

Why we need estrogen

In this section we look at why a woman needs estrogen and how she makes it.

Estrogen - an introduction

Of the dozens of different types of hormones that our bodies depend on to work, estrogen has to be the most remarkable, if only because of the broad diversity of its roles. Most hormones perform narrow functions – eg. insulin regulates sugar metabolism, growth hormone promotes growth, prolactin promotes milk production – while estrogen has so many functions that it is impossible to pigeonhole it into any one category. It used to be categorised as a *female sex hormone*, but we now realise that that term severely short-changed its broader function.

The role that it is universally recognised for is that of female sexuality. A woman is a woman because of estrogen. The physical developments that define her as a female - her breasts, ovaries, uterus and vagina - are the result of having high levels of estrogen.

But that is just the start. Beyond those are the secondary female effects of this hormone – such as her shape (fat around the hips and thighs) and her lustrous skin and hair. And even beyond those to tertiary effects such as personality characteristics associated with being a woman like gentleness and softness and a sense of nurturing.

And in the ultimate in multi-skilling, estrogen plays an important part in the functioning of every tissue in the body – from bones, to the heart, arteries, kidneys, liver, skin and bladder. No tissue escapes the nourishing effects of estrogen.

That integration of estrogen into a woman's overall health and the day-to-day functioning of all parts of her body come at a price, which is that anything that disturbs normal estrogen function for more than a trivial amount of time has the potential to disrupt the wellbeing of all parts of the body. We are well aware of the long-term health implications when a single-purpose hormone such as insulin malfunctions. How much more then will be the impact of a malfunction of a hormone like estrogen where its tentacles spread to every part of the body?

Later on in the book we look at how your body regulates its estrogen levels and the consequences of disturbing that regulatory system. But for the moment we need to focus on why we need estrogen, where it comes from, and how it works. There is a reason for doing this, and it's not just out of academic interest. If we are to understand what has gone wrong with the system, then we need to start by understanding how the system is meant to work in the first place.

Where estrogen comes from

Estrogen starts life as cholesterol. For all the bad press that cholesterol gets, it actually is a vital compound that our bodies need to manufacture a wide range of compounds including steroid hormones, vitamin K and bile salts.

Because it comes from cholesterol, estrogen belongs to a chemical class of hormones known as *steroids*, a chemical term meaning that they come from *cholesterol* which chemists refer to as having a 'sterol' structure. Other hormones in the steroid class include testosterone, progesterone and cortisone.

The first step in the production of steroidal hormones is the conversion of cholesterol to the pre-hormone, *androstenedione*. This takes place in the adrenal glands (two small glands attached to the kidneys). The adrenals release the androstenedione into the bloodstream where it gets picked up by a wide range of tissues and converted into the final steroid such as estrogen or testosterone.

One of the amazing facts emerging over recent years about estrogen is that it is manufactured by virtually every part of the body. The ovaries are the primary source, accounting for about 80% of all estrogen produced in a younger woman's body. The remainder comes from tissues as diverse as fat, muscle, hair follicles, the lining of the gut, brain, bone and artery walls. Of these secondary sources, fat is the dominant one. Any sort of fat is capable of manufacturing estrogen, but fat in the breasts and on the hips and thighs has particularly strong estrogen-producing capacity.

In a pre-menopausal woman, the ovaries are the main source of estrogen. This is why Maryanne had an early and instant menopause when her ovaries were removed. That surgery took away 80% of the estrogen in her body in one move, inducing a waterfall-like drop in her estrogen levels. After menopause, or after surgical removal of the ovaries in younger women, the body relies on the secondary sources (estrogen coming from all of the other tissues) for estrogen, the result being that the total amount of estrogen being produced in the post-menopausal body is about one-fifth that of the pre-menopausal body.

Fat has a couple of relevancies in terms of its estrogen production. One is that women with greater body fat tend to pass through the menopause with fewer acute symptoms than thinner women. (Although that is where the benefits of high body fat end, with the estrogenic benefits of high body fat tending to be offset in later life by an increased risk of cardiovascular disease and diabetes).

Another relevance of local estrogen production by fat is that the (usually) large amount of fat within the breasts with its strong hormone-producing qualities means that the breast is to a large extent independent of the rest of the body in terms of estrogen production. The breasts go on making estrogen well into menopause, exposing breast tissue to much higher levels of estrogen than the rest of the body is experiencing. This is why estrogen-dependent breast cancer still can strike post-menopausal women despite low levels of estrogen in the body as a whole.

The largest amount of estrogen that a woman will ever make in her life on a daily basis comes during pregnancy when the placenta takes over that function from the ovaries. The placenta is a veritable powerhouse of estrogen production, yielding extraordinarily high levels of estrogen in the body. Following birth and the removal of the placenta, estrogen levels tend to fall precipitously, with the sudden loss of the 'feel good' effects of estrogen producing the post-natal lows that many women experience after birth.

This diversity of estrogen-manufacturing sites simply reinforces the way that Nature has integrated estrogen into the whole fabric of the body and made it such an indispensable hormone to a woman's overall health.

