**ENDOCRINE BLOCK**

**ACADEMIC YEAR: 2015-2016**

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**I. INTRODUCTION**

The endocrine system is a complex, highly integrated group of organs that have a central role in the maintenance of normal bodily functions. More specifically, the endocrine system plays an important part in the regulation of reproduction, growth and development, maintenance of the internal environment, and energy production, utilization and storage. Disorders of the endocrine system are therefore important because they have far reaching and devastating effects, which in some cases can be life-threatening (e.g. addisonian crisis, diabetic ketoacidosis). At the heart of the endocrine system are the endocrine glands, which includes the pituitary, adrenals, the thyroid, parathyroid, and pancreas. Endocrine glands synthesize and secrete hormones into the bloodstream, via which they are carried to distant sites to exert their effects. In this way the endocrine glands are able to influence the function of distant target organs and tissues. Disorders of the endocrine system are usually due to their over reproduction or under reproduction of a particular hormone, or mass lesions, and to aid understanding. The pathology will be presented in a similar scheme.

**Lectures 1 and 2: Pathology of diabetes mellitus.**

*Learning Objectives*

* Understand the structure of the pancreas and have a basic understanding of its function
* Know the various hormones secreted by the pancreas
* Have an understanding of the classification, pathogenesis, clinical features and complications of diabetes mellitus and have a basic knowledge of the theories of its pathogenesis.

**Structure and function of endocrine pancreas.**

The pancreas consists of two separate functional units, the exocrine pancreas, which secretes digestive enzymes in the duodenum and the endocrine pancreas which secretes a number of different hormones. The endocrine pancreas consists of – 1 million islets of Langerhans, which are scattered throughout the gland. Each islet is composed of a cluster of a number of different cell types, each cell type synthesizing and secreting a different hormone (table 1).

Insulin and glucagon are the hormone responsible for maintaining blood sugar levels; insulin exerts a hypoglycaemic effect and glucagon exerts a hyperglycaemic effect. The two main disorders of the islet cells are diabetes mellitus and islet cell tumors.

**Diabetes and mellitus.**

Diabetes mellitus is a condition characterized by an absolute or relative deficiency of insulin and/or insulin resistance, inducing hypoglycaemia.

**Classification**

**There are two main types of diabetes mellitus:**

* **Type 1 diabetes – juvenile-onsite diabetes;** insulin dependent diabetes (IDDM), which accounts for 10% of all cases.

*Table I. The cell types of the pancreas.*

|  |  |  |
| --- | --- | --- |
| Cell type | Hormone synthesized | Action hormone |
| β (beta) | Insulin | * Increases glucose entry into cells * Promotes glycogen synthesis and prevents breakdown * Promotes lipolysis |
| α (alpha) | Glucagon | * Promotes glycogen breakdown * Promotes gluconeogenesis |
| δ (delta) | Somatostatin | * Inhibits secretion of insulin and glucagon |
| PP | Pancreatic polypeptide | * Exerts a number of gastrointestinal effects |
| Enterochromaffin cells | Vasoactive intestinal polypeptide | * Stimulates intestinal fluid secretion |
| D1 | Serotonin | * Potent vasodilator * Increases intestinal motility |

* **Type 2 diabetes – adult – onset diabetes;** non-insulin dependent diabetes (NIDDM), which accounts for 80 – 90% of all cases. Gestational diabetes and maturity – onset diabetes of the young (MODY) are rare cases of diabetes mellitus. MODY is due to a genetic defect in β cell function.

**Pathogenesis**

**Type I diabetes**

Type I diabetes, which typically presents in childhood, is characterized by a complete lack of insulin. Insulin secretion is inadequate because of destruction of the β cells in the islets. Three separate but inter-related mechanisms appear to have a role in this destructive process:

* Genetic susceptibility
* Autoimmune reaction
* Environmental event

It has been postulated that genetic susceptibility predisposes certain individuals to the development of an autoimmune reaction against the β cells of the islets, and that this autoimmune reaction is triggered by an environmental event (e.g. viral infection, exposure to chemical toxins).

**Type II diabetes**

This type of diabetes usually presents in middle age. The precise pathogenic mechanisms is unknown, but obesity and genetic factors are important. Two mechanisms have been postulated.

