Second Year Endocrinology

**Hyposcretion of Anterior Pituitary Hormones**
by Professor John Laycock

The hypothalamo-adenohypophysial axis comprises the hypothalamus, anterior pituitary and various endocrine glands. Hormones are secreted from the hypothalamus to stimulate or inhibit the release of hormones from the anterior pituitary. Anterior pituitary hormones then have their effects on the body and on endocrine glands which may be stimulated to release primary hormones.

Disorder at the endocrine gland results in primary endocrine gland disease. Disorder at the anterior pituitary results in secondary endocrine gland disease. Disorder at the hypothalamus results in tertiary endocrine gland disease.

Hypopituitarism is the decreased production of all anterior pituitary hormones (Panhypopituitarism), or the decreased production of specific hormones. Panhypopituitarism a rare case caused by congenital defects or gene mutations (e.g. PROP1 mutations). It can also occur after radiotherapy. In adults, it is the progressive loss of pituitary secretion, often (but not invariably) in the following order:

- Gonadotrophins (LH and FSH)
- GH
- Thyrotrophin
- Corticotrophin
- (Prolactin deficiency is uncommon)

The first description of hypopituitarism was made in 1914 by the German physician Dr Morris Simmonds. Simmonds’ disease is insidious (slow) in onset, caused by various things including infiltrative processes (e.g. lymphocytic), pituitary adenomas, craniopharyngiomas, cranial injury and following surgery.

- Symptoms are due mainly to decreased thyroidal, adrenal and gonadal function. The result is secondary amenorrhoea or Oligomenorrhoea (women), impotence (men), loss of libido, tiredness, waxy skin, loss of body hair, hypotension, etc.
- Diagnosis of hypopituitarism is made using basal plasma values of pituitary or target endocrine gland hormones. These are particularly useful if measured after a stimulation or ‘provocation’ test, for example using a combined function test involving rapid iv sequential administration of GHRH, CRH, GnRH and TRH. For individual hormones, more specific tests can be used e.g. insulin-induced hypoglycaemia for GH.

Sheehan’s syndrome is hypopituitarism specific in women. It develops acutely following post-partum haemorrhage, whereby blood loss and hypovolaemic shock causes vasoconstrictor spasm of hypophysial arteries, leading to ischaemia and subsequent necrosis of the pituitary gland (enlarged during pregnancy).

Pituitary apoplexy is a similar infarction or haemorrhage of the pituitary gland in the presence of a pituitary adenoma. It often has dramatic presentation with pre-existing pituitary tumours which suddenly infarct. Many patients can be treated with supportive treatment alone. In some cases surgical decompression can be necessary although indications for intervention are controversial.

It is possible to have a deficiency in a single adenohypophysial hormone, resulting in secondary endocrine gland failure. For example, lack of gonadotrophins leading to hypogonadism; lack of thyrotrophins leading to hypothyroidism; lack of corticotrophin leading to hypoadrenocorticalism (loss of glucocorticoids).

Lack of somatotrophin (GH) in children results in pituitary dwarfism or short stature. In adults, the effect of the loss of GH is uncertain because by that point most of the growing is complete. Causes of short stature include genetic determination, malnutrition, emotional deprivation, endocrine disorders and other various and often unknown causes.
GH deficiency in children can be congenital but this is rare. It can be due to deficiency of hypothalamic GHRH; mutations of the GH gene (very rare); or developmental abnormalities (e.g. aplasia or hypoplasia of the pituitary). Acquired GH deficiency is more common, and can be due to tumours of the hypothalamus or pituitary; other intracranial tumours nearby (e.g. optic nerve glioma); secondary to cranial irradiation; head injury; infection or inflammation; or severe psychosocial deprivation.

It must be remembered that the hormone can only work if the receptor and post-receptor mechanisms are working, so it is not always a disorder of hormone production.

Tertiary hypopituitarism involves specific hypothalamic hormone defects. For example, Kallmann’s syndrome is caused by a deficiency of GnRH and leads to decreased functioning of the glands that produce sex hormones. Prader-Willi syndrome is a rare genetic disorder in which seven genes on chromosome 15 are deleted or unexpressed on the paternal chromosome, one of the symptoms manifests itself as hypogonadism.

**Diagnosis**

To diagnose pituitary deficiency, a provocative challenge (i.e. stimulation) test is done. A preliminary diagnosis may be made on the bases of the signs and symptoms the patient presents with. However, a definitive diagnosis requires biochemical measurement of the hormone concerned. Since hormones are secreted periodically and the normal range may be broad, tests for pituitary insufficiency normally involve measurement of circulating hormone levels before and after a provocative challenge.

For example, growth hormone (GH) insufficiency may be diagnosed by measuring plasma GH before and after one of the following:

- GHRH (iv)
- Insulin (iv)
- Arginine (iv)
- Exercise (e.g. 10 minute step climbing)

The graph shows typical GH responses to insulin in a normal subject and one with GH deficiency. This is known as insulin-induced growth hormone secretion. 2 hours is the window needed to see the GH level response to administration of insulin.

The principal aim of the treatment of pituitary deficiency is to restore homeostasis by replacing missing hormones. An accurate diagnosis is therefore critical. ACTH, TSH and LH/FSH produce their biological actions largely through stimulating the production of hormones by the adrenal cortex, thyroid and gonads respectively. As these hormones (or analogues) are easier to administer than the pituitary hormones themselves, they are used in preference in replacement therapy.

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**Growth hormone therapy** in children accelerates linear growth and decreases body fat. The effects are most marked in the first year of treatment and younger children respond better and obese children respond better. However, resistance may develop (antibody formation). If GH deficiency is associated with generalised
hypopituitarism, replacement therapy with other hormones will be required. In growth hormone therapy, the **preparation** is human recombinant GH (approved name ‘somatotropin’). The **administration** is a subcutaneous or intramuscular injection given daily, or 4-5 times per week, and the dose is adjusted to the patient’s size. The **absorption** and **distribution** gives a maximal plasma concentration in 2 to 6 hours. **Metabolism** is hepatic or renal, and the half-life is short (approximately 20 minutes). The **duration of action** lasts well beyond plasma clearance with peak IGF-1 levels at approximately 20 hours.

The adverse effects of growth hormone therapy include **lipoatrophy** at injection site; intracranial **hypertension;** **headaches;** increased incidence of **leukaemia.**

Growth hormone deficiency in adults presents with various signs and symptoms. This includes reduced lean mass, increased adiposity, increased waist to hip ratio, reduced muscle strength/bulk, reduced exercise performance, decreased plasma HDL-cholesterol, raised LDL-cholesterol, impaired ‘psychological well being’, and reduced quality of life. GH production tends to decrease in people over 60. A diagnosis is made by a lack of response to GH stimulation test (e.g. to insulin), low plasma IGF-1 and low plasma IGF-BP3.

The **potential benefits** of GH therapy in adults include improved body composition, improved muscle strength and exercise capacity, normalisation of HDL-cholesterol, increased bone mineral content, and improved psychological well being and quality of life.

The **potential risks** of GH therapy in adults include increased risk of cardiovascular accidents, increased soft tissue growth (leading to e.g. cardiomegaly), and increased susceptibility to cancer.
Hypersecretion of anterior pituitary hormones
by Professor John Laycock

Hyperpituitarism is usually due to isolated pituitary tumours but can also be due to ectopic (i.e. from non-endocrine tissue) hormone production. It can quite often be associated with visual field and other (e.g. cranial nerve) defects, as well as endocrine-related signs and symptoms. The symptoms are associated with excess production of adenohypophysial hormones.

Bitemporal (heteronymous) hemianopia occurs when the pituitary tumour presses nerves, which leads to the disruption of vision.

Excess of pituitary hormones can result in a number of different scenarios. For example, excess corticotrophin (ACTH) can lead to Cushing’s disease; excess thyrotrophin (TSH) can lead to thyrotoxicosis; excess gonadotrophins (LH and FSH) can lead to precocious puberty in children; excess prolactin can lead to hyperprolactinaemia; and excess somatotrophin can lead to gigantism or acromegaly.

Hyperprolactinaemia is caused by excess circulating prolactin when not due to a physiological cause such as pregnancy or breast feeding. It is usually due to a prolactinoma (often microadenomas less than 10mm in diameter). In women this results in galactorrhoea (milk production), secondary amenorrhoea or oligomenorrhoea, loss of libido and infertility. In men this results in galactorrhoea (uncommon since appropriate steroid background usually inadequate), loss of libido, impotence and infertility.

Excess somatotrophin (growth hormone) in childhood results in gigantism, and in an adult results in acromegaly. Acromegaly is insidious in onset, with signs and symptoms progressing gradually over many years (can remain undiagnosed for 15-20 years). Untreated, gigantism and acromegaly are associated with an increased morbidity and mortality due to cardiovascular and/or respiratory complications.

Acromegaly involves increased growth of periosteal bone, cartilage, fibrous tissue, connective tissue and internal organs (cardiomegaly, splenomegaly, hepatomegaly, etc.). The metabolic effects include an increased plasma insulin response to oral glucose load, which leads to increased insulin resistance, which results in an impaired glucose tolerance test in 50% of patients and diabetes mellitus in 10% of patients.

Common clinical manifestations include enlargement of supraorbital ridges and nose, hands and feet, thickening of lips and general coarseness of features; excessive sweating; mandible growth (leading to protrusion of lower jaw aka prognathism); carpal tunnel syndrome and joint pain; barrel chest and curvature of spine (kyphosis); galactorrhoea; menstrual abnormalities; decreased libido and impotence; hypertension; abnormal glucose tolerance; and symptoms of diabetes mellitus.

Diagnosis of pituitary hypersecretory states uses suppression tests. As for pituitary underactivity, preliminary diagnosis may be made on the basis of the signs and symptoms the patient presents with. However, a definitive diagnosis requires biochemical measurements of the hormone concerned. Since hormones are secreted episodically and the normal range is broad, tests for pituitary overactivity normally involve measurement of circulating hormone levels before and after treatment with an agent which normally causes suppression of hormone release. For example, acromegaly may be diagnosed by measuring plasma GH before and after an oral glucose load.

Treatment options are variable, including somatostatin analogues such as Octreotide and dopamine agonists such as Bromocriptine. Octreotide can be used as short-term treatment before pituitary surgery.
(transphenoidal), or as long-term treatment in those not controlled by other means. As it inhibits GH release, it can also be used to treat other neuroendocrine tumours e.g. carcinoid tumours.

Octreotide is administered subcutaneously or intramuscularly 3 times per day, with a depot preparation once GH levels are under control. The dose is adjusted according to need. It is distributed by being retained in the extracellular fluid, and metabolism is hepatic / renal with a half life of 2 to 4 hours. Unwanted side-effects may include GI tract disturbances, initial reduction in insulin secretion; transient hyperglycaemia; and in rare cases gallstones.

Hyperprolactinaemia is treated using dopamine receptor agonists to decrease prolactin secretion and reduce tumour size. Examples of dopamine agonists include Bromocriptine and Cabergoline. Bromocriptine is a D₂ agonist, administered by mouth once daily; it is highly plasma protein bound (93%) with a typical half life of about 7 hours (hepatic metabolism). Unwanted effects of Bromocriptine include nausea/vomiting/abdominal cramps; dyskinesias; psychomotor excitation; postural hypotension; vasospasm in fingers and toes (caution Raynaud’s disease). Other uses of Bromocriptine include suppression of lactation, cyclical benign breast tumours, acromegaly and Parkinson’s disease. Cabergoline is a D₂ receptor agonist with moderate D₁ receptor activity. It is longer lasting than Bromocriptine, taken orally once or twice a week with a half life of over 45 hours. The unwanted effects are those of Bromocriptine, but less pronounced.
Neurohypophysial Disorders
by Professor John Laycock

In the hypothalamo-neurohypophysial system, secretions are released into the general circulation. The supraoptic and paraventricular nuclei (cell bodies) are located in the hypothalamus, and the axons pass through the median eminence through to the capillary network.

The neurohypophysis secretes vasopressin and oxytocin.

The principal action of vasopressin is the antidiuretic effect. It acts on the V2 receptors of renal cortical and medullary collecting ducts, where it stimulates the insertion of aquaporin 2 into the membranes of the principal cells to increase water transport (water reabsorption) from the tubular fluid into the general circulation. Increasing the amount of water retained in the body is an antidiuretic effect.

V1 receptors are specific to corticotrophs. Vasoconstrictor activity of vasopressin is brought about by V1a receptors. Corticotrophin (ACTH) release is associated with V1b receptors. V2 receptors are involved in the production of Factor VIII and von Willebrand factor. There is currently ongoing research into the central effects of vasopressin, including treatment for conditions to do with social behaviour such as autism.

The principal actions of oxytocin include constriction of myometrium at parturition, and also the milk ejection reflex. There may also be central effects. In high amounts of vasopressin and oxytocin there is overlap of pharmacological conditions and actions.

Lack of neurohypophysial hormones
Oxytocin - parturition and milk ejection effects induced/replaced by other means.
Vasopressin - DIABETES INSIPIDUS.

Diabetes notes that the amount of urine being produced is large. Unlike diabetes mellitus where there is high glucose in the blood, insipidus (non-sweet) is due to a lack of vasopressin in the circulation, which results in the body being unable to reabsorb water in the collecting ducts. Simply the lack of circulating vasopressin leads to central (cranial) diabetes insipidus. Another pathway depends on the presence of receptors and correctly functioning post-receptor mechanisms. End-organ resistance to vasopressin (e.g. don’t have V2 receptors or mutated receptors or intracellular problems) leads to nephrogenic diabetes insipidus.

Central (cranial) diabetes insipidus is caused by anything that leads to the damage of the neurohypophysis. This can be due to injury, surgery, central thrombosis, tumours (intrasellar and suprasellar), and also granulomatous infiltrations of the median eminence. It can also be idiopathic, and familial diabetes insipidus is rare. A Brattleboro rat was shown to have a vasopressin gene mutation - the perfect form of diabetes insipidus. This rat produced roughly its own body weight in urine each day. Rats have very long nephrons and therefore have greater concentrating abilities than humans, so in humans body weight quantities of urine are not produced, but enough is produced to seriously disrupt the day and night. Nephrogenic diabetes insipidus can be familial, but this is rare (e.g. receptor defects).

Drugs (e.g. lithium, dimethyl-chlortetracycline DMCT) can cause nephrogenic too, and so drugs such as lithium which is still used in the treatment of various psychiatric disorders have to be considered for the effects of diabetes insipidus.

Diabetes Insipidus and Psychogenic Polydipsia
The signs and symptoms of diabetes insipidus include large volumes of urine (polyuria); very dilute urine (hypo-osmolar); thirst and increased drinking (polydipsia); dehydration if fluid intake not maintained; possible disruption to sleep with associated problems; and possible electrolyte imbalance.
The lack of vasopressin leads to polyuria, causing a reduction of extracellular volume and an increase in plasma osmolality (sodium increase). This affects the thirst centre, so you seek water and drink to replace the fluid lost to extracellular fluid, which should switch off vasopressin, but in this case there isn’t any and so you enter the vicious circle.

The normal (hydrated) range of plasma osmolality (mOsm.kg H₂O⁻¹) is about 280. In diabetes insipidus this becomes about 290, and in polydipsia this becomes 270. In psychogenic polydipsia, a central disturbance combined creates the sensation of thirst and leads to increased drinking (polydipsia), leading to the expansion of extracellular fluid volume and a decrease in plasma osmolality. It also leads to increased urine excretion, and this leads to a reduction of extracellular fluid volume, which increases plasma osmolality. This combined with the central disturbance increases the sensation of thirst and the vicious circle is entered.

To distinguish between four different patients, a fluid deprivation test is done.

In a normal person, fluid deprivation will lead to concentrated urine being produced. This is the normal physiological response by increasing vasopressin due to changes in plasma osmolality.

The polydipsic patient usually has a normal vasopressin system, so they can concentrate their urine, but not as well as a normal person. This is because the kidneys will become used to being driven in such a way that the urea is lost in the kidneys so the concentrating ability is lost to a certain degree over time.

A patient with central diabetes insipidus cannot concentrate urine, so prolonged fluid deprivation will just kill them as they can’t control the amount of urine produced and so their body weight will just reduce over the hours. It is very important not to let them dehydrate for too long, otherwise this could result in coma and death.

A patient with nephrogenic diabetes insipidus has vasopressin, but it won’t work. The obvious way to distinguish between the two types of diabetic patient is to replace the vasopressin. The patient with nephrogenic diabetes insipidus won’t be able to concentrate urine despite being given vasopressin.