How estrogen works

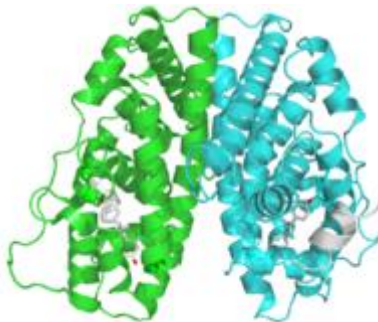
There is one thing that all of the hundreds of different hormones in the body have in common, and that is how they work. The final outcomes might all be different (eg. the target cell might be made to multiply, or to make something, or even to stop doing something), but the initial step involves a common mechanism. That mechanism is that the hormone needs to dock with a receptor and to activate that receptor.

Each hormone has its own individual chemical structure and that individuality means that each hormone has its own specific receptor. Hence the estrogen receptor will only recognise estrogen. The male equivalent of estrogen, testosterone, has a remarkably similar structure to estrogen, but it is unable to dock with the estrogen receptor.

The analogy usually used to describe the action of hormones and their receptors is that of a key and a lock. The lock (*receptor*) must be a perfect physical fit for the key (*hormone*) before it is accepted and allowed to undo the lock.

The hormone receptor is a protein, and like all proteins, is in the shape of a long ribbon that is bunched up.

Estrogen receptor



The hormone needs to thread its way through the jumble of the ribbon and lodge into a specific docking area that is made to the exact size and shape of the hormone. Only then will the hormone lock into place.

Each cell in the body has thousands of estrogen receptors, probably hundreds of thousands. These receptors are located inside each cell on the membrane surrounding the nucleus. Once the hormone attaches itself to the estrogen receptor, a series of events ensues leading to particular genes within the nucleus being activated. Depending on the type of cell involved, different genes are activated. In the case of a breast cell, the genes responsible for making the cell divide are activated. In the case of a bone cell, it is the genes responsible for leading the cell to make bone. In the case of a smooth muscle cell in the wall of an artery, it is the genes responsible for making the cell relax (thus lowering blood pressure).

With that basic science behind us, we can now move on to look at how and why the body is dependent upon estrogen.

Estrogen and reproduction

Before we launch into a review of the connection between estrogen and a woman's reproductive system, just a quick detour to look at the broader picture of hormones and reproductive development.

Testosterone. The hormone blamed for much of mankind's problems. Testosterone is often seen as the counterpart of estrogen...the ying and yang of the reproductive system. Whereas in fact the two hormones work hand in hand. Men are just as reliant on estrogen for general health as are women, and women are just as reliant on many of the effects of testosterone as are men. Where they differ is their effect on the reproductive tracts.

Testosterone is an important sex hormone in women. It is responsible for some general functions that we normally associate with masculinity such as facial hair growth and muscle building, and the fact that women make only about 1/10th the amount of testosterone that men make accounts for the difference in muscle mass between the sexes. But even this relatively low amount of testosterone has an important role to play in women. Apart from the effects on hair and muscle, testosterone makes a significant contribution to a woman's femininity and sexuality. For example, testosterone is responsible for the development of certain parts of her reproductive apparatus such as the outer lips (labia) of the vagina and the clitoris, which is essentially a rudimentary penis. It also plays an important role in libido. In women whose libido is flagging, an injection of testosterone often does wonders for their sex lives, which from a philosophical viewpoint is rather ironic when you think that a woman's desire for sex should be so dependent on male sex hormone. That dependency even goes one step further in that the production of estrogen in the ovaries and fat requires that androstenedione first be converted into testosterone, which then is converted into estrogen. I am not sure what philosophers would make of all that, but it just seems a quirky bit of biology to me.

Equally, estrogen plays a role in male reproduction. We know a good deal less about the role of estrogen in men than we do about the role of testosterone in women, but it seems that the healthy development of the male reproductive system in young men, along with the production of sperm and the ongoing function of male sex glands such as the prostate, depend in some way on the presence of estrogen.

But back to our subject...the role of estrogen in the development and function of the female reproductive system.

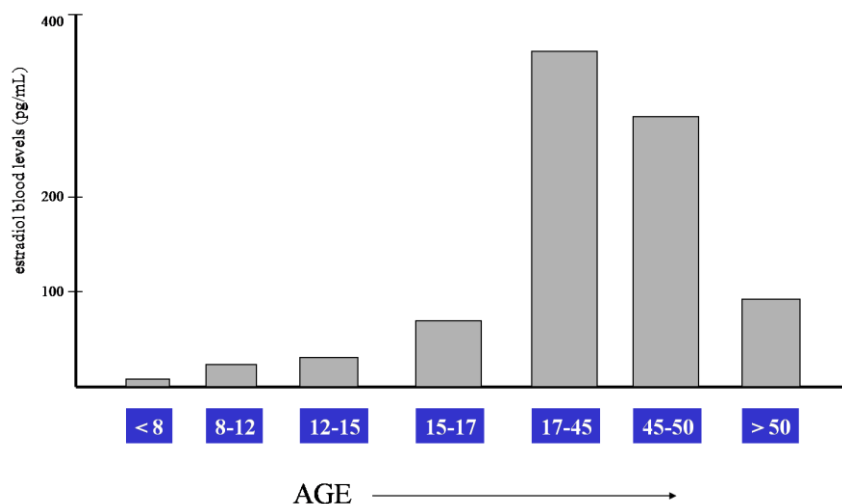
Estrogen show signs of stirring about the age of 10. At this time, the ovaries are flickering into action and starting to produce estrogen. As a result, the female form begins to evolve in most girls between the ages of 11 and 14. The breasts and nipples grow into almost their full

