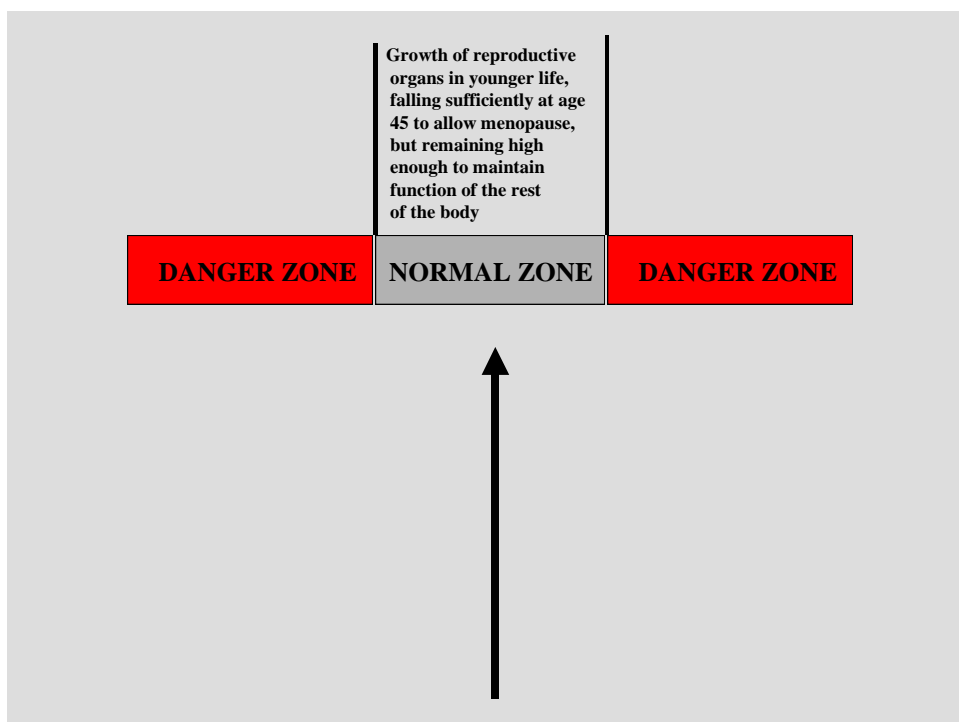


The body's *estrogen-balancing* mechanism



Here we look at how the body balances its estrogen activity throughout life to cope with the different stages of life.

9

Estrogen – the hormone with a split personality

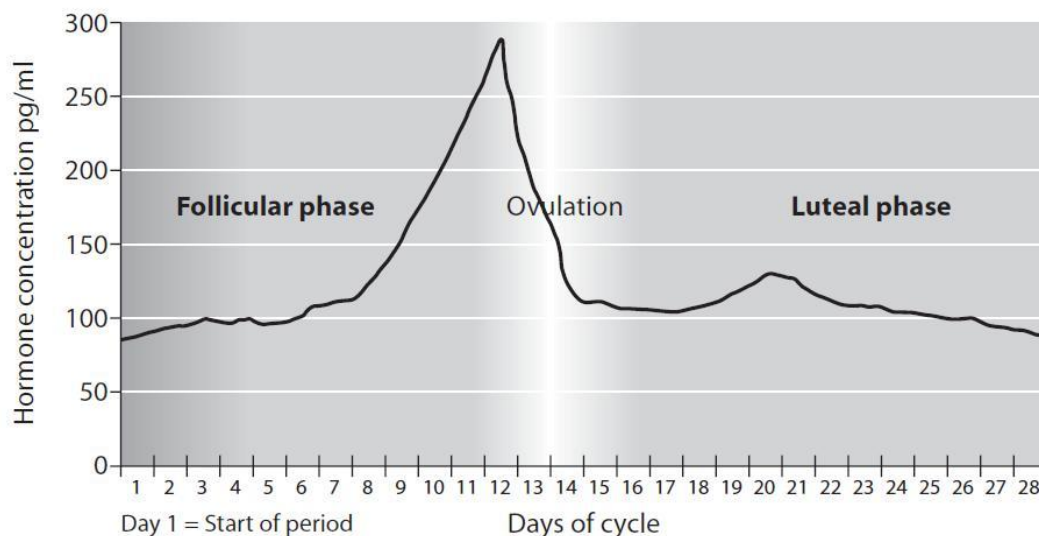
Nature had a problem. It had created a hormone with a split personality. On the one hand it had created a hormone that provided nourishing and fine-tuning effects on virtually every part of the body. Those effects weren't essential to life, but they certainly made life better. From stimulating bone growth, to keeping the lining of our blood vessels smooth and their walls relaxed, to helping to regulate the moisture level in our body, to helping our brains feel good, this was a hormone destined to play a big role in helping the body function normally throughout life.

The amount of estrogen required for each of those nourishing functions wasn't high... modest amounts were all that were needed. And because the functions were constant, the demand for estrogen was constant...estrogen needed to be present on a continuous basis at a constant level throughout life.

This wasn't a problem for the male of the species – the adrenals would go on pumping out androstenedione throughout life at a fairly constant rate, and because the stepping-stone in estrogen production was androstenedione → testosterone → estrogen, then as long as a man was capable of making testosterone, then he could also make estrogen. The result is that estrogen levels in men show little change over their lifetime. But the female of the species presented a special problem. In her, estrogen had an even more critical role, and that was to regulate her reproductive capacity. That meant that for a woman, this side of the hormone's personality was always going to be dominant. This was a far more aggressive and unpredictable personality trait. Instead of the even, moderate amounts of estrogen required on a day-to-day basis by the rest of the body, the reproductive system was going to need enormous fluctuations in estrogen activity. The first need occurred at puberty when the reproductive system had to be developed to a state of readiness for pregnancy. This meant bringing estrogen levels in the blood up to reasonably high levels. Then once the ovaries were fully functioning, a regular menstrual cycle meant exposing the body to a monthly tidal flow of estrogen. During pregnancy, estrogen levels would need to climb even higher and be sustained at those levels for 9 months. And then when a woman reached the age of about 50, Nature decreed that she should stop bearing children and the only way to do this was to largely shut down estrogen production.

