Chapter 14
Cell differentiation

Unit
2B

Unit content

Cells, metabolism and regulation
Genes determine a cell's structure and function. Differentiation of stem cells produces different cells and tissues.

Differentiation:

- differentiation forming embryonic germ layers
- tissues formed from the primary germ layers
- types of stem cells and their potency
- importance of stem cells e.g. cord blood.

The relevance of human biology to everyday life
The rate of change in human biology means that there is a range of alternative treatments available. Each treatment has its risks, ethical concerns and benefits based on individual variations and the condition being treated.

Medical technologies:

- stem cell collection for future use e.g. cord blood banks.

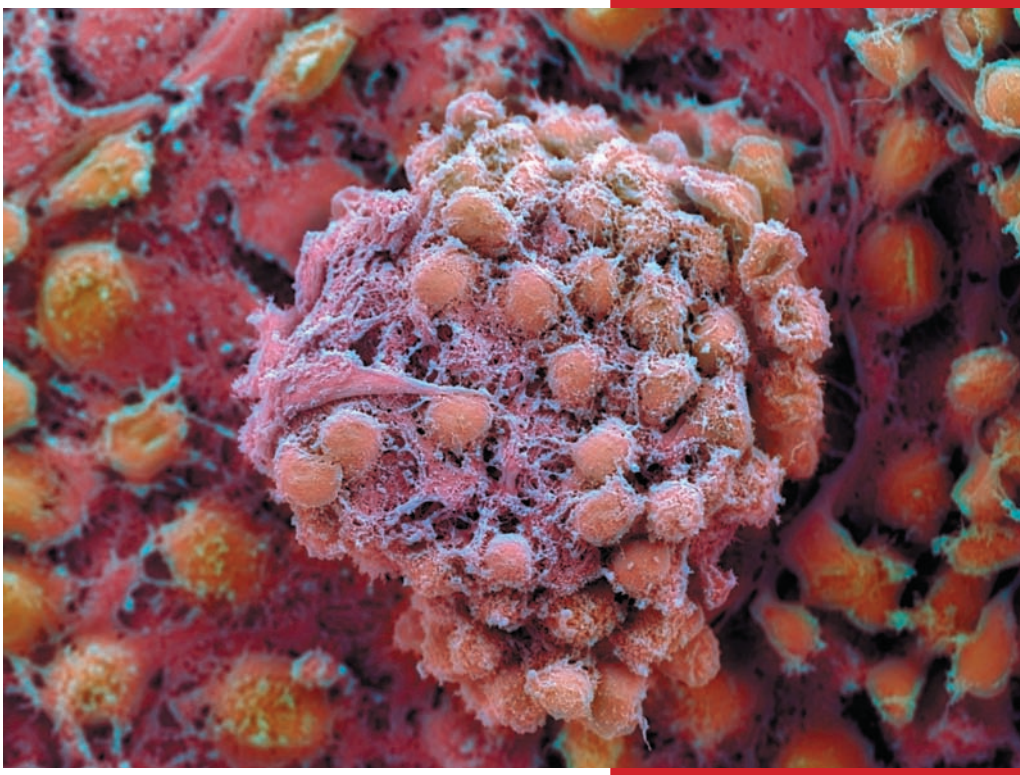

Figure 14.1 Human embryonic stems cells (scanning electron micrograph)

A **zygote** is the single cell that results from the fertilisation of an egg by a sperm. The zygote has the potential to grow into a new individual human. From that one initial cell develop all of the more than 200 types of cells that occur in the human body. How does this happen?

As the zygote travels down the uterine, or Fallopian, tube, it begins to divide by mitosis. The process of mitosis results in the formation of two cells exactly the same as the original parent cell (see Chapter 5). These two cells divide again by mitosis into four, then eight, then sixteen, and so on. By about six days after fertilisation the original zygote has reached the uterus and has developed into a **blastocyst**. The blastocyst is a hollow ball of cells that surround a cavity filled with fluid (see Fig. 14.2). At one side of the cavity is a group of about 30 cells called the **inner cell mass** (sometimes known as the **embryoblast**). The inner cell mass will develop into the **embryo** and the cells that compose it are termed **stem cells**. These stem cells are able to produce any of the different types of body cells.

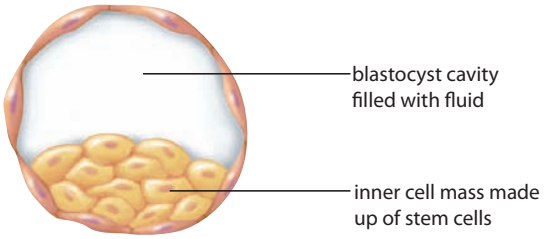

Figure 14.2 The blastocyst with inner cell mass

Cell differentiation

Stem cells are very different from other cells. They are not specialised for any particular role, they are capable of repeated division by mitosis, and, given the right conditions, they can differentiate into specialised cells. When cells replicate themselves many times over it is called **proliferation**. **Differentiation** is the process by which unspecialised cells develop the characteristics and the functions of particular types of cells, such as blood cells, muscle cells, nerve cells and bone cells. From the stem cells of the inner cell mass develop all of the 200 or more types of cells that make up a mature human body. These types of cells are known as tissues. A **tissue** is a group of cells that have a similar structure and which work together to perform a common function (Fig. 14.3).

The events of mitosis ensure that each daughter cell receives the same genetic information that is contained in the parent cell; therefore, every cell in the body must have the same genes. However, some cells, such as those in the stomach, secrete enzymes for digestion, whereas others, such as those in the skin, produce pigment, and nerve cells become specialised for the transmission of information. It seems that as stem cells proliferate (i.e. undergo division by mitosis) different genes become activated. This results in differentiation into specialised cells that are able to perform particular functions.