size at this stage; the vagina expands and its walls thicken and the secretory glands in the vaginal wall start to make a lubricating mucus; a fat pad develops above the vagina (to act as a cushion for the pelvic bone during intercourse); and the hips and waist start to take on a distinctive female shape. All of these changes are the direct result of estrogen. In concert, testosterone also starts to appear at this stage, promoting the development of the labia and clitoris and pubic hairs.

Internal changes are also underway. The cervix and uterus and ovaries are growing to their full size. As estrogen levels rise, a point eventually is reached where the lining of the uterus grows sufficiently to result in menstruation. Ovulation normally is incomplete at this time, so that periods up to the age of 14 can be erratic. The menstrual cycle usually doesn't establish its regular routine until ovulation settles into a normal cycle between the ages of about 14-16.

Once full sexual development is achieved, the role of estrogen switches from development to maintenance. Estrogen after the age of about 17 is still stimulating the cells of the reproductive system to divide, but this is replacement of cells rather than growth of tissue. For most cells of the female reproductive system, estrogen is the trigger that keeps them actively dividing and turning over. That is why women when they enter menopause experience shrinking of their reproductive tissues. Without estrogen, these tissues simply stop multiplying and eventually become largely non-functional. In menopausal women, the breasts typically show some shrinkage, but the ability of the breast fat to go on making estrogen locally means that the breasts can retain relatively normal size and shape in older women for some years, long after they have stopped cycling, and despite at this time the uterus shrinking away to become just a small ball of fibrous tissue, the ovaries becoming essentially inactive and fibrous, the vagina becoming thinner and drier, and the fat pad above the vagina essentially disappearing.

Relative estrogen levels in blood with age are shown below.



Ovarian function – the menstrual cycle

The menstrual cycle is the monthly cycle of preparing the uterus for pregnancy and then de-commissioning it when pregnancy does not eventuate. It is a cycle that depends on the close co-operation and synchronisation of the two ovaries and the uterus. The menstrual cycle is not exclusively human because certain types of monkeys also menstruate. But there is little

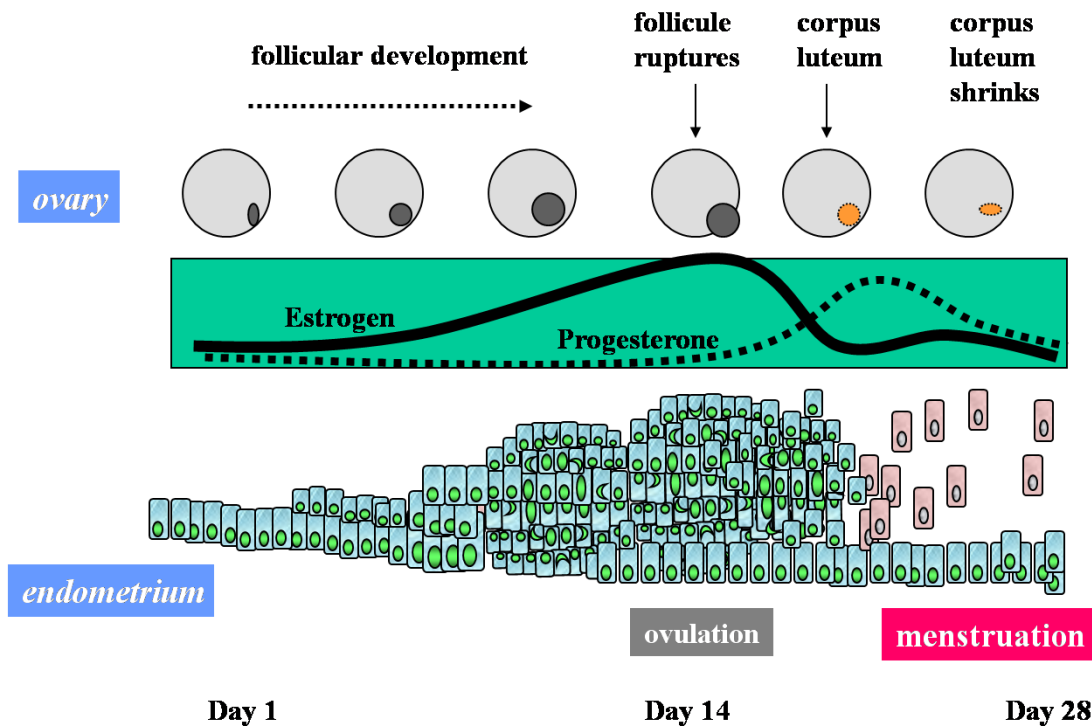
doubt that the human female has developed the menstrual cycle into an art form compared to all other animals.

