediates a range of hormonal and environmental influences on reproduction. The hypothalamus in turn acts mostly via the **pituitary gland**.

The pituitary

The pituitary gland, or **hypophysis**, lies at the base of the brain to which it is attached by the **pituitary stalk**, or **infundibulum** (Figure 1.9). It has two main lobes in humans (Figure 1.10). A posterior lobe derived embryologically from a brain outgrowth (the **neurohypophysis**), and a larger anterior lobe derived embryologically from the dorsal pharynx (the **adenohypophysis**). The infundibulum connects the pituitary anatomically and functionally to the overlying hypothalamus in the region of the **median eminence** (Figure 1.10). The adenohypophysis contains several types of hormone-secreting cells, the two of most reproductive importance being the **gonadotrophs** (site of **gonadotrophin** production) and **lactotrophs** (site of **prolactin** production), whilst the neurohypophysis, being nervous in origin, secretes small neuropeptide hormones such as **oxytocin**.

The hypothalamus

The hypothalamus is a relatively small but complex region at the base of the brain, lying between the midbrain and the forebrain (Figure 1.10). Its boundaries are ill-defined, conventionally being described as: (1) superiorly the **hypothalamic**

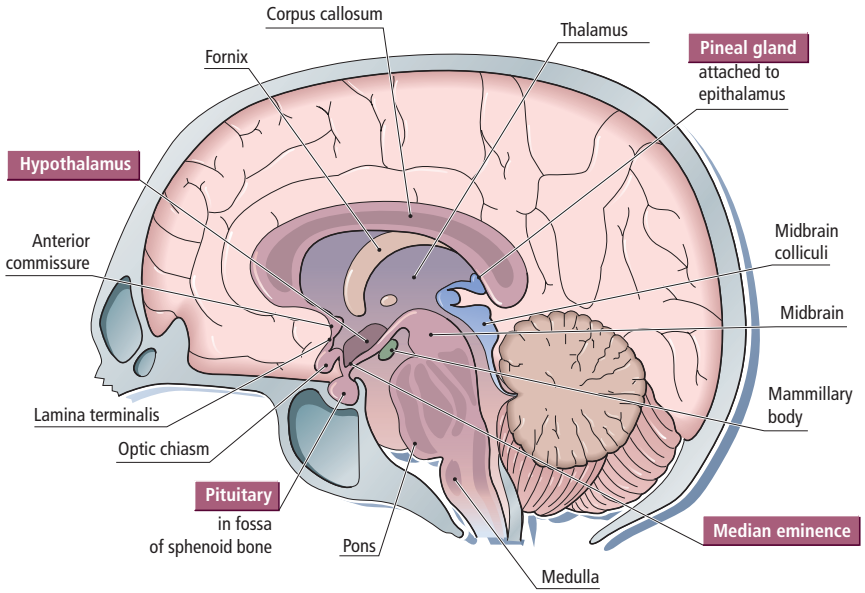


Figure 1.9 A sagittal section through the human brain with the pituitary and pineal glands attached. Note the comparatively small size of the hypothalamus and its rather compressed dimensions ventrally. The pineal is attached by its stalk to the epithalamus (habenula region) and lies above the midbrain colliculi. The third ventricle is a midline slit-like structure, which has been opened up by the midline cut exposing the medial surface of the brain. The thalamus (above) and the hypothalamus (below) form one wall (the right in this view) of the third ventricle, which are better viewed in Figure 1.10.

