**Homeostasis** literally means “same state” and it refers to the process of keeping the internal body environment in a steady state, when the external environment is changed. The importance of this cannot be over-stressed, as it allows enzymes etc to be ‘fine-tuned’ to a particular set of conditions, and so to operate more efficiently. Much of the hormone system and autonomic nervous systems is dedicated to homeostasis, and their action is coordinated by the hypothalamus. In Module 2 we saw how the breathing and heart rates were maintained (N.B. Synoptic questions probable!). Here we shall look at three more examples of homeostasis in detail:

- temperature,
- blood glucose and
- blood water.

All homeostatic mechanisms use negative feedback to maintain a constant value (called the set point). This is the most important point in this topic! Negative feedback means that whenever a change occurs in a system, this automatically causes a corrective mechanism to start, which reverses the original change and brings the system back towards the set point (i.e. ‘normal’). It also means that the bigger the change the bigger the corrective mechanism. Negative feedback applies to electronic circuits and central heating systems as well as to biological systems. When your oven gets too hot, the heating switches off; this allows the oven to cool down. Eventually it will get too cold, when the heating will switch back in, so raising the temperature once again.

So, in a system controlled by negative feedback, the set level is never perfectly maintained, but constantly oscillates about the set point. An efficient homeostatic system minimises the size of the oscillations. Some variation must be permitted, however, or both corrective mechanisms would try to operate at once! This is particularly true in hormone-controlled homeostatic mechanisms (and most are), where there is a significant time-lag before the corrective mechanism can be activated. This is because it takes time for protein synthesis to commence, the hormone to diffuse into the blood-steam, and for it to circulate around the body and take effect.

**Temperature Homeostasis (thermoregulation)**

One of the most important examples of homeostasis is the regulation of body temperature. Not all animals can do this physiologically. Animals that maintain a fairly constant body temperature (birds and mammals) are called endotherms, while those that have a variable body temperature (all others) are called ectotherms. Endotherms normally maintain their body temperatures at around 35 - 40°C, so are sometimes called warm-blooded animals, but in fact ectothermic animals can also have very warm blood during the day by basking in the sun, or by extended muscle activity (e.g. bumble bees, tuna). The difference between the two groups is thus that endothermic animals use internal corrective mechanisms, whilst ectotherms use behavioural mechanisms (e.g. lying in the sun when cold, moving into shade when hot). Such mechanisms can be very effective, particularly when coupled with internal mechanisms to ensure that the temperature of the blood going to vital organs (brain, heart) is kept constant. We use both!

In humans, body temperature is controlled by the thermoregulatory centre in the hypothalamus. It receives input from two sets of thermoreceptors: receptors in the hypothalamus itself monitor the temperature of the blood as it passes through the brain (the core temperature), and receptors in the skin (especially on the trunk) monitor the external temperature. Both sets of information are needed so that the body can make appropriate adjustments. The thermoregulatory centre sends impulses to several different effectors to adjust body temperature:
Our first response to encountering hotter or colder condition is voluntary - if too hot, we may decide to take some clothes off, or to move into the shade; if too cold, we put extra clothes on - or turn the heating up! It is only when these responses are not enough that the thermoregulatory centre is stimulated. This is part of the autonomic nervous system, so the various responses are all involuntary.

When we get too hot, the heat loss centre in the hypothalamus is stimulated; when we get too cold, it is the heat conservation centre of the hypothalamus which is stimulated.

Note that some of the responses to low temperature actually generate heat (thermogenesis), whilst others just conserve heat. Similarly some of the responses to cold actively cool the body down, while others just reduce heat production or transfer heat to the surface. The body thus has a range of responses available, depending on the internal and external temperatures.