Neurohypophysial hormone excess

The Syndrome of Inappropriate ADH (SIADH) by definition is when the plasma vasopressin concentration is inappropriate for the existing plasma osmolality. Excess vasopressin causes excess water reabsorption, and retaining more water than normal leads to diluted plasma. Sodium ions play important roles in the body, and hyponatraemia is very dangerous. The decreased urine volume (small concentrated amount) associated with SIADH means there is actually an increased loss of sodium relatively, which worsens the hyponatraemia. The body tries to compensate for this by making more urine (natriuresis) to restore urine output, but this decreases sodium still because of the excess vasopressin.

The signs of SIADH include raised urine osmolality, decreased urine volume, and hyponatraemia due to increased water reabsorption. It can be symptomless, however if p[Na⁺] is less than 120mM, then there can be generalised weakness, poor mental function and nausea. If the sodium ion concentration becomes lower, below certain levels cells start responding badly. Less than 110mM can present with confusion, leading to coma and ultimately death.

Causes of SIADH are varied. Tumours (ectopic secretion) are the main cause. Vasopressin was one of the first molecules to be shown to be associated with an outside tumour (in the lung) producing excess amounts of vasopressin. Neurohypophysial malfunction (e.g. meningitis, cerebrovascular disease) can also be a cause, as
well as thoracic disease (e.g. pneumonia); endocrine disease (e.g. Addison’s); physiological i.e. non-osmotic stimuli (e.g. hypovolaemia, pain, surgery); drugs (e.g. chloropropamide); or indeed it can be idiopathic.

Once the cause of SIADH is identified (e.g. tumour) then the appropriate treatment (e.g. surgery) can be applied. The main aim of treatment is to reduce the immediate concern i.e. hyponatraemia. This is done with immediate fluid restriction, and in the longer term drugs are used which prevent vasopressin action in the kidneys e.g. lithium, di-methyl-chlor-tetracycline, and also V2 receptor antagonists.

**Pharmacology of Vasopressin and its Analogues**

All vasopressin receptors will be activated in response to exogenous vasopressin. V1 receptors are found on vascular smooth muscle, non-vascular smooth muscle, the anterior pituitary, the liver, platelets and in the CNS. V2 receptors are found in the kidneys and on endothelial cells.

One of the main pharmacological actions of vasopressin is **natriuresis**. It is V2-mediated, but the mechanism is unclear. It is evident with high doses only, and may contribute to hyponatraemia. Another main action is the **pressor action**. This is V1-mediated, and affects vascular smooth muscle. Not all beds are equally sensitive, but the effect on coronary vessels is important (may cause cardiac ischaemia or anginal attacks). Contraction of non-vascular smooth muscle (e.g. gut motility) is via V1a receptors. Increased ACTH secretion is via V1b receptors. Increased Factor VIII and von Willebrand factor production is via V2 receptors.

Selective vasopressin receptor agonists include **Terlipressin** for V1 receptors, and **Desmopressin (DDAVP)** for V2 receptors. Clinically, desmopressin is used in cranial diabetes insipidus, nocturnal enuresis, and in haemophilia. It is administered nasally or orally. Oral desmopressin produces a prompt and sustained decrease in urine volume and increase in urine osmolarity. Desmopressin has a long term effect over many hours (because it is more potent than vasopressin).

The distribution of desmopressin involves it being retained in extracellular fluid, and the metabolism is hepatic and renal with a typical half life of about 5 hours. The unwanted effects of desmopressin include fluid retention and hyponatraemia; abdominal pain; headaches; and nausea. V2 receptor agonists cause fluid retention, although it is unknown why abdominal pain, headaches and nausea are caused. It could be to do with the high doses affecting the V1 receptor system.

Clinically, terlipressin is useful in haemorrhages in oesophageal varices. **Felypressin** is also used to prolong the action of local anaesthetics. In both cases the drugs are useful for the vasoconstrictor effect.

Treatment of nephrogenic diabetes insipidus uses **thiazides** such as bendroflumethiazide. The possible mechanism involves inhibiting the Na⁺/Cl⁻ transport in the distal convoluted tubule, which leads to a diuretic effect. There is volume depletion and a compensatory increase in Na⁺ reabsorption from the proximal tubule (plus a small decrease in GFR, etc) which causes increased proximal water reabsorption. Consequently, less fluid reaches the collecting duct and there is reduced urine volume. Thiazides reduce urine output by up to 50%, which seems paradoxical as it is a diuretic.

Drugs such as **nicotine** increase vasopressin secretion, and drugs such as **alcohol** or **glucocorticoids** decrease vasopressin secretion.
**Thyroid Disorders**

by Professor Karim Meeran and Dr Glenda Gillies

**Hypothyroidism**

Primary hypothyroidism (myxoedema) is caused by autoimmune damage to the thyroid. Thyroxine levels decline and TSH levels climb. The basal metabolic rate falls, and so everything slows down. Symptoms include confusion, slow thinking, depression and tiredness, slow responses, coarsening and deepening voice, heart slows down, feel cold all year round, oedema of face and eyelids, slow pulse, ascites, weakness, weight gain with reduced appetite, constipation and also blood pressure climbs due to increasing stroke volume (caused by Bradycardia).

In replacement therapy, there are a few drugs that can be used. **Levothyroxine sodium** is usually the drug of choice (T4 analogue), but **Liothyronine sodium** (T3 analogue) can be used for a more rapid action in myxoedema coma by intravenous administration, although this is rare.

**Hypothyroid conditions**

1. **Primary hypothyroidism (myxoedema).** The leading cause of this is autoimmune disease (Hashimoto’s disease). There is circulating anti-thyroglobulin, anti-thyroid peroxidise and TSH receptor blocking antibodies; as well as the invasion of lymphocytes and macrophages into the gland. This leads to an inability to produce hormones. Primary hypothyroidism affects around 1% of the adult population.

2. **Consequences of therapy of thyroid tumours with radioiodine** (T4).

3. **Iatrogenic** (resulting from treatment) hypothyroidism e.g. glucocorticoids, thiourylenes, lithium.

4. **Myxoedema coma** (rare) - a complication of hypothyroidism (T3).

Every cell in the body depends on thyroid hormones for regulation of metabolism, i.e. energy production. The actions of T3 and T4 are largely to do with the metabolism of carbohydrates, fat and protein. The direct effect is to increase metabolism and sources of energy, and there are also indirect effects via insulin, glucagon, glucocorticoids, catecholamines, and adrenocceptor expression.

Thyroid hormones cause **basal metabolic rate** to increase - oxygen consumption and heat production increase, particularly in the heart, liver and kidneys more than in the gonads, brain and spleen. Cardiac output and heart rate also increase due to sympathetic effects.

**Growth and development** are also dependent on thyroid hormones, not only in skeletal development, but also in CNS development. Neonatal screening for hypothyroidism means that treatment is possible if necessary to prevent mental retardation and dwarfism (cretinism). The heel prick test may reveal that the neonate needs to be treated with thyroid hormones.

Thyroid hormone receptors belong to the nuclear receptor superfamily. T4 can be considered a **prohormone**. This prohormone doesn’t act on cell surface receptors, it has a specific receptor inside the cell, which transfers into the nucleus and affects DNA production to regulate the activity of that cell. T4 is the main circulating thyroid hormone, but it is often converted to T3 which binds more readily to the **intracellular receptor**.

**Dosage** of replacement hormones must be monitored by checking **TSH levels** every 6 to 12 months to ensure that the correct dosage is being given. Treatment usually starts with a low dose and works up slowly. Too much will lead to unwanted side-effects of hyperthyroidism. Signs and symptoms of hyperthyroidism include high BMR, increased temperature, sweating, sensitivity to heat, nervousness, and increased appetite but loss of weight. There are many unwanted consequences of enhanced activity in the sympathetic nervous system due to hyperthyroidism including tremor, risk of precipitating angina pectoris, cardiac dysrhythmias or cardiac failure.

Thyroid hormones are **active orally**. T4 has a plasma half life of 6 days, has its peak effect at 9 days, and the half life for the decline of the response is 11 to 15 days. T3 has a plasma half life of 2 to 5 days, has its peak effect within 1 or 2 days, and has a half life for decline of response of 8 days. These properties illustrate why T3 acts faster and why the hormones accumulate if given daily, therefore treatment begins with a low dose. Almost 100% of the hormone is bound to plasma proteins, mainly **thyroxine binding globulin**. TBG is a
glycoprotein synthesised in the liver (not to be confused with thyroglobulin). Plasma binding proteins increase in pregnancy and on prolonged treatment with oestrogens and phenothiazines. Certain co-administered drugs (e.g. phenytoin, salicylates) compete for protein binding sites. There is 10 times more T4 in the plasma than T3. Some T4 is converted to T3 in tissues, and further metabolism occurs in the liver (de-iodination, deamination, conjugation). Free and conjugated hormone is secreted in the bile and urine - T3 is cleared in hours, T4 in about 6 days.

**Hyperthyroidism**
The autoimmune condition of hyperthyroidism was first described by Robert Graves in 1796 (Graves' disease). It was much more prevalent in Ireland than in other parts of the world. A nodular goitre was noted as Plummer's disease. Graves' disease is autoimmune, whereby antibodies bind to and stimulate the TSH receptor in the thyroid. The gland is caused to make more thyroxine than is needed and this results in a smooth goitre and hyperthyroidism which causes lid lag. It is actually possible to hear blood flowing through the smooth goitre, as it is a very dynamic gland. In hyperthyroidism, the patient feels sweaty and hot, they lose weight with increased appetite, body temperature climbs, muscle wasting, shortness of breath, rapid pulse, tremor, palpitations and tachycardia, breast enlargement and also antibodies bind to muscles at the back of the eyes causing them to swell up - exophthalmos. Other antibodies cause pretibial myxoedema (hypertrophy). Pretibial myxoedema is the swelling (non-pitting) that occurs on the shins of patients with Graves' disease in the form soft tissue growth. This is not to be confused with myxoedema, which is hypothyroidism!

Plummer's disease is a toxic nodular goitre. This is not an autoimmune condition, but is a benign adenoma that is overactive at making thyroxine. The patient does not present with pretibial myxoedema, and does not present with exophthalmos either as there are no antibodies involved.

**Thyroxine** affects the nervous system in many ways. For example, it sensitises $\beta$ adrenoceptors to ambient levels of adrenaline and noradrenaline, thus there is apparent sympathetic activation. This leads to tachycardia, palpitations, tremor in the hands and lid lag. A thyroid storm is a medical emergency as there is a 50% chance of mortality if it is untreated. Blood results confirm hyperthyroidism. In a thyroid storm, the patient can present with hyperpyrexia (a temperature of over 41°C), accelerated tachycardia/ arrhythmia, cardiac failure, delirium/frank psychosis, hepatocellular dysfunction and jaundice. This needs aggressive treatment. Treatment options include surgery (thyroidectomy), radioiodine, and the use of drugs.

There are a few treatment options in terms of drugs. Beta blockade is very important, and so propranolol can be used. Anti-thyroid drugs include Carbimazole and Propylthiouracil. Other than using drugs there is also radioiodine and surgery (thyroidectomy).

**Viral (de Quervain's) thyroiditis** presents with painful dysphagia, hyperthyroidism, pyrexia and raised erythrocyte sedimentation rate (ESR). The patient will have tender pretracheal lymph nodes and a tender and palpable thyroid, which will be enlarged more on one side. A virus attacks the thyroid gland causing pain and tenderness, consequently the thyroid stops making thyroxine and makes viruses instead. Thus there is zero iodine uptake, and also zero radioiodine uptake. A thyroid scan in Graves' will be very dark, but a thyroid scan in viral thyroiditis will be blank as there is no iodine uptake. This means the gland is not working. Since there is zero radioiodine uptake, the stored thyroxine is released. Four weeks later the stored thyroxine is exhausted and this results in hypothyroidism. After a further month, resolution occurs (like in all viral diseases) and the patient then becomes euthyroidism (normally functioning thyroid gland) again.

In the cases of both papillary and follicular thyroid cancers, radioiodine is taken up. An adenocarcinoma is usually bad news, and medullary is rare. Papillary and follicular thyroid carcinomas both may be stimulated to grow by TSH, and they both take up radioiodine. Treatment of thyroid carcinoma includes total thyroidectomy, giving large dose of radioiodine (ablation), and giving enough thyroxine to suppress TSH.

**Thiourylenes** e.g. Propylthiouracil and Carbimazole are used in the daily treatment of hyperthyroid conditions. It is mainly used in diffuse toxic goitre/Graves disease/exophthalmic goitre, where IgG acts against components of the follicle cell membrane (possibly the TSH receptor) and stimulates T3 and T4 secretion. Benign neoplasms/toxic nodular goitre/Plummer’s disease is usually treated surgically if necessary.
Thiourylenes are used as treatment prior to surgery, for the reduction of symptoms while waiting for radioactive iodine to act.

The mechanisms of action of thiourylenes are based on the inhibition of thyroperoxidase and peroxidise transaminase and hence T3 and T4 synthesis and secretion. The biochemical effect is within hours but the clinical effect lasts for weeks. The treatment regime may include propranolol, which rapidly reduces tremor and tachycardia. Thiourylenes may also suppress antibody production in Graves’ disease, and reduce the conversion of T4 to T3 in peripheral tissues.

There are, however, unwanted actions of thiourylenes including rashes, headaches, nausea, jaundice and joint pain. Agranulocytosis/granulocytopenia (reduction or absence of granular leukocytes) are rare effects and are reversible on withdrawal of the drug.

They are orally active drugs. Carbimazole is a pro-drug which first has to be converted to methimazole. The plasma half life is between 6 and 15 hours, and it has the ability to cross the placenta as well as being secreted in milk. The drugs are metabolised in the liver and secreted in the urine.

Iodide (usually in the form of potassium iodide) doses can also be given as treatment at least at 30 times the average daily requirement. Iodide is used in preparation of hyperthyroid patients for surgery, and it would also be used in a severe thyrotoxic crisis (thyroid storm).

Its actions include inhibiting iodination of thyroglobulin and inhibiting thyroperoxidase generation. Thyroid hormone secretion is thus inhibited, and hyperthyroid symptoms reduce within 1 or 2 days. Vascularity and the size of the gland reduces within 10 to 14 days.

There are, however, unwanted actions of iodide including allergic reaction (e.g. rashes, fever, angio-oedema). Iodide is given orally and has its maximum effects after 10 days of continuous administration.

Radioiodine \( (^{131}\text{I}) \) given in high doses treats hyperthyroidism and thyroid tumours. The mode of action involves the isotope being processed in the same way as stable iodide. It becomes incorporated into thyroglobulin and therefore concentrates in the colloid of the thyroid gland. The isotope emits \( \beta \) particles (very short range) and x-rays, but the cytotoxic effects are limited to thyroid follicular cells.

Radioiodine is administered as a single oral dose in a capsule. In Graves’ disease this is 370 - 555MBq (10 - 15 mCi). In thyroid cancer this is circa 3000MBq. The radioactive half life of radioiodine is about 8 days, and the radioactivity is negligible after 2 months. The maximum effect is at around 2 to 3 months. Exposure to pregnant patients can have teratogenic effects on the baby, so patients are advised to avoid children and pregnant women. If for scans only (not for treatment), then 99-Tc pertechnetate is an option. Otherwise, a very low tracer dose of radioiodine can be used to test thyroid function. This is administered intravenously, and has negligible toxicity.
Oxytocic Drugs and the Pregnant Uterus
by Dr Glenda Gillies

Clinical uses of drugs acting on the pregnant uterus:
- Induction and augmentation of labour
- Control of post-partum haemorrhage and uterine atony
- Therapeutic abortion
- Delay of premature labour

Drugs acting on the pregnant uterus
Oxytocics: increase motility
- Oxytocin
- Ergometrine
- Prostaglandins

Abortifacients:
- Prostaglandins
- Progesterone antagonists

Tocolytics:
- β-adrenoceptor agonists

Oxytocin
Oxytocin stimulates contraction of smooth muscle cells (myoepithelial cells) in breasts, which results in contraction and milk ejection during lactation. Oxytocin also stimulates contraction of uterine smooth muscle (myometrial cells) during labour, which results in the delivery of a baby. The neuroendocrine reflex arc of oxytocin begins with the stimulus of suckling, and receptors around the nipple signal via the neural afferent limb to the hypothalamus. Oxytocin is released from the posterior pituitary, which travels to the breast and has its effect via the endocrine efferent limb to cause milk ejection.