Scientists are just beginning to understand the signals inside and outside cells that trigger stem cell differentiation. The internal signals are controlled by a cell's **genes**, which are interspersed across long strands of DNA and carry coded instructions for all the structures and functions of a cell (see Chapter 17). The external signals for cell differentiation include chemicals secreted by other cells, physical contact with neighbouring cells, and certain molecules in the cell's immediate surroundings, its **microenvironment**.

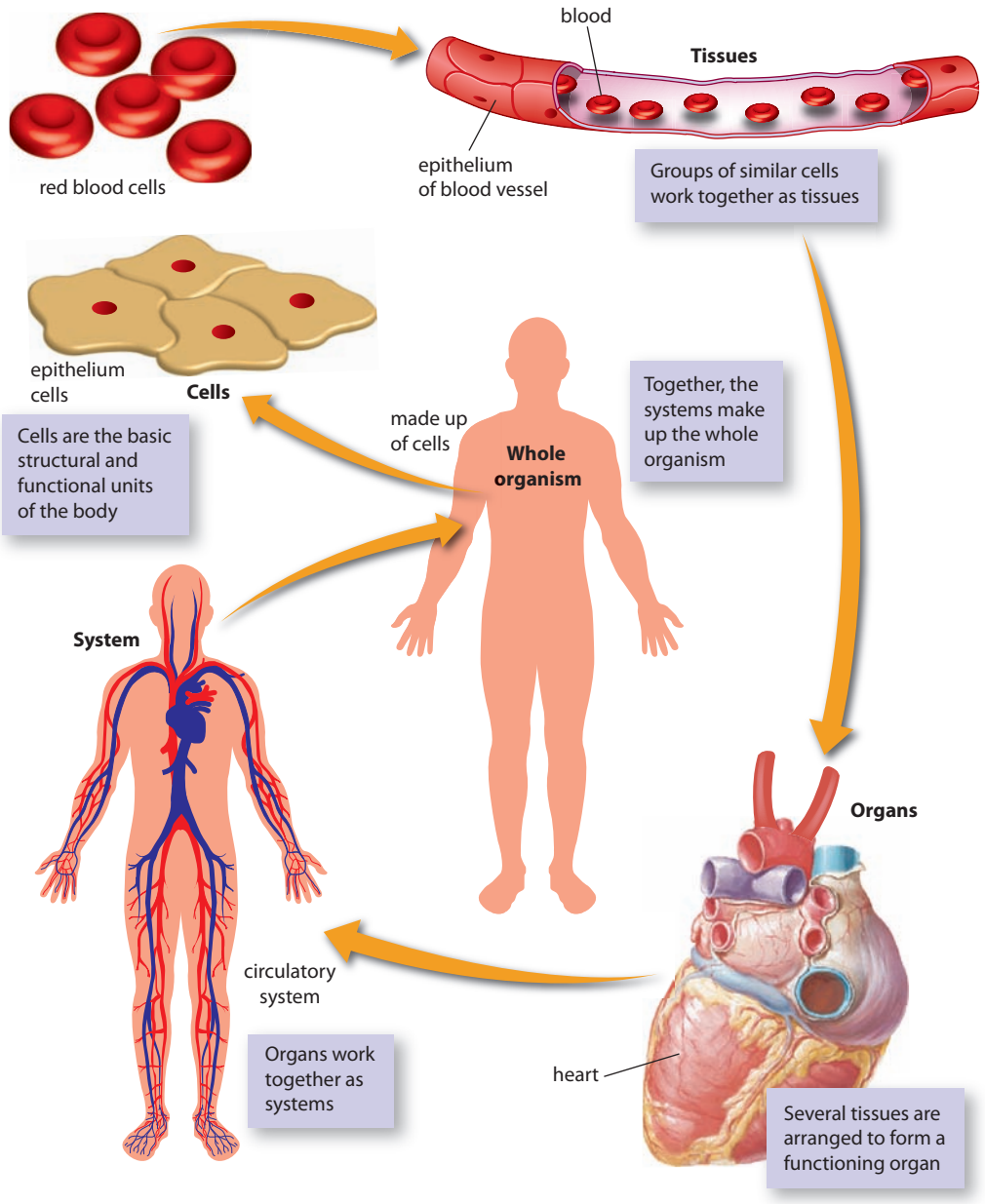

Figure 14.3 Tissues are one of the structural levels of body organisation. Groups of tissues make up organs that function together as systems

The process of differentiation

Stem cells have the ability either to divide for indefinite periods in culture to create more stem cells, or to give rise to specialised cells. Because of their ability to develop into any cell type, they could potentially provide an unlimited source of adult cells, such as bone, muscle, liver or blood cells. Several types of stem cells exist, and these will be described in the context of the ways humans develop (Fig. 14.4).

After a sperm fertilises an egg, a zygote is formed, which then has the potential to develop into a complete embryo. At this point, the fertilised egg is a **totipotent** stem cell, which means that it has the potential to create any type of cell necessary for embryonic development, including the embryo itself, and all of the membranes associated with embryonic development.