The exact responses to high and low temperatures are described in the table below:
<table>
<thead>
<tr>
<th>Effector</th>
<th>Response to low temperature</th>
<th>Response to high temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth muscles in arterioles in the skin.</td>
<td>Muscles contract causing vasoconstriction. <strong>Less heat</strong> is carried from the core to the surface of the body, maintaining core temperature. Extremities can turn blue and feel cold and can even be damaged (<strong>frostbite</strong>).</td>
<td>Muscles relax causing <strong>vasodilation</strong>. <strong>More heat</strong> is carried from the core to the surface, where it is lost by convection and radiation (<strong>conduction</strong> is generally low, except when in water). Skin turns red.</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>No sweat produced.</td>
<td>Glands secrete sweat onto surface of skin, where it <strong>evaporates</strong>. Since water has a high <strong>latent heat of evaporation</strong>, it takes heat from the body. <strong>High humidity</strong>, and <strong>tight clothing made of man-made fibres</strong> reduce the ability of the sweat to evaporate and so make us uncomfortable in hot weather. <strong>Transpiration</strong> from trees has a dramatic cooling effect on the surrounding air temperature.</td>
</tr>
<tr>
<td>Erector pili muscles in skin (attached to skin hairs)</td>
<td><strong>Muscles contract</strong>, raising skin hairs and trapping an <strong>insulating layer of still, warm air</strong> next to the skin. <strong>Not very effective in humans</strong>, just causing &quot;goosebumps&quot;.</td>
<td><strong>Muscles relax</strong>, lowering the skin hairs and allowing air to circulate over the skin, encouraging convection and evaporation.</td>
</tr>
<tr>
<td>Skeletal muscles</td>
<td><strong>Shivering</strong>: Muscles contract and relax repeatedly, generating heat by friction and from metabolic reactions (respiration is only 40% efficient: 60% of increased respiration thus generates heat).</td>
<td>No shivering.</td>
</tr>
<tr>
<td>Adrenal and thyroid glands</td>
<td><strong>Glands secrete adrenaline</strong> and thyroxine respectively, which <strong>increases the metabolic rate in different tissues</strong>, especially the liver, so generating heat.</td>
<td><strong>Glands stop secreting</strong> adrenaline and thyroxine.</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Curling up, huddling, finding shelter, putting on more clothes.</td>
<td>Stretching out, finding shade, swimming, removing clothes.</td>
</tr>
</tbody>
</table>

The thermoregulatory centre normally maintains a set point of 37.5 ± 0.5 °C in most mammals. However the set point can be altered in special circumstances:

- **Fever.** Chemicals called **pyrogens** released by white blood cells raise the set point of the thermoregulatory centre causing the whole body temperature to increase by 2-3 °C. This helps to kill bacteria, inhibits viruses, and explains why you shiver even though you are hot.
- **Hibernation.** Some mammals release hormones that reduce their set point to around 5°C while they hibernate. This drastically reduces their metabolic rate and so conserves their food reserves e.g. hedgehogs.
- **Torpor.** Bats and hummingbirds reduce their set point every day while they are inactive. They have a **high surface area/volume ratio**, so this reduces heat loss.
Blood Glucose Homeostasis

**Glucose** is the transport carbohydrate in animals, and its concentration in the blood affects every cell in the body. Its concentration is therefore strictly controlled within the range 0.8 – 1g per dm$^3$ of blood, and very low levels (hypoglycaemia) or very high levels (hyperglycaemia) are both serious and can lead to death.

**Blood glucose concentration is controlled by the pancreas.** The pancreas has glucose receptor cells which monitor the concentration of glucose in the blood, and it also has endocrine cells (called the Islets of Langerhans), which secrete hormones. The $\alpha$-cells secrete the hormone glucagon, while the $\beta$-cells secrete the hormone insulin. These two hormones are antagonistic, and have opposite effects on blood glucose:

- **insulin** stimulates the uptake of glucose by cells for respiration, and in the liver it stimulates the conversion of glucose to glycogen (glycogenesis). It therefore decreases blood glucose.
- **glucagon** stimulates the breakdown of glycogen to glucose in the liver (glycogenolysis), and in extreme cases it can also stimulate the synthesis of glucose from pyruvate. It therefore increases blood glucose.

![Diagram of blood glucose homeostasis](image)

After a meal, glucose is absorbed from the gut into the hepatic portal vein, increasing the blood glucose concentration. This is detected by the pancreas, which secretes insulin from its $\beta$-cells in response. **Insulin causes glucose to be taken up by the liver** and converted to glycogen. This reduces blood glucose, which causes the pancreas to stop secreting insulin.

If the glucose level falls too far, the pancreas detects this and releases glucagon from its $\alpha$-cells. Glucagon causes the liver to break down some of its glycogen store to glucose, which diffuses into the blood. This increases blood glucose, which causes the pancreas to stop producing glucagon.

Because blood glucose levels are allowed to deviate from the set point by about 20% before any corrective mechanism is activated, glucagon and insulin can never both be produced at the same time.
Diabetes Mellitus

Diabetes is a disease caused by a failure of glucose homeostasis. There are two forms of the disease.

In type 1 diabetes (30%) (also known as insulin-dependent or early-onset diabetes) there is a severe insulin deficiency due to an autoimmune reaction, killing off the β-cells. This appears to be an inherited condition, possibly triggered by a virus. In this form of the diabetes, no insulin is produced.