Menstruation is something of a luxury in biological terms - it means that the uterus can be well and truly prepared for pregnancy. Most other mammalian species are far more efficient than this. First, they don't ovulate as often as humans do. Ovulation in many species coincides with the seasons so that birthing takes place when food is most plentiful. Or it only occurs when a male is around, so ensuring that there is help with rearing the young. Second, other species only ovulate when a male is present, or in some cases (like members of the cat family), only by the act of mating. All of this means that that most mammals only bother to prepare the uterus for pregnancy once they know that they are reasonably certain of falling pregnant.

We humans have taken a different approach. We assume that pregnancy is going to take place every time we ovulate and so we prepare the uterus for pregnancy before we even know if we are going to mate, and even whether or not a male is nearby ready to mate. This means thickening the lining of the uterus to provide a blood-rich, luxuriant bed for the embryo to embed itself in, thus maximising the chances of a successful pregnancy.

Having prepared this lush environment for the embryo means that if fertilization doesn't take place, then the body needs to de-commission the waiting uterus. De-commissioning requires expelling the blood-rich tissue and returning the uterus to its resting state. For most animals that would present a major problem because it would mean that they would leave a trail of blood and heavy scent that would be irresistible to predators. Menstruation would have been a major negative in evolutionary terms because for most animals it would have threatened their very survival. The fact that humans have retained this capacity may simply reflect the fact that we have become the dominant predator of the world rather than the prey. Hence the earlier term 'luxury' - we have the luxury of being able to prepare our bodies for pregnancy on a regular basis without concerns about the expelled bloody tissue.

The menstrual cycle is the result of an intricate dance between the two hormones, estrogen and progesterone. The main source of these two hormones is the ovary, and the source within the ovary is the follicle (or immature egg). Each ovary contains thousands of immature eggs known as follicles, and each follicle, no matter how small, is manufacturing a small amount of estrogen. Each month, one or two follicles from the thousands present are selected to grow into a mature egg. That growth takes place over about 14 days, and during this time the designated and rapidly expanding follicle is pumping out an increasingly large amount of estrogen. The final, mature follicle is about the size of a grain of rice containing the mature egg (known as an *ovum*) suspended in estrogen-rich fluid. By this time, the follicle is sitting hard up against the surface of the ovary. The pressure in the follicle finally reaches the point where the follicle ruptures. The egg is released and travels down the Fallopian tubes to the uterus where it has its rendezvous with a sperm cell.



Once the follicles ruptures, it collapses to form a structure known as the corpus luteum (Latin for *yellow body*, because of its colour). This structure remains active for about another 14 days, during which time it switches from manufacturing estrogen to manufacturing progesterone. If pregnancy takes place, then the corpus luteum remains active throughout pregnancy. If pregnancy does not occur, then the corpus luteum stops functioning and disappears. This cycle of 14 days of follicular development followed by 14 days of corpus luteum activity represents a woman's menstrual cycle of about 28 days. The decline in progesterone levels if pregnancy doesn't take place triggers the brain to release the hormone, *follicle stimulating hormone* (FSH), to start the whole cycle again.

The different events of the ovarian cycle are reflected in the tidal levels of estrogen in the blood. Each ovulation brings a surge in estrogen levels, almost all coming from the 1 or 2 follicles that are growing and competing with each other to release their egg.

Preparation for pregnancy

The *reason* for this estrogen surge is to prepare the body for pregnancy.

uterus: the lining of the uterus (the *endometrium*) multiples and thickens. By the middle of the cycle, it is about three times its original thickness as a result of estrogen both increasing the number of endometrial cells and increasing the size of each cell. Estrogen also increases the number of the size of blood vessels servicing the uterus, leading to a considerable increase in the amount of blood flowing to and from the uterus. All of this is to prepare a lush environment for the impending implantation of a fertilised ovum.

[Following menopause, without sufficient levels of estrogen in the body to stimulate uterine tissue, the uterus shrinks to just a fibrous ball.]

cervix: estrogen induces a series of changes in the cervix in order to promote the ability of sperm to exit the vagina and reach the ovum in the Fallopian tube. Estrogen causes the cervix to make more mucus to provide a conduit for sperm, and it changes the nature of the mucus in making it more 'stringy' to provide tunnels for the sperm to track along.

vagina: estrogen slightly thickens the wall of the vagina and increases the amount of mucus being produced, outcomes designed to provide a friendlier environment for sperm. Estrogen also lowers the pH of the vaginal secretions, an effect thought to provide an antiseptic effect.

