Laura Campbell

The ups and downs of hormones

This article explains, with particular reference to the female reproductive system, what happens to hormone levels as we age, the effect these changes can have on the body, how these changes can lead to an increased risk of developing certain diseases, and how our knowledge is being used to develop new treatments to target diseases associated with the menopause.

Key words

Endocrine system
Hormone
Oestrogen
Menopause
Hormone replacement therapy (HRT)
Chronic wounds

The **endocrine system** is an information signal network that uses chemicals — hormones — to communicate. It is key to body function — regulating mood, development, metabolism and reproductive processes.

Hormones are released from endocrine glands located throughout the body (see Figure 1). They enter the blood and are carried to specific target organs, cells or tissues, where they induce a response.

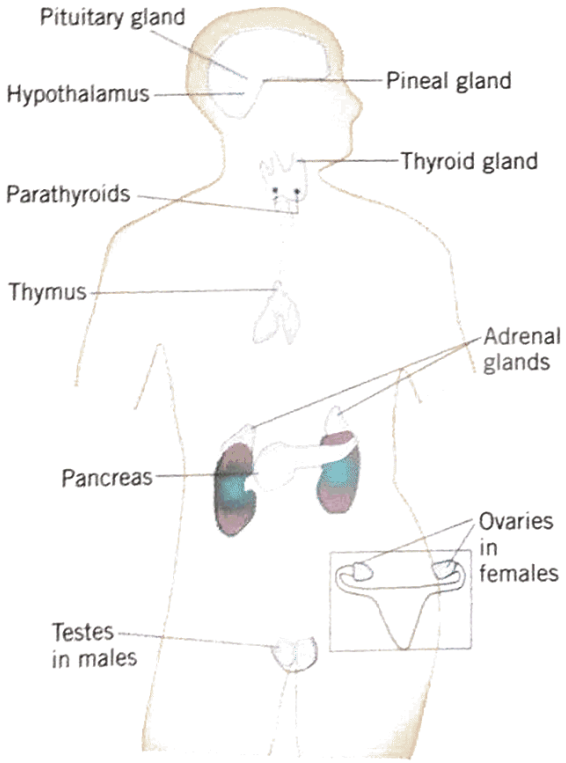


Figure 1 Glands of the endocrine system.

This type of signalling is slow to begin with, but can lead to prolonged responses, often measured in days.

Each hormone has a defined structure that is recognised by specific binding sites — called hormone receptors — on the target cell. Binding of a hormone to its receptor triggers a cascade of secondary effects inside the target cell, ultimately activating the expression of genes in that cell (see Box 1).

Hormone synthesis and release is controlled by positive and negative feedback mechanisms, which maintain or restore **homeostasis**. A well-known example is the female menstrual cycle. This involves a signalling network comprising the brain and ovaries (see Biological Sciences Review, Vol. 25, No. 1, pp. 23–27).

The menstrual cycle

The menstrual cycle of a healthy pre-menopausal woman lasts an average of 28 days, resulting in the release of a fertilisation-competent **oocyte**. The cycle can be split into three distinct phases, characterised by tightly regulated fluctuations in hormone concentrations (see Figure 2 on p. 32). The follicular phase spans the first day of menstruation through to ovulation. It begins with an increase in follicle stimulating hormone (FSH) concentration. This stimulates around 15–20 follicles to mature and secrete increasing quantities of oestrogen, which in turn inhibits further FSH secretion by **negative feedback**. Usually, a single follicle emerges and oestrogen concentrations peak towards the end of