The major effects of oxytocin give it a therapeutic advantage for use in the uterus or mammary gland myoepithelial cells. In the uterus it causes rhythmic contractions from the fundus to the cervix, and also causes the dilation of the cervix. Uterine actions of oxytocin are suppressed by progesterone, enhanced by oestrogen, and are most marked in the later stages of pregnancy. In the mammary glands, oxytocin causes contraction of myoepithelial cells which leads to milk ejection.

Minor effects can be unwanted, such as those on the cardiovascular system and kidneys. Oxytocin can cause transient vasodilation and tachycardia, as well as constriction of umbilical arteries and veins. In the kidneys it causes anti-diuresis and secondary hyponatraemia, i.e. vasopressin like actions. Additional physiological effects are on the CNS, as oxytocin has been shown to be linked with maternal/paternal behaviour, social recognition, bonding and trust.

Clinical uses of oxytocin:
- Induction of labour at term, using a controlled intravenous infusion
- Prevention treatment of post-partum haemorrhage, using a slow intravenous injection/infusion (local pressor action in the uterus suppresses bleeding).
- Facilitation of milk let-down, using an intranasal spray.

Oxytocin is administered in a variety of ways, for example by infusion/slow injection or by an intranasal spray in the case of milk let-down. Distribution is in the extracellular fluid, and metabolism is in the liver, kidneys and also in the plasma (placenta-derived enzyme). The half life is short, about 5 minutes or so.

Oxytocin overdose in labour has unwanted effects. There can be compromised placental exchange of oxygen and nutrients which causes foetal distress; the foetus can be forced against an undilated cervix (which could cause lacerations and trauma); there can be uterine rupture; transient but serious hypotension with reflex tachycardia; and water intoxication of mother and foetus.
Because of the CNS actions of oxytocin, it is known as the hormone of love, generosity and well-being.

**Ergometrine**
Ergot is derived from the fungus *Clarium purpurea*. It comprises many biologically active alkaloids. Ergot derived alkaloids are used to treat e.g. Parkinson’s disease, hyperprolactinaemia and migraine. The principal oxytocic agent was identified in 1935 as ergometrine.

The principal actions of ergometrine include increasing tone in the myometrium with a prolonged series of contractions, and also effects on the blood vessels e.g. constriction of umbilical and placental vessels.

**Clinical uses of ergometrine:**
- Routine management of 3rd stage of labour, intramuscular +/- oxytocin.
- High risk post-partum haemorrhage, intravenous after delivery of the shoulders.
- Post-partum atony of the uterus - oral administration.
- Contra-indications
  - Pregnancy prior to the 3rd stage of labour
  - Pre-eclampsia and other vascular disease

Administration of ergometrine is intravenous, intramuscular or oral. It is well distributed, and is metabolised in the liver after a duration of 3 to 4 hours. Unwanted effects of ergometrine include abdominal pain, hypertension, anginal pain and nausea/vomiting.

**Prostaglandins**
Abortifacients induce abortion; these include prostaglandins and progesterone receptor blockers. Prostaglandins stimulate contractions in the uterus throughout pregnancy and induce cervical ripening (i.e. softening of the tissue).

**Prostaglandin preparations:**
- Dinoprostone: PGE2 (vasodilator)
- Gemeprost: PGE1 derivative
- Carboprost: 15-methyl - PGF2α (vasoconstrictor)

**Clinical uses of prostaglandins in pregnancy:**
- **Induction of abortion**
  - Dinoprostone - intravaginally administered as a gel or tablet
- **Induction of cervical ripening**
  - At term dinoprostone is used, but prior to abortion gemeprost vaginal pessaries are used
- **Post-partum haemorrhage in those resistant to oxytocin and ergometrine**
  - Carboprost intramuscular administration

Unwanted effects of prostaglandins include potentiation of actions of oxytocin, nausea, vomiting, diarrhoea, hypertension (PGF2α), hypotension (PGE2), and pyrexia.

**Progesterone receptor blockers** e.g. mifepristone (RU486) are competitive antagonists of progesterone at the progesterone receptor with weak agonist activity. Clinically, this can be used to induce an early therapeutic abortion (up to 63 days). The mechanism is mifepristone involves blockade of uterine progesterone receptors, which causes detachment of the blastocyst and reduced hCG production. Consequently there is reduced progesterone production by the ovarian corpus luteum, and this leads to accentuated decidial breakdown and increased uterine prostaglandin production. Mifepristone is also used in softening and dilating the cervix prior to suction abortion, or in therapeutic abortion at 13 - 20 weeks in combination with gemeprost.

Administration of mifepristone is oral, it has good bioavailability. It enters cells, but distribution is limited by plasma protein binding. Metabolism is hepatic/enterohepatic and metabolites are excreted mainly in the
faeces. The half life is 20 to 40 hours. Unwanted effects of mifepristone include vaginal bleeding and headaches.

**Tocolytics (reduce motility)**
These are β₂-adrenoceptor agonists. Receptor activation increases intracellular cyclic AMP and this causes relaxation of the uterine muscle.
**Hyperadrenal Disorders**
by Professor Karim Meeran and Dr Glenda Gillies

**Cushing’s syndrome** is caused by too much cortisol. The clinical features include centripetal obesity, moon face, buffalo hump, proximal myopathy, hypertension, hypokalaemia, red striae, thin skin, bruising, osteoporosis and diabetes. Cushing’s can be caused by taking too many **steroids**, a pituitary tumour (which causes **Cushing’s disease**), an **ectopic tumour** (e.g. in the lung) secreting ACTH, or an **adrenal adenoma** secreting cortisol.

Investigations to determine the cause of Cushing’s syndrome include a 24 hour urine collection for urinary free cortisol and blood diurnal cortisol levels. Cortisol is usually highest at 9am and lowest at midnight if asleep in normal patients, but in Cushing’s syndrome cortisol levels are constantly high. A **low dose dexamethasone suppression test** is done to investigate Cushing’s. Dexamethasone is an artificial steroid, which is taken every 6 hours for 48 hours in a 0.5mg dose. **Normal patients will suppress cortisol to zero**, but any cause of Cushing’s will fail to suppress the cortisol. A **high dose dexamethasone suppression test** is used to distinguish pituitary Cushing’s from the other types. Only pituitary Cushing’s will suppress to 50%, whereas ectopic ACTH and adrenal tumours will not suppress at all.

Diagnosis of Cushing’s is made using the results of these suppression tests. For example, a patient may have a basal (9am) cortisol of 800nM. After the low dose test cortisol is 680nM and after the high dose test cortisol is 235nM. This patient has Cushing’s disease. Treatment involves pharmacological manipulation of steroids, for example using enzyme inhibitors and receptor blocking drugs.
Metyrapone inhibits the enzyme 11β-hydroxylase, and in doing so cuts off the production of corticosterone and cortisol. Cortisol synthesis is blocked, ACTH secretion increases and plasma deoxycortisol levels are increased. Steroid synthesis in the zona fasciculata and reticularis is arrested at the 11-deoxycortisol stage. 11-deoxycortisol has no negative feedback effect on the hypothalamus and pituitary gland.

Metyrapone is used to treat some causes of Cushing's syndrome, for example bronchial tumours that are inaccessible to surgery. Oral doses may be tailoried to corticosteroid production, and corticosteroid replacement therapy may be necessary with high doses. Metyrapone is a useful drug for controlling Cushing's symptoms prior to surgery.

There are, however, some unwanted actions such as nausea, vomiting, dizziness, sedation, and also hypoadrenalism, hypertension on long-term administration. Caution is given against impaired performance of skilled tasks e.g. driving and operating machinery. As for the hypertension, deoxycorticosterone accumulates in the zona glomerulosa and has aldosterone-like (mineralocorticoid) activity, leading to salt retention and hypertension.

Trilostane blocks the activity of the enzyme 3β-hydroxysteroid dehydrogenase and therefore prevents the production of glucocorticoids, mineralocorticoids and sex steroids. So aldosterone, corticosterone, cortisol and androstenedione production are all cut off.

Trilostane is used in Cushing's syndrome, particularly in primary Hyperaldosteronism. It is not easy to tailor a dose to corticosteroid production. Circulating corticosteroids and plasma electrolytes are monitored and replaced with glucocorticoids and mineralocorticoids when necessary. Trilostane is also used in the reduction of sex steroid hormone production e.g. in post-menopausal breast cancer which has relapsed after initial therapy with anti-oestrogens. Unwanted actions include nausea, vomiting, diarrhoea and flushing.

Ketocnazole is mainly used as an antifungal agent. At higher concentrations, it inhibits steriodogenesis due to non-specific inhibition of cytochrome P450 enzymes. It blocks the production of glucocorticoids, mineralocorticoids and sex steroids. Its uses are similar to those of Metyrapone in Cushing's syndrome. Ketocnazole is used in the treatment and control of symptoms prior to surgery, and is an orally active drug.

Unwanted actions of ketoconazole include nausea, vomiting, abdominal pain, alopecia, gynaecomastia, oligospermia, ventricular tachycardias, liver damage (possibly fatal, so monitor liver function clinically and biochemically), and also reduced androgen production.

Aminoglutethamide works by inhibiting the conversion of cholesterol to pregnenolone (very toxic). This blocks the production of glucocorticoids, mineralocorticoids and sex steroid hormones. It is used in adrenocortical carcinoma (malignant), and also in prostate cancer (malignant, NB replace corticosteroids). It is an orally active drug.

Treatment of Cushing's depends on the cause, and can be pituitary surgery (transphenoidal hypophysectomy), bilateral adrenalectomy or unilateral adrenalectomy for adrenal mass. Metyrapone and ketoconazole are both used in medical treatment.

Conn's syndrome is a benign adrenal cortical tumour in the zona glomerulosa, which causes aldosterone to be in excess, leading to hypertension and hypokalaemia. Diagnosis is made when the patient presents with primary hyperaldosteronism. The renin-angiotensin system should be suppressed, which excludes secondary hyperaldosteronism. Treatment of Conn's syndrome has various options. An aldosterone receptor antagonist such as spironolactone can be used, or surgical intervention may be appropriate to image and remove the adenoma, or if bilateral adrenal hyperplasia the patient can stay on spironolactone.

Spironolactone is used in primary hyperaldosteronism and is also used in the treatment of oedema, congestive heart failure, nephritic syndrome and cirrhosis of the liver. Spironolactone (a prodrug) is rapidly converted to canrenone, a competitive antagonist of the mineralocorticoid receptor. This blocks Na" resorption and K" excretion in the kidney tubules (potassium sparing diuretic). Spironolactone is orally active, and is given daily in a single or divided dose. It is highly protein bound and is metabolised in the liver.
Unwanted actions include menstrual irregularities, gynaecomastia (androgen receptor binding), and also GI tract irritation. Contraindications are renal and hepatic diseases.

**Phaeochromocytomas** are tumours of the adrenal medulla which secrete catecholamines adrenaline and noradrenaline. Clinical features include hypertension in young people and episodic severe hypertension (after abdominal palpation). It is more common in certain inherited conditions. Severe hypertension can cause myocardial infarction or stroke, and high adrenaline can cause ventricular fibrillation and death, thus this is a medical emergency.

A phaeochromocytoma will eventually need surgery, but the patient needs careful preparation as anaesthetic can precipitate a hypertensive crisis. Alpha blockade is the first therapeutic step. Patients may need intravenous fluid as alpha blockade commences. Beta blockade is added to prevent tachycardia. 10% of phaeochromocytomas are extra-adrenal (sympathetic chain), 10% are malignant, 10% are bilateral, and are extremely rare.
**Hypoadrenal Disorders**
by Professor Karim Meeran

There are two cases where the cause of adrenocortical failure is due to the adrenal glands being destroyed, and one case where it is due to enzymes in the steroid synthetic pathway not working. Tuberculosis Addison’s disease is the commonest cause worldwide, but in the UK the most common cause is autoimmune Addison’s disease. Another cause of adrenocortical failure is congenital adrenal hyperplasia.

The consequences of adrenocortical failure include fall in blood pressure, loss of salt in urine, increased plasma potassium, fall in glucose due to glucocorticoid deficiency, high ACTH resulting in increased pigmentation, and eventual death due to severe hypotension. The increased pigmentation is because ACTH is made from the precursor POMC (pro-opio melanocortin). This is synthesised and broken down to ACTH and MSH (melanocyte stimulating hormone) and endorphins and enkephalins and other peptides.

Addison’s can be tested for if 9am cortisol is low and ACTH is high. A short synACTHen test is done (synthetic ACTH), whereby 250μg of synACTHen is given intramuscularly, and the cortisol response is measured. For example if 9am cortisol was 100 (normal 270-900), and after an intramuscular injection of synACTHen, cortisol at 9.30am could be found as 150 (normal >600), in which case the patient can be diagnosed with Addison’s.

The commonest cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency. This can be complete or partial. It is an inherited enzyme deficiency whereby cortisol and aldosterone are consequently deficient.

In complete 21-hydroxylase deficiency, the patient can survive for less than 24 hours or so as sodium will be lost in urine. This presents as floppy baby. Sex steroids and testosterone are in excess as the 17-OH progesterone follows through to becoming sex steroids. Presentation as a neonate will be with a salt losing Addisonian crisis. Before birth (while in utero), the foetus gets steroids across the placenta. Girls might have ambiguous genitalia (virilised by adrenal testosterone).

In partial 21-hydroxylase deficiency, cortisol and aldosterone are slightly low. There is a high ACTH and a high 17-OH progesterone, which leads to there being a high testosterone and again sex steroids are in excess. Patients in this case, however, can present at any age as they survive. The main problem later in life is Hirsutism and virilisation in girls and precocious puberty in boys due to adrenal testosterone.

11-deoxycorticosterone behaves like aldosterone. In excess it can cause hypertension and hypokalaemia. In 11-hydroxylase deficiency, cortisol and aldosterone are deficient while 11-deoxycorticosterone levels are high. Sex steroids and testosterone and 11-deoxycorticosterone are in excess, and problems include virilisation, hypertension and hypokalaemia.

In 17-hydroxylase deficiency cortisol and sex steroids are deficient, while 11-deoxycorticosterone and aldosterone (mineralocorticoids) are in excess. Problems include hypertension, low potassium, sex steroid deficiency and glucocorticoid deficiency (low glucose).
Adrenal Steroids as Anti-Inflammatory and Immunosuppressive Drugs
by Dr Pat Cover

Control of adrenal steroid production is influenced by many factors including circadian stimuli and stress. These lead to CRH being released from the hypothalamus, which stimulates the release of ACTH from the anterior pituitary. Aldosterone is secreted from the adrenal gland when stimulated by the renin-angiotensin system.

The glucocorticoids (cortisol and synthetic cortisol analogues) are an important group of drugs and are used:
- for replacement therapy in patients with adrenocortical insufficiency
- to provide replacement therapy and quench ACTH (and hence adrenal androgen production) in congenital adrenal hyperplasia
- in differential diagnosis of Cushing’s syndrome
- to control inflammation
- to produce immunosuppression in hypersensitivity, autoimmune disease and transplant patients (prevention of rejection)
- in the treatment of neoplastic disease
- to mature the foetal lung prior to pre-term birth

Inflammation
Glucocorticoids are a powerful defence response, which enables the body to deal with pathogens. Organisms that are not normally pathogenic may initiate an inflammatory response if the host defence system is inadequate or suppressed by drugs. An inappropriate inflammatory response may produce damage and constitute part of a disease process, for example in hypersensitivity reactions like anaphylaxis, or in chronic disease such as rheumatoid arthritis.

At the macroscopic level, inflamed tissue is red, hot, swollen and painful due to vasodilation, increased blood flow, local oedema and activation of sensory afferents. In addition, local tissue function is impaired (e.g. restricted movement of joints) or altered (e.g. bronchospasm in asthma). If tissue damage like cell death or ulceration occurs, then local repair processes are initiated and scarring may occur as local cells become fibrous connective tissue. If the pathogen persists, the condition proceeds to chronic inflammation which additionally involves the destruction of local tissue and proliferation of local cells, fibrous connective tissue and blood vessels. Mechanisms of inflammation can be innate or acquired.

Innate (non-immunological) responses comprise vascular and cellular events which are triggered by pro-inflammatory mediators derived from plasma (e.g. complement factors) and from local and invading cells (e.g. histamine, eicosanoids, nitric oxide and cytokines).