* Defective secretion of insulin β cells
* Resistance of peripheral tissues to the effects of insulin

**Clinical Features**

**Type I diabetes**

The clinical features are related to increased gluconeogenesis and hyperglycaemia resulting from a lack of insulin.

* Polyuria – due to glycosuria with osmotic diuresis.
* Polydipsia – extracellular hyperosmolarity causes osmotic depletion of intracellular water and triggers osmoreceptors in the brain, with resultant severe thirst.
* Polyphagia - breakdown of proteins and fats for gluconeogenesis causes an increased appetite.
* Weight loss and weakness – despite increased dietary intake, breakdown prevails over storage.

Severe insulin deficiency may lead to diabetic kectoacidosis lipolysis results in elevated free fatty acids, which are oxidized to produce ketone bodies in the liver. The rate of formation to ketone bodies exceeds the rate at which they are utilized, resulting in ketonuria and ketoanemia. If there is superimposed dehydration, metabolic ketoacidosis results. The condition is life-threatening. Infection, which increases insulin requirements, often precedes development of diabetic ketoacidosis.

**Type 2 diabetes**

The diagnosis of type 2 diabetes is usually made after routine serum or urine testing in an asymptomatic patient. The metabolic derangements are much less severe than in type I diabetes, and metabolic ketoacidosis does not occur. Instead, patients in the decompensated state develop hyperosmolar non-ketotic coma, which results from severe dehydration due to insufficient water intake in the face of polyuria. Other clinical features of types 1 and 2 diabetes are related to the complications of longstanding diabetes.

**Complications of Diabetes Mellitus**

Although the two major types of diabetes have different pathogenesis and clinical presentations, the long term systemic complications are the same and are the major causes of morbidity and mortality in these patients.

***Vascular system***

***Aterosclerosis* –** There is severe accelerated atherosclerosis in the aorta and large and medium-sized arteries. Myocardial infarction, stroke and gangrene of the lower limbs are responsible for ῀80% of deaths due to diabetes in adults.

***Hyaline arteriosclerosis*** *–* Hyaline thickening of the wall of arterioles with narrowing of the lumen.

***Diabetic microangiopathy* –** This is characterized by diffuse thickening of the capillary vascular basement membranes. Affected vessels are more leaky to plasma proteins. The change is most evident in the capillaries of the retina and kidney and may account for some of the changes seen in the peripheral nerves.

***Diabetic nephropathy***

* Glomerular changes – includes diffuse basement membrane thickening, nodular expansion of mesangial regions and exudative lesions.
* Vascular changes – renal atherosclerosis and arteriosclerosis
* Parenchymal changes – pyelonephritis with increased propensity to develop necrotizing papillitis.

***Diabetic retinopathy***

Diabetic retinopathy can be non-proliferative (background) or proliferative. The non-proliferative changes are:

* Thickening of the capillary basement membrane (microangiopathy) with development of micro aneurysms (dots)
* Retinal hemorrhages (blots)
* Retinal edema and exudates (cotton wool spots)
* Venous dilatation

The proliferative changes are neovascularization and fibrosis, which may lead to retinal detachment and blindness.

***Diabetic neuropathy***

Neuropathies seen include symmetric peripheral neuropathy, affecting both motor and sensory nerves and autonomic neuropathy, which may cause impotence and bladder and bowel dysfunction***.***

***Infections***

People with diabetes have an increased tendency to develop infections.

***Skin complications***

These include necrobiosis lipoidica diabeticorum and granuloma annulare.

***Pregnancy***

Pregnant women with diabetes are at a higher risk of developing pre-eclampsia and tend to have large babies.

**Lecture 3 and 4. Pathology of the disease of the thyroid gland**

*Learning objectives*

You should

* Know the structure and function of the thyroid gland
* Know the ways in which thyroid disorders present
* Know the major causes of hypo and hyperthyroidism
* Know the causes of goiter
* Know the causes of a solitary nodule in the thyroid
* Understand the classification and behavior of thyroid carcinoma

**Structure and function of The Thyroid Gland**

The thyroid gland develops from an evagination at the root of the tongue (foramen caecum), which grows downwards anterior to the trachea to reach its final position in front of the thyroid cartilage. During its descent, the thyroid gland is attached to the root of the tongue by means of thyroglossal duct, which eventually undergoes atrophy. Persistence of this duct is this basis of thyroglossal cysts.