The following graph shows the extent of the estrogen surge each ovulation, with estrogen levels typically ranging each month between about 80 – 400 units. In men, estrogen levels throughout life range between about 10 – 60 units.

Normal estrogen levels during the month (as indicated by estradiol)



This immediately presented a problem of what was going to happen to all those non-reproductive tissues with their requirement for a gentle, constant amount of estrogen. At one level, how were they going to cope with being exposed to fluctuating amounts of estrogen in the blood? In particular, how would they cope with occasional huge amounts of estrogen at each ovulation and in pregnancy? Wouldn't the different fine-tuning functions of estrogen suddenly become overactive? What would prevent blood vessels from relaxing to the point of the body being unable to adjust blood pressure to deal with physical activity? What would stop the kidneys from retaining so much water that the body would become water-logged?

But it was with menopause that the challenge became even more serious. There may have been sound biological reasons behind the decision to create a menopause, but that had an inevitable outcome which meant exposing the rest of the body to the consequences of the loss of a much needed, nourishing hormone.

So that was the challenge for Nature – how to reconcile three apparent paradoxes. Having made a hormone with a split personality, the task then was:

in younger women

- how to protect the sexual organs from uncontrolled growth coming from monthly tidal surges in estrogen levels?
- how to protect the non-sexual organs, with their need of a constant, medium level of estrogen, from the wild fluctuations in estrogen levels?

in older women

- how to meet the estrogen needs of the non-sexual organs?

Understanding the designs that Nature incorporated into a woman's body to manage these paradoxes is the next stage of our journey.

To meet this challenge, Nature came up with an **estrogen balancing mechanism** that is designed to smooth out the lumps and bumps in estrogen levels and to ensure that the separate and distinct needs of the sexual organs and all other tissues are met without

prejudicing each other. When functioning normally, the mechanism should be sufficient to deliver the Female Bill of Rights for the great majority of women. The story of this book is that this master mechanism is not functioning the way it should, leaving women exposed to the stimulatory effects of ‘too much’ estrogen in younger life, and ‘too little’ estrogen in later life.

The mechanism is elegant in the simplicity of its design, but it is not infallible, as the current epidemic of reproductive dysfunctions and menopausal symptoms shows.

It has two components – an *involuntary* component and a *voluntary* component. The fallibility of the system lies with the voluntary component that is within our control to change and which unfortunately we have changed for the worse in modern times. The involuntary component, as the name suggests, is largely outside of our control, but it remains just as functional today as it did thousands of years ago.

A warning...the terms *involuntary* and *voluntary* estrogen balance mechanisms are not in the textbooks. They are the writer’s terms. In fact, the notion of there even being two parts to this mechanism is not in the textbooks, and I fully expect it to be highly controversial. There is nothing contentious about the involuntary component. It has been the subject of considerable scientific research over several decades. I think most scientists would acknowledge that we probably have only scratched the surface in understanding its fine detail, but there is general agreement on the fact that it exists and on its broad details. The problem is that this component is only looked at in isolation when it comes to a discussion about estrogen function. And when you do so, it becomes difficult to repudiate the argument that Eve did have a design fault. For if this is the best the body could do to balance estrogen, then it very clearly has failed.

The concept that this author is proposing is that there is nothing wrong with the voluntary component. It is a perfectly validly designed and functioning system. But it is only half the story, and it is only when we include the other half that we can put into context why things have gone wrong.

The following chapters in this section lay out the argument and the facts for the concept of there being two halves to the estrogen story ... I leave it up to the reader to accept them or dismiss them.

The involuntary mechanism

Part 1

The involuntary estrogen-balancing mechanism is not unique to humans. It occurs in all mammals. It's as fundamental to how estrogen works in the body as insulin is to the control of blood sugar levels and growth hormone is to body height.

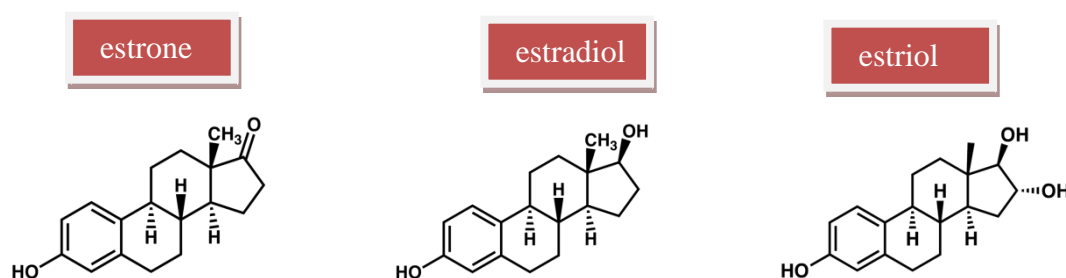
The involuntary system has three distinctive design features. The first feature is that the body has different kinds of estrogens with different strengths. The second allows the reproductive organs and the rest of the body to have a degree of independence by allowing them to respond to estrogen in different ways. The third feature is how estrogen is stored in the body.