[Following menopause, the drop in estrogen levels predisposes the vagina to becoming thinner and drier.]

breasts: estrogen stimulates most aspects of breast tissue and function. The glandular (milk-producing) cells in the breast start to mature and to divide in preparation for lactation, resulting in increased breast size. Blood flow to the breasts is enhanced and the nipples and areola enlarge.

connective tissue: estrogen softens the collagen in connective tissue. In the uterus, relaxation of the fibrous tissue in the uterine wall makes the uterus more expandable to allow it to accommodate a growing foetus. Later in pregnancy it will help relax ligaments in the pelvic joints ahead of childbirth.

Biological significance of estrogen and no pregnancy

The *reason* for the estrogen surge as part of the menstrual cycle is preparation for pregnancy. The modern reality, however, is that pregnancy doesn't follow the great bulk of surges. This modern reality is at the heart of this story, or more particularly the biological significance for the younger woman of being exposed to repeated estrogen surges. There is nothing intrinsically wrong about the *surge*... it is a perfectly normal event, even a desirable and necessary event. It is just that Nature could not have foreseen a situation where the body would be bombarded with many hundreds of such surges over a lifetime. A dozen or so surges, yes, just to ensure the survival of the species, but certainly not the repeated, relentless, continuous *surges* every month for 30 years or more. We are now living with the consequences of this estrogen bombardment.

It is not unusual for hormone levels to fluctuate, sometimes quite wildly. The hormone *insulin* being a case in point. For most of the time, insulin levels in the blood are maintained within a fairly narrow range. They temporarily fall outside of that range when we eat or when we undergo very strenuous exercise.

Insulin levels in the blood rise and fall in relation to when we eat. A temporary tidal flow of that nature, where blood levels fall outside of a narrow range for no more than an hour or so at a time, is perfectly normal and not harmful to the body. But when insulin levels fall outside of that narrow range more than they are in it, then it becomes a problem. That is the case with diabetes, where people with Type 2 diabetes can suffer *insulin resistance* (elevated insulin levels) and people with Type 1 diabetes (juvenile-onset diabetes) suffer low insulin levels. The adverse biological consequences of either scenario are widespread and significant.

In the same way, the modern pre-menopausal female is suffering the consequences of an estrogen system that is outside of its normal range more than it is in it. The reasons for this and the way to address the problem are the subject of the second half of this book. But for the moment, in order to truly understand the problem, we need to stay focused on why we need estrogen.

Estrogen and general health

As we noted earlier, the classification of estrogen for much of the last century as a *female sex hormone* did this hormone an enormous disservice. Estrogen was first described in the late-1920s and its role in the development and function of the female reproductive system gradually came to be understood over the next 50-60 years. But it is only in the last 20 years or so that we have come to appreciate it for its important contribution to overall human health.

The realisation that estrogens affect the health and function of virtually every tissue in the body must rank as one of the defining moments of medical science this last century. The catalyst for this discovery was the development of estrogen replacement therapy. Chemically synthesised estrogens or natural estrogens extracted from the urine of pregnant horses began to be used widely in women in the early 1980s as a means of easing the passage through the menopause. Within the limits of our knowledge at the time, this approach was based on simple and logical reasoning. And that was, that if the sudden onset of menopause symptoms such as hot flashes, night sweats, mood swings and so on was precipitated by the sudden loss of production of estrogen by the body, then putting estrogen back into the body should help. And to the everlasting gratitude of millions of women since, it did. [The notion that a natural phenomenon such as menopause is an ‘estrogen deficiency’ disease that needs to be managed by putting a hormone back into a body that has deliberately stopped producing it, needs its own chapter. But that’s for later].

Something unexpected and positive came out of the use of estrogen replacement therapy. Women who took estrogen supplementation for a number of years began to show health benefits other than simply reversal of hot flashes. Positive effects began to be seen in tissues outside of the reproductive system – on tissues and biological functions that scientists had no idea had any connection to estrogen. Women whose blood cholesterol levels or blood pressure had deteriorated following menopause began seeing an improvement - their levels of ‘good’ cholesterol started to rise and levels of ‘bad’ cholesterol fell. Their blood pressure that had risen alarmingly following menopause also began to return to the sort of levels they had before the menopause. And it appeared that these cardio-vascular responses (lower cholesterol, lower blood pressure) translated into lower risk of heart attack and stroke. Treated women also showed improvements in bone strength, and this raised hope that it would lower the risk of osteoporosis and bone fracture. A number of often distressing problems such as urinary incontinence and thinning of the vaginal wall were also found to improve following estrogen therapy. A whole range of mental and emotional benefits from an improved ability to concentrate, through to just feeling ‘better’ with more energy and a more positive attitude to life were often reported. All of these responses were attributed to higher levels of estrogen in the blood.