In the first few hours after fertilisation, the fertilised egg undergoes several cell divisions that produce identical totipotent cells. Because these cells are still totipotent, any one of them has the potential to develop into an entire human being. In fact,

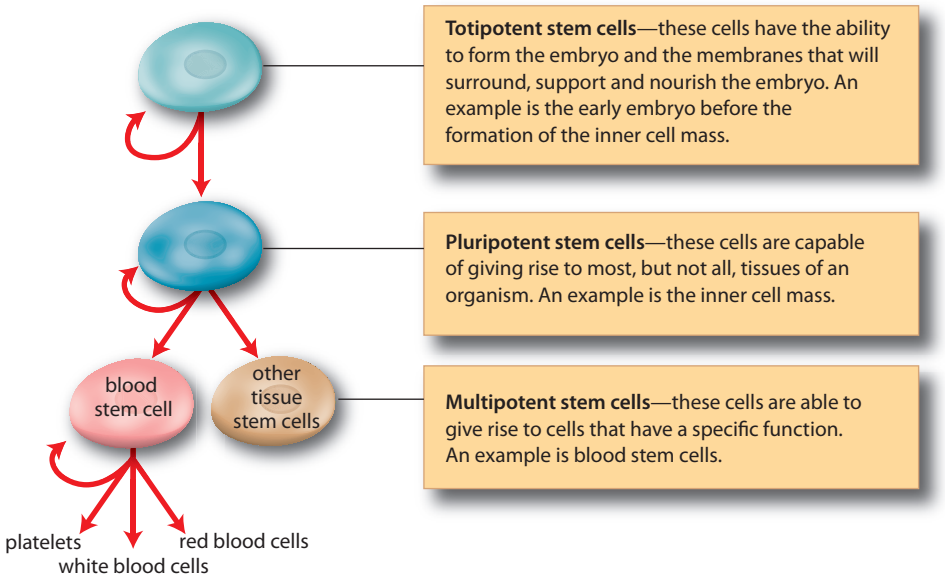

Figure 14.4 The process of cell differentiation

identical twins are formed when two totipotent cells separate and develop into two genetically identical embryos.

The totipotent cells undergo several rounds of cell division. About five days after fertilisation, they begin to specialise and form a **blastocyst** (see Chapter 12). The blastocyst is a ball of cells consisting of a hollow outer layer of cells, within which is a cluster of cells called the **inner cell mass** (see Fig. 14.2).

The outer layer of cells will eventually form the placenta and other tissues that are needed for the support and development of the foetus. The inner cell mass will form all of the tissues of the human body; therefore, these are the cells that develop into the foetus. The cells of the inner cell mass are **pluripotent**. This means that they are able to give rise to many, but not all, cell types necessary for foetal development. For example, they are able to give rise to foetal tissues, but not placental tissue. Pluripotent stem cells are currently under investigation for medical use.

For a brief video on cell differentiation see http://www.teachersdomain.org/resources/tdc02/sci/life/stru/different/index.html

Each pluripotent cell then undergoes further specialisation into another type of stem cell, a **multipotent** stem cell. Multipotent stem cells give rise to cells that have a particular function, for example, blood stem cells give rise to red blood cells, white blood cells and platelets, and skin stem cells give rise to the different types of skin cells. Multipotent stem cells exist in both embryos and adults, the best understood example being the blood stem cell. In each person's bone marrow, blood stem cells exist that constantly replenish the supply of red blood cells, white blood cells and platelets (see Chapter 6 for a description of blood cells).

Table 14.1 Potency of stem cells

Totipotent stem cells	Can give rise to all of the cell types that make up the human body and also all of the cell types that make up the membranes that surround the developing embryo (including the placenta)
Pluripotent stem cells	Can give rise to all of the cell types that make up the body but **not** the cell types that make up the embryonic membranes
Multipotent stem cells	Can develop into more than one of the cell types that make up the body but **not** all cell types

Primary germ layers

While the blastocyst is implanting in the lining of the uterus (see Chapter 12) the inner cell mass undergoes changes, resulting in the formation of three layers of cells, the **primary germ layers**. These layers, called the **ectoderm**, **mesoderm** and **endoderm** (Fig. 14.5), are the embryonic tissues that will differentiate into all the tissues and organs of the body. Table 14.2 lists the structures that are formed by the three primary germ layers.