After our previously simple overview of estrogen and how it works, this might sound a bridge too far in terms of what the reader needs to know. It isn't. It's remarkably simple and logical as long as we stay with the bigger picture. And if the reader is to understand the whole picture of how it should be working and why it isn't, then we need to delve into a bit more detail than we have looked at before.

To ease the learning process, each of the three designs features of the involuntary mechanism has its own chapter. This chapter is about the different forms of estrogen.

Estrogen. *Not one, but many*

Up until now we have used the term 'estrogen' as though it is a single hormone. In fact there are a dozen or so different estrogens. There are 3 main ones, and these are the only ones we need to know about for the moment. They are known as



Also known as



because that is the order in which they are produced in the body.

The relevance of this conversion into different forms of estrogen is that they all have different levels of strength. Estradiol is the strongest of the three and is the reference estrogen against which any other compound, hormone or otherwise, with estrogenic activity is measured. The relative strengths of the three main estrogens are as follows.



Estradiol

Estradiol is the powerhouse of the estrogen family. When we refer generically to *estrogen*, we really are referring to this hormone. Estradiol drives the development of the reproductive organs at puberty and then maintains them in functioning order through until menopause.

The great bulk (90-95%) of estradiol comes from the ovaries, hence the switching on of ovarian function at puberty and the switching off of ovarian function at menopause explains why estradiol levels are highest in the 10-50 years age range. The other 5-10% of estradiol in the body of a young woman comes mainly from her fat tissues (particularly around the thighs and buttocks and breasts).

At menopause when the ovaries stop producing eggs, estradiol levels drop by about 80%, and it is this dramatic fall that triggers menopause and leads to the subsequent shrinkage of a woman's reproductive organs.

In the pre-menopausal woman, the body is focused on producing estradiol, and it does this in two ways. The first way is to convert androstenedione directly into estrone and then to convert estrone into estradiol. The second way is to convert androstenedione into testosterone and then to convert testosterone into estradiol.

The ovaries favour the androstenedione → estrone → estradiol route, while the androstenedione → testosterone → estradiol route is favoured by the fat tissues. There is even a difference within the fat tissues, with fat on the buttocks and thighs being more capable of converting testosterone → estradiol compared to the fat around the abdomen and in the breasts.

Estrone

The major role of estrone in the pre-menopausal woman is to act as a source of estradiol. The blood of a pre-menopausal woman contains similar levels of estrone and estradiol, but with estrone only being one-fifth as strong as estradiol, estradiol is by far the dominant estrogen.

It is after menopause that estrone comes into its own. With the dramatic fall in estradiol levels, estrone now becomes the main source of estrogen function for the post-menopausal woman.

Estriol

The third estrogen, estriol, is the weakest of the three main estrogens. It is only about 1% as active as estradiol. Estriol is the main breakdown product of estradiol and estrone, and is the way that the body eliminates estrogen from the body in urine. When the last two hormones have served their purpose, they are broken down in the liver to this very weak estrogen and then eliminated from the body.

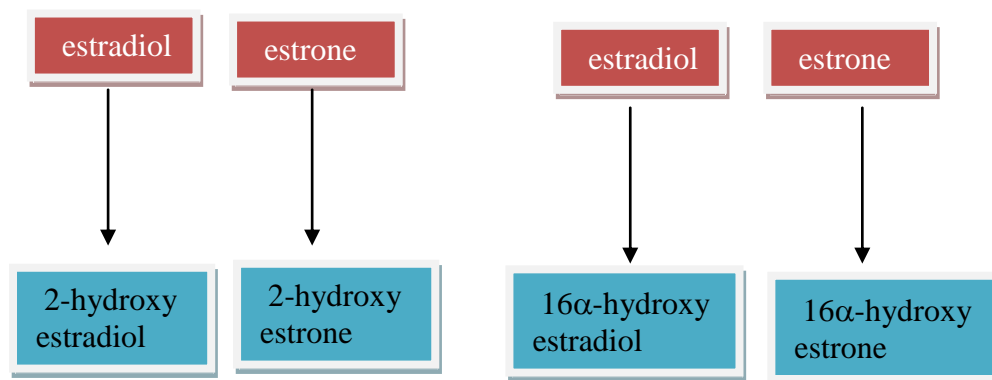
Estriol levels in the body are relatively low compared to estradiol and estrone, except during pregnancy when estriol levels in the body surge, reaching levels up to 300x higher than estradiol and estrone levels.

Estrogen metabolites

Estradiol and estrone are the two primary estrogens produced by the body. If you were to have a blood test for estrogen levels, they would be the ones measured. But there are dozens of others, all coming from various parts of the body as the result of these two primary estrogens being broken down. The end-products of that breaking down process are known as *estrogen metabolites*. Estriol is by far the most common of these metabolites and ranks as an important estrogen in its own right because of its prevalence in blood.

But estriol isn't the only metabolites, although the dozens of other estrogens occur at such low levels in the blood that they are regarded as minor hormones only in terms of their effect on the body as a whole. However their real significance lies in their estrogen effects locally within the tissues where they are made, mostly the sexual organs. Although their levels might be quite low in blood, they can be present in relatively high levels within tissues such as the breasts, to the point where they are exerting a major estrogenic effect. In fact, these so-called minor estrogens are thought to play a significant role in the development of breast diseases such as breast cancer.

Estrone and estradiol go down two separate pathways of metabolism as shown below.



The two 2-hydroxy metabolites are very weak estrogens, even weaker than estriol. The two 16 α -hydroxy metabolites, on the other hand, are very powerful estrogens, having about twice the potency of estradiol. The dominance of the 16 α -hydroxy metabolites over the weaker 2-hydroxy metabolites is thought to be a primary risk factor in the development of breast diseases.