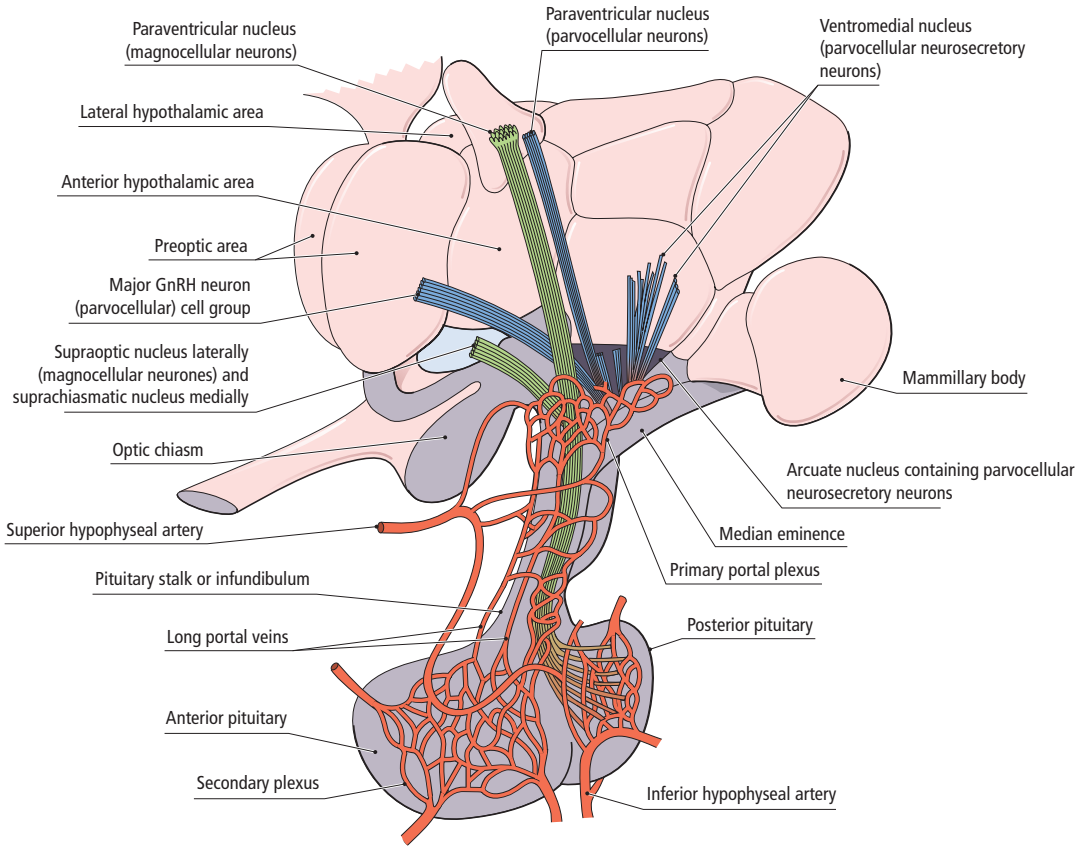


Figure 1.10 A highly schematic and enlarged view of the human hypothalamus and pituitary. Note the portal capillary system (red) derived from the superior hypophyseal artery and running from the median eminence/arcuate nucleus region of the hypothalamus above to the anterior lobe of the pituitary below. The anatomically and functionally well-defined paraventricular, ventromedial and arcuate nuclei contain the cell bodies of parvocellular neurons whose axons (blue) terminate in close association with the portal capillaries. Parvocellular neurons also arise in the less well-defined anterior hypothalamic/preoptic areas continuum and send axons to the portal plexus. Magnocellular neurons (green) are also located in the paraventricular nuclei, with a second group in the supraoptic nuclei, and send axons along the infundibulum to the posterior pituitary. (Source: Heimer L. (1983) The Human Brain and Spinal Cord. Reproduced with permission from Springer-Verlag, Berlin.)