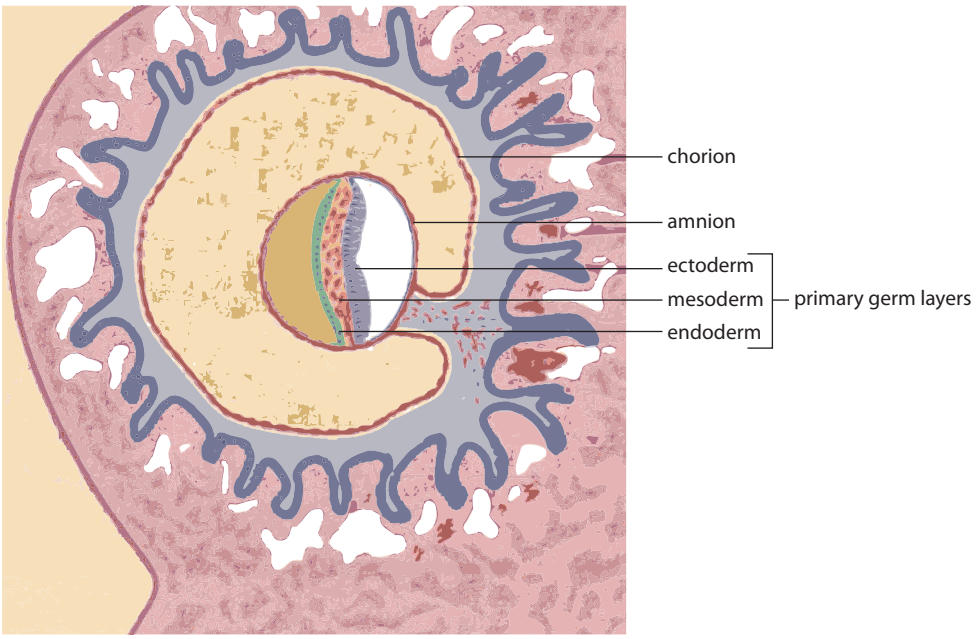

Figure 14.5 Formation of the embryonic germ layers

Table 14.2 Structures formed by the three primary germ layers

Endoderm	Mesoderm	Ectoderm
Epithelium of alimentary canal and its glands (e.g. liver and pancreas)	Skeletal, smooth and cardiac muscles	Epidermis of skin
Epithelium of urinary bladder, urethra and gall bladder	Cartilage, bone, blood and other connective tissue	Hair, nails, glands of skin
Epithelium of pharynx, auditory canal, larynx, trachea, bronchi and lungs	Lymphoid tissue	Lens, cornea and muscles of the eye
Epithelium of tonsils, thyroid, parathyroid and thymus glands	Endothelium of blood vessels and lymphatics	Receptor cells of the sense organs
Epithelium of vagina and associated glands	Epithelium of the body cavity and joint cavities	Epithelium of mouth, nostrils, sinuses, glands of mouth, and anal canal
	Epithelium of kidneys and ureters	Enamel of the teeth
	Epithelium of ovaries, testes and reproductive tracts	Entire nervous system
	Epithelium of adrenal cortex	Anterior lobe of the pituitary gland
	Dermis of skin	Adrenal medulla

Sources of stem cells

Stem cells have the potential to be used as a form of therapy to replace damaged or degenerated tissues, for example, in Parkinson's disease, diabetes and spinal injuries. There are three sources of stem cells.

1. *Umbilical cord blood and placental stem cells*. Stem cells are present in the blood in the umbilical cord and the placenta. Once a baby is born, these cells can be extracted from the discarded tissue and used for the benefit of children and adults who suffer from devastating bone marrow and blood diseases. They can also be stored in case the baby requires replacement tissues or organs later in life. These stem cells are obtained after the baby is born and are multipotent. There is no harm to the mother or child.

   In Australia there is a national network of umbilical cord blood banks called AusCord. Parents can choose to donate their baby's cord blood to one of AusCord's public cord blood banks. The donated blood is then available to any suitable recipient. If parents wish to ensure that the cord blood is available for their own baby later in life, they can pay to have the cord blood stored at a private blood bank.
2. *Embryonic stem cells*. Embryonic stem cells (see Fig. 14.1) are cultured from frozen embryos (Fig. 14.6) that are obtained from in-vitro fertilisation clinics. Unused embryos from in-vitro fertilisation may be donated to research because the couple no longer desires additional children, does not wish to continue

There are many websites that deal with stem cells, for example:
- http://www.sumanasinc.com/webcontent/animations/content/stemcells_scnt.html
- http://learn.genetics.utah.edu/units/stemcells/index.cfm

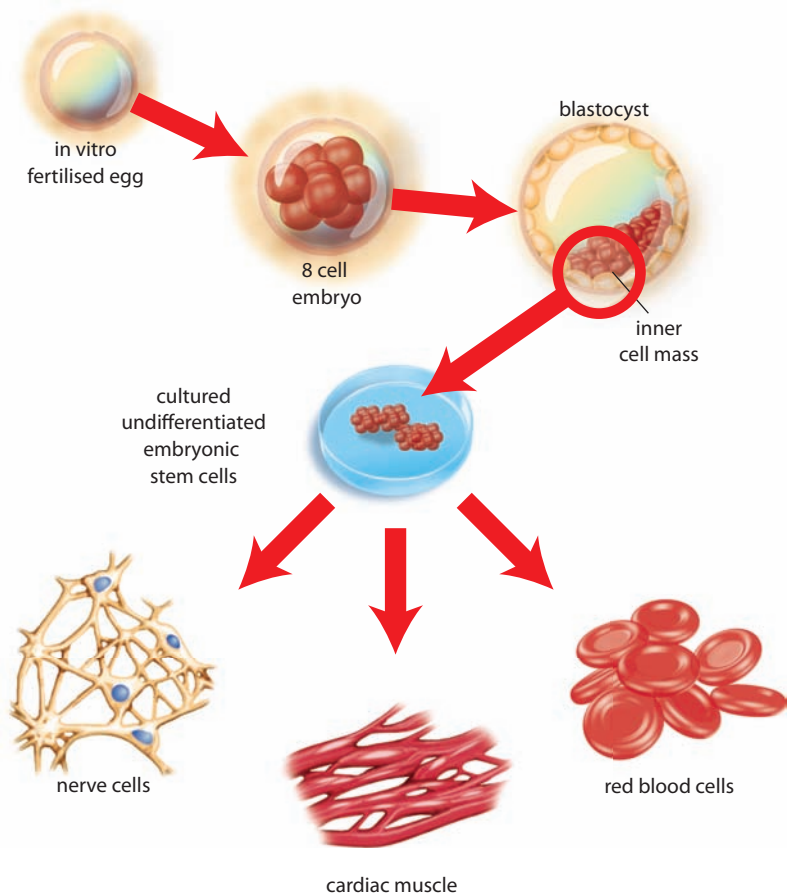

Figure 14.6 Culturing embryonic stem cells may allow scientists to grow replacement tissues and organs for patients

storage, or does not want to give them up for use by another infertile couple. However, there are significant ethical issues related to the use of embryonic stem cells because obtaining them requires destruction of an embryo, and governments have strict regulations in place for controlling this type of technology. A potential advantage of using embryonic stem cells is that they are pluripotent. They can become any of the cell types of the body and are therefore more versatile than adult stem cells. A disadvantage is that they come from embryos that are not derived from the patient's own cells and the patient's body may therefore reject them.