How estrogens manage to have different strength

In our discussion earlier about the estrogen receptor, we spoke of how the estrogen hormone needed to fit into the receptor precisely like a key in a lock before the receptor could be triggered. In the case of the estrogen receptor, that lock-and-key analogy certainly applies to any other steroid hormone like testosterone or progesterone or cortisone. Despite all of these hormones sharing a very close structural relationship with estrogen, they are just too different to be accepted by the receptor. But that isn't the case with the different estrogens. They are all sufficiently similar that they are accepted by the estrogen receptor. The estrogen receptor is not that rigid a lock ... it will accept very minor variations of the one key.

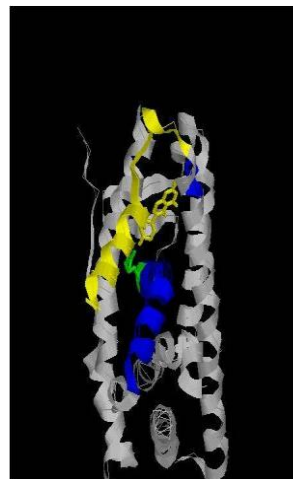
But that is where the analogy of the lock-and-key example ends, because a key either opens the lock or it doesn't – there is no half-way measure. Even if the key has a poor fit, with a bit of jiggling it might be possible to make it work and to open the lock. The estrogen receptor does not have this all-or-nothing approach to life.

A more appropriate comparison is that of a pistol. Most hormone systems in the body are like a gun. If the gun's trigger is pulled, then the bullet either leaves the barrel or it doesn't, and if it does, then the velocity is always the same. In the same way, hormone receptors are either triggered or not, and if they are, then the response of the cell is always the same.

The estrogen receptor is more like a water-pistol. With a water-pistol, the force at which water leaves the pistol depends entirely up the force being applied to the trigger. With the estrogen receptor, different estrogens are able to apply different levels of pressure to the trigger to produce different levels of response. This trigger releases a spring, and the strength of the response relates to how much the spring is released. Estradiol causes the spring to be released completely; estrone causes it to be released slightly less; estriol hardly moves the spring at all.



Estrogen receptor interacting with estradiol. Note the yellow trigger arm has been released to its full extent.



Estrogen receptor interacting with a weaker estrogen. Note the yellow trigger arm is only partially released.

This means that pound-for-pound, the various members of the estrogen family have widely different abilities to make the estrogen receptor respond. They vary from those that are barely capable of triggering any response, through to those that produce a dramatic response.

Why estrogens have different strength

We've looked at how the different estrogens vary in their strength. The next question is why Nature has developed this function.

The answer is, so that the body can regulate estrogen function through the process of *competitive inhibition*.

'Competitive inhibition' is a biological term. It refers to a situation where two different chemicals of different strength (a weak one and a strong one) compete on an equal footing for a single target site – if the stronger one gets there first, then it is able to produce its normal strong outcome; but if the weaker one gets there first, it will exert a weaker effect, but in the process of occupying the receptor, it has effectively blocked the ability of the stronger compound to have any effect. The net result is a weaker outcome than might have been the case.

Such is the case with the different estrogens in the body. Consider the different forms of estrogen

- the very weak estrogens - *estriol, 2-hydroxyestrone, 2-hydroxyestradiol*
- the weak estrogen - *estrone*
- the powerful estrogen – *estradiol*
- the very powerful estrogens – *16-hydroxyestrone, 16-hydroxyestradiol*.

All these different estrogens are members of a soup where each component of that soup is competing for binding to the same estrogen receptors.

Let's take the example of a single breast cell in a non-pregnant young woman that is simply sitting there quietly in an immature state, minding its own business. Inside the cell are thousands of estrogen receptors, waiting to be activated by estrogen. Once so activated, the receptors will move into the cell's nucleus and instruct the relevant genes to cause the cell to mature, to grow to full size, and then to divide into two daughter cells.

The speed of that response, and the degree of the response depends entirely on how many of the receptors are activated, and whether they are fully activated or not. If most of the receptors get activated by a strong estrogen such as estradiol, then the cell's response will be rapid (within minutes), with two new cells being produced within a day or so. If, on the other hand, the majority of receptors are activated by estrone (only one-fifth as strong as estradiol), then the response will be more sluggish and take several days to complete. Going one step further, if estriol or 2-hydroxyestrone manages to get to the majority of receptors first, then the breast cell may not respond at all, or if it does, then it could take up to a week to complete the response.

Each form of estrogen has roughly the same chance of attaching to the receptor once it gets near to the receptor, so the final outcome comes down mainly to the proportion of the different estrogens gaining access to the cell. That is competitive-inhibition, and that is one of the main ways that the body controls how estrogen works.

Contribution made to estrogen balance by different estrogens

Competitive inhibition means that the 3 major estrogens, estrone, estradiol and estriol, are counterbalancing each other, particularly when it comes to the reproductive tissues. The weaker estrogen, estrone, is cushioning the effect of estradiol, and estriol is cushioning it even more. And the levels of these 3 hormones tend to remain in balance because the body needs to make estrone (E1) before it can make estradiol (E2), and the more E1 and E2 are made, the more estriol (E3) is made as this is the form in which the majority of E1 and E2 end up.

Between puberty and menopause, this mixture of estrogens provides a cushion against the excesses that could result from the periodic dramatic rises in estradiol levels associated with the menstrual cycle. Estradiol levels are rising at these times for good reason the need to promote the growth of the reproductive tissues in preparation for pregnancy. But by having a mix of very weak, weak and strong estrogens together, the sudden rises and falls in estradiol levels during the menstrual cycle are cushioned and evened out to a large degree.