This unexpected outcome caused doctors to throw out the old, conventional thoughts about estrogen and to look with fresh eyes at just how estrogen was working in the body. Helping this fresh look was the discovery in the 1950s of the existence of the estrogen receptor, and the progressive realisation of the next 50 years that estrogen receptors are present on almost all body cells. To discover that estrogen was influencing the function of tissues such as brain, bone, liver, skin, gut wall, arteries and muscle, all tissues that have little or nothing to do with the reproductive system, has been one of the great medical discoveries of our age. No matter where they look, scientists continue to find evidence that estrogen plays a role in the function of that particular tissue.

Estrogen and bone health

Estrogen helps to maintain the density of bone in both women and men. On the surface this may sound odd because we tend to think of bone as an inert material, just like metal or stone – that once it is formed when we finish our growth, then that is it. However, bone is a living tissue that is a dynamic state, constantly undergoing change. Our bones are forever being remodelled, with older bone being broken down and replaced with new bone.



The body doesn't wait for bone to become damaged before it replaces it... it just replaces it anyway. In this way, we replace our entire bones on a regular basis, and this is a process that continues throughout life, even in old age.

This bone-replacement process is under the control of two types of bone cells called *osteoclasts* and *osteoblasts*. The osteoclasts are the 'destroyers' – they release an acid that dissolves bone, creating a little cavity in the bone. The osteoblasts are the 'builders' – they follow along after the osteoclasts and deposit new bone. The two types of cells are scattered throughout our bones and are constantly wandering around together to ensure that all bone gets replaced on a regular basis.

Up to our early-20s, the 'building forces' are more active than the 'destroying forces' and this ensures that our bones get larger and stronger. From early-20s to early-40s, the two forces are roughly in equilibrium, which means that our bones are maintaining their size and strength. From about our mid-40s onwards, advancing age brings a gradual dominance of the 'destroying forces'.

Estrogen inserts itself into this scenario in two ways:

First, estrogen regulates the activity of both types of bone cells. It increases the activity of osteoblasts (the 'bone builders') and suppresses the activity of osteoclasts (the 'bone destroyers'). The result is that bone loss is matched by bone production.

The reason that Maryanne was at risk of developing osteoporosis after her surgery to remove her ovaries was that the resulting drop in estrogen levels would tip the balance of power in her bones towards the osteoclasts, causing bone to be destroyed at a faster rate than it could be replaced.

The second way that estrogen helps bone strength is by increasing the amount of calcium that our bodies absorb from our diet. Calcium and phosphorus are the two main minerals in bone, providing bone with its tensile strength. The amount of calcium in the diet and our ability to absorb this calcium are therefore important factors to maintaining that strength. Estrogen promotes the amount of calcium we absorb from food in the gut by playing a role in how vitamin D works. Vitamin D is essential for the absorption of calcium from the gut, and estrogen influences this by promoting the production of a form of vitamin D that has enhanced calcium-absorbing properties. This means that a post-menopausal woman needs proportionally more calcium in her diet than a younger woman, just to compensate for her reduced efficiency in the absorption of calcium.

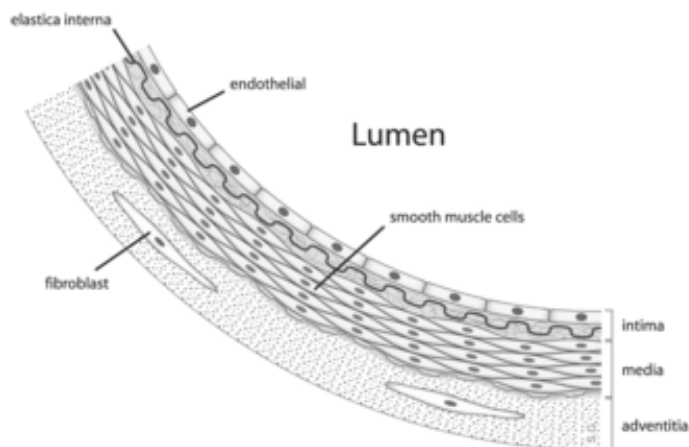
Estrogen and cardiovascular health

The cardiovascular system comprises the heart, arteries and veins. Estrogen helps to maintain a normal, healthy environment across all parts of the cardiovascular system in 3 key ways.



(a) Blood pressure. Estrogen is important in helping to maintain flexibility and a state of relaxation in our arteries, key factors in lowering blood pressure.

The vessels that carry blood away from the heart to the rest of the body are not rigid tubes. They need to be flexible in order to expand and absorb the pressure each time the heart pumps. The degree of flexibility in arteries is determined by smooth muscle cells within the walls of the arteries as shown in the following cross-section of an artery wall.



If these muscles contract, then the arteries become more rigid and blood pressure rises; if the muscles relax, then the arteries become more flexible and blood pressure falls. The effect of estrogen is to make the smooth muscle cells relax.

Following menopause, low estrogen levels have the effect of predisposing women to high blood pressure because menopausal arteries are considerably less flexible than those in

younger women. The lower estrogen levels in men also accounts in large part for their generally higher levels of blood pressure compared to women of the same age.