Vascular events:
- vasodilation and increased blood flow
- increased capillary permeability → leakage of plasma into the tissue
- activation of enzyme cascades in the exudate with the consequent release of mediators (bradykinin and complement factors) which:
  o cause pain
  o induce further increases in vascular permeability and in mediator release from local cells (e.g. histamine, eicosanoids)
  o act as spasmogens
  o are chemotactic and activate phagocytic cells
  o cause bacterial lysis

Cellular events:
(local)
- mast cells: release pro-inflammatory mediators e.g. histamine, eicosanoids and cytokines in response to complement and antigen
- tissue macrophages: release cytokines, chemoattractants and other mediators, engulf debris, dead cells, and micro-organisms; kill pathogens
- **endothelial cells**: release vasodilators and other mediators (e.g. cytokines); contribute to angiogenesis
- **fibroblasts**: produce matrix proteins and lay down fibrous tissue in areas of healing and chronic inflammation

*(migrate from blood into tissue)*

- **polymorphonuclear leukocytes**: neutrophils and subsequently eosinophils are recruited by chemoattractants; they kill invading pathogens by releasing toxic oxygen products and (if activated inappropriately) will damage host tissue
- **monocytes**: these enter at a later stage and are transformed into and function as tissue macrophages
- **platelets**: release eicosanoids, free radicals; also contribute to tissue repair processes

Acquired (specific) immunological responses may also contribute to the inflammatory response. Such responses may be initiated by antigenic products of invading micro-organisms which reach the lymph nodes; hypersensitivity (inappropriate) reactions to exogenous substances; or hypersensitivity reactions to endogenous proteins that are normally innocuous (i.e. autoimmunity).

The induction and effector phases of lymphocyte activation:

![Diagram of lymphocyte activation](image)

The antigen is presented by **antigen presenting cells** to naïve CD4⁺ T-helper cells which respond by expressing IL-2 receptors and IL-2 protein. IL-2 acts as an **autocrine** agent causing **proliferation** of the cells and the subsequent generation of a clone of activated T-cells (Th0). Th0 cells differentiate into either Th1 or Th2 subsets. Th1 cells produce IL-2 and IFN-γ which cause the cells to proliferate and differentiate into CD8⁺ T-cells which effect cell mediated responses. Th2 cells produce IL-4 which acts on B cells causing them to proliferate and generate antibodies which mediate humoral immune responses.

Drugs that are used to treat inflammation include **non-steroidal anti-inflammatory drugs** (NSAIDS) for example aspirin, and **steroidal anti-inflammatory drugs** like glucocorticoids. Glucocorticoids inhibit the early and late stages of the inflammatory response by modifying vascular events and cellular events. In terms of vascular events they **inhibit the vasodilator** response and **reduce fluid exudation**. They modify cellular events by reducing the influx and activity of PMNs, inhibiting the recruitment and activity of mononuclear cells, inhibiting angiogenesis, blocking clonal proliferation of T-cells (therefore reducing T-cell dependent immunity), and also by inhibiting fibroblast function.
These responses reflect the ability of steroids to:

- inhibit the production of a number of pro-inflammatory mediators, including histamine, eicosanoids (prostanoids, leukotrienes and PAF), cytokines which drive immune responses, complement components and nitric oxide.
- stimulate the production of anti-inflammatory proteins such as annexin-1.
- suppress the production of extracellular matrix formation by inhibiting matrix factors such as collagen and glycosaminoglycans, and also by enhancing the production of degrading enzymes e.g. collagenase.

Glucocorticoids exert their actions mainly through interactions with intracellular receptors termed glucocorticoid receptors (GR). When activated by ligand, these receptors act directly or indirectly as transcription factors and up or down regulate the expression of specific target genes.

The number of the genes the glucocorticoids target is large and includes many of those concerned with host defence processes. They include for example:

- genes encoding inflammatory cytokines
- enzymes required for the biosynthesis of pro-inflammatory mediators
- proteins which modify the activity of these enzymes

Examples of Drugs

Hydrocortisone (the approved name for cortisol) is used clinically in the treatment of inflammatory disease. However, when given systemically in doses sufficient to produce a beneficial clinical effect, it binds to mineralocorticoid receptors (MR) and produces unwanted aldosterone-like effects. Modifications to the cortisol molecule have led to the development of analogues with a higher degree of selectivity for the glucocorticoid receptor, for example prednisolone and dexamethasone.

Administration of these steroids are all effective orally but may also be given parenterally (e.g. intravenous, intramuscular, subcutaneous) if required. In addition, they may be administered locally, for example, to the respiratory tract (inhalation), to the skin (as ointments or creams) or in inflamed joints by local injection. Hydrocortisone binds to a specific carrier protein (corticosteroid binding globulin, CBG) and also to albumin.
Approximately 90-95% in the blood is protein bound. The free steroid penetrates all compartments of the body. Prednisolone also binds to CBG but dexamethasone binds only weakly to albumin.

The steroids are metabolised mainly in the liver, the principal step being reduction of the A ring and then further modifications such as conjugation before excretion via bile and urine. Hydrocortisone has a plasma half life of around 8 hours. The effects of prednisolone persist for longer (up to 12 hours) while dexamethasone is long acting (over 36 hours) because metabolism is slow.

Clinically, glucocorticoids are used in treating disorders of the HPA axis (Addison’s disease, congenital adrenal hyperplasia, differential diagnosis of Cushing’s syndrome/disease). They are also used in pregnancy to mature the foetal lung for pre-term birth. They are used in anti-inflammatory and immunosuppressive therapy:

- Asthma
- Inflammatory conditions of the skin, nasal mucosa, ear, eye, joints
- Autoimmune/inflammatory disease, e.g. rheumatoid arthritis
- Other autoimmune disease, e.g. myasthenia gravis
- To prevent rejection following organ or bone marrow transplants

Glucocorticoids are also used in treatment of neoplastic disease:

- In combination with cytotoxic drugs in specific malignancies, e.g. acute lymphocytic leukaemia
- To reduce cerebral oedema in patients with brain tumours
- As a component of anti-emetic treatment with chemotherapy
- To elevate mood in terminally ill subjects

The unwanted effects of glucocorticoids are usually due to the effects of prolonged glucocorticoid excess, which leads to iatrogenic Cushing’s syndrome.

The typical symptoms will include potassium loss, sodium and water retention, hypertension, muscle wasting, centripetal obesity, moon face, buffalo hump, hyperglycaemia (leading to steroid diabetes), increased appetite, osteoporosis, increased risk of infection, poor wound healing, easy bruising, impaired growth, disorders of menstruation, suppression of the hypothalamo-pituitary-adrenocortical axis, mood changes, normally euphoria but sometimes depression, increased risk of cataracts and peptic ulcers, and also suspected actions on the foetus/neonate that may predispose the individual to diseases in adulthood such as hypertension and type 2 diabetes.

Ways to minimise the unwanted effects of corticosteroids:

- Administer locally where possible
- Use minimum effective dose
- Use a GR-selective steroid
- Use ACTH in children to reduce growth suppression
- Recommend patients carry a steroid card
- Withdraw steroids slowly

Euphoria
(though sometimes depression or psychotic symptoms, and emotional lability)

Buffalo hump
(Hypertension)

Moon face, with red (plethoric) cheeks

Increased abdominal fat

(Avascular necrosis of femoral head)

Easy bruising

Poor wound healing

Thinning of skin

Thin arms and legs: muscle wasting

(Benign intracranial hypertension)

(Cataracts)

Also:

Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
Increased susceptibility to infection
Obesity
**Therapeutic Use of Adrenal Steroids**
by Dr Glenda Gillies

The adrenal cortex produces three types of steroid hormone:

- **Glucocorticoids** (principal steroid = cortisol).
- **Sex steroids**, mainly androgens (principal steroid = dehydroepiandrosterone, DHEA).
- **Mineralocorticoids** (principal steroid = aldosterone).

The synthesis of both the glucocorticoids and the adrenal androgens is driven by ACTH which is produced by the anterior pituitary gland. The secretion of cortisol follows a circadian rhythm with the highest levels occurring just before waking (which leads to increased awareness and brain function, cortisol primes the body to deal with stress). In addition, substantial amounts of cortisol are released in response to stress (e.g. infection) to have protective actions. Failure of adequate cortisol response to stress is potentially fatal. The synthesis of aldosterone is controlled by the renin-angiotensin system which is sensitive to changes in blood K⁺ and Na⁺, renal blood flow and sympathetic activation.

**Glucocorticoids** represent an important group of drugs. They are used clinically:
- For replacement therapy in patients with adrenocortical insufficiency
- To provide therapy and to quench ACTH and hence adrenal androgen production in congenital adrenal hyperplasia
- In the differential diagnosis of Cushing’s syndrome (dexamethasone suppression test)
- To control inflammation
- To produce immunosuppression in hypersensitivity, autoimmune disease and transplant patients (prevention of rejection)
- In the treatment of neoplastic disease
- To mature the foetal lung prior to preterm birth

**Adrenal androgens** are not used clinically in the UK.

**Aldosterone derivatives** have an important place in the treatment of certain types of adrenocortical insufficiency while aldosterone receptor antagonists are used to control primary hyperaldosteronism and (normally in combination with other drugs) as diuretics in the treatment of oedema.

**Cortisol**
This hormone exerts widespread actions in the body, e.g. influencing metabolism (increased hepatic gluconeogenesis, protein breakdown in e.g. muscle and soft tissues, lipid mobilisation), host defence processes, bone turnover, mood and behaviour. Importantly, cortisol provides protection from stress-induced hypotension, shock and death. **Failure to release adequate amounts of cortisol in stress is potentially fatal.** The mechanisms underlying these life-maintaining actions are not well understood, but appear to involve both permissive and protective actions of the steroids.

**Permissive actions:** these actions are evident at low levels of cortisol (i.e. those which occur in the absence of stress) and serve to prime the body to respond to and deal with a stressful insult. For example, cortisol up-regulates cytokine receptors; these receptors are essential for an organism to mount an effective immune response and combat an infection.

**Protective actions:** these actions are evident at higher concentrations of cortisol, such as those which occur in stress, and serve to check the body’s response to stress and prevent it proceeding to a point where it damages the host. For example, cortisol suppresses the release of inflammatory mediators which, if unchecked, may
cause e.g. hypotension, oedema and tissue damage. These actions of cortisol are responsible for the anti-inflammatory properties of the glucocorticoids which are exploited clinically in the treatment of inflammatory diseases such as asthma and rheumatoid arthritis.

Adrenal Androgens
The physiological role of the adrenal androgens is poorly understood although there is evidence that they contribute to the development and maintenance of secondary sexual hair pattern and growth in the female; excessive adrenal androgen production is however problematical as exemplified by congenital adrenal hyperplasia.

Aldosterone
This hormone acts mainly on the kidney, causing potassium loss and sodium retention, and as water follows sodium, water is also retained.

Mechanism of Corticosteroid Action
Adrenal steroids exert their actions mainly through interactions with intracellular receptors which, when activated by ligand, act as transcription factors and up or down regulate the expression of specific target genes.

The proteins whose expression is altered are responsible for affecting the biological responses to the steroids.

The biological response of exogenous steroids are thus usually slow in onset (1 or 2 hours) with a long duration of action (about 8 hours).

Receptors for Adrenal Steroids
The receptors for cortisol and aldosterone are frequently called corticosteroid receptors; there are two classes which differ in their distribution, their steroid specificity and their affinity for cortisol.

Glucocorticoid receptors (GR) have a wide distribution and are selective for glucocorticoids and they have a low affinity for cortisol.

Mineralocorticoid receptors (MR) have a discrete distribution, particularly in the kidneys. They do not distinguish between aldosterone and cortisol. They have a high affinity for cortisol.

In normal circumstances mineralocorticoid receptors in the kidneys and sweat glands are protected from cortisol by 11β-hydroxysteroid dehydrogenase (11βHSD) which inactivates cortisol in the target cell by converting it to cortisone. However, when present in high concentrations cortisol gains access to the receptors and exerts mineralocorticoid activity.

Adrenal androgens, which in many cases are metabolised to testosterone in the peripheral tissues, exert their actions via androgen receptors. Androgenic steroids are not used in the treatment of adrenal dysfunction.

Drugs
Cortisol (hydrocortisone) - glucocorticoid with mineralocorticoid activity at high doses
Prednisolone - glucocorticoid with weak mineralocorticoid activity
Dexamethasone - synthetic glucocorticoid with no mineralocorticoid activity
Fludrocortisone - aldosterone analogue used as an aldosterone substitute


**Hydrocortisone** is used clinically for replacement therapy and also in the treatment of inflammatory disease.

However, as its use in the latter is frequently associated with unwanted mineralocorticoid activity, synthetic steroid analogues which show more selectivity for the glucocorticoid receptor are frequently used in preference to control inflammation, to produce immunosuppression and in the treatment of neoplastic disease.

These analogues are also used in the treatment of congenital adrenal hyperplasia and in the diagnosis of adrenal disease. Examples include:
- **Prednisolone** which shows only weak mineralocorticoid activity
- **Dexamethasone** which has no mineralocorticoid activity

Aldosterone is not used clinically as it is not effective when given by mouth. An aldosterone analogue termed **Fludrocortisone** is used as a substitute.

**Pharmacokinetics**

**Administration:** these steroids are all effective by mouth but hydrocortisone, prednisolone and dexamethasone may also be given parenterally (IV, IM) if required.

**Distribution:** hydrocortisone binds to a specific carrier protein (corticosteroid binding globulin CBG) and also to albumin. Approximately 90-95% in the blood is protein bound. The free steroid penetrates all compartments of the body. Prednisolone also binds to plasma protein but dexamethasone and Fludrocortisone bind only weakly to albumin.

**Metabolism:** the steroids are metabolised mainly in the liver, the principal step being reduction of the A ring and other modifications, conjugation, and excretion via bile and urine. Hydrocortisone and Fludrocortisone have a plasma half life of about 1.5 hours but a duration of action of about 8 hours. The effects of prednisolone persist for longer (up to 12 hours) while dexamethasone is long acting (more than 36 hours) because metabolism is slow.

**Replacement Therapy**

**Primary adrenocortical failure**, or chronic adrenal insufficiency (Addison’s disease) is when patients are deficient in both cortisol and aldosterone. It is therefore necessary to replace both hormones, i.e. use hydrocortisone and fludrocortisone in titrate doses.

**Secondary adrenocortical failure (ACTH deficiency)** is when patients are lacking cortisol but not aldosterone. They are therefore treated with hydrocortisone only in titrate doses.

Emergency treatment in **acute adrenocortical failure** means a parenteral route of administration is needed. Hydrocortisone or dexamethasone (longer duration) is given intravenously or intramuscularly, and saline is given to rehydrate the patient. Glucose is also given.

**Congenital adrenal hyperplasia** arises as a result of an enzyme deficiency in the adrenal cortex. The most common deficiency is a lack of 21-hydroxylase, leading to a deficiency of both cortisol and aldosterone. Deficiencies in other enzymes are rare. A lack of 11β-hydroxylase is often associated with hypertension as 11-deoxycorticosterone has mineralocorticoid activity.

The reduction in cortisol production reduces the negative feedback inhibition. ACTH secretion is thus increased and adrenal androgen production is therefore enhanced markedly.
The objectives of therapy are to replace cortisol, suppress ACTH (and thus adrenal androgen production), and to replace aldosterone in salt wasting forms. Oral dexamethasone can be given daily at night. It is a long-acting steroid and will therefore not only replace cortisol but also effectively suppress the morning rise in ACTH. Adrenal androgen production will therefore be suppressed. Alternatively, hydrocortisone or prednisolone may be used (twice daily with a higher dose at night) in doses which are sufficient to reduce ACTH secretion. Fludrocortisone is also given orally in two divided doses in salt wasting forms.

The effectiveness of dexamethasone, hydrocortisone and prednisolone in suppressing androgen production may be monitored by measurement of adrenal androgens or the 17β-hydroxyprogesterone response to exogenous ACTH.

Dexamethasone is not recommended for children as it impairs growth. The neonatal kidney is relatively insensitive to fludrocortisone, therefore higher doses are needed in infants.

Protective Measures for patients with Adrenocortical Insufficiency

Normal subjects produce about 20mg of cortisol per day, but in severe stress production may rise to 200-300mg per day. Subjects with adrenocortical insufficiency are unable to produce cortisol in conditions of stress, e.g. in response to minor infections or surgery. It is therefore important to provide additional exogenous steroid to protect them if they are vulnerable to stress.