Box 1 Types of hormones

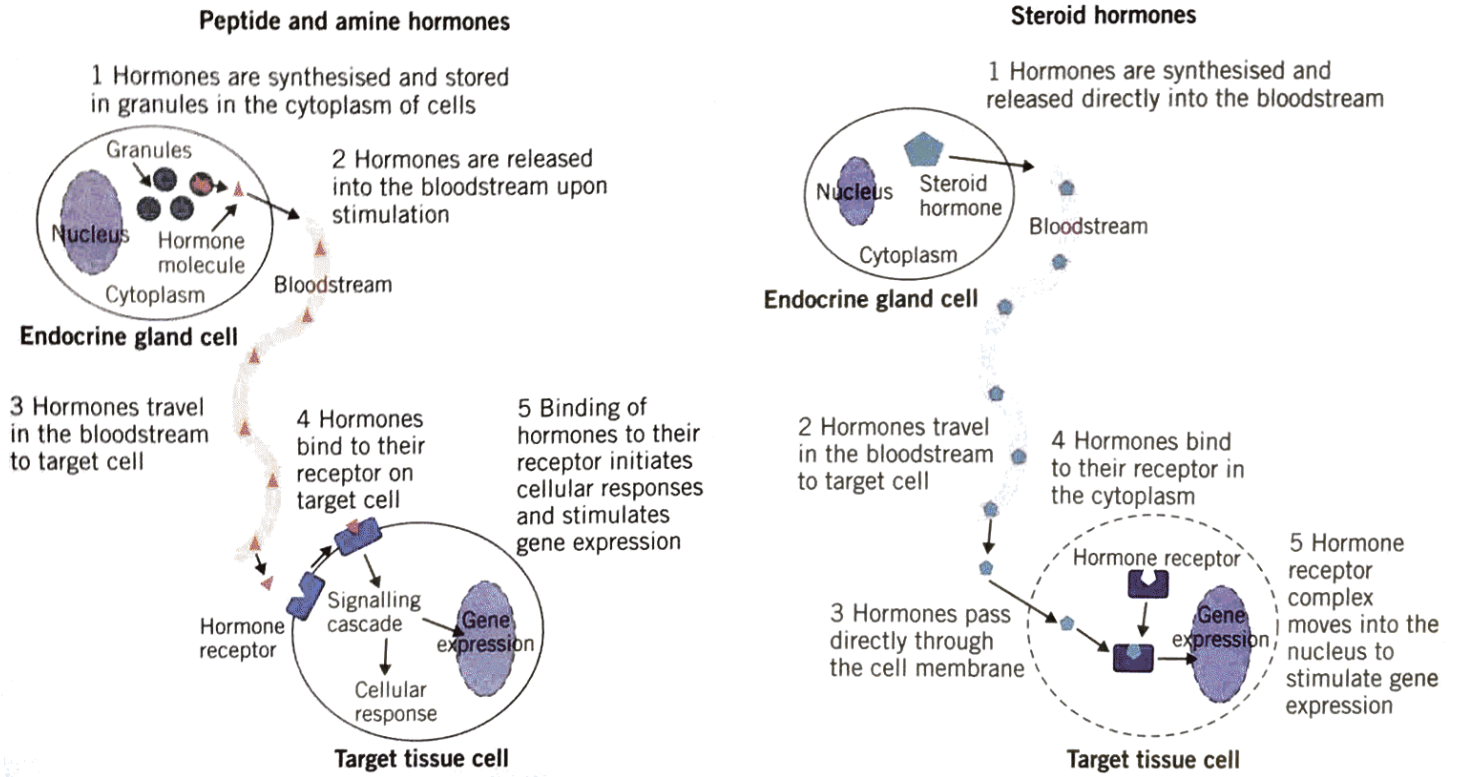
Stretch and challenge

Hormones can be grouped broadly into steroids, amines and peptides/proteins (see Table 1). Hormones in each group tend to function in a similar fashion.

Peptides and proteins — the largest class — are variable in size, ranging from three to 50 amino acids in length. Most peptide hormones are synthesised in the endoplasmic reticulum of cells contained within the endocrine organ as larger biologically inactive precursors, termed pro-hormones. They are stored in secretory granules and are released into the bloodstream when stimulated by a specific signal.

Amines are water-soluble molecules derived from amino acids. Amines are also stored in secretory granules. Once these hormones are released into the bloodstream they travel to a target tissue where they bind to receptors on the outside surface of the target cell.