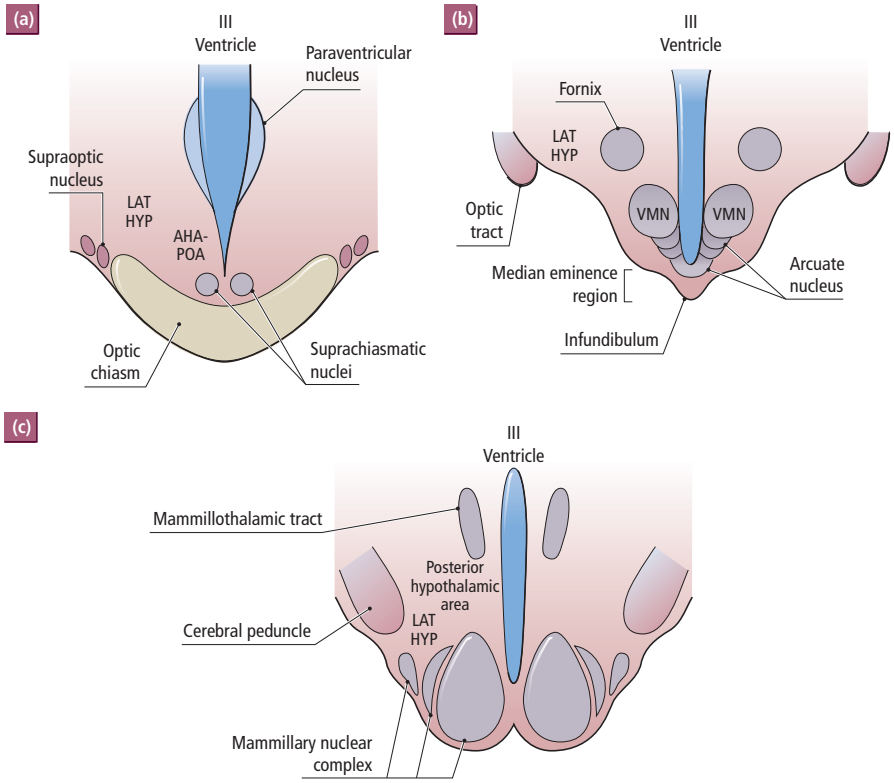


Figure 1.11 Three coronal sections at different anterior–posterior levels of the human hypothalamus (consult Figure 1.10 to construct the planes of sections). (a) Through the optic chiasm, note the third ventricle in the midline flanked by the anterior paraventricular (magnocellular) nuclei, which, together with the laterally placed supraoptic nuclei, synthesize oxytocin and vasopressin. The latter are then transported along the hypothalamo–hypophyseal tract (axons of neurons with cell bodies in these nuclei) to the posterior pituitary. The region of the suprachiasmatic nuclei and the anterior hypothalamic–preoptic area (AHA–POA) are also shown. (b) Through the infundibulum and median eminence, and showing the relationship between the parvocellular arcuate and ventromedial nuclei (VMN). The capillary loops of the portal plexus are found in this region. (c) Through the level of the mammillary bodies and showing the mammillary nuclear complex. The area labelled LAT HYP in all three sections is the lateral hypothalamus, and is composed of many nerve fibres ascending (largely aminergic) from the brainstem and descending from the rostral limbic and olfactory areas. This pathway represents a major input/output system for the more medially placed hypothalamic nuclei.

sulcus separating it from the **thalamus**; (2) anteriorly the **lamina terminalis**; and (3) posteriorly a vertical plane immediately behind the **mammillary bodies** (Figure 1.10). It is split symmetrically into left and right halves in the midline by the **third ventricle**, containing cerebrospinal fluid, such that the ventricle's floor and walls are formed by the hypothalamus (Figure 1.11). The hypothalamus has many different functions, only some of which are reproductive. Each function is associated with various **hypothalamic areas** or **nuclei** (Figures 1.10 and 1.11), those particularly concerned with reproductive functions being the **supraoptic, paraventricular, arcuate, ventromedial** and **suprachiasmatic nuclei**, and also two less easily defined areas, the **medial anterior hypothalamic** and **medial preoptic areas**.

The hypothalamic connections with the pituitary

The hypothalamic nuclei and areas have **either direct neural or indirect vascular connections with the pituitary gland**. Large neurons (the so-called **magnocellular neurosecretory system**) are located in the supraoptic and paraventricular nuclei (Figures 1.10 and 1.12a), and are the site of synthesis of the small peptide hormone, **oxytocin** (plus a second neuropeptide, **vasopressin**). Each hormone is synthesized in a distinctive subset of neurons, and pass along axons projecting from their cell bodies directly to the posterior lobe of the pituitary via the **hypothalamo–hypophyseal tract**, to be stored in the posterior lobe (see Figure 1.19c), before release into the bloodstream.