In a similar way, the very high levels of estriol associated with the dramatic increase in estradiol production during pregnancy is a shock-absorbing effect, preventing sky-rocketing estradiol levels from over-stimulating the body's tissues, reproductive as well as non-reproductive.

At a local level such as the breast, the presence of the weak metabolites again is off-setting the potentially damaging effects of the stronger metabolites.

The fall-off in estradiol levels over the age of about 45 allows menopause to occur. The withdrawal of estradiol removes the main estrogen stimulation for the reproductive tissues, and the remaining estrone and estriol have insufficient strength to continue to support these tissues. However, they do have sufficient estrogenic strength to continue to meet the needs of the non-reproductive tissues.

By this process of competitive-inhibition, Nature is able to allow estrogen levels to fluctuate enormously with minimal risk of over-stimulation of the reproductive tissues to the point of damage at a younger age, and under-stimulation of the non-reproductive tissues at an older age.

The involuntary mechanism

Part 2

Just as there is more than one type of estrogen, there is more than one type of estrogen receptor. Fortunately this part of the story is nowhere near as complicated as the different estrogen hormone story.... there are only two types of estrogen receptor.

This is the second design feature of the involuntary estrogen balancing mechanism. And it is one that Nature cleverly came up with to deal with the fact that estrogen had been created for multiple purposes.

(a) On the one hand, estrogen was given responsibility for driving the growth and function of the female reproductive tissues. This role required estrogen to have dramatic effects on the reproductive organs – to be able to transform those organs within a matter of days from a resting state to a state of readiness for an impending pregnancy. Estrogen had to be able to make the cells in the ovaries, breasts and uterus mature and grow so that those organs could expand and prepare for pregnancy.

(b) On the other hand, estrogen was asked to be a nourishing and invigorating hormone, encouraging bones to remain strong, arteries to relax, skin to remain hydrated, ligaments and tendons to remain supple, muscles to remain strong, and the brain to experience a sense of wellbeing. For this role, estrogen was not required to make cells grow. If it did, then our bones and arteries and brain would grow to 2-3 times their normal size during pregnancy in the same way that the breasts and uterus do. Instead of making these cells multiply, estrogen was required to do nothing more than stimulate them to work harder.

To separate this dual role, Nature created two different types of estrogen receptors – scientists refer to these as *alpha* and *beta* estrogen receptors. The *alpha* estrogen receptor is the one found on cells in the reproductive organs, while the *beta* estrogen receptor is the dominant receptor in the rest of the body.

Estrogen doesn't distinguish between the two types of estrogen receptor. It has the same ability to trigger the receptor whether it is an *alpha* or a *beta* receptor. The difference between these two receptors lies in their response. When the *alpha* receptor is triggered, the cell matures, works harder and multiplies. When the *beta* receptor is triggered, the cell only works harder, but it does not divide.

The effect of estrogen on different tissues in the body is a consequence of what type of receptors that they express. All tissues contain a mixture of both *alpha* and *beta* receptors, but the proportion of each varies tremendously from tissue to tissue.

Where the *alpha* receptor dominates

eg. breast, uterus, ovary, vagina.

The overwhelming response of these tissues to estrogen is cell growth and cell division.

Where the *beta* receptor dominates

eg. bone and muscle.

The general response of these tissues is increased cell activity, with little or no increase in cell numbers. In the case of bone, the response is to increase osteoblast activity (more bone laid down) and decrease osteoclast activity (less bone resorption). In the case of smooth muscle in the wall of arteries, the response is muscle relaxation; in the case of muscle surrounding the neck of the bladder, the response is contraction.

Where there is a mixture of *alpha* and *beta*

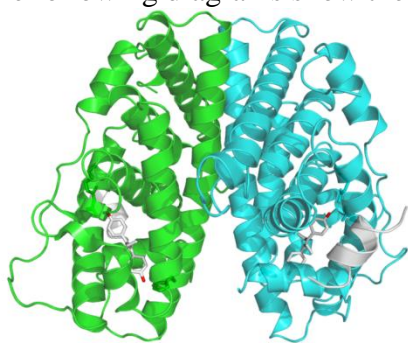
eg. skin, mucous membranes, brain.

In the case of skin, those epithelial cells expressing the *alpha* receptor respond by dividing, those expressing the *beta* receptor respond by holding more water (and therefore expanding), and those dermal fibroblasts expressing beta receptors respond by producing more collagen. The sum total of these three effects is to increase skin thickness.

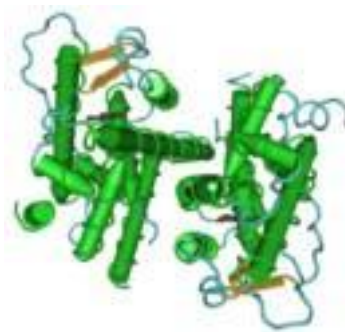
In the case of mucous membranes (lining the vagina, bladder etc), the response, as with skin, is a mixture of increasing cell numbers and increasing the production of mucous secretions.

In the case of the brain, stimulation of cells expressing the *beta* receptor is thought to be associated with improved cognitive function and mood. The response of brain cells expressing the *alpha* receptor to estrogen is unknown.

The following diagrams show the shapes of the two receptors.



α -estrogen receptor



β -estrogen receptor

Contribution to estrogen balance made by the two receptors

This advanced design feature of having two different estrogen receptors was important in allowing the reproductive and non-reproductive tissues to go their own ways as far as estrogen was concerned. The best way to appreciate this is to consider what is happening in a woman's body at different stages of her life.