Steroid hormones, produced by the adrenal gland, ovaries or testes, are not stored in endocrine cells and are released immediately they are made. Steroid hormones are lipid-soluble so they can diffuse directly across the plasma membrane of the target cell. Once inside the cytoplasm, steroid hormones bind to their receptors, forming a complex. This complex then moves into the nucleus where it binds to target genes, turning protein expression on or off.



How the different classes of hormones work.

Table 1 Types of hormones

Type	Form	Where produced (see Figure 1)	Example
Steroid	Lipid-soluble	Adrenal gland, ovaries, testes	Oestrogen, testosterone
Amines	Water-soluble	Adrenal medulla, thyroid gland, pineal gland	Epinephrine, dopamine
Peptides and proteins	Water-soluble	Pituitary gland, hypothalamus, pancreas, parathyroid gland, thymus gland	Insulin, follicle-stimulating hormone, luteinising hormone

the follicular phase. The high levels of oestrogen stimulate the production of luteinising hormone, LH (**positive feedback**). This is required for the second phase, ovulation, in which the developing female gamete, or oocyte, is ejected from the ovary and migrates down the oviduct.

In the final, luteal, phase, a **corpus luteum** develops, which secretes mainly progesterone with some oestrogen. High progesterone concentrations inhibit the production of FSH and LH. In the absence of FSH and LH stimulation, the corpus luteum undergoes cell death and reabsorption. As oestrogen and progesterone concentrations fall, the negative feedback control on FSH is removed, concentrations begin to rise, and the next menstrual cycle is initiated. This cycle begins at puberty and lasts throughout the reproductive phase of every woman until the onset of the menopause.

Ageing and the menopause

The menopause is the stage in a woman's life when her ovaries stop producing gametes and she is no longer fertile. The menopause occurs because the ovaries no longer respond to FSH and LH

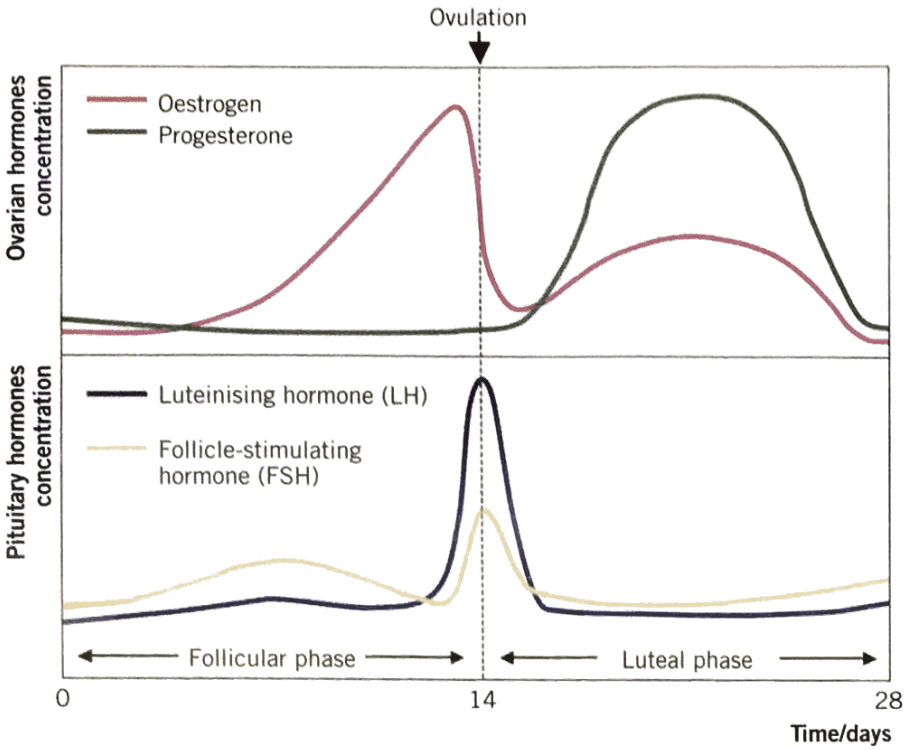


Figure 2 Hormonal regulation of the menstrual cycle. There are three distinct phases. (1) The follicular phase is characterised by increasing levels of FSH, which results in maturation of ovarian follicles, which in turn produce oestrogen, where levels peak at the end of the phase. (2) Ovulation occurs due to high levels of oestrogen having a positive effect on LH concentrations resulting in the ejection of an oocyte from the ovary. (3) The luteal phase is characterised by the production of a corpus luteum, which secretes high levels of progesterone.