In type 2 diabetes (70%) (also known as non insulin-dependent diabetes or late-onset diabetes) insulin is produced, but the insulin receptors in the target cells don’t work, so insulin has no effect. This is often a response to years of over-production of insulin, caused by a high-sugar diet. It is estimated that 40% of UK adults over 70 are diabetic to some extent. In both cases there is a very high blood glucose concentration after a meal, so the active transport pumps in the proximal convoluted tubule of the kidney can’t reabsorb it all from the kidney filtrate, and glucose is excreted in urine.

This leads to the symptoms of diabetes:

- high thirst due to osmosis of water from cells to the blood, which has a low water potential.
- copious urine production due to excess water in blood.
- poor vision due to osmotic loss of water from the eye lens.
- tiredness due to loss of glucose in urine and poor uptake of glucose by liver and muscle cells.
- ‘ketone breath’ caused by the body breaking down lipids to supply energy
- muscle wasting due to gluconeogenesis caused by increased glucagon.

Type I diabetes can be treated by injections with insulin (typically 4 per day, after each meal). Care must be taken not to over-dose, or a hypoglycaemic coma will be induced.

Type II diabetes can be treated by careful diet (balancing sugar intake with exercise), or by tablets that stimulate insulin production or increase the sensitivity of the liver cells to the hormone. Until the discovery of insulin in 1922 by Banting and Best, diabetes was an untreatable, fatal disease.
Blood Water Homeostasis (Osmoregulation)

The water potential of the blood must be regulated to prevent loss or gain of water from cells. Blood water homeostasis is controlled by the hypothalamus. It contains osmosreceptor cells, which can detect changes in the water potential of the blood passing through the brain. In response, the hypothalamus controls the sensation of thirst, and it also secretes the hormone ADH (antidiuretic hormone). ADH is stored in the pituitary gland, and its target cells are the endothelial cells of the collecting ducts of the kidney nephron. These cells are unusual in that water molecules can only cross their membranes via water channels called aquaporins, rather than through the lipid bilayer. ADH causes these water channels to open. The effects of ADH are shown in this diagram:
Excretion and Homeostasis

Excretion means the removal of waste products from cells. There are five important excretory organs in humans:

**Skin**  
**Lungs**  
**Liver**  
**Gut**  
**Kidneys**

- **Skin** excretes sweat, containing water, ions and urea
- **Lungs** excrete carbon dioxide and water
- **Liver** excretes bile, containing bile pigments, cholesterol and mineral ions
- **Gut** excretes mucosa cells, water and bile in faeces. (The bulk of faeces comprises plant fibre and bacterial cells, which have never been absorbed into the body, so are not excreted but **egested**.)
- **Kidneys** excrete urine, containing urea, mineral ions, water and other “foreign” chemicals from the blood.

This section is mainly concerned with the excretion of nitrogenous waste as urea. The body cannot store protein in the way it can store carbohydrate and fat, so it cannot keep excess amino acids. The “carbon skeleton” of the amino acids can be used in respiration, but the nitrogenous amino group must be excreted.

Amino Acid Metabolism

Amino acid metabolism takes place in the liver, and consists of three stages:

1. **Transamination:** In this reaction an amino group is transferred from an amino acid to a keto acid, to form a different amino acid.

   \[
   \text{Amino acid 1 + Keto acid 2} \leftrightarrow \text{Keto acid 1 + Amino acid 2}
   \]

   In this way scarce amino acids can be made from abundant ones. In adult humans only 11 of the 20 amino acids can be made by transamination. The others are called **essential amino acids**, and they must be supplied in the diet.

2. **Deamination:** In this reaction an amino group is removed from an amino acid to form ammonia and a keto acid. The most common example is glutamate deamination (see right):

   This reaction is catalysed by the enzyme **glutamate dehydrogenase**. Most other amino acids are first transaminated to form glutamate, which is then deaminated. The NADH produced is used in the respiratory chain; the a-ketoglutarate enters the Krebs cycle; and the ammonia is converted to urea in the urea cycle.

3. **Urea Synthesis**

   In this reaction surplus amino-acids are converted to urea, ready for excretion by the kidney. Ammonia is highly toxic, and stops the Krebs cycle; urea is less toxic than ammonia, so it is safer to have in the bloodstream. The disadvantage is that it “costs” 3 ATP molecules to make one urea molecule. This is not in fact a single reaction, but is a summary of another cyclic pathway, called the **ornithine cycle** (or urea cycle). It was the first cyclic pathway discovered.

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