Childhood (0-10 years)

Up to the age of about 7 or 8, the reproductive system is rudimentary. There is virtually no breast tissue, the uterus hardly exists, and the ovaries are little more than specks. With the reproductive system being in such an immature and quiescent state, it is highly desirable for the body to keep estrogen levels low so that the *alpha* receptors are not activated.

But that still leaves the rest of the body - the bones, skin, brain etc. with their *beta* receptors. How are these tissues going to get their estrogen needs satisfied? The answer is that these tissues in a young body don't need anything like the amount of estrogen to maintain normal function as they do when we become older. The reason for this is that when we are young, most of the growth and invigoration of function in the young body is being supplied by a whole raft of growth hormones. It is only once we stop growing in about our early 20s that those growth hormones drop away, leaving estrogen to take over the task of maintaining their youthful vigour. Happily, this coincides with the rise in estrogen levels after puberty.

The overall outcome of this situation is one that allows the body to grow and mature without waking up the reproductive tissues.

But puberty beckons, and towards the end of childhood the reproductive organs need to be induced into activity on their passage into a fully developed system capable of creating another human life. This can only happen through the production of more estrogen. This process starts with the ovaries spluttering into life as they start the process of developing follicles. This is a process that goes on over a number of years and is characterised by inconsistent estrogen levels as some of the follicles start developing but never go on to full maturity and ovulation.

Adolescence (10-18)

As more and more follicles start to develop, estrogen levels gradually get higher. Finally, they reach a level that fully kicks the ovary into life, resulting in ovulation. This happens about the age of 13-15 years. Even before that full activity is reached, the ovaries have been spluttering along for a couple of years, producing ever-increasing amounts of estradiol. Those gradually rising estrogen levels, with their activation of *alpha* estrogen receptors on the reproductive tissues, have gradually brought about increasing feminisation of the body with progressive development of the breasts and the vagina and the labia (vaginal lips). Out of sight, the cervix and uterus and Fallopian tubes also have been growing in response to this rising estrogen tide.

As far as the rest of the body is concerned with its *beta* estrogen receptors, it is beginning to gain the benefit of this same rising estrogen tide. Stimulation of these receptors in our bones, blood vessels, brain etc. produces an additional benefit on top of that being provided by the myriad of growth hormones that are still circulating on our bodies at that age. The combined effect of estrogens + growth hormones produces a level of health in our adolescent years

which regrettably is not to be repeated at any other stage of our lives. This stage of life truly represents the prime of a woman's life in terms of her physical health.

(c) The reproductive years (19-50)

With the onset of full, regular ovarian function, there are more than adequate levels of estrogen around to satisfy all of the *alpha* and *beta* receptors in our bodies.

The reproductive tissues with their predominance of *alpha* receptors are responding directly to the tidal flow of estrogen by following a pattern of growth and 'un-growth' each month. In addition to the estrogen being produced by the ovaries and elsewhere in the body, the breast in particular is able to make a reasonable amount of additional estrogen in its fat, adding to the total amount of estrogen that is acting on this tissue.

The various other tissues such as the skin and mucous membranes with their mixture of *alpha* and *beta* receptors also are being stimulated to grow as well as to maintain normal function. But unlike the breast, these tissues lack the fat reserves to make additional estrogen and so their growth response is going to be more muted compared to the breast or uterus.

All the various non-reproductive tissues that are expressing predominantly *beta* receptors, such as bone, arteries, brain and liver, are responding by maintaining normal function.

(d) Menopause (> 50)

In the mid-40s, the ovaries begin to slow down their production of estrogen as they exhaust their supply of follicles. Eventually estrogen levels fall below a critical threshold, at which point there is insufficient estrogen to activate the *alpha* receptors to keep the reproductive organs functioning. At that point, those organs stop responding and start to shrink, marking the onset of menopause and the loss of reproductive capacity. Without enough estrogen to maintain the growth of cells in the reproductive organs, the breasts, ovaries and uterus gradually shrink as new cells are not being made at an adequate rate to replace the death of older cells, the result being a net loss of cells.

For the same reason, the *alpha* receptors in tissues such as the skin, vagina and mucous membranes (lining of the bladder) fail to be adequately stimulated, leading to thinning and drying of these structures.

The dramatic withdrawal of estrogen from the body when menopause starts also affects those parts of the brain involved in regulating body temperature and which display both *alpha* and *beta* receptors. The sudden loss of estrogen for these cells leads to confusion, causing the cells to believe the body is cold when it isn't. After 6 months or so, this part of the brain acclimatizes to low estrogen levels and restores normal temperature-regulating function.

Outside of the brain, other tissues expressing the *beta* receptors also now start to suffer as estrogen is withdrawn. The response of these tissues to low estrogen levels is not quite as dramatic as that of the tissues expressing mainly *alpha* receptors because the *beta* receptor tissues are not as dependant as the *alpha* receptor tissues on estrogen for their survival, but they still show a slowing down in function. Thus, we see in the aging woman,

- gradual hardening of the arteries (producing increasing blood pressure) as the ability of estrogen to relax muscles in the walls of the arteries diminishes

- an increasing risk of heart disease as the high blood pressure joins with a reduction in the level of 'good' cholesterol in the body
- gradual loss of bone density leading ultimately to osteoporosis and bone fractures
- gradual hardening of the lens in the eye leading ultimately to cataract formation
- gradual loss of strength in the muscles in the bladder wall, leading to incontinence.

The involuntary mechanism

Part 3, and summary

This is the third (and final) plank of the involuntary estrogen balancing mechanism, and arguably the most potent in terms of cushioning the impact of estrogen on the body.

Nature has developed a simple method of locking up most of the estrogen that is produced by the body in an inactive form. In pre-menopausal women, the body is making far more estrogen than it could possibly use at any one time, and the reason it can do this is because the bulk of the estrogen manufactured in the body is stored in an inactive form and only slowly released to become an active form.