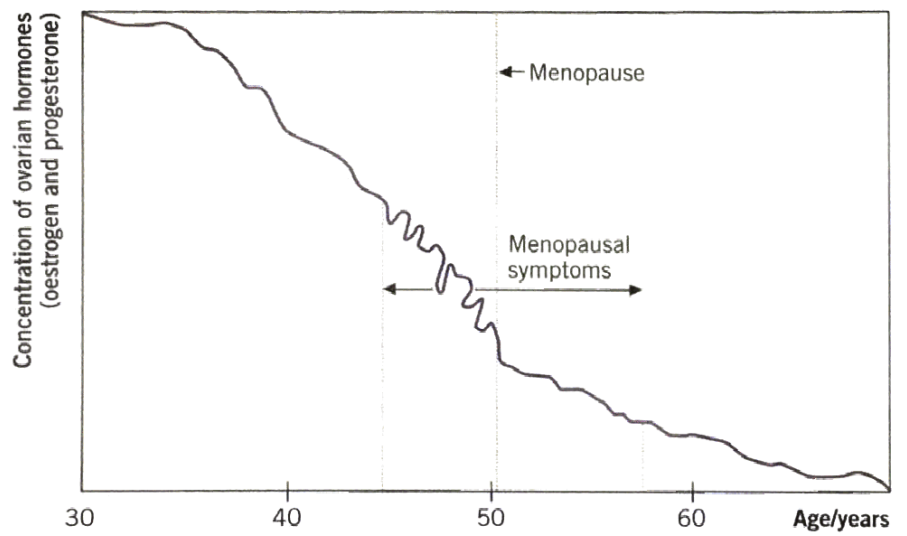


Figure 3 Mean levels of ovarian hormones as women age.

Table 2 Increased health risks associated with the menopause

Tissue	Conditions
Brain	Stroke, Alzheimer's disease
Bone	Osteoporosis
Breast	Breast cancer
Heart	Heart attack, heart disease
Bladder	Urinary incontinence
Skin	Delayed wound repair

released from the pituitary gland, even though they continue to be released throughout her life. Lack of ovulation results in reduced concentrations of circulating oestrogen and progesterone. Oestrogen concentrations usually begin to fall from around 35 years of age. However, the most pronounced changes occur around the menopause (see Figure 3).

It is the fall in these hormones that gives rise to the characteristic symptoms of the menopause — irregular menstruation, night sweats, hot flushes, vaginal dryness. The average age of menopause is 51 — so women now live the last third of their lives with low oestrogen concentrations, resulting in increased risk of developing several **chronic diseases** (see Table 2). For example, the menopause is closely associated with an increased risk of developing osteoporosis — a reduction in bone strength leading to higher chance of fractures. Reduced concentrations of oestrogen result in increased bone reabsorption and decreased levels of new bone being deposited, which ultimately results in lower bone density.