3. *Adult stem cells*. Multipotent adult stem cells can form cells of many kinds of tissue. An important potential advantage of using adult stem cells to treat disease is that a patient's own cells could be used for treatment. Risks would be reduced because patients' bodies would not reject their own cells. A disadvantage of most adult stem cells is that they are pre-specialised, that is, blood stem cells make only blood and brain stem cells make only brain cells. It appears that most organs of the body have stem cells so that they can replace dead or damaged cells. For example, bone marrow contains multipotent stem cells that give rise to all the cells of the blood. It is, therefore, a good source of adult stem cells (Fig. 14.7).

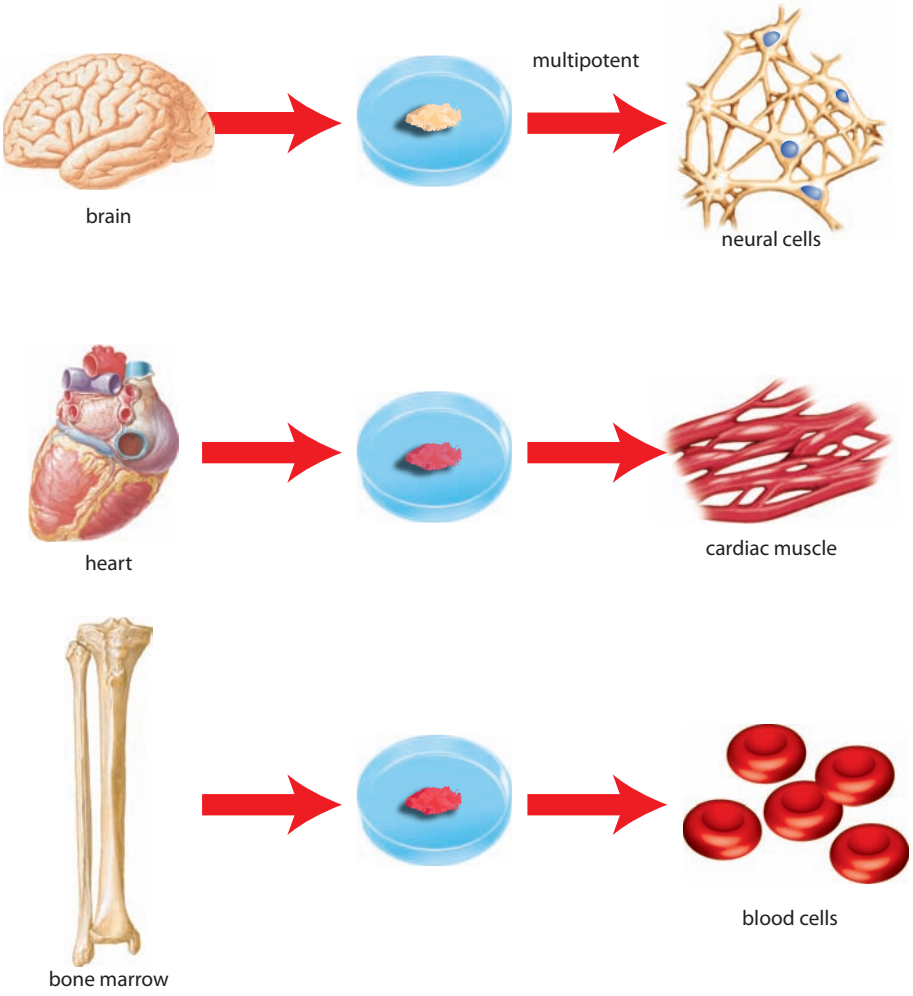

Figure 14.7 Examples of adult stem cells. Adult stem cells are now thought to be multipotent

EXTENSION

Every nucleus in every cell in your body has the same set of genes because they have all arisen by mitosis from the original zygote. In order for cells to differentiate and become different from one another, certain genes must be activated while others remain inactive. If the process of gene activation could be controlled it would have the potential to cure many diseases.

Find out:

- how genes are turned on and off
- the lines of research into controlling gene activation
- some of the diseases that could be treated if gene activation could be controlled.

Stem cell research

As we have seen, stem cells have three characteristics that distinguish them from other cells. They have not yet undergone differentiation, that is, they are not specialised for any particular role; they are capable of repeated division by mitosis for long periods of time; and, given the right conditions, they can differentiate into specialised cells.

There are two types of stem cells. **Embryonic stem cells** are present in 3–5-day-old embryos and give rise, through differentiation, to the different types of specialised cells in the body—muscle cells, nerve cells, skin cells, bone cells and all the other cells that make up the body tissues.

Adult stem cells occur in adult tissues such as the bone marrow, muscle and the brain. In these tissues the adult stem cells are able to produce new cells to replace those that are worn out, injured or diseased. Normally, adult stem cells give rise to cells that are the same as the tissue in which they are located. For example, adult stem cells in the skin differentiate into new skin cells. Recently it has been discovered that adult stem cells can, if given the right conditions, differentiate into quite different tissues from the one in which they are located. For example, stem cells in the bone marrow could become heart muscle cells, or stem cells in the liver could become pancreatic cells producing insulin.