The adult thyroid gland comprises two lobes connected by an isthmus and consists of follicles lined by cuboidal epithelial cells and filled with colloid. The main function of these epithelial cells is to synthesize and secrete the two thyroid hormones - T₄ (thyroxine) and Tɜ. The secretion of T₄ and Tɜ is under negative feedback control by TSH, which is secreted by the anterior pituitary. Scattered throughout the thyroid are C-cells, which synthesise and secrete the hormone calcitonin. Calcitonin is involved in the regulation of body calcium levels.

Disorders of the thyroid manifest in four main ways:

* Hypofunction (hypothyroidism)
* Hyperfunction (hyperthyroidism)
* Enlargement of the gland (goiter)
* Solitary masses

These groups are not mutually exclusive. For example, goiters can be associated with either hyperfunction or hypofunction of the thyroid gland, and hyperthyroidism may be associated with a goiter.

**Hyperthyroidism (thyrotoxicosis)**

Excess circulatingTɜ and T₄ induce a hypermetabolic state, the resulting clinical syndrome being known as thyrotoxicosis.

***Aetiology***

The three commonest causes of thyrotoxicosis are as follows:

* Graves’ disease (80%)
* Functioning adenoma
* Toxic nodular goiter

Graves’ disease (Graves’’ thyroiditis)

Graves’ disease typically affects young women who present with the clinical features of thyrotoxicosis and mild goiter. If the patient develops proptosis (protrusion of the eyes) or pretibial myoxoedema, the diagnosis of Graves’ disease is almost certain since these changes are not seen in the thyrotoxicosis due to other causes. Graves’ thyroiditis is an ‘organ- specific’ autoimmune disease; autoantibodies bind to the TSH receptor on thyroid epithelial cells and mimic the stimulatory action of TSH. Histologically, there is an increase of the number of cells lining the follicles and a reduction in the amount of stored colloid.

***Functioning adenoma***

Rarely, functioning thyroid adenomas have enough secretory activity to induce thyrotoxicosis. Such adenomas may also present as solitary thyroid masses.

***Toxic nodular goiter***

Rarely, one or more nodules in a multinodular goiter may develop hypersecretory activity, resulting in thyrotoxicosis.

**Clinical features of thyrotoxicosis**

The systemic features of thyrotoxicosis are as follows:

* Eye changes (exophthalmos, lid lag, lid retraction)
* Hair loss, weight loss
* Anxiety, tremor, diarrhea, warm moist hands
* Cardiac manifestations (tachycardia, palpitations, atrial fibrillation)
* Pretibial myxoedema (accumulation of mucopolysaccharides in the skin)
* Menorrhagia, osteoporosis
* Proximal myopathy

Exophthalmos and pretibial myxoedema occur only in thyrotoxicosis due to Graves’ disease.

**Hypothyroidism**

Insufficient circulating T₄ and Tɜ lead to a hypometabolic state resulting in the clinical syndrome known as hypothyroidism. If hypothyroidism occurs during infancy, it results in a condition known as cretinism, in which mental and physical development is impaired. This condition is now rare. If hypothyroidism occurs in older children or adults it results in a condition known as myxoedema, in which skin appears oedematous and doughty due to the accumulation of mucopolysaccharides in the dermis.

***Aetiology***

There are many causes of hypothyroidism and the commonest cause in adults in Hashimoto’s thyroiditis. Most of the remaining cases of hypothyroidism are due to radiotherapy or surgery or are drug induced.

***Hashimoto’s thyroiditis***

Like Graves’ disease, Hashimoto’s thyroiditis is an organ specific autoimmune disease. Antibodies directed against thyroid tissue and thyroglobulin have been detected in patients with this condition. Hashimoto’s thyroiditis may present in a number of ways:

* With goiter, which after time recedes due to atrophy and fibrosis of the gland as a result of autoimmune destruction
* With hypothyroidism
* With thyrotoxicosis-in the early stages of the disease, damage to the thyroid follicles may lead to a transient rise in thyroid hormone levels.