The vast majority of hormones in the body are made on demand, usually via a feed-back loop. For example, the cells in the pancreas that produce insulin are induced to do so by rising levels of glucose in the blood. We eat, and the body responds by making insulin.

Compare that to estrogen.

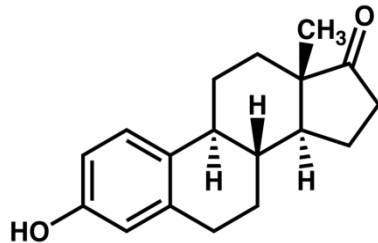
- Estrogen is required by a vast array of different tissues in the body at totally different amounts.
- Estrogen is made by a wide array of tissues (eg. fat) without any regulation.
- Estrogen has different effects on different tissues.
- Estrogen levels fluctuate wildly.

Making estrogens of different strengths and separating a cell's response to estrogen by creating two different estrogen receptors were important design features in being able to meet this challenge. The third design feature was the creation of an estrogen reservoir to hold any excess estrogen and to allow tissues to access this pool as and when required.

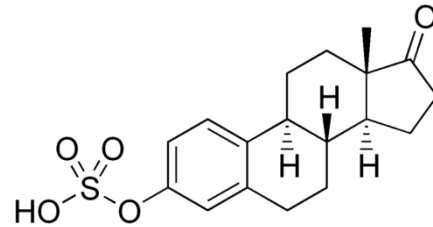
The reservoir is created by a process known as '*sulfation*.' Sulfation refers to the chemical process where a sulfate chemical group is attached to the estrogen molecule. This simple addition to estrogen has a couple of outcomes. First, it makes it more water-soluble, and second, it renders the estrogen inactive.

On the matter of water-solubility, estrogen is very poorly water-soluble. That is a feature of all steroids. Chemicals with a sterol structure like cholesterol are by nature fatty and therefore poorly soluble in water. Estrogen is just a minor chemical version of cholesterol, so it too is fatty and poorly water-soluble. So for estrogen to be moved around the body in blood (mostly water) and then to reach individual cells (surrounded by a watery fluid), it needs to be made water-soluble. It also needs to be made water-soluble so that it can be excreted finally from the body in urine.

The body has two ways of solubilising estrogen. The first way is to attach it to a blood protein made specifically for this purpose. The protein is known as *sex hormone binding globulin* (or SHBG). This protein, like all the blood proteins, mixes very well in water. Estrogen attaches itself loosely to this protein and then un-attaches itself when it reaches its final target. The second way to make estrogen water-soluble is to attach a sulfate chemical group as shown below.



Estrone



Estrone sulfate

About 40% of estrogen in blood is attached to protein and about 60% is sulfated. The protein-bound estrogen is far more readily accessible for tissues. The estrogen is only loosely attached to the protein, and readily falls off the protein when it reaches an individual cell. At that time, it is ready to enter a cell and to seek out an estrogen receptor.

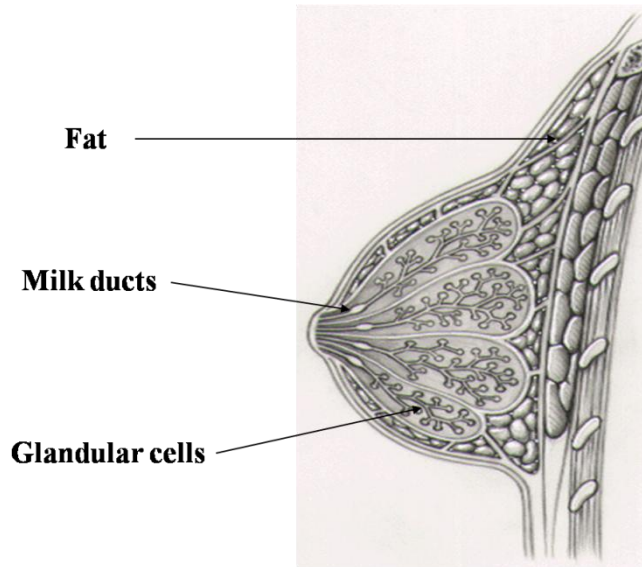
The sulfated form, on the other hand, is a permanent state. It cannot dissociate itself from the sulfate group at will, and it cannot interact with the estrogen receptor in that form, so for all intents and purposes it is locked up in a biologically inactive form. The only way that it is released from this state is to have the sulfate group cleaved off by the action of an enzyme known as *steroid sulphatase*. This enzyme is found inside of most cells and its degree of activity is regulated by a number of factors, including the voluntary estrogen balancing mechanism that we will be looking at shortly.

The whole process of transporting steroid hormones by the twin methods of blood protein and sulfation is not limited to estrogen... it is common to all steroid hormones such as testosterone, progesterone and cortisone. The protein transport method is the body's way of delivering hormones to tissues to be available for use immediately. The sulfated form simply buys the body time. The release of estrogen from its inactive sulfated state) will occur given enough time, but there is a delay, and this delay is long enough to act as an important cushion to estrogen surges.