A source of adult stem cells is umbilical cord and placental blood from newborn babies (known as cord blood). Although from infants, they are considered to be adult stem cells because they do not come from embryos. These **cord blood stem cells** can differentiate into red blood cells and cells of the immune system. Cord blood stem cells, stored at birth, could be used to treat conditions such as leukaemia, anaemia and immune system diseases should the donor baby suffer from those conditions later in life. If the stored cells are a suitable match they can also be used to treat other patients. For conditions like leukaemia, the most suitable transplant is another person's cord blood because the patient's own cord blood may have the potential to develop leukaemia.

Due to their ability to differentiate into cells of many different types, stem cells are the subject of intense scientific research. It is hoped that ways may be found to use stem cells in **cell-based therapies** to treat disease (Fig. 14.8). If stem cells could be made to differentiate into particular cell types, they could provide replacement tissues for treating conditions such as stroke, spinal cord injury, burns, heart disease, diabetes, arthritis, Alzheimer's disease and Parkinson's disease. In addition to use in cell-based therapies, stem cells could be used for such things as testing new drugs, testing toxins and for understanding the causes of birth defects.

Research into stem cells is particularly aimed at identifying, firstly, how stem cells are able to remain undifferentiated and self-renewing for several years, and secondly, the signals that stimulate stem cells to begin differentiation.

Embryonic stem cell research

Over 20 years ago scientists learned how to obtain stem cells from early mouse embryos, but it was not until 1998 that they were able to isolate stem cells from human embryos and grow them in the laboratory.

Embryonic stem cells for research are obtained from embryos produced by in-vitro fertilisation (IVF; see Chapter 12). The embryos have been produced to assist an infertile couple but are no longer needed for possible implantation into the female's uterus. They are made available for research with the informed consent of the donors.

Embryos from which embryonic stem cells are obtained are four or five days old and are at the blastocyst stage of development (see Fig. 14.2). The inner cell mass of about 30 cells is transferred to a culture dish containing a nutrient solution. Over a few days the cells divide, spread over the surface of the culture medium, and begin to fill the dish. At this stage they are removed and placed in several fresh culture dishes. This **subculturing** can be repeated many times over a number of months, developing what is called a **stem cell line**. In six months the 30 cells from the original inner cell mass can develop into cultures containing millions of embryonic stem cells. The cultures can be frozen and made available for research in other laboratories.

Therapeutic cloning is a controversial method of obtaining embryonic stem cells. A **clone** is two or more cells, tissues or organisms that are genetically identical. Dolly, a sheep born in 1997, was the first animal produced that was a clone of its mother.

In therapeutic cloning a nucleus from a patient's body cell is inserted into a donor's egg from which the egg nucleus has been removed. The resulting cell develops into a blastocyst from which the stem cells can be harvested (Fig. 14.9). Those stem cells are genetically identical to the cells of the patient from whom the nucleus came. Any tissues developed from the stem cells and transplanted into the patient will not be rejected—a big advantage over tissues from other sources. The procedure is controversial because the cloned embryo, if allowed to develop, could potentially develop into a person, who would be a clone of the patient.

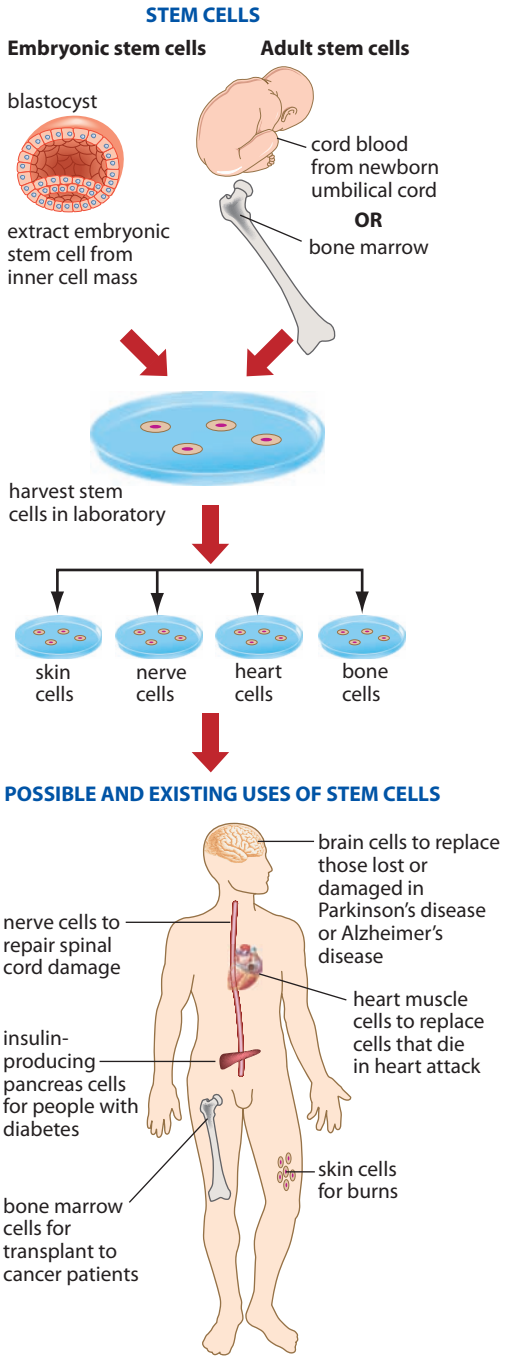

Figure 14.8 The process of culturing stem cells and their possible uses

Adult stem cell research

Research on adult stem cells began in the 1960s when it was discovered that bone marrow contains two different types of stem cells—those that give rise to blood cells and those that differentiate into bone, cartilage and fat storage tissues. Bone marrow stem cells that differentiate into blood cells have been used in transplants for over 30 years. Most research has centred on these bone marrow stem cells.