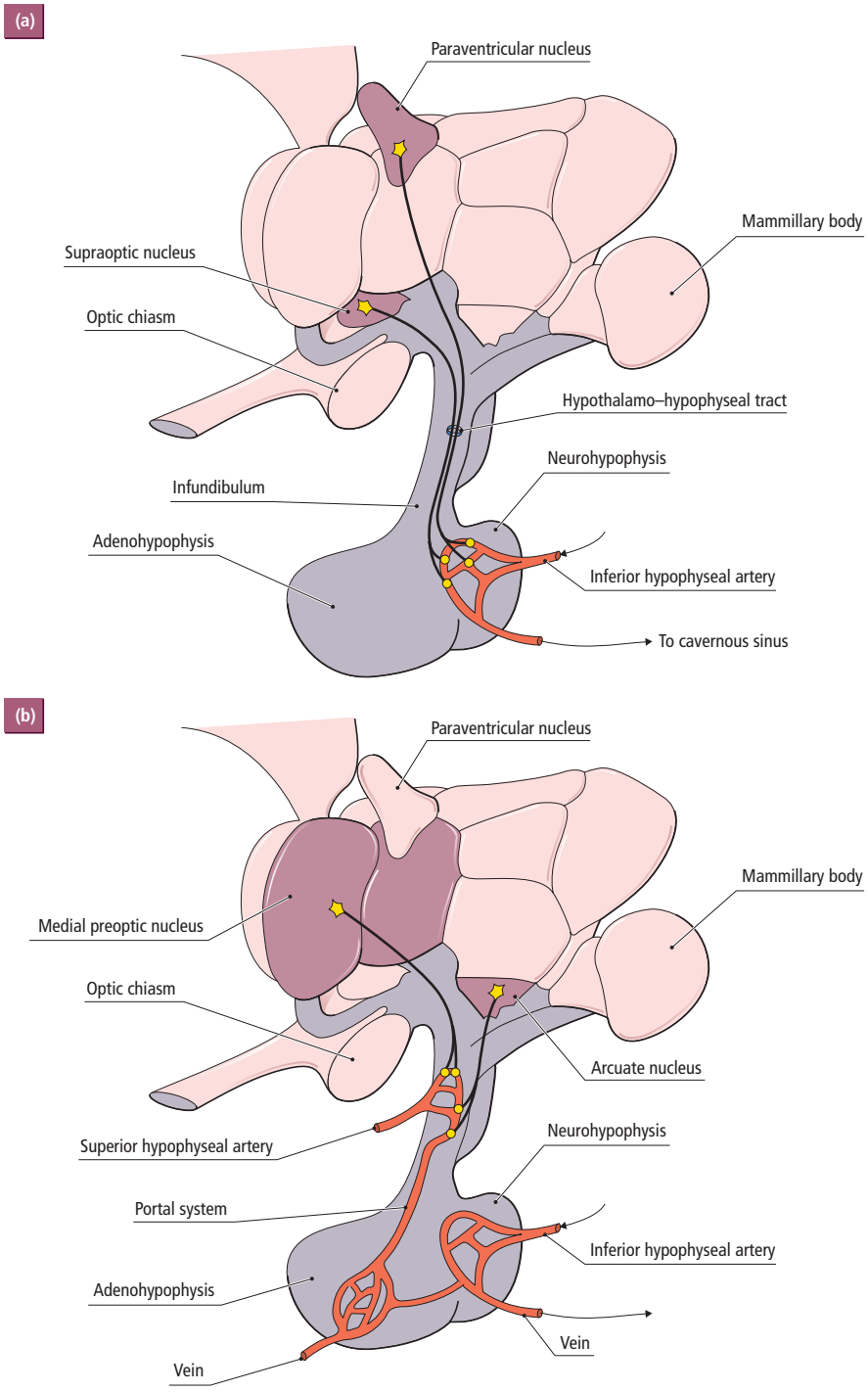


Figure 1.12 (a) Schematic representation of the magnocellular neurosecretory system. Neurons in the supraoptic and paraventricular nuclei send their axons via the hypothalamo–hypophyseal tract and infundibulum to the neurohypophysis, where terminals lie in association with capillary walls, the site of neurosecretion. (b) Schematic representation of the parvocellular GnRH neurosecretory system. Neurons in the medial preoptic and anterior hypothalamic areas, and in the arcuate nucleus send axons down to the portal vessels in the external layer (palisade zone) of the median eminence, where neurosecretion occurs.

The anterior pituitary, in contrast, receives its hypothalamic input indirectly by a vascular route (Figure 1.11). A variety of small neuropeptide hormones, including **GnRH**, is synthesized in the **parvocellular** (i.e. small-celled) **neurosecretory system** of the hypothalamus. In primates, parvocellular neurons are clustered mainly in the arcuate nuclei (Figure 1.12b), whilst others are more diffusely located in the medial preoptic and anterior hypothalamic areas (Figures 1.11 and 1.12b). Axons of these neurons project to the median eminence, where they terminate in the pericapillary space of the **primary portal plexus**. These vessels pass from the hypothalamus to the anterior pituitary, carrying the released neuropeptides in the **portal blood** where they act on the gonadotrophs.