In minor illnesses the hydrocortisone dose is increased two or three times above the normal dose. In surgery, hydrocortisone is administered intramuscularly (100mg) with the pre-anaesthetic medication and repeated at 6 to 8 hour intervals. The dose is slowly reduced thereafter until the normal maintenance dose is reached. In preparation for adrenalectomy or hypophysectomy the same regime is used as for surgery.

In addition to the causes detailed above, adrenal insufficiency may also be caused by long-term treatment with high doses of glucocorticoids in, for example, chronic inflammatory disease. This is iatrogenic adrenocortical failure. These patients also require protection with exogenous glucocorticoids during surgery. Patients on corticosteroid therapy are advised to carry a steroid card detailing their dosage and condition. Iatrogenic failure may also be seen in patients on inhibitors of steroid synthesis e.g. Metyrapone.
Oral Contraceptives, HRT and SERMs
by Dr Glenda Gillies

There are some clinically useful oestrogens and progestogens/progestins used in practice, namely there is 17-β oestradiol and its esters (e.g. valerate).

Oestradiol and its esters are well absorbed but they undergo extensive first pass metabolism. Oestradiol esters may be given by injection, usually intramuscularly in oil. The oil vehicle delays absorption, maintains plasma levels over extended periods and prolongs the duration of action. Conjugated oestrogens are excreted in bile and urine.

Oestriol is a natural, orally active oestrogen.

Oestrone sulphate is a ‘conjugated’ oestrogen (natural and Premarin), which is orally active and is hydrolysed to a more active oestrogen within peripheral tissues. Ethinyl oestradiol is a semi-synthetic oestrogen. It is an oestradiol with an ethinyl group on carbon 17. It is an orally active drug of choice that is resistant to metabolism. Most oestrogens can also be administered via transdermal skin patches, as oestrogens readily cross membranes and a skin patch avoids first pass metabolism. In terms of bioavailability, 70% of circulating oestrogens are bound to plasma proteins such as sex steroid hormone binding globulin and albumin.

Clinically used progestogens fall into two groups:
- Progesterone and its analogues such as medroxyprogesterone acetate. Progesterone is poorly absorbed, and is also rapidly metabolised by the liver. It can be given by intramuscular injection in an oily vehicle as a depot preparation.
- Testosterone analogues such as norethisterone. A variety of orally active synthetic progestogens are available (like norethisterone). These bind to SHBG and albumin in circulation. Synthetic progestogens are variously metabolised to other biologically active steroids.

Combined Oral Contraceptives
These are usually a combination of an oestrogen (ethinyl oestradiol) with a second - or third - generation progestogen (e.g. norethisterone). This combination provides additive and synergistic pharmacology to maximise efficacy at minimal drug concentrations to suppress ovulation via multiple mechanisms.

For example, there are feedback actions of oestrogen and progesterone at the hypothalamus and pituitary to influence the LH surge and ovulation and suppress menstrual cycling. Also, progesterone thickens the cervical mucus to provide an environment inhospitable to sperm. Oestrogen up regulates progesterone receptors to enhance sensitivity to progesterone and oestrogen also counteracts the androgenic effects of synthetic progesterone to prevent masculinisation.

A combined oral contraceptive is usually taken for 21 days and then stopped for 7 days. At doses that produce inappropriate (unphysiological) hormone concentrations, fertility is disrupted. Monophasic means there is one concentration taken throughout. Triphasic means there are 3 step-wise changes in the oestrogen/progesterone ratio.

There are unwanted effects of oestrogen on blood clotting factors. Clotting factors are increased, and so there is increased incidence of thromboembolic disease (chronic usage of high doses). There are also unwanted effects on the
endometrium, as there is increased proliferation and so an increased risk of endometrial cancer. This is reduced by co-administration of progestogens. There are also unwanted effects on the breast. Patients often experience breast discomfort and there is an increased risk of breast cancer (controversial). In the kidney there is increased salt and water retention, which may cause oedema and accentuate oedema due to other causes e.g. cardiac failure or kidney disease. This also contributes to hypertension and weight gain. There are also unwanted effects in the chemoreceptor trigger zone and vomiting centre of the brain, which causes nausea and headaches. Weight generally increases due to fat deposition.

Progestogen-Only Contraceptives
These may be used when oestrogens are contra-indicated in patients. For example, if they have CVS problems, a history of thrombosis, if they are prior to major surgery or during lactation. They are administered orally, or long acting preparations may be given by deep intramuscular injection (e.g. medroxyprogesterone acetate / Depot-Provera) or via an intra-uterine system.

“Emergency” Contraception (Post-Coital Pill/Morning After Pill)
These are combined oestrogen and progestogen (prescription only) pills or progestogen alone (over the counter) pills, at doses higher than those used in normal combined oral contraceptives. Two doses are taken 12 hours apart, beginning as soon as possible and within 72 hours of intercourse. A single one-step double strength tablet is also available. Side effects include nausea and vomiting, in which case the dose should be repeated if necessary, and it may require the co-administration of an anti-emetic.

In terms of effectiveness, they prevent 75-85% of pregnancies that might otherwise occur after unprotected intercourse. As for risks if unsuccessful, there are no reported harmful effects to the woman, the course of her pregnancy, or the foetus. Caution should be taken, as it is ineffective in terminating an established pregnancy, and so it should not be used with a known or suspected pregnancy.

Menopause is the permanent cessation of menstruation resulting from the loss of ovarian follicular activity and 12 months of amenorrhea at the time of midlife. The average age for this is 51, with the range being between 45 and 55. Premature menopause (or premature ovarian failure) is menopause occurring before the age of 40, and this occurs in 1% of women. Causes of premature menopause includes surgical and autoimmune (family history & investigate for other associated autoimmune conditions). Other causes of secondary amenorrhea should be excluded, such as pregnancy or a pituitary problem like a prolactinoma.

Climacteric = the period of transition from predictable ovarian function through the post-menopausal years. There is waning ovarian function and a dramatic decline in oestrogen production.

The symptoms of menopause begin with irregular cycles and hot flushes (head, neck, upper chest). Women experience an increased pulse rate and profuse sweating. These flushes often last about 4 minutes, and occur at night (insomnia). 80% of women are affected in this way. Most flushes resolve within a year. Women may also experience psycho-social symptoms like depression, mood swings and a loss of energy. They get thin, translucent skin because of the oestrogen deficiency causing a loss of collagen. Women also experience a decreased libido, and also urogenital atrophy (increased urgency, nocturia, incontinence, dryness of the vagina, and discomfort with intercourse aka dyspareunia). These symptoms usually diminish and disappear with time.
There are a few complications of menopause. One major and well known complication is osteoporosis. Oestrogen deficiency leads to a loss of bone matrix. Post-menopausal women may lose 1-3% of bone mass per year, and they have a 10 fold increased risk of fracture. Another complication is cardiovascular disease.

Menopause treatments are available for control of these symptoms. The main treatment is hormone replacement therapy (HRT). Oestrogen-only HRT is given to women who have had a hysterectomy. All others are combined HRT (oestrogen and progestogen) to prevent endometrial hyperplasia. HRT formulations may be orally administered, given as a transdermal patch or gel, a percutaneous slow release implant, an intranasal spray or may be intravaginal oestrogens. Hormone replacement therapy provides agonists of oestrogen to act on receptors on bone, breast and endometrium.

The advantages of HRT are that vasomotor symptoms like flushing are controlled, and osteoporosis is delayed. HRT is the first line choice only if vasomotor symptoms are a problem, otherwise alternatives like bisphosphonate or raloxifene are tried first. Although not proven, there may also be protective effects against ischaemic heart disease, symptoms of Alzheimer’s disease and colon cancer. There are, however, disadvantages of HRT. Oestrogen promotes endometrial proliferation and increases the risk of endometrial carcinoma. Including progestogens in the HRT formulation will reduce the risk of endometrial cancer. A woman who has a uterus must never take unopposed oestrogen. HRT also increases the risk of breast cancer after 5 years of use. HRT is therefore contra-indicated if there has been a previous diagnosis of breast cancer. HRT also increases the risk of gallstones, and the risk of venous thromboembolism. HRT is therefore contra-indicated if the patient has a high risk of VTE (overweight, family history, past history). There are also increased risks of cardiovascular accidents.

Whether or not to take hormone replacement therapy is the patient’s decision after education and counselling. Benefits of treatment should outweigh the risks, but 50% of women discontinue HRT after 1 year. It is common to treat normal menopausal women for 5 to 7 years, and to treat premature menopause until a normal menopause age.

Tibolone is a synthetic prohormone of oestrogen, progestogen and androgen (weak). As a synthetic prohormone it is a “designer HRT”. It provides relief of vasomotor symptoms of menopause, and is as effective as HRT. It increases bone density, and we are still waiting on data regarding fractures and the link with endometrial and breast cancer.

SERMs are selective oestrogen receptor modulating drugs. They do not have the classical steroid structure and their actions are tissue selective. They are thought of as “designer oestrogens”. They bind to oestrogen receptors (α and β) with high affinity, and therefore displace oestradiol. This means that they activate oestrogen metabolic pathways (agonist), but in some tissues by binding to the receptor they effectively block the ability of oestrogen (antagonist).

Tamoxifen is a commonly used SERM that has agonist activity in bone and uterus, but antagonistic activity in breasts. Tamoxifen is an anti-cancer drug used to treat oestrogen-dependent breast tumours and metastatic breast cancers. It has oestrogen like effects on the liver (lower cholesterol), bone (increase density) and on endometrial tissue (unfortunately increased risk of cancer). Side effects of Tamoxifen include endometrial changes (hyperplasia, polyps, cancer); bone pain with bony metastases; hot flushes; menstrual irregularities; and gastrointestinal disturbances.

Raloxifene has agonist effects on bone, but antagonist effects on breast and uterus. It is used in the treatment and prevention of postmenopausal osteoporosis, reducing the risk of vertebral fractures and breast cancer. Unfortunately it is associated with increased risk of fatal stroke, venous thromboembolism, and it doesn’t reduce vasomotor symptoms.

Clomiphene is a fertility drug used in women who are infertile due to a lack of ovulation. It is anti-oestrogenic in the hypothalamo-pituitary axis, as it blocks normal negative feedback to increase GnRH, LH and FSH secretion. Side effects include ovarian hyperstimulation, hot flushes, nausea, vomiting and headaches.
**Endocrine Infertility**
by Dr Waljit Dhillo

Normal reproductive physiology in males involves GnRH from the hypothalamus acting on the pituitary to release LH and FSH, which have different effects on the testes. In females, the normal 28 day menstrual cycle includes the follicular phase, ovulation and the luteal phase. LH and FSH released from the pituitary affect the ovaries, and regulate the production of oestrogen and progesterone. If implantation does not occur, then the endometrium is shed (menstruation). If implantation does occur, then this leads to pregnancy.

**Infertility** is the inability to conceive after 1 year of regular unprotected sex. It is a condition that affects 1 in 10 couples. In 30% of cases it is caused by abnormalities in the male, in 45% of cases the female, and in 25% of cases the cause of abnormality is unknown.

**Primary gonadal failure** is where there is high GnRH and therefore also high LH and FSH, but the testes or ovaries are unresponsive, leading to low testosterone or oestradiol. In hypopituitary disease there is low GnRH, which means there is low LH and FSH and so consequently the effects on the testes and ovaries are small, leading to low testosterone and low oestradiol.

**Disorders in Males**

A disorder in the male is hypogonadism. The clinical features of hypogonadism include loss of libido, impotence, small testes, a decrease in muscle bulk, and osteoporosis. It can be caused by hypothalamic-pituitary disease (hypopituitarism), for example a tertiary hypopituitarism is Kallmann’s syndrome caused by low GnRH. In a 16 year old boy Kallmann’s syndrome would present with testes originally undescended and a low to normal stature. It can also be caused by illness and being underweight. **Primary gonadal disease** is usually congenital, for example Klinefelter’s syndrome (XXY), where there is 5α-reductase deficiency. It can be acquired, for example by testicular torsion or chemotherapy. **Hyperprolactinaemia** is another cause of hypogonadism, as is androgen receptor deficiency.

There are a couple of investigations that can be carried out in male hypogonadism. Firstly **LH, FSH and testosterone** should be measured, if all are low then perhaps an MRI scan of the pituitary could confirm. **Prolactin levels** could be measured, a sperm count conducted (azoospermia is the absence of sperm in ejaculate, oligospermia is reduced numbers of sperm in ejaculate), and also a chromosomal analysis could confirm Klinefelter’s.

Treatment involves replacement **testosterone** for all patients. For fertility (if hypothalamic-pituitary disease) then replacement **GnRH and gonadotrophins** (LH and FSH) should be given. Hyperprolactinaemia can be treated with **dopamine agonists**.

**Androgens**

Endogenous sites of androgen production include interstitial Leydig cells of the testes, adrenal cortex, ovaries, placenta and tumours. The main actions of testosterone are in the development of the male genital tract. The hormone maintains fertility in adulthood and controls secondary sexual characteristics. It also has anabolic effects in building muscle and bone.

In the circulation, testosterone is 98% protein bound following tissue-specific processing. 5α-reductase converts testosterone into dihydrotestosterone (DHT) which acts via the androgen receptor (AR). Aromatase converts testosterone into 17β-oestradiol (E2) which acts via the oestrogen receptor (ER) e.g. in the brain and in adipose tissue. The mechanism of action of both these hormones is via nuclear receptors.

Testosterone also has clinical uses, for example in adulthood it will increase lean body mass, muscle size and strength, bone formation and bone mass, and also libido and potency. It will not restore fertility, which requires treatment with gonadotrophins or pulsatile GnRH to restore normal spermatogenesis.
Disorders in Females

Amenorrhoea is the absence of periods. Primary amenorrhoea means there is failure to begin spontaneous menstruation by the age of 16 years. Secondary amenorrhoea means absence of menstruation for 3 months in a woman who has previously had cycles. Oligomenorrhoea is irregular long cycles.

The main cause of amenorrhoea is pregnancy / lactation. However a cause can also be ovarian failure. This can be premature ovarian failure, it can be due to ovariectomy or chemotherapy, and it can be due to ovarian dysgenesis (Turner’s 45X where a chromosome is lacking, 1 in 5000 live births). Turner’s syndrome in a 12 year old girl would present with short stature, cubitis valgus (wide carrying angle), and gonadal dysgenesis.

Gonadotrophin failure is also a cause of amenorrhoea. This can be because of hypothalamic-pituitary disease, Kallmann’s syndrome, low BMI or it could be post pill amenorrhoea. Amenorrhoea can also be caused by hyperprolactinaemia, as well as androgen excess (gonadal tumour).

A number of investigations can be done. The first is a pregnancy test, then if that is negative LH, FSH and oestradiol levels, day 21 progesterone, prolactin and thyroid function tests. Androgens can also be measured (testosterone, androstenedione, DHEAS), and chromosomal analysis may prove useful in confirming Turner’s 45X. Ultrasound scans of the ovaries and uterus can also be carried out.

Treatment is by treating the cause (e.g. low weight). Primary ovarian failure will lead to infertility, and should be addressed with hormone replacement therapy. Hypothalamic-pituitary disease can be treated with GnRH and gonadotrophins (LH and FSH).

Polycystic ovarian syndrome (PCOS) has an incidence of 1 in 12 women of reproductive age. It is associated with increased cardiovascular risk and also insulin resistance. PCOS can be diagnosed by seeing polycystic ovaries on an ultrasound scan, if the patient presents with anovulation, and by measuring clinical/biochemical androgen excess. Clinical features of PCOS include Hirsutism, menstrual cycle disturbance, and an increased BMI.

Treatment of PCOS uses Metformin, as well as reverse circadian prednisolone, which suppresses pituitary ACTH production which drives adrenal androgen production to increase regular cycles. Clomiphrene is also used. This is a fertility drug, an anti-oestrogenic in the hypothalamo-pituitary axis. It binds to oestrogen receptors in the hypothalamus thereby blocking the normal negative feedback, resulting in an increase in the secretion of GnRH and gonadotrophins. PCOS is also treated using gonadotrophin therapy.

Hyperprolactinaemia is another common disorder in females. The use of anti-emetics and anti-psychotics, and other dopamine antagonist drugs can cause hyperprolactinaemia. A prolactinoma could also be the cause, and the patient may present with acromegaly. Stalk compression due to a pituitary adenoma can also cause hyperprolactinaemia. Other causes include PCOS, hypothyroidism, oestrogens, pregnancy, lactation, or it can be idiopathic.