More recently it has been revealed that stem cells probably exist in all body tissues but that there are only a small number in each tissue. Scientists are now trying to find ways of growing cultures of adult stem cells and inducing them to differentiate into particular cell types for use in treatment of injury or disease. If a patient's own stem

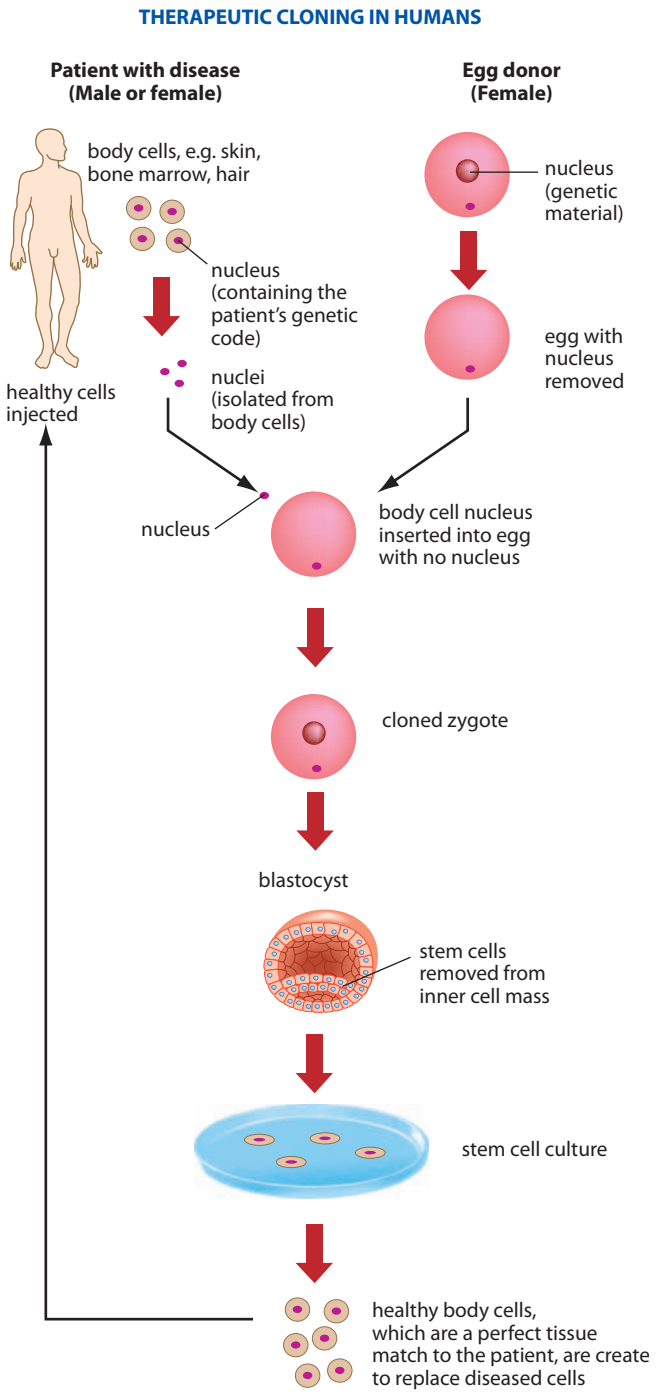

Figure 14.9 The process of therapeutic cloning in humans

cells could be cultured and then reintroduced into the body, the introduced cells would not be rejected by the patient's immune system.

Recent discoveries that adult stem cells may be able to differentiate into tissues different from the one in which they are located have given much impetus to adult stem cell research. There is a need to learn much more about how adult stem cells can be stimulated to differentiate into multiple cell types.

Ethical considerations of stem cell research

The most promising lines of research involve the use of human embryos. Embryonic stem cells can be cultured in the laboratory and are able to differentiate into any other type of cell. Research on human embryos, however, raises many ethical questions.

Therapies that may result from embryonic stem cell research have the potential to alleviate much human suffering. Prevention of suffering is an important moral principle in human societies. Another important moral principle is respect for the value of human life. Thus, in embryonic stem cell research we have a conflict of values. To achieve the goal of developing new and potent therapies that will help suffering humans, we must destroy human embryos, which are potential human lives. Which of these values is more important?

Each of us must make up our own minds about where we stand on this issue according to our own beliefs and values. Listed below are some of the arguments for and against embryonic stem cell research that need to be considered before you arrive at a conclusion. (For more information, see the discussion in Chapter 12 on when human life begins.)

- Production of replacement tissues and organs for transplant will be of great benefit because the organs available for transplant are always in short supply.
- The benefits of stem cell research are only *potential* benefits. The outcomes of scientific research are unpredictable and the goals may prove to be unattainable or many decades away.
- Adult stem cells can be used for research, thus avoiding the destruction of human embryos.
- Tissues developed from a person's own stem cells would not provoke an immune response when transplanted into the person's body.
- Compared with embryonic stem cells, therapies from adult stem cells will take many more years to develop because adult stem cells cannot yet be easily harvested and cultured in the laboratory.
- At present embryonic stem cell research uses surplus embryos from IVF programs. These embryos would have eventually been destroyed anyway.

- In the future, embryos may be produced just for research purposes. This could ultimately lead to a trade in human embryos.
- Allowing human embryos to be routinely destroyed may mean that society will become desensitised to the destruction of human life.
- Embryos used in stem cell research are pre-implantation blastocysts that would not be able to develop into a human unless implanted into a female's uterus.
- There is no difference between prevention of implantation of an embryo using an IUD or the morning-after pill and the destruction of an embryo for research purposes.