(b) Coagulation



Estrogen promotes coagulation of blood. This is via a number of different mechanisms, one of them being by increasing the stickiness of platelets. Estrogen also increases the body's production of key coagulation factors such as fibrinogen. While this is a healthy outcome designed to maintain a normal ability to coagulate blood and so prevent haemorrhage, excess estrogen can lead to increased risk of abnormal clotting

as seen in the increased risk of stroke associated with long-term use of the oral contraceptive pill.

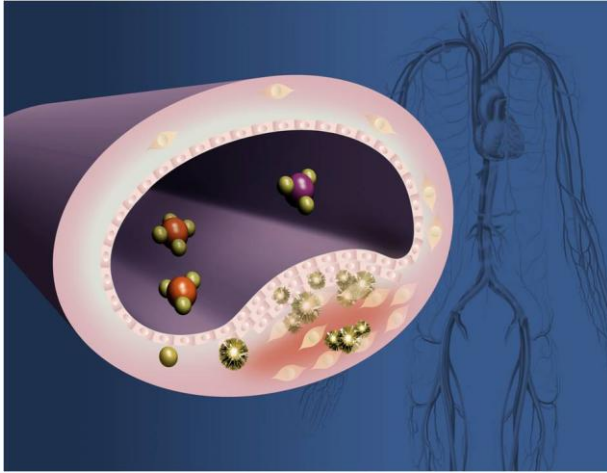
(c) Cholesterol metabolism

Maintaining a normal cholesterol balance is a cornerstone of cardiovascular health. Once cholesterol levels get out of balance, the usual outcome is an accumulation of cholesterol in artery walls and a subsequent narrowing of the artery. That condition is known as atherosclerosis and it is the major cause of heart disease and death in women in Western societies. Estrogen plays a critically important role in how our bodies make and use cholesterol, and in so doing has a key impact on the overall health of our cardiovascular system.

Cholesterol is an important structural material that all cells in our body need, and so it needs to be transported around the body in order to be used. The liver prepares cholesterol for transport in blood, and it does this by attaching cholesterol to a protein. The combined structure of cholesterol + protein is known as a *lipoprotein*. Lipoproteins come in two main forms – high-density lipoprotein (abbreviated to HDL) and low-density lipoprotein (abbreviated to LDL). The *density* tag simply refers to the number of cholesterol molecules joined together – LDL has more cholesterol molecules per lipoprotein structure than HDL.

Cholesterol is delivered to tissues in the LDL form, and then collected again and returned to the liver for further processing in the HDL form. Providing that there is a normal ratio of LDL to HDL in blood, cholesterol usage is in balance, meaning that it is being delivered to various parts of the body, used, and then collected and returned to the liver for recycling. The 'normal' balance usually requires that blood contain no more than about twice as much LDL as HDL.

Problems start when this 2:1 ratio starts to rise. Going beyond a 2:1 ratio means that cholesterol is being delivered to tissues faster than it can be collected and recycled (remembering that HDL is carrying less cholesterol than LDL). This results in a back-up of cholesterol, and the one tissue that is capable of storing excess cholesterol is the artery. The problem with used cholesterol is that it tends to be oxidised, and oxidised cholesterol is irritant to tissues. So any LDL accumulating in the artery wall begins to irritate the wall



resulting in an inflammatory response (and swelling) as shown in the diagram on the left. This protrusion into the lumen of the blood vessel is the condition atherosclerosis.

Estrogen impacts on this area of health by being the main regulator of HDL production by the liver. High levels of estrogen cause the liver to make sufficient HDL to ensure that waste cholesterol is

collected and returned liver in a timely and efficient manner. Low estrogen levels is one of the most important risk factors for the development of heart disease in post-menopausal women.

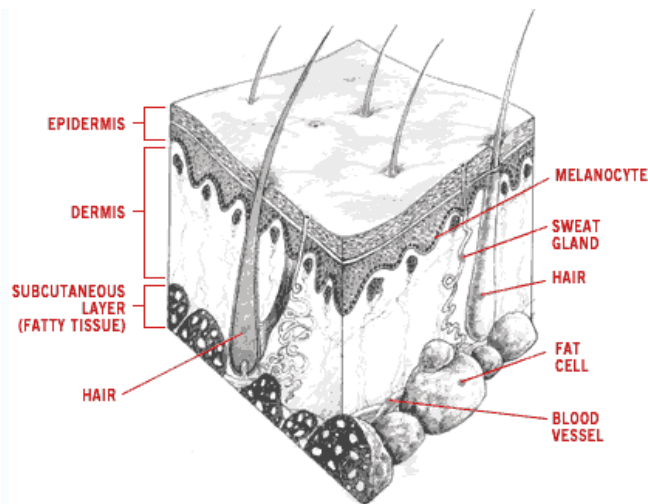
Estrogen and water balance

The amount of water held in our body at any one time is governed by a complex regulatory system involving the kidneys and a number of different hormones. Estrogen is one of those hormones, as any woman who has suffered bloating due to water retention at various stages of the menstrual cycle or following HRT therapy knows only too well.