Histologically, the gland is infiltrated by lymphocytes and plasma cells. There are lymphoid aggregates, often with germinal centers. The thyroid epithelial cell’s become eosinophilic and granular, at which time they are termed oncocytes. In advanced cases, the gland is shrunken and fibrotic.

**Clinical features of hypothyroidism**

The clinical features are as follows:

* Myoxoedematous face
* Loss of the outer third of the eyebrows
* Dry hair
* Hoarse voice
* Slowed physical and mental activity, lethargy, weight gain
* Psychosis
* Cold intolerance
* Constipation, muscle weakness, carpal tunnel syndrome, menstrual irregularities.

***Goiter***

The term goiter denotes enlargement of the thyroid gland. There are two main causes:

* Simple and multinodular goiter
* Inflammation of the thyroid (thyroiditis)

***Simple and multinodular goiter***

Simple goiters are characterized by diffuse hypertrophy and hyperplasia of the thyroid gland, without the production of discrete nodularity. Nearly all longstanding simple goiters develop into multinodular goiters, where tracts of fibrosis separate hyperplastic areas, producing nodularity.

Simple goiters are thought to arise from overstimulation of the thyroid tissue by excess TSH. The over secretion of TSH is due to a deficiency of the thyroid hormones. The compensatory rise in the TSH levels usually renders the individual enthyroid, although hypothyroidism may occur Goiters can arise in four main settings:

1. Endemic goiters due to iodine deficiency. These are usually localized to geographic areas where the soil contains little iodine (e.g. the Derbyshire hills, some mountainous areas). Iodine is necessary for the synthesis of the thyroid hormone.
2. Ingestion of certain foodstuffs. In individuals whose iodine uptake is suboptimal, ingestion of foodstuffs such as cabbage and turnips may produce a goiter
3. Rare inherited defects in thyroid hormone synthesis
4. Drug-induced goiters, e.g. amiodarone, lithium

***Thyroiditis***

Thyroiditis is a rare cause of goiter. There are four main forms of thyroiditis.

* Hashimoto’s thyroiditis (discussed above)
* Subacute granulomatous (giant cell or de Quervain thyroiditis
* Riedel’s thyroiditis
* Acute bacterial thyroiditis

***Subacute granulomatous thyroiditis***

As its name implies, the thyroid in subacute granulomatous thyroiditis is infiltrated by multinucleate giant cells admixed with other inflammatory cells. The cause of the condition is uncertain. Patients usually present with an abrupt onset of thyroid swelling and tenderness on palpation. There may be a fever. The condition is self-limiting.

***Riedel’s thyroiditis***

Riedel’s thyroiditis is exceptionally rare. It is characterized by replacement of the thyroid by fibrous tissue, often with involvement of adjacent tissues. The aetiology is unknown. Patients present with an enlarged thyroid, which is hard and immobile on palpation thereby mimicking carcinoma. The condition may be associated with retroperitoneal fibrosis.

***Acute bacterial thyroiditis***

Acute inflammation of the thyroid can result from direct bacterial spread from adjacent tissues or by blood-borne spread. Patients present with thyroid pain, tenderness and enlargement. There may be systemic features of infection. The condition usually resolves with antibiotic treatment.

***Solitary masses***

The differential diagnoses of solitary thyroid masses are as follows:

* One dominant nodule in a multinodular goiter
* Thyroid cysts
* Asymmetrical enlargement due to non-neoplastic disease (e.g. Hashimoto’s thyroiditis)
* Thyroid neoplasm

***Thyroid neoplasms***

Thyroid neoplasms can be benign or malignant. Most thyroid tumors are non-functioning and therefore appear ‘cold’ on scintigraphy (i.e. they do not take up radioactive iodine). However, a minority are functioning, appearing ‘warm’ or ‘hot’ on scintigraphy and possibly causing thyrotoxicosis.

***Benign***

Almost all benign tumors of the thyroid gland are follicular adenomas. The tumors are well-encapsulated and have an expansile growth pattern, compressing the adjacent normal thyroid tissue. These features differentiate a follicular adenoma from a dominant nodule in a multinodular goiter. Histologically, they may show a variety of appearances, the most common being a microfollicular architecture comprising multiple closely follicles with little colloid.