Stem cell research in Australia

Two acts of parliament govern stem cell research in Australia. The *Research Involving Human Embryos Act 2002* permits research on surplus embryos from IVF programs. Researchers have to apply for a licence to do the research and it is carefully regulated to make sure that ethical standards are observed. Written permission must be obtained from the female (and her partner where appropriate) for whom the embryo was created.

The *Prohibition of Human Cloning Act 2002* totally banned human cloning, including cloning for therapeutic purposes. The only purpose for which human embryos could be created in Australia was to achieve pregnancy in a woman.

Written into both of those Australian Acts was a provision for a review after three years. The review began in the second half of 2005. It recommended that the present regulatory frameworks be maintained and therapeutic cloning be allowed under strict ethical regulations. The Australian Parliament, in December 2006, passed a bill that will now allow cloning of human embryos for therapeutic purposes.

The situation in other countries varies. Since 2002, scientists in the United Kingdom have been able to obtain licences to create therapeutic human clones. In the United States, government funding is currently only available for research on embryos that were already in existence in 2001.

Cell-based therapies using stem cells offer exciting possibilities for the treatment of many diseases. However, there are still many ethical issues that divide society. Even if these can be overcome, the technical obstacles are still enormous and many years of painstaking research will be required before any of the dreams become a reality.

EXTENSION

The latest Australian legislation on human embryo research and cloning allows therapeutic cloning and cloning for harvesting stem cells. It has been recommended that a national stem cell bank be established.

- What is a stem cell bank and what would be the advantages of such a bank?
- Comment on the changing attitudes in Australian society that led to the recommendation that therapeutic cloning be allowed.
- If therapeutic cloning does occur in Australia, what further changes in attitude are likely?

Working scientifically

Activity 14.1 A briefing paper

Imagine that you are employed by a member of parliament who is to participate in a debate about the desirability of stem cell research. You have been asked to prepare a briefing paper for the member. He/she will need to know such things as:

- what stem cells are
- what lines of research are currently being carried out
- what diseases could potentially be cured or alleviated as a result of the research
- the ethical arguments for and against stem cell research
- any other relevant information.

Your task is to compile a briefing paper for the member, including all the information that you think will be necessary to engage in a meaningful debate.

Activity 14.2 Designer babies

> In June 2003, Michelle Whitaker gave birth to a baby boy, James, in a hospital in Sheffield, UK. During the birth doctors took a sample of James's umbilical cord blood and banked it for later use. The intended recipient wasn't James: it was his older brother Charlie, who suffers from a rare form of anaemia and whose only hope of a cure was an injection of tissue-matched stem cells.
>
> James was a 'designer baby', conceived by IVF and selected from among many embryos to ensure that he would be a suitable donor for Charlie, using a technology called pre-implantation genetic diagnosis. PGD involves taking a single cell while the embryo is at an early stage—just 4 to 10 cells—and scrutinising its genome. It has been used thousands of times since its first success in 1990, but the Whitakers' case broke new ground.
>
> Until James, PGD had been almost exclusively used to reject embryos carrying undesirable genes for diseases or disabilities including Huntington's, cystic fibrosis, sickle cell anaemia and even a predisposition to cancer. The Whitakers' case showed it can also be used to positively select for desirable traits. And that, some people believe, marks the beginning of a world where parents can start to choose their children's genetic make-up.

From an article titled 'The New Incredibles' by Graham Lawton, *New Scientist*, 13 May 2006.

- Discuss, in small groups, the advantages and disadvantages of parents being able to choose their children's inherited characteristics.
- Report a summary of your arguments to the whole class.
- Create a two-column list of advantages and disadvantages of 'designer babies'.

REVIEW QUESTIONS

1. Distinguish between proliferation and differentiation.
2. Explain the difference between the three types of stem cells—totipotent, pluripotent and multipotent.
3. **(a)** What are the three embryonic germ layers?
   (b) Give two examples of tissues that develop from each of the germ layers.
4. What are three sources of stem cells?
5. **(a)** In what ways do stem cells differ from ordinary body cells?
   (b) What are the differences between embryonic and adult stem cells?
6. What are cell-based therapies? How could they be used to treat certain diseases?
7. Explain how a stem cell line is created.
8. What is therapeutic cloning? How could therapeutic cloning be used to treat disease?

APPLY YOUR KNOWLEDGE

1. The categorisation of stem cells is based on the potency, or ability, of that cell to produce a range of other cells. Look at the three types and describe how the name fits the range of cells it is able to produce.
2. Which source of stem cell is likely to be most useful in developing therapies for diseases?
3. An umbilical cord blood bank was established in Australia in 1995. Parents can voluntarily have a sample of their baby's cord blood stored for later use. What would be the advantages of such a bank?
4. Describe five examples of situations where there is a strained relationship between groups in society over the use of devices or procedures that have been developed through advances in human biological science.
5. Research into cell-based therapies using stem cells is occurring in many laboratories around the world, with new advances being made all the time. Find out the latest information available with particular reference to which diseases are the most likely to benefit from such research.
6. 'The rate of change in human biology can cause tensions requiring individuals to make decisions that will have consequences for individuals and society.' Discuss this statement with particular reference to research on embryonic and adult stem cells.
7. It was reported in the media in late 2007 that several top Australian sporting teams were considering storing their players' stem cells so that they could be helped to recover quickly from serious injury. Stem cells would be taken from the bone marrow in a player's spine, cultured in the laboratory and then stored. The cells could be transplanted to the player should an injury occur. What sort of injuries could be treated using such a technique?