The exact mechanism in operation here is not fully understood, but appears to involve estrogen regulating the kidney's ability to excrete sodium into the urine. By holding onto sodium, less urine is produced, and water levels in the body rise. One of the main benefits of this is that blood volume expands.

Estrogen and skin

Estrogen contributes to skin health via a number of underlying mechanisms, most of which have been discovered by estrogen replacement therapy in post-menopausal women. The ultimate benefit of estrogen is to maintain the thickness, elasticity and moisture of skin, in much the same way that it does with another epithelial structure - the lining of the vagina.



Estrogen stimulates the activity of fibroblasts, the main cell in the dermis (the connective tissue layer that provides the thickness of skin). As a result of this stimulation, collagen production is increased (collagen adds ‘plumpness’ to skin), hyaluronic acid production is increased (this chemical helps keep water in tissues), and sebum production is increased (leading to oilier, healthier skin).

And in the same way that estrogen promotes elasticity of collagen in tissues of the reproductive system, it does the same with skin collagen, reducing the susceptibility of skin to wrinkling.

Estrogen and muscles

Estrogen is not responsible for building muscles. That is the role of testosterone. But estrogen appears to play a role in helping to maintain muscle tone, particularly for muscles in the reproductive tract and bladder. This is a totally different effect to that of estrogen on the muscles in the wall of arteries. Artery wall muscles are a special kind of muscle (known as *smooth muscle*) and their response to estrogen is to relax. The muscles in the pelvis that we are referring to here are of a type known as *striated muscles* and they respond to estrogen in the opposite way by contracting.

Pelvic muscles supporting the uterus and vagina lose muscle tone following menopause, predisposing the uterus to prolapse and the vagina to sagging.

In the case of the bladder, there is a small muscle surrounding the external opening to the bladder known as the sphincter muscle. This muscle normally needs to stay contracted in order to close off the bladder and prevent urine from escaping. Estrogen maintains this sphincter in a state of constant contraction until we consciously tell it to relax. In the absence of estrogen, the sphincter muscle relaxes and allowing urine to be released when abdominal pressure is increased when sneezing or coughing or lifting something. This is known as urinary *incontinence*.

Estrogen and brain function

The human brain loves estrogen and responds very positively to its presence. The precise mechanisms of this are not well understood, but are thought to involve a group of brain ‘feel

good' hormones known as *endorphins*. Endorphins have a major influence on our mood and on our perception of pain. They belong to the chemical family of opiates, of which opium and morphine are also members. All these chemicals stimulate opioid receptors on brain cells, affecting a broad range of brain functions including pain, mood, sexual behaviour, learning and memory.

Estrogens are thought to affect brain function by increasing the brain's rate of production of endorphins. During the menstrual cycle, endorphin levels rise and fall in parallel estrogen levels, causing a woman to experience fluctuations throughout her cycle in her mood, her sense of confidence, her sense of well-being, and even her ability to concentrate and to learn.

Long-term lowering of estrogen levels is associated with mood lowering. The 'baby blues' that some women experience immediately after giving birth is due to a sudden drop in endorphin levels stemming from a plummeting estrogen level once the placenta stops pumping out huge amounts of estrogen. Coming off an estrogen/endorphin high that is pregnancy is inevitably going to predispose a woman to depression to some degree. There also is some evidence to suggest that obsessive-compulsive disorder is associated with low estrogen levels.

Another role of endorphins is a contribution to regulation of body temperature. Endorphins increase body temperature slightly by reducing blood flow to the skin (hence reducing heat loss) and increasing the metabolic rate. This slight temperature rise accounts for the small but detectable rise in body temperature at the time of ovulation when estrogen levels peak. The involvement of estrogen and endorphins in body thermoregulation is also thought to be behind the hot flushes experienced by many women going through menopause. While the exact mechanics of this are not understood, it is thought to represent an adjustment in the setting of the internal thermostat in the brain following the sudden withdrawal of estrogen.

Estrogen – a hormone for all seasons

The functions that we have looked at are just some of the better known functions of estrogen in the body and it is far from being the definitive list. They are the most obvious functions that we see lost when estrogen is withdrawn from the body and restored when estrogen is replaced. But it is likely that there are many other functions that have escaped our attention to date because they are too subtle to detect.

This makes estrogen arguably the most broadly acting hormone in the body. From making breast cells multiply, to making bone cells lay down bone, to making skin hold more water, this remarkable hormone has become so integrated and interwoven into the general functioning of the body that it is difficult to imagine a bodily function that it not either directly or indirectly controlled or influenced by this hormone. And given our dependency on this hormone, one would imagine that Nature also did not intend that we would be liable to dysfunction of such a critically important hormone. Yet the one thing that distinguishes estrogen from any other hormone is that it is in a constant state of flux. There isn't another hormone that undergoes the dramatic and irregular changes in blood levels that estrogen undergoes. Modern medicine would have us believe that this is the legacy of a design fault in Eve? This book aims to disprove this notion.