The lactotrophs are also regulated via the portal plexus but quite differently from the gonadotrophs. Thus, unlike other pituitary hormones, prolactin is secreted spontaneously in large amounts when the vascular links between the pituitary and hypothalamus are **disconnected**. This observation means that regulation of secretion is mainly by **inhibition**, and has led to the search for the hypothalamic **prolactin inhibitory factor** (**PIF**). PIF is the catecholamine **dopamine**, and is found in neurons of the arcuate nucleus, the axons of which project to the portal capillaries in the medial and lateral palisade zones of the external layer of the median eminence (Figure 1.13; Box 1.3). It is secreted into the portal blood from the terminals of this **tuberoinfundibular dopamine (TIDA) system** and carried to the lactotrophs, where it depresses prolactin secretion.

Having described the main anatomical and physiological features concerned with reproduction, we can now examine the nature of the key hormones in more detail.

Reproductive messengers

In this volume, you will be introduced to many reproductive messengers, but here we focus on a few key hormones. We start with the sex steroids, introduced above (see page 12), which are the central players in reproduction. Here, a more detailed account of this family is given.

The sex steroids

These steroids make up a large group of molecules all derived from a common sterol precursor: **cholesterol** (Figure 1.14). There are four main families of steroid: the **progestagens**, **androgen**s, **oestrogens** (American spelling estrogens) and **corticosteroids** (Figure 1.15), of which only the first three are identified as **sex steroids**. In **steroidogenic** tissues, most steroid is synthesized from acetate with cholesterol as an intermediate product (Figure 1.14). The **steroid biosynthetic pathway** is illustrated in Figure 1.15, which also provides a visual framework of the molecular relationships of the different steroid family members. The conversion of cholesterol to **pregnenolone** is the first and rate-limiting step in steroid synthesis, and so an important point of regulation. Although there are three distinctive classes of sex steroid, they are related structurally to each other. Indeed, they can be seen as different generations of a biosynthetic family, the progestagens being 'grandparental' and the androgens being 'parental' to the oestrogens (Figure 1.15). Interconversion from one class of steroid to another is undertaken by a series of enzymes arranged together as a **biosynthetic unit**, taking in substrate and passing the molecule along a production line with little 'leakage' of any intermediates. For example, the enzymes 17α-hydroxylase, 17,20-desmolase, 17-ketosteroid reductase and 3β-hydroxy steroid dehydrogenase would form an enzyme package for the synthesis of testosterone from pregnenolone. This close relationship between the different classes of steroids means that an enzymatic defect at one point in the synthetic pathway may have far-reaching effects, as will be seen in Chapters 2 and 3.

Within each class of sex steroid, there are several natural members. The criteria for membership of each class are similarity of chemical structure that then reflects their common functional properties. Tables 1.1–1.3 summarize the principal natural progestagens, androgens and oestrogens, together with some of the functional characteristics of each class. It is often said that progestagens are associated with the preparations for pregnancy and its maintenance, androgens with the development and maintenance of male characteristics and fecundity, and oestrogens with the development and maintenance of female characteristics and fecundity. Although broadly correct, this statement is a simplification, and a number of exceptions will be encountered, e.g. androgens stimulate secondary sex patterns and behaviour in females (see Chapters 4 and 5) and oestrogens stimulate epididymal function in males (see Chapter 10).

Sex steroid receptors

Whether or not a particular steroid affects a tissue, and how it affects it, depends mainly on whether that tissue expresses a steroid **receptor**. The interaction between the two, like a key in a lock, then leads to secondary changes in the receptor (or in a molecule adjacent to it) that alert the cell to the arrival of the hormone. Steroids, being lipid soluble, can pass freely *into* a target cell nucleus to combine with an **intranucleoplasmic receptor**, thereby activating it (Figure 1.16). Activation involves phosphorylation of the receptor and a conformational change. This steroid–receptor complex, but not the steroid or receptor alone, can then bind to specific DNA sequences in the chromatin: the so-called acceptor sites or **steroid response elements (SREs)** specific for each steroid (e.g. ARE, PRE and ERE for androgens, progestagens and oestrogens, respectively). Binding of adjacent transcription factors also occurs, leading to a rapid rise in the activity of RNA polymerase II, production of mRNA species specific for the steroid and, in the continuing presence of the complex, a more general stimulation of nucleolar and transfer RNA synthesis. Steroid action through this so-called **'classical' pathway** has recently been supplemented by evidence of a **non-classical pathway**, in which the steroid