Hormone replacement therapy

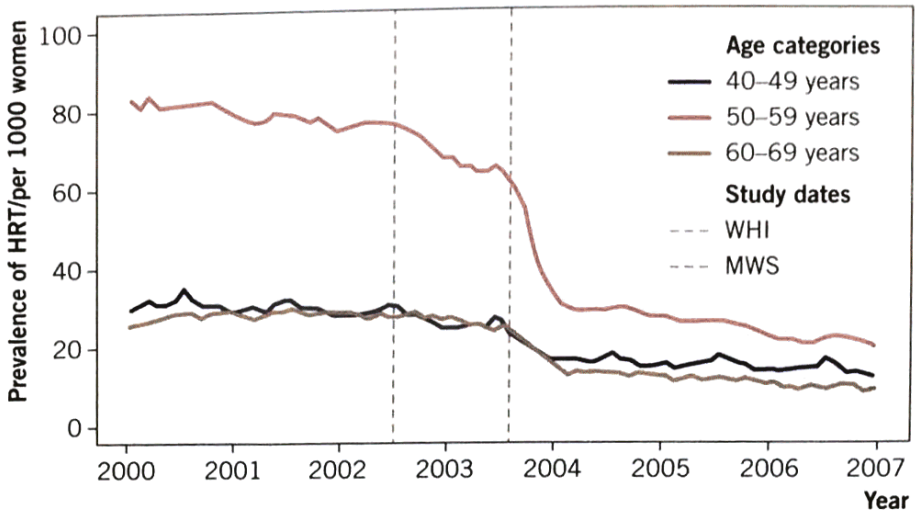
Women can be prescribed hormone replacement therapy (HRT) to alleviate the symptoms of menopause and reduce the risk of developing chronic diseases. HRT can be taken as a combined oestrogen–progesterone therapy or as an

Woman applying oestrogen patch.

oestrogen-only therapy (for women who have had a hysterectomy), and can be administered by tablet, patch or implant. HRT can prevent osteoporosis by reducing bone loss and delay skin ageing in post-menopausal women. Two large-scale studies (the Women's Health Initiative, WHI, and the Million Women Study, MWS) looked at the effect of HRT on the health of post-menopausal women. The WHI was conducted in the USA on more than 160000 volunteers between the ages of 50 and 79. These volunteers were randomly given either a **placebo** or HRT. The study was due to end in 2005 but was terminated prematurely in 2002 when it was found that the HRT group had a slightly increased risk of developing breast cancer, stroke and coronary heart disease compared with the placebo control group.

The MWS was conducted in the UK on more than 1 million post-menopausal women aged over 50. This study confirmed findings from the WHI of an increased risk of stroke, breast cancer and coronary heart disease in women prescribed HRT compared with those who were taking a placebo. This study also confirmed an increased risk of uterine cancer in women prescribed oestrogen-only HRT.

After the publication of these studies and the extensive media publicity that followed, the number of HRT prescriptions declined dramatically (see Figure 4). However, when the data were re-analysed, taking into account the length of time women were post-menopause before they started treatment, it was clear that women who began taking HRT around the onset of menopause were at a *decreased* risk of heart disease. These new findings have highlighted the potential difference of taking HRT at different times during menopause. The reasons for this are still unclear and are the subject of much investigation.



From: Vegter, S., Kolling, P., Toben, M., Visser, S. T. and de Jong-van den Berg, L. T. (2009) 'Replacing hormone therapy — is the decline in prescribing sustained?', *Menopause*, Vol. 16, pp. 329–35.

Figure 4 Number of HRT prescriptions. This graph shows that the number of HRT prescriptions fell dramatically after the publication of two studies (the Women's Health Initiative in 2002 and the Million Women Study in 2003). This decrease was particularly pronounced in women aged 50–59 years, which is the average age of women entering menopause and therefore at most risk of developing menopausal symptoms.

Hormones and wound healing

As people age, they have an increased risk of developing wounds that fail to heal properly — chronic wounds (see Figure 5). These wounds lead to pain, reduced mobility and social isolation. It is estimated that 1 in 20 elderly people will develop a chronic wound at some point in their lifetime. There are three main types of chronic wound:

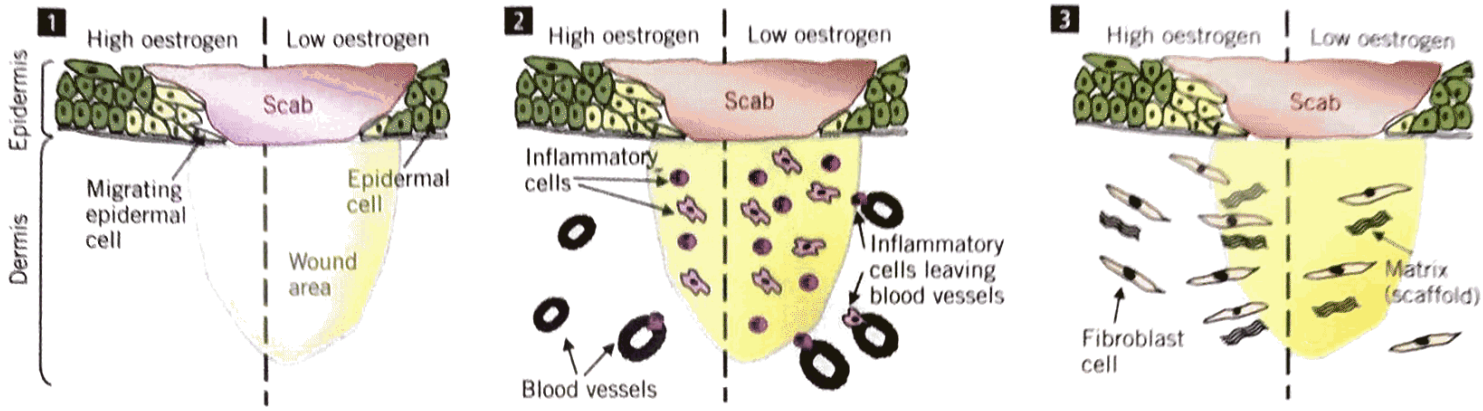
- pressure ulcers, usually found in the pelvic region
- venous ulcers, common in the lower part of the leg
- diabetic foot ulcers, caused by an inability to feel pain resulting in damage to tissues in the foot

Chronic wounds have a major impact on the NHS, with annual treatment costs estimated at over £3 billion. Currently, there are no effective treatments.

One of the main reasons that these wounds heal so slowly is the decrease in oestrogen concentrations in elderly men and women, rather than age itself.

Figure 5 Examples of chronic wounds (diabetic foot ulcers).

If patients are given HRT to increase the levels of oestrogen circulating around the body, healing is accelerated and these patients do not develop chronic wounds. Recent studies have shown that



Oestrogen promotes cells in the top layer of skin (epidermal cells) to move over the surface of the wound, therefore promoting healing.

Inflammatory cells are released into the wound area from blood vessels in the skin. These inflammatory cells release factors that delay healing. Oestrogen reduces the number of inflammatory cells and so promotes healing.

Fibroblast cells deposit matrix (which acts as a scaffold to be able to reform the skin structure). Oestrogen increases the number of fibroblast cells, resulting in higher levels of matrix.

Figure 6 Oestrogen promotes wound healing. The epidermis is the outer layer of cells in the skin; the dermis is the layer of skin below the epidermis. The left-hand side of each panel shows what happens when oestrogen levels in the circulation are high; the right-hand side shows what happens when oestrogen levels in the circulation are low.

Further reading

For general information about hormones and endocrine diseases go to: **www.hormone.org**

For detailed reading about the two large-scale research studies into the effects of HRT go to:
www.millionwomenstudy.org

www.nhlbi.nih.gov/whi

Terms explained

Chronic disease A disease that develops gradually and is persistent or lasts a long time (months to years).

Corpus luteum A temporary endocrine structure that develops from the ovarian follicle and secretes high levels of progesterone.

Endocrine system The system in the body that is responsible for the production of hormones.

Epidermis The outer layer(s) of cells in a multicellular organism.

Homeostasis The maintenance of constant internal conditions.

Negative feedback A mechanism whereby the body can regulate levels of hormones through their own influence, i.e. when a hormone reaches a high level it can inhibit further secretion of itself.