SUMMARY

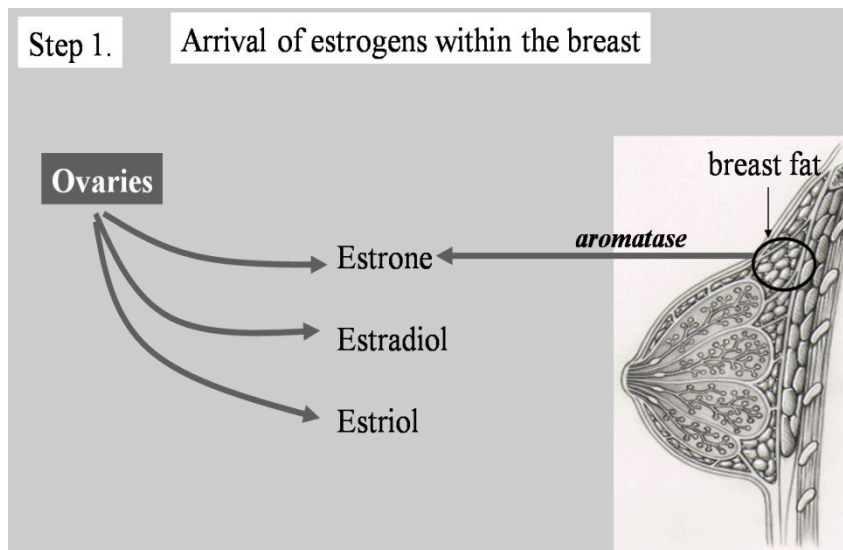
Now it's time to bring all three parts of the involuntary estrogen balancing mechanism together to see how the three are integrated. For this, we will use the example of the breast, although the following steps apply generally across all parts of the body.

First, a quick look at the breast anatomy.



Step 1.

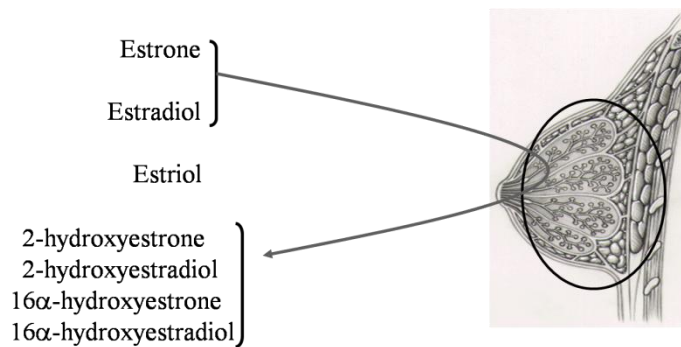
The pre-menopausal breast is presented with the three primary estrogens, estrone, estradiol, estradiol. These mostly have arrived via the bloodstream, but some also have been manufactured locally by the breast fat tissue, with testosterone being converted by the enzyme, *aromatase*, into estrone.



Step 2.

The breast tissue then converts a reasonable proportion of the estrone and estradiol into the various hydroxy estrogen forms. The breast tissue then ends up containing at least 7 different types of estrogens.

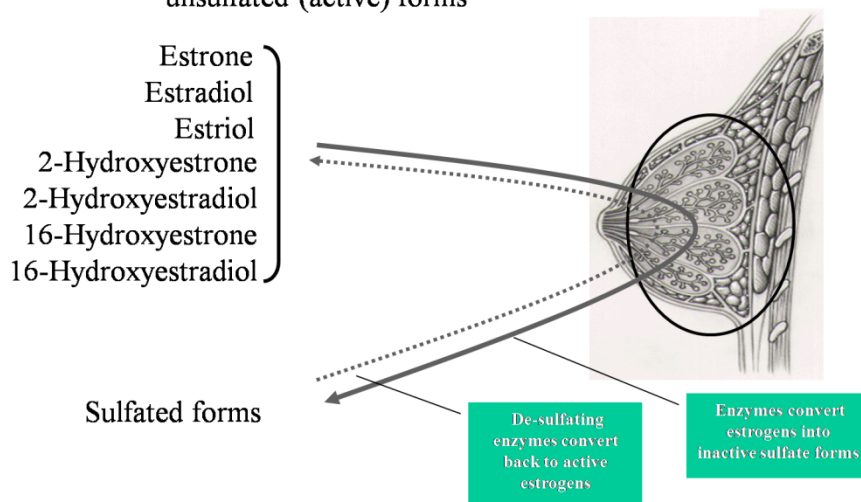
Step 2. Estrogens are metabolised within the breast



Step 3.

The various forms of estrogen then encounter an enzyme system (*estrogen sulfotransferase*) within the breast that converts about two-thirds of these estrogens into an inactive, sulfated form. When required, another enzyme (*steroid sulphatase*) removes the sulfate group, releasing the active form of estrogen.

Step 3. Enzymes within the breast convert the estrogens into sulfate (inactive) forms and then back to unsulfated (active) forms



Step 4.

The various forms of free estrogen then engage the estrogen receptors on breast cells. The level of response by the breast cells to having their estrogen receptors stimulated is a function of what types of estrogen are doing the stimulation. The presence of the weak estrogens (estriol, estrone, 2-hydroxyestrone and 2-hydroxyestradiol), suppresses the action of the more potent estrogens (estradiol, 16α-hydroxyestrone, 16α-hydroxyestradiol) by the process of competitive-inhibition. A correct balance of weak:strong estrogens ensures that the estrogenic response is moderate. A greater proportion of strong:weak will cause an excessive response.

Step 5.

The effects of estrogen on the different parts of the breast is determined by the presence of different estrogen receptors. The glandular cells of the breast with their *alpha* receptors will respond by multiplying. The other types of tissues within the breast with their predominantly *beta* receptors, respond by increasing their function. In the case of blood vessels, this means greater relaxation; in the case of the ligaments and muscles, it means greater strength.

Step 5.

Different parts of the breast respond differently to the same estrogens because of the presence of *alpha* and *beta* receptors.

beta
LIGAMENTS AND
FIBROUS TISSUE
STRENGTHEN

MUSCLE TONE
STRENGTHENED

Alpha
GLANDULAR
CELLS MULTIPLY