***Malignant***

Carcinoma of the thyroid is uncommon, and together with the fact that these tumors often have a good prognosis, they are responsible for less than 1% have of all cancer deaths. Thyroid carcinoma is two to three times more common in females than males. The four main types of thyroid carcinoma are as follows:

* Papillary carcinoma (75%)
* Follicular carcinoma (10-20%)
* Anaplastic carcinoma (rare)
* Medullary carcinoma (5%)

***Papillary carcinoma***

Papillary carcinoma typically occurs in women in the third or fourth decade. The tumors are un-encapsulated, infiltrative and may be multifocal. Histologically, papillary carcinomas can exhibit a wide range of appearances. The diagnosis depends on the presence of certain cytological features:

* Large hypochromatic nuclei termed “Orphan Annie” nuclei
* Nuclear grooves
* Eosinophilic cytoplasmic inclusions
* Psammoma bodies (calcified glycoprotein bodies)

Cervical lymph node metastases are present in as many as 50% of cases at presentation. However, because these tumors often pursue an indolent course, the overall prognosis is excellent.

***Follicular carcinoma***

Follicular carcinoma occurs in older age groups. Histologically, they are solitary encapsulated tumors most commonly consisting of closely packed small follicles, and may therefore be difficult to distinguish from follicular adenomatous. Invasion of the capsule or vascular invasion indicate malignancy. Metastatic spread has occurred in 15% cases at presentation, most commonly involving the lung or bones. The prognosis for theses tumors is poorer than for papillary carcinomas.

***Anaplastic carcinoma***

Anaplastic carcinoma tends to occur in elderly individuals. The tumors are poorly differentiated histologically, have a rapid growth rate, and metastasize widely. The prognosis is very poor.

***Medullary carcinomas***

Medullary carcinomas are derived from the C-cells within the thyroid, and are therefore neuroendocrine tumors. Most secrete calcitonin but oversecretion of this hormone does not usually produce any clinical effects. Rarely, the tumor other secrete hormones (e.g. ACTH, or 5-hydroxytryplamine). Histologically, the tumor consists of nests or sheets of tumor cells in a characteristic amyloid stroma. These tumors may pursue an indolent or aggressive course. Most medullary carcinomas are sporadic, but around 20% are hereditary and occur as part of one of the MEN syndromes.

**Parathyroid glands**

*Learning objectives*

You should:

* Know the structure and function of the parathyroid glands
* Know the various subtypes of hypothyroidism and their causes

**Structure and function**

Most individuals have four parathyroid glands. In the adult, the upper two glands almost always lie close to the upper posterior aspect of the thyroid gland, but the lower two may be found anywhere between the lower posterior aspect of the thyroid gland and the mediastinum. The glands are composed predominantly of chief cells, which secrete parathyroid hormone (PTH). PTH:

* Mobilizes calcium from bone
* Increases renal tubular resorption of calcium
* Promotes the production of 1, 25-dihydroxyvitamin D₁ (the active form of vitamin D) in the kidney
* Enhances phosphate excretion by the kidney

Overall, serum calcium levels are controlled by the actions of three hormones – PTH, calcitonin and vitamin D. PTH and vitamin D have a hypercalcaemic effect and calcitonin has a hypocalcaemic effect. The most important disorders of the parathyroids are hyperparathyroidism, hypoparathyroidism and tumors.

**Hyperparathyroidism**

Hyperparathyroidism can be divided into primary, secondary and tertiary types:

* Primary – hypersecretion of PTH by a parathyroid lesion
* Secondary – a physiological increase in PTH in response to hypocalcaemia
* Tertiary – development of a hypersecretory parathyroid adenoma in an individual with longstanding secondary hyperparathyroidism

***Primary hyperparathyroidism***

This condition can be caused by the following:

* An adenoma in one of the parathyroid glands (75-80%)
* Hyperplasia of all of the parathyroid glands (10-15%)
* Parathyroid carcinoma (<5%)

The clinical features, with the exception of the bone changes are due