The clinical features of hyperprolactinaemia include galactorrhoea, reduced GnRH secretion/LH action, and a possible prolactinoma which also causes headaches and visual field defects.

First line treatment is to treat the cause, for example to stop taking dopamine antagonist drugs. Instead, dopamine agonist drugs should be given to treat the hyperprolactinaemia (Bromocriptine and Cabergoline). A prolactinoma can be treated with dopamine agonist therapy, and rarely pituitary surgery.
Endocrinology of Pregnancy
by Professor John Laycock

Fertilisation
The voyage of the spermatozoon from testis to oviduct is a long one: 100,000 times its own length, which is comparable to 150km for a 1.5m human being! It is also one taken very much against all odds of success, as less than one spermatozoon per 100,000,000 actually reaches the ovum.

Within the male reproductive tract, most tubular fluid is reabsorbed within rete testis and early epididymis under oestrogen control (oestrogen mainly in tubular fluid produced by Sertoli cells). Nutrients and other molecules (e.g. glycoproteins) are secreted into the epididymal fluid under the influence of androgen to provide energy for the impending possible journey, and to coat the surface of the spermatozoa (possible protection from hostile environment). These secretory products are vital for the maturation process.

Semen is ejaculated into the female tract (usually into the vagina, sometimes into the cervical canal). Semen consists of spermatozoa (15-120x10^6/ml), seminal fluid (2-5ml), leukocytes, and potentially viruses like hepatitis B or HIV.

Seminal fluid has a small contribution of components such as inositol, carnitine and glycerylphosphorylcholine from the epididymis/tests, but is mainly from the accessory sex glands. These are the seminal vesicles which contribute fructose and fibrinogen, and the prostate, which contributes citric acid (Ca^{2+} chelator), acid phosphatase, fibrinogenase and fibrinolytic enzyme). Other accessory organs include the ampulla and bulbourethral glands.

Taken from the seminiferous tubule, spermatozoa are quiescent and incapable of fertilizing an ovum. Taken from the vas deferens, spermatozoa are capable of movement (‘whiplash’ activity) and have some capability for fertilizing an ovum. However, full activity and fertilizing capacity is only achieved within the female reproductive tract. This is known as capacitation.

Capacitation of sperm has a number of steps. Firstly, there is the loss of the glycoprotein coat. Then there is a change in the surface membrane characteristics, leading to the acrosome reaction when in close proximity to an ovum. Then there are further whiplash movements of the tail. This takes place in the ionic and proteolytic environment of the oviduct, i.e. it is oestrogen-dependent. All components of capacitation are Ca^{2+} dependent. Note that only 1% of the spermatozoa in ejaculate enter the cervix.

In the acrosome reaction there is a Ca^{2+} influx into sperm stimulated by progesterone following the binding of sperm to ZP3 (short lived). This results in the Ca-dependent acrosome reaction. This enables an exposed spermatozoon binding site to bind to a second glycoprotein (ZP2). Subsequently the spermatozoon penetrates the zona pellucida (e.g. by releasing hyaluronidase and other proteolytic enzymes).

Fertilization normally occurs within the fallopian tube. It results in the expulsion of a second polar body, and leads immediately to the zona reaction, in which cortical granules release molecules that degrade zona pellucida (including ZP2 and ZP3) to prevent further binding of other sperm. This is also Ca^{2+} dependent. Once diploidy is established, the zygote starts dividing to form the initial 2-cell conceptus.

The conceptus continues to divide as it moves down the Fallopian tube to the uterus. This process takes 3 to 4 days. Until implantation the developing conceptus receives its nutrients from uterine secretions.
This free-living phase can last for about 9 to 10 days. The conceptus first compacts to an 8 to 16 cell **morula**, then into a **blastocyst** (inner cell mass becomes **embryo** and outer trophoblast becomes **chorion**). Transfer to the uterus is facilitated by increasing the progesterone to oestrogen ratio (luteal phase). It then establishes physical and nutritional contact with maternal tissues.

**Implantation** in humans is **invasive**. It involves the initial **attachment phase** when the outer trophoblast cells contact the uterine surface epithelium. Within a few hours, it results in **decidualization** of the underlying uterine stromal tissue. This requires **progesterone domination** in the presence of oestrogen.

In **attachment**, leukaemia inhibitory factor (LIF) from the endometrial secretory glands (and blastocyst) stimulates adhesion of the blastocyst to endometrial cells.

Interleukin-11 (IL11) is also released into uterine fluid and may be involved.

Many other molecules are involved in this process.

**Decidualization** involves the **invasion** of the underlying uterine stromal tissue by the trophoblast cells of the blastocyst. Within hours this results in increased **vascular** permeability in the invasion region associated with **oedema** of tissues, localised changes in **intracellular composition** and progressive sprouting and growth of **capillaries**. This is the decidualization reaction.

Factors involved in the decidualization reaction include mainly **interleukin-11** (IL11), histamine, certain prostaglandins, and TGF-β which promotes angiogenesis.

**Pregnancy**

During the first 5-6 weeks of pregnancy, the maternal ovaries release gonadal steroids that are essential for the developing fetoplacental unit.

The circulating progesterone and oestradiol concentrations are high and rising during this period, and the release of maternal LH and FSH are inhibited by negative feedback.

The stimulatory role of gonadotrophins on the corpus luteum is taken over by human chorionic gonadotrophin (hCG), which is produced by the developing implanting blastocyst (syncytiotrophoblast).

From day 40 onwards an ovariectomy will have no effect on pregnancy.

Maternal hormones such as thyrotrophin, corticotrophin, prolactin, growth hormone, iodothyronines, adrenal steroids and PTH increase.

Others like gonadotrophins decrease, and hGH decreases as the placental hGH-Variant increased towards term.
Parturition

Lactation
There are a number of vitamin D metabolites, the main one being 1,25(OH)$_2$D$_3$, or calcitriol. This is the most important metabolite, but 25(OH)D$_3$ can become important in excess where there is vitamin D intoxication. The principal effect of calcitriol is to stimulate intestinal absorption of Ca$^{2+}$ (and Mg$^{2+}$) and PO$_4^{3-}$. This provides the ions necessary for normal bone mineralisation. Calcitriol also stimulates osteoclast formation from precursors in bone and stimulates their activity as well as stimulating osteoblasts for matrix protein synthesis (e.g. osteocalcin) or repression (e.g. type 1 collagen). All the time bone is remodelling, and it is estimated that 10% of our bones are broken down and rebuilt every year.

A vitamin D deficiency state is defined as a lack of mineralisation in the bone. This results in softening of bone, deformities, pain, and severe proximal myopathy. Effects on skeletal muscle are recovered when vitamin D is replaced. In vitamin D deficiency the bone doesn’t have its normal strength, and this is seen particularly in the weight bearing bones of the body. In children the effect is very pronounced as rickets, and in adults the same condition is known as osteomalacia. The difference is that in adults the bones are fully formed as opposed to developing in the child. Bowing legs is characteristic of rickets. Other deformities also occur, such as rachitis, which is seen as wrist widening (increased cartilaginous growth in the absence of vitamin D).

Causes of vitamin D deficiency are varied, ranging from poor diet or lack of exposure to sunlight to gastrointestinal malabsorptive states, renal failure (this can be receptor defects).

A fault can occur at a variety of points in the diagram on the right, which will cause vitamin D deficiency:
- Lack of UV light
- Poor ergocalciferol intake in the diet
- Liver disease (impact on 25 OH-D$_3$
- Renal disease (impact on 1α-hydroxylase)
- Malabsorption disorders in the gut
- Receptor defects

When diagnosing vitamin D deficiency, the patient will usually have low plasma 25(OH)D$_3$ and low plasma Ca$^{2+}$ (unless secondary hyperparathyroidism has been induced when it may appear normal). PTH levels in the plasma will be high, and plasma phosphate will be low. The radiological findings are variable, for example you may see widened osteoid seams.

Decreased renal function has two main implications that will lead to hypocalcaemia. The first is decreased production of calcitriol, which causes decreased calcium absorption. The second is decreased phosphate excretion which leads to a higher plasma phosphate (which causes extra-skeletal calcification). The resulting hypocalcaemia means decreased bone mineralisation and increased levels of PTH being released into the circulation. The PTH causes increased bone resorption and diseases such as osteitis fibrosa cystica.

On the other hand, vitamin D excess (intoxication) can lead to hypercalcaemia and hypercalciuria due to increased intestinal absorption of calcium. Vitamin D excess can occur as a result of excessive treatment with active metabolites of vitamin D, as in patients with chronic renal failure. It can also occur as a result of granulomatous diseases, such as sarcoidosis, leprosy and tuberculosis, where the granulomatous tissues can convert 25(OH)D to the active metabolite 1,25(OH)$_2$D.

Paget’s disease is defined as very active (increased), localised, but disorganised bone metabolism. It is usually slowly progressive. The disease is characterised by the presence of abnormal, large osteoclasts. It has a significant genetic component, as up to 30% of cases are autosomal dominant, although there is evidence for a viral origin. Men and women are affected equally, although men may be more symptomatic. The disease is usually not apparent under the age of 50-60. More than 10% of over-60s are affected (but the majority have no symptoms). It is apparently more common in the UK than elsewhere.
Symptoms of Paget’s disease include:
- Increased Vascularity (warmth over affected bone).
- Increased osteoclast/osteoblast activity; initially osteoclast activity (increased deformity and fracture risk); followed by increased osteoblast activity (thickening of deformed bone).
- Pelvis, femur, spine, skull (associated with hearing loss), and tibia are most commonly affected.
- Fractures.
- Bone pain (nerve entrapment, joint involvement)

In the diagnosis of Paget’s disease, plasma calcium levels are usually normal. Plasma alkaline phosphatase levels are usually increased. Radiology demonstrates variable features including loss of trabecular bone, increased density and deformity. A radioisotope (Technetium) scanning of the bone can indicate the areas of involvement.
**Drugs used to treat Metabolic Bone Disorders**
by Dr Glenda Gillies

**Calcium Salts**
For example, calcium chloride and calcium gluconate are used in the treatment of osteoporosis. This is a condition of reduced bone mass and a distortion of bone microarchitecture which predisposes to fracture after minimal trauma.

Bone stores over 95% of the body’s calcium. The inorganic mineral component forms 65% of bone mass, and is comprised of calcium hydroxyapatite crystals filling the space between collagen fibrils. The other 35% is organic components (osteoid), made 95% of collagen fibres. Plasma calcium concentration increases if there is circulating PTH and sufficient vitamin D. Plasma calcium concentration decreases if there is calcitonin in the blood.

A pre-disposing condition for osteoporosis includes postmenopausal oestrogen deficiency. There is a constant balance of osteoblast activity (synthesising osteoid and participating in mineralisation/calcification of osteoid) and osteoclast activity (releasing lysosomal enzymes which break down bone). PTH increases plasma Ca$^{2+}$ by shifting the balance towards osteoclast activity. Oestrogen (E2) blocks the effects of PTH. Another predisposing factor is age-related deficiency in bone haemostasis, e.g. raised PTH levels and osteoblast senescence. The number of osteoblasts decreases with age, and PTH levels actually increase with age. Another pre-disposing factor is raised glucocorticoid levels. This can also be iatrogenic or due to Cushing’s syndrome. Glucocorticoids reduce osteoid formation and bone mineralisation, and also stimulate osteoclasts.

Calcium salts are also used in hypocalcaemias due to a variety of things. For example: dietary deficiency of calcium; malabsorption of calcium; hypoparathyroidism; and hypocalcaemic tetany (iv). Calcium salts may be used in combination with vitamin D preparations, bisphosphonates and/or calcitonin and with oestrogens and calcitonin in postmenopausal osteoporosis. Calcium salts are also used in cardiac dysrhythmias caused by severe hyperkalaemia.

Calcium chloride is administered intravenously (slow infusion). This could cause peripheral vasodilation, cutaneous burning sensations and a moderate fall in blood pressure. It should not be used orally, as it is a gastric irritant, and calcium salts should not be injected directly into tissues (e.g. intramuscular) as they could cause tissue necrosis.

Calcium gluconate is orally active and does not cause gastric irritation. It is administered intravenously for severe hypocalaemic tetany.

**Bisphosphonates/diphosphonates**
These are analogues of pyrophosphate. For example, sodium etidronate and alendronate inhibit the recruitment of osteoclasts and promote the apoptosis of osteoclasts, i.e. they reduce bone turnover. They also indirectly stimulate osteoblast activity.

Bisphosphonates are used to treat Paget’s disease, where there is increased bone turnover leading to alterations in bone structure. Management of hypercalcaemias are associated with malignancy. Bisphosphonates are used in cancer treatment to delay bone metastases.

They are also used in osteoporosis induced by high pharmacological concentrations of glucocorticoids, and may be used in preference to calcitonin.

Bisphosphonates are orally active but poorly absorbed. They should be taken on an empty stomach, as food (especially milk) reduces drug absorption generally. They accumulate at the site of bone mineralisation and remain part of a bone until it is resorbed months or years later. They are excreted in urine unmetabolised.

Unwanted actions include the increase in non-mineral osteoid predisposition to fractures, gastric pain and GI upsets, oesophagitis, and bone pain.
Oestrogen receptor (ER) ligands
These include:
- Oestrogens e.g. ethinyl oestradiol (ER agonist)
- Tissue selective ER antagonists/antioestrogens e.g. tamoxifen, which antagonises ERs in breast but has oestrogenic activity in bone
- Tissue selective ER agonists e.g. raloxifene has been further developed for its selectivity on bone.

Prevention of post-menopausal osteoporosis requires the inhibition of osteoclast recruitment and opposition of PTH. This is what ER ligands can provide to maintain bone integrity.

Unwanted actions include increased risk of endometrial cancer (aim for bone-selective SERMs), possible increased risk of breast cancer, minor gastro-intestinal problems, and a small increased risk of venous thromboembolism and pulmonary embolism.

Calcitonin
This is a 32 amino acid peptide hormone produced by the parafollicular (C) cells of the thyroid gland. It acts via a 7-transmembrane, G-protein coupled receptor to reduce calcium and phosphate resorption. Calcitonin decreases plasma calcium, and has a negative impact on osteoclasts and kidney 1α-hydroxylase.

It is used in Paget’s disease to relieve bone pain and neurological complications. It is also used in osteoporosis, both post-menopausal and glucocorticoid induced, and also in treating hypercalcemia, (e.g. in primary hyperparathyroidism (diseases of PTH excess), vitamin D intoxication (excess), neoplasias, malignancies, osteolytic bone metastases).

Calcitonin is important in the treatment of life-threatening hypercalcemic emergency with arrhythmia, coma and cardiac arrest. The treatment should involve rehydration, diuresis, bisphosphonates and calcitonin (subcutaneous or intramuscular).

Synthetic salmon and human calcitonin are available for clinical use. The route of administration is usually subcutaneous or intramuscular in Paget’s disease, or intranasally in post-menopausal osteoporosis. Resistance due to antibody formation may develop after a few months.

Unwanted actions of calcitonin include inflammatory reactions at the sight of injection, nausea, vomiting, facial flushing, tingling sensation in hands, and an unpleasant taste in the mouth.

Vitamin D
This is a fat soluble vitamin. It plays an important physiological role in maintaining plasma calcium and regulating cell growth.

Vitamin D is used in the treatment of diseases associated with hypocalcaemia. Ergocalciferol is used to prevent osteomalacia (defects in bone mineralisation due to vitamin D deficiency) and rickets (in children) and disorders of vitamin D absorption. It is also used to treat hypocalcaemias associated with hypoparathyroidism (preferable to PTH treatment which is expensive, parenteral and has more side effects).

Calcitriol is used to treat osteodystrophy arising as a result of decreased calcitriol production due to chronic renal failure. Calcitriol binds to its intracellular receptors which belong to the superfamily of nuclear receptors. In the small intestine it enhances transcription of Ca²⁺ transporter protein so intestinal absorption of Ca²⁺ and phosphate are increased. In the kidney it increases reabsorption of Ca²⁺ and phosphate. In the bone it promotes healthy mineralisation, growth and remodelling. It also plays a role in cell growth and differentiation in many tissues, especially bone marrow.

Other drugs used to treat hypercalcemia include diuretics and anti-inflammatory glucocorticoids.
Diabetes Mellitus

Pathophysiology and Treatment of Type 1 Diabetes
by Dr David Gable

Type 1 diabetes is characterised by absolute insulin deficiency, which can either by immune mediated or idiopathic.

Type 2 diabetes is characterised by insulin resistance and relative insulin deficiency.

Other specific types of diabetes include specific gene abnormalities (MODY), genetic defects, and diseases of the exocrine pancreas secondary to other endocrine disorders.

In type 1 diabetes, usually a genetic predisposition leads to abnormal antigen presentation and recognition of a viral infection which leads to pancreatic islet cell destruction and hypoinsulinemia. This results in hyperglycaemia, which has systemic microvascular, macrovascular and metabolic consequences.

There is a genetic background to type 1 diabetes that predisposes people to developing the illness. There is a HLA association pattern (HLA-DR3 and DR4 associated), and HLA-DR2 has been found to be protective. This is 30 - 50% in concordance in twin studies, and in family studies if HLA-DR is identical this increases risk 90 fold.

There are also various theories about environmental factors that contribute to the aetiology of type 1 diabetes. It is suggested that there is a viral trigger for immune insulitis, whereby direct infection leads to pancreatic β cell death. The viral proteins could incorporate themselves into the β cell membrane, and alter the β cell antigen expression and immune mechanisms.

There is some evidence that certain types of virus when incorporated into the relevant risk HLA-types, on a molecular basis, may look like parts of various bacterial agents. This “mimicry” confuses the immune system. Once the β cell becomes immunogenic, it is destroyed by the immune system.

The biochemical aspects of diabetes all result from effects of insulin deficiency. In the absence of insulin there is increased hepatic production, reduced muscle uptake and utilisation, proteolysis, lipolysis, ketogenesis, dyslipidaemia, and impaired growth.

Keeping blood glucose up in the absence of food:
Patients with type 1 diabetes present with symptoms such as **polyuria, nocturia, polydipsia, blurring of vision, ‘thrush’, weight loss and fatigue**. Signs include **dehydration, cachexia, hyperventilation, smell of ketones, glycosuria, and ketonuria**.

The aims of treatment in type 1 diabetes are to **reduce early mortality**, as well as to **avoid acute metabolic decompensation** (DKA / hypoglycaemia), and also to **prevent long term complications** such as retinopathy, nephropathy, neuropathy and vascular disease.

It is important for the patient to control their **diet**, for example reducing calories as fat and refined carbohydrate, and increasing calories as complex carbohydrate and soluble fibre. Patients should aim for a balanced distribution of food over the course of the day with regular meals and snacks.

Most patients are now treated with human **insulin** available in various formulations, e.g. soluble (short acting), NPH (intermediate acting), and pre-mixed combinations of the two. Insulin analogues are also now available with special properties, e.g.
- Lispo/novorapid: very rapid onset and short duration action
- Glargine: long-acting with ‘flat’ 24 hour action profile

There are many different **regimes** possible. A common regime is twice daily mixed soluble and NPH insulin (bd regime), or NPH insulin at bedtime and soluble insulin with meals (‘basal bolus regime’), or continuous subcutaneous infusion of soluble insulin or rapid acting analogue (CSII). An **insulin pump** gives continuous insulin delivery. It has pre-programmed basal rates and bolus for meals. However, it doesn’t measure glucose and so there is no completion of the feedback loop. So patients assess glycaemia using a little machine and a pick test.

**HbA1c** red cells react with glucose, as it does with all proteins. Irreversible, non-covalent binding depends on:
- Lifespan of red cell, about 120 days
- Rate of glycation, faster in some individuals
- Haemoglobinopathy, renal failure etc
- Level of glucose

It therefore forms an ideal measure of long term **glycaemic control** and has been shown to be related to risk of complications. Furthermore, lowering HbA1c is associated with a lower risk of complication particularly microvascular complication.

Symptoms are of little use in monitoring diabetes control, which is why the common method is **home capillary glucose monitoring**. Glycated proteins like HbA1c are currently the ‘gold standard’, but fructosamine is useful in patients with haemoglobinopathy and in pregnancy.

An acute complication is **ketoacidosis**. A rapid decompensation of type 1 diabetes leads to hyperglycaemia and ketone production, which causes metabolic acidosis and dehydration. This can cause new presentation, insulin omission and infection or other illness. Incidence is from 1 - 8% of diabetic patients per year, with a mortality rate of 5 - 10%. DKA results from insulin deficiency, leading to reduced tissue glucose utilisation, increased hepatic glucose production, circulating NEFA, circulating acetoacetate & hydroxybutyrate, and it also leads to osmotic dehydration and acidosis.

Occasional **hypoglycaemia** (hypos) is inevitable as a result of treating diabetes. This is, unfortunately, a major cause of anxiety in patients and families, and is also a source of major misconceptions in the media. Hypoglycaemia is defined as a **plasma glucose of less than 3.6mmol/l**. Severe hypoglycaemia is any hypo requiring the help of another person to treat it.

Most mental processes are impaired at less than 3mmol/l, and consciousness is impaired at less than 2mmol/l. Severe hypoglycaemia may contribute to arrhythmia and sudden death, or may have long-term effects on the brain. Recurrent hypos result in a loss of warnings - “hypoglycaemia unawareness”.

The main risk factor of hypos is the **quality of glycaemic control**. Hypos are more frequent in patients with low HbA1c. They can occur at any time, but there is often a clear pattern. Pre-lunch hypos are common, nocturnal
hypos are very common and often are not recognised. They can occur because of unaccustomed exercise, missed meals, inadequate snacks, alcohol, or an inappropriate insulin regime.

Hypoglycaemia symptoms and signs due to increased autonomic activation include palpitations (tachycardia), tremor, sweating, pallor/cold extremities and anxiety. Symptoms due to impaired CNS function include drowsiness, confusion, altered behaviour, focal neurology and coma.

Hypoglycaemia treatment:
- **Oral**: glucose is rapidly absorbed as solution or tablets, and complex carbohydrates will maintain blood glucose after the initial treatment.
- **Parenteral**: if consciousness is impaired, intravenous dextrose (10% glucose infusion) and 1mg Glucagon (intramuscular) is used to treat the patient. Avoid concentrated solutions if possible (e.g. 50% glucose).

**Aetiology and Treatment of Type 2 Diabetes**

by Dr Stephen Robinson

Diabetes mellitus can be defined as a state of chronic hyperglycaemia sufficient to cause long-term damage to specific tissues, notably the retina, kidneys, nerves and arteries. Type 2 diabetes mellitus is not ketosis prone, it is not mild, and it often involves weight, lipids and blood pressure.

75g of glucose is administered orally in a glucose tolerance test.

Below 6.0, fasted glucose is normal. Between 6.0 and 7.0, the patient has an Impaired Fasting Glucose (IFG), and above 7.0 the patient has diabetes.

After 2 hours, below 7.8 the patient has a normal glucose tolerance. Between 7.8 and 11.1 the patient has an Impaired Glucose Tolerance (IGT), and above 11.1 the patient is diabetic.

Impaired values do not give microvascular risk, although they do predict macrovascular risk.

**Type 2 diabetes mellitus** is the most common cause of diabetes in the UK and in the world. Type 1 diabetes is less common, and even less common are Maturity Onset Diabetes of the Young (MODY) and Latent Autoimmune Diabetes of Adults (LADA).

Diabetes is prevalent, mostly being T2DM. It is seen mainly with increasing age, but now it is also being found in children. The prevalence varies enormously, but it is occurring and being diagnosed younger. It is greatest in ethnic groups that move from an urban to a rural lifestyle.

Maturity Onset Diabetes of the Young (MODY) is relatively uncommon but gives useful metabolic insights into how diabetes can come about. T2DM can be caused by genes and intrauterine environment (seen by studies using mono- and dizygous twins) and of course adult environment. It is associated with insulin resistance and insulin secretion defects. Fatty acids are important in the pathogenesis and complications.
There are several hereditary forms (1-8) of MODY. It is an autosomal dominant condition where there is ineffective pancreatic \( \beta \) cell insulin production. It is caused by mutations of transcription factor genes and the glucokinase gene. There is usually a positive family history, not necessarily with obesity. There is specific treatment depending on the type of diabetes.

Twin studies have shown that T2DM appears to be a genetic disorder. The genes for T2DM predispose the individual to becoming obese, and obesity in turn causes insulin resistance (which means glucose is not taken up by muscles because they use fat instead) and \( \beta \) cell failure. These genes are linked to intra-uterine growth restriction. Long before the patient has high blood sugar, in diabetes HDLs are predisposed to become low and LDL levels higher - this is known as dyslipidaemia and can lead to various macrovascular complications such as coronary heart disease, cerebrovascular disease and peripheral vascular disease. The \( \beta \) cell failure causes hyperglycaemia, which leads to various microvascular complications and also means the patient has an insulin requirement. According to a study by Hales in 1991 on children in Hertfordshire, babies that are born lighter are at higher risk of developing T2DM, so perhaps intra-uterine growth restriction programmes diabetes for later life.

To a certain degree, insulin resistance is part of the ageing process. However, developing T2DM at a younger age of around 40 is because the patient will already have poor \( \beta \) cells, and so the natural \( \beta \) cell reserve decline is exacerbated, causing increasing insulin resistance.

T2DM is heterogeneous and presents usually with obesity, insulin resistance and insulin secretion deficit, hyperglycaemia and dyslipidaemia, and also the acute and chronic complications associated with diabetes such as sudden blindness, renal failure, heart attacks and stroke.

Blood sugar becomes high because the insulin is less effective in muscles for glucose uptake. Insulin secretion deteriorates with progressive impairment of glucose tolerance. Decreased glucose disposal and increased hepatic glucose production (output) contribute to increased plasma glucose in type 2 diabetes. Pancreatic islet dysfunction leads to hyperglycaemia. \( \beta \) cells can only compensate for insulin resistance up to a certain limit of normal glucose tolerance, after which there is impaired glucose tolerance and eventually type 2 diabetes, because with fewer \( \beta \) cells, \( \alpha \) cells hypertroph and there is insufficient insulin, which causes excess glucagon and increased hepatic glucose output.

Measuring waist circumference is an easy way to predict diabetes. Increased waist circumference is more important than overall weight in T2DM. Central or omental obesity is more than a precipitant of diabetes. 80% of type 2 diabetics are obese. Waist circumference also predicts ischaemic heart disease. Above 35 inches for a woman and above 40 inches for a man increases the risk of diabetes. Cholesterol should ideally be under 4 for a diabetic, the normal being 5.5. Triglycerides should be 2 and HDLs should be above 1.

Weight reduction is useful treatment, although unfortunately weight gain is a common side effect of diabetes treatments.

Type 2 diabetes also presents with osmotic symptoms of polyuria and polydipsia and increased infections (bacteria like the sugar going round the body) such as foot ulceration. Diabetes can be picked up on early in a screening test, or later at presentation of a complication (acute could be hyperosmolar coma, chronic could be ischaemic heart disease or retinopathy suddenly going blind in one eye due to a vitreous haemorrhage). Visual disturbances can also occur if the aqueous humour becomes more concentrated.
**Microvascular** complications include retinopathy, nephropathy or neuropathy. Nephropathy can be checked by dipstick testing urine for micro-albumin urea, proteinurea, and also creatinine levels for renal failure. Peripheral neuropathy could be tingling fingers; autonomic neuropathy could be postural hypotension (difference of 20/10 after 2 minutes). **Macrovascular** complications include ischaemic heart disease, cerebrovascular disease, renal artery stenosis, or peripheral vascular disease. **Metabolic** complications include lactic acidoses and hyperosmolarity. Complications may also arise as a result of treatment - hypoglycaemia.

The basic management of T2DM involves education, diet, pharmacological treatment of glucose, blood pressure and dyslipidaemia and also complication screening. Diabetes is treated to reduce the symptoms and to reduce the chance of acute metabolic complications (although unlikely in T2DM), and also to reduce the chance of long term complications (there is a good evidence base for this - UK Prospective Diabetes Study). Education is essential in all of this.

Most diabetes patients are overweight. The patient should control total calories and increase exercise to control their weight. They should reduce refined carbohydrates such as sugar and increase complex carbohydrates like rice, as well as reducing fat as a proportion of calories (less insulin resistance). They should increase unsaturated fat as their proportion of fat intake to avoid ischaemic heart disease, and they should increase soluble fibre intake so that it takes longer to absorb carbohydrates.

Things to monitor during the treatment of T2DM include weight, glycaemia, blood pressure and dyslipidaemia. Various drugs have been used to control weight. **Orlistat** is the one that is still available and licensed in the UK; it works by reducing fat absorption in the gut. **Sibutramine** has been taken off the market, but it used to work by causing the re-uptake of NA to influence central satiety in the hypothalamus and β3 thermogenesis in muscle. **Rimonabant** also acts on central satiety, but also causes central fat loss is adipose tissue.

An **α-Glucosidase inhibitor** such as Acarbose delays the absorption of oligosaccharides, and so allows insulin secretion to cope. It does, however, cause flatulence. **Post-prandial glucose regulators** such as Repaglinide and Pramlitide slow gastric emptying and inhibit glucagon release. Pramlitide is a Glucagon-like peptide agonist. Glucagon-like peptide-1 is a gut hormone secreted in response to nutrients in the gut, and it stimulates insulin release, suppresses glucagon, and increases satiety. **Sulphonylureas** and **Metaglinides** also assist in controlling acute insulin release by acting on β cells. **Glucagon-like peptide DPP4 inhibitors** stimulate β cell differentiation and insulin biosynthesis. **Metformin** acts on the liver to increase hepatic insulin sensitivity and inhibit gluconeogenesis. **Thiazolidinediones** increase muscle insulin sensitivity, and act on adipose for favourable fat redistribution and suppression of fatty acid release. Thiazolidinediones include Pioglitazone and Rosiglitazone, which unfortunately have side effects of increased CVS complications and increased osteoporosis.

**Metformin** is a biguanide insulin sensitizer. It is a very effective drug used commonly in an overweight patient with T2DM where diet alone has not succeeded. It reduces insulin resistance by reducing hepatic glucose output and by increasing peripheral glucose disposal by increasing the ability of glucose to get into muscle. There are some GI side effects such as diarrhoea, however Metformin does not cause weight gain, and it does not cause hypos as it doesn’t increase the amount of insulin. It should not be used if there is severe liver, cardiac or mild renal failure, and if the patient is on Metformin and they have an IV contrast, they are likely to develop lactic acidoses and so patients are warned to stop taking the drug before coming into hospital.

**Glibenclamide** is a sulphonylurea, and works by inhibiting ATP-sensitive potassium channels in pancreatic beta cells. This inhibition causes cell membrane depolarization, which causes voltage-dependent calcium channels to open, which causes an increase in intracellular calcium in the beta cell, which stimulates insulin release. It is usually used in lean patients with T2DM where diet alone has not succeeded. Side effects include hypoglycaemia and weight gain. Despite treatments though, β cells...
inevitable continue to decline. This happens regardless of intervention in T2DM. Other aspects of control include blood pressure (possibly 90% of diabetics) as there are clear benefits to treatment such as a reduced chance of heart disease and stroke; and also the control of diabetic dyslipidaemia where cholesterol and triglycerides are high and HDLs are low. Again, there are clear benefits to treatment.

The problem with diabetes is the associated mortality, morbidity and cost of living with diabetes. Screening programmes are unclear in terms of specifics - which test should be done how often on who? It’s quite a difficult situation.

**Diabetes Comparison:**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>0.25%</td>
<td>4-7%</td>
</tr>
<tr>
<td>Typical Age</td>
<td>Child, Adolescent</td>
<td>Middle age +</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Gradual</td>
</tr>
<tr>
<td>Habitus</td>
<td>Lean</td>
<td>Often Obese</td>
</tr>
<tr>
<td>Family History</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Geography</td>
<td>Europids</td>
<td>Less Europids</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>Usual</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Ketosis Prone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Serum Insulin</td>
<td>Low or Absent</td>
<td>Variable</td>
</tr>
<tr>
<td>HLA Association</td>
<td>DR3, DR4</td>
<td>None</td>
</tr>
<tr>
<td>Islet β cells</td>
<td>Destroyed</td>
<td>Function</td>
</tr>
<tr>
<td>Islet Antibodies</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

**The Pathophysiology of Diabetic Ketoacidosis (DKA)**

by Dr Stephen Robinson

The primary defect in T1DM is deficient insulin secretion from the pancreatic β cells. Diabetic ketoacidosis could be precipitated by various factors. For example, new diagnosis of T1DM, not taking insulin, intercurrent stress (pneumonia, heart attack), and also fasting and not taking enough insulin.

With deficient insulin, there is high hepatic glucose output and deficient muscle glucose uptake, and with high plasma glucose, the glucose exceeds the proximal convoluted tubule ability for reabsorption.

When insulin is low, there is an increased lipolysis rate and fatty acids are used to produce ketone bodies in the liver.

**Bicarbonate** production is linked to H⁺ excretion. In the distal convoluted tubule, Na⁺ excretion is linked to H⁺ or K⁺ excretion. In metabolic acidosis, the plasma pH becomes low where the basic lesion is low bicarbonate, and compensatory low CO₂. In metabolic alkalosis, plasma pH is high, where the basic lesion is high bicarbonate and compensatory high CO₂. In respiratory acidosis, the plasma pH is low where the basic lesion is high CO₂, with compensatory high bicarbonate. In respiratory alkalosis, plasma pH is high where the basic lesion is low CO₂ and compensatory low bicarbonate.

In metabolic acidosis with diabetic ketoacidosis there is a reduction in bicarbonate concentration because of the impaired production and the increased H⁺ buffering.

Anion gap

\[ [\text{Na}^+] + [\text{K}^+] = [\text{HCO}_3^-] + [\text{Cl}^-] + [\text{A}^-] \]
45

\[140 + 4 = 25 + 100 + 19\]

Increase in single cation other than Cl
\[\text{[Na}^+\text{]} + \text{[K}^+\text{]} = \text{[HCO}_3^-\text{]} + \text{[Cl}^-\text{]} + \text{[A}^-\text{]} + \text{[X}^-\text{]}\]
\[140 + 4 = 15 + 100 + 19 + 10\]

\[\text{pH} = 6.1 + \log \frac{\text{[HCO}_3^-\text{]}}{\text{PCO}_2 \times 0.23}\]

There is also electrolyte disturbance because water is lost in urine, and so Na\(^+\) is lost in urine and K\(^+\) is lost in urine. Although acidosis shows high concentration of K\(^+\), the total body K\(^+\) is low.

The clinical features of diabetic ketoacidosis include dehydration, insulin deficiency, total body K\(^+\) deficiency (although high plasma K\(^+\)), acidic, and risk of arrhythmia, infection and dilated stomach. The patient presents with polyuria and polydipsia due to the osmotic diuresis. They also present with dehydration, hyperventilation, abdominal pain, vomiting, or possibly coma. It is important to look for the precipitating factor. They will present with glycosuria and ketonuria.

Investigations include capillary glucose, plasma glucose, creatinine, K\(^+\), Na\(^+\), full blood count, arterial blood gases, amylase (triglyceride), ECG, chest x-ray and a septic screen.

Treatment of diabetic ketoacidosis involves fluid, insulin, potassium, bicarbonate and other measures if necessary. Water (100ml/kg) should be given with sodium at 8mmol/kg (3 to 8 litres in 24 hours) as normal saline. 500ml in 15 minutes, after 20 minutes twice, 60 minutes twice and then after 120 minutes.

**Insulin** is given intravenously using a sliding scale with capillary glucose depending on how low the glucose is. Potassium is given 4-5mmol/l, it is mainly intracellular

> 6 mmol/l >>> give non and check
5mmol/l >>> 10mmol/hr
4mmol/l >>> 20mmol/hr
3mmol/l >>> 25mmol/hr
<3 large K\(^+\) and recheck

**Potassium** is given 4-5mmol/l, mainly intracellular, loss usually 4mmol/kg (200-800mmol).

**Bicarbonate** is given bearing in mind the risks of hypokalaemia, hypernatraemia, rebound alkalosis, CSF acidosis and impaired oxyhaemoglobin dissociation. However, the dangers of acidaemia include negative inotropism, peripheral vasodilation, hypotension and cerebral inhibition.

**Other measures** include cardiac monitoring for arrhythmias, catheterisation, antibiotics, NG tube (gastroparesis), consider heparin, consider arterial line (very acidotic) and central line (elderly or when cardiac failure).

When glucose is less than 10mmol/l change to 5% dextrose, continue insulin, continue potassium and the patient may need more saline.

Causes of death in DKA include overwhelming disease, self-neglect, social factors, delay in seeking help, delay in primary care, or inappropriate treatment.

DKA can be prevented by good education, never stopping insulin, checking glucose and modifying insulin if ill, and admission if vomiting.

DKA is less common now, but understanding its physiology helps treatment and prevention.
**Microvascular Complications of Diabetes Mellitus**
by Professor Karim Meeran and Dr Andrew Frankel

Diabetes damages blood vessels. We now know that poor control of diabetes causes a higher risk of both microvascular and macrovascular complications. Microvascular complications occur mainly in the retinal arteries, in the glomerular arterioles (kidney), and in the vasa nervorum (tiny blood vessels that supply nerves). These complications manifest themselves as diabetic retinopathy, nephropathy and neuropathy.

**Diabetic Retinopathy**
The blood supply of the retina has got many very small blood vessels, ad when these get blocked, retinopathy results. In diagnosing diabetic retinopathy, we can visualise both the retinal arterioles and the retina for signs of ischaemic damage. On normal inspection of the retina, the fovea should be visible as a slightly darker region in the middle, and the optic disc (blind spot) will also be visible with blood vessels emerging. Arteries are slightly narrower and a brighter red than the veins.

With background diabetic retinopathy, the things to look for are hard exudates (cholesterol), microaneurysms (dots), and blot haemorrhages. In pre-proliferative diabetic retinopathy, cotton wool spots are also visible. These are also known as “soft exudates”, and are in fact areas of ischaemia and infarction.

In an area of ischaemia, the thing to worry about is that new blood vessels will grow, and it is important to look out for this in proliferative retinopathy slides. Little arcades of lots of new thin vessels will try to supply blood to where the ischaemia is. These new vessels are very thin and very weak, and so even minor trauma could easily cause the vessels to tear, leading to complete sudden blindness.

In maculopathy, hard exudates form near the macula. It is the same disease as background retinopathy, but the hard exudates are near or on the macula. This might threaten direct vision, for example, the patient won’t be able to read.

In the management of diabetic retinopathy, it is important to improve the control of blood glucose. The patient should be warned that signs are present that high sugar is causing damage to the eye. Pre-proliferative retinopathy (cotton wool spots) suggests the whole retina is generally ischaemic, and if left alone new vessels will inevitably grow (which is proliferative retinopathy). This will need treatment by pan retinal photocoagulation. Essentially the retina is made less ischaemic by deliberately infarcting some of the outer area using laser treatment. In this way, the retina is less ischaemic and new vessels will be less likely to develop. Central vision is maintained, and there is less risk of going blind. In a maculopathy, there is only a problem around the macula. This is treated with a subtle grid of photocoagulation (laser therapy) instead of pan retinal photocoagulation.

**Diabetic Nephropathy**
This is a very important associated morbidity and cause of mortality in diabetes. Diabetic nephropathy accounts for 40% of people on dialysis, and there is a high risk of developing end stage kidney disease. The clinical hallmark of diabetic nephropathy is proteinuria. Proteinuria is associated with cardiovascular morbidity.

Worldwide rates of diabetes mellitus show that it is a growing epidemic, with figures only expected to increase in the next few years.

The histological features visible in nephropathy are mainly glomerular changes such as mesangial expansion, basement membrane thickening and glomerulosclerosis. There are also vascular changes and tubulo-interstitial changes.
Diabetic nephropathy occurs in about 30-40% of type 1 diabetics after 30 to 40 years of diabetes. The incidence of nephropathy in type 2 diabetes depends on racial factors, age at presentation and loss due to cardiovascular morbidity. The clinical features include progressive proteinuria, increased blood pressure and deranged renal function.

Proteinurea:
- Normal range = < 30mg/24hrs
- Microalbuminuric range = 30 - 300mg/24hrs
- Asymptomatic range = 300 - 3000mg/24hrs
- Nephrotic range = > 3000mg/24hrs

Patients with diabetes who are likely to develop nephropathy can be identified at an early stage by the presence of small increases in proteinurea termed microalbuminuria and by abnormalities of blood pressure control. Intervention is most successful if commenced at an early stage of the process and it is important to identify diabetes at risk of developing this disorder. Patients with clinical nephropathy usually go on to end stage renal failure within a period of 2 to 7 years of the appearance of significant proteinurea.

Strategies for intervention include diabetic control, blood pressure control and inhibition of the activity of the renin-angiotensin system. The last one is because angiotensin II has vasoactive effects in the mediation of glomerular hyperfiltration and increased tubular uptake of proteins. Capillary pressure is affected and this damages the kidney, leading to a reduced GFR. ACE inhibitors have been shown to have a beneficial effect on diabetic nephropathy, with a reduction in the progression of proteinurea and a reduction in cardiovascular morbidity. Another important strategy for intervention is stopping smoking if the patient is a smoker.

Diabetic Neuropathy
Small vessels supplying nerves are called vasa nervorum. Neuropathy results when these get blocked. Diabetic neuropathy can manifest itself as peripheral polyneuropathy, mononeuropathy, mononeuritis multiplex, radiculopathy, autonomic neuropathy and also diabetic amyotrophy.

The actual mechanism of blood vessel damage is not known. Possible mechanisms for vascular damage include sorbitol, which is thought to be produced in excess in individuals with high plasma glucose because glucose is reduced to sorbitol by the enzyme aldol reductase.

Another possible mechanism is the production of advanced glycation end products (AGE). Glycation is the term used for non-enzymatic addition of hexoses to protein and glycosylation is the term used when the process is enzymatic. Glycation of haemoglobin to form HbA1c is well recognised. A similar process is known to affect other proteins, in particular the lens protein (causing cataracts), fibrin and collagen. The latter might be responsible for microangiopathy. Fructosamine is another example of a glycated protein. We can use both HbA1c and fructosamine to get an idea of long term glucose control.

Peripheral neuropathy is where the long nerves are affected first and over time this becomes more proximal. It is usually bilateral and symmetrical. The longest nerves supply the feet, and so this is where there is often a loss of sensation. The danger is that patients will not sense an injury to the foot (e.g. stepping on a nail). Peripheral neuropathy is more likely to occur in tall patients and patients with poor glucose control. It can be tested for, as the patient will have a loss of ankle jerks, loss of vibration sense (use tuning fork), and could have multiple fractures on a foot x-ray (Charcot’s joint).

Mononeuropathy is single nerve loss. This is usually noted as sudden motor loss, for example a wrist drop or a foot drop, as single sensory nerve loss is rarely symptomatic. There can be cranial nerve palsy, for example double vision due to 3rd nerve palsy, with the eye drooping “down and out” as the 6th nerve pulls the eye out and 4th nerve pulls it down. It is known as “pupil sparing third nerve palsy” because the pupil does respond to light. The parasympathetic fibres alongside the third nerve are on the outside, thus they do not easily lose blood supply in diabetes. In contrast, an aneurysm causing third nerve palsy is a space occupying lesion, and so will press on the parasympathetic fibres too, first causing a fixed dilated pupil.

Mononeuritis complex is a random combination of peripheral nerve lesions. Radiculopathy is pain over spinal nerves, usually affecting a dermatome on the abdomen or chest wall.
Autonomic neuropathy results in loss of sympathetic and parasympathetic nerves to GI tract, bladder and cardiovascular system. The GI tract effects will result in difficulty swallowing, delayed gastric emptying, constipation / nocturnal diarrhoea and bladder dysfunction. A common sign of autonomic neuropathy however is postural hypotension. This can be disabling for the patient, collapsing on standing. In terms of cardiac autonomic supply there have been instances of sudden cardiac death. Autonomic neuropathy can be measured by changes in heart rate in response to the Valsalva manoeuvre. Normally there is a change in heart rate. Look at the ECG and compare R-R intervals.

Diabetic amyotrophy is asymmetrical painful proximal motor loss (affects quads), which also leads to muscle wasting.

The Macrovascular Complications of Diabetes
by Dr Stephen Robinson

The main macrovascular complications of diabetes include ischaemic heart disease, cerebrovascular disease, renal artery stenosis and peripheral vascular disease.

Hyperglycaemia is part of a spectrum of an arterial disease that significantly reduces life expectancy. There are many factors such as a fasting glucose above 6.0mmol/l, HDLs below 1, hypertension above 135/80, microalbumin and insulin resistance, and a large waist circumference that all contribute to and play a role in diabetes. Life expectancy is greatly reduced if diagnosed with diabetes aged 30 to 40, as relative risk of things such as cardiovascular events is increased in diabetes.

Patients with diabetes die from diseases of big arteries. Macrovascular disease is a systemic disease and is commonly present in multiple arterial beds. Ischaemic heart disease is twice as likely to be the cause of death in a diabetic than in a non-diabetic person. It is the major cause of morbidity and mortality in diabetes. The mechanisms are similar with and without diabetes. Cerebrovascular disease is another problem that can occur earlier than without diabetes, and is also more widespread in diabetics. It means that stroke is more likely to occur at a younger age. Peripheral vascular disease contributes to diabetic foot problems and neuropathy. Renal artery stenosis can be seen as narrowing on an angiogram and may contribute to hypertension in some.

Treatment targeted to blood glucose alone does not significantly offset the increased risk of cardiovascular disease. Prevention of macrovascular disease requires aggressive management of multiple risk factors. Non-modifiable risk factors for macrovascular disease include age, sex, birth weight, family history and genes. Modifiable risk factors include dyslipidaemia, high blood pressure, smoking and diabetes.

Glycated haemoglobin is a series of Hb components formed by adduction of glucose or glucose derived products to normal adult HbA0. It is associated with the risk of complications.

Blood pressure management:

**Targets**

- If kidney, eye or cerebrovascular damage, set a target < 130/80 mmHg.
- Others, set a target < 140/80 mmHg.

**If on antihypertensive therapy at diagnosis of diabetes**

- Review BP control and medication use.
- Make changes only if BP is poorly controlled or current medications are inappropriate because of microvascular complications or metabolic problems.

**If the person’s BP reaches and consistently remains at the target**

- Monitor every 4–6 months and check for possible adverse effects of antihypertensive therapy (including those from unnecessarily low blood pressure).
Management of blood lipids:

The complications of diabetes that predispose the patient to foot disease include neuropathy and peripheral vascular disease. The prevalence of current or past foot ulceration in diabetes is about 5-7%, and the risk of amputation is up to 60 times diabetes, with poor subsequent prognosis. 10% of NHS bed occupancy is due to diabetes related problems (50% of this is foot disease).

Signs include clawed toes (because of mismatched power of lower leg muscles) and the prayer sign (not being able to bring palms together and thickening of fascia). Another sign is plantar flexion that is fixed in an abnormal position.

The usual pathway to foot ulceration starts with motor neuropathy, causing limited joint mobility. This in combination with autonomic neuropathy can lead to unnoticed trauma (repeated minor or discrete episodes) because of sensory neuropathy. There is also peripheral vascular disease and a reduced resistance to infection. Foot ulceration can also occur in combination with other diabetic complications like retinopathy.

The neuropathic foot is numb, warm and dry, with palpable foot pulses and ulcers at points of high pressure loading. The ischaemic foot is cold, pulseless and has ulcers as foot margins. The neuro-ischaemic foot is numb, cold, dry, pulseless and has ulcers at points of high pressure loading and at foot margins.

Assessing the foot of a diabetic patient should start with appearance. Are there any deformities? Are there any calluses? Shiny skin is characteristic of peripheral vascular disease. Then how does it feel? Is it hot/cold? Is it dry? Then foot pulses should be checked (dorsalis pedis / posterior tibial pulse). Finally neuropathy should be checked - vibration sensation, temperature, ankle jerk reflex, fine touch sensation.

Preventative management of foot disease means controlling hyperglycaemia, hypertension, dyslipidaemia, smoking and education. Specific foot care measures involve checking feet daily, having feet measured when buying shoes, buying shoes with square toe box and laces, inspecting the inside of shoes for foreign objects, attending a chiropodist, cutting nails straight, taking care with heat and never walking barefoot.

Management of foot ulceration will require a multi-disciplinary team approach, needing perhaps a diabetologist, nurse, chiropodist, vascular surgeon, orthopaedic surgeon, orthotist (supplies and fits shoes) and a limb fitting centre. The first thing is relief of pressure (bed rest, although risk of DVT and heel ulceration), then the patient should be treated with antibiotics, debridement, revascularisation (angioplasty, arterial bypass surgery), and possibly amputation may be the appropriate option.