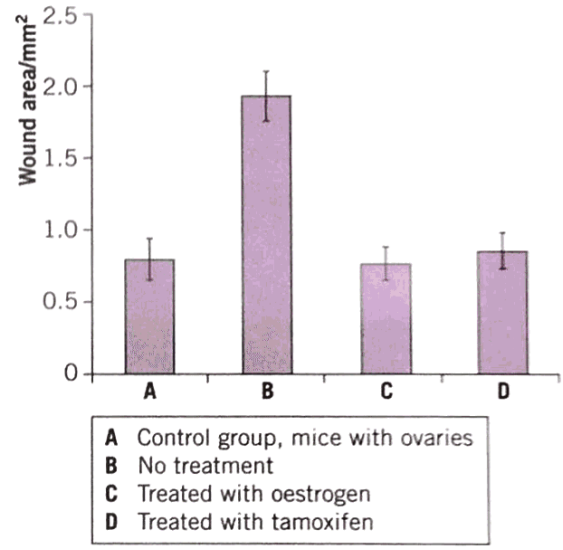
Oocyte Immature egg cell produced from the ovary.

Placebo An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a drug.

Positive feedback The opposite of negative feedback, whereby levels of hormone can have positive effects on the secretion of itself or other hormones.

SERMs Class of compounds that act through the oestrogen receptor.

Box 2 SERMS promote wound healing in mice



Adapted frrom Hardman, M. J., Emmerson, E., Campbell, L. & Ashcroft, G. S. (2008) 'Selective oestrogen receptor modulators accelerate cutaneous wound healing in ovariectomised female mice', *Endocrinology*, Vol. 149, No. 2, pp. 551–557. Copyright 2008, The Endocrine Society.

Scientists investigated the effects of tamoxifen on wound healing in mice that did not have ovaries (mimicking the menopause). These mice were given oestrogen or tamoxifen and the wounds were left to heal. Mice with intact ovaries were used as controls; their wounds were left untreated for the same length of time. The size of the wounds was measured and the results obtained are presented in the graph as mean wound area ± standard error of the mean. These results show that tamoxifen promotes wound healing in mice without ovaries to a similar extent as oestrogen.

oestrogen can increase wound healing in several ways (see Figure 6). For example, oestrogen:

- promotes the migration of cells in the **epidermis**, which helps to close the wound
- reduces the number of inflammatory cells that release harmful factors
- increases the production of new skin by fibroblasts

However, because of the controversy surrounding the use of HRT, this treatment is not usually prescribed for elderly patients suffering with chronic wounds. Instead, compounds called 'selective estrogen receptor modulators' — **SERMs** — are being developed. Although these drugs are being developed primarily to treat menopause-associated symptoms, they may also be useful for the treatment of other hormone-related diseases, including chronic wounds. SERMs bind to oestrogen receptors and promote oestrogen-like beneficial effects such as reducing bone reabsorption during osteoporosis, without oestrogen's detrimental side effects, such as increasing risk of breast cancer. Several SERMs are in current clinical use, including tamoxifen for the treatment of cancer (see Biological Sciences Review, Vol. 24, No. 1, pp. 38–41) and raloxifene for the prevention of osteoporosis. Interestingly, recent research has shown that SERMs can also improve wound healing in rats and mice to the same extent as oestrogen (see Box 2). Clinical trials are now being performed to determine whether SERMs can also promote wound healing in chronic wound patients.

Laura Campbell is a final year PhD student working with Dr Matthew Hardman in the Healing Foundation Centre at the University of Manchester. Their research interests are focused on the role of hormones in delayed wound healing in the elderly.

Key points

- Hormones are chemical messengers released from endocrine glands to regulate body functions.
- Hormone release is tightly controlled by positive and negative feedback loops. A good example is the system controlling the female menstrual cycle in which hormones fluctuate on a monthly cycle.
- As women age, their hormone levels decline, leading to the menopause. HRT alleviates symptoms of menopause but is also associated with a slightly increased risk of developing conditions such as breast cancer.
- Low oestrogen in post-menopausal women increases the risk of developing a number of diseases, such as chronic wounds, osteoporosis, heart disease and stroke.
- Current therapies exploiting our knowledge of oestrogen signalling are being developed to target diseases associated with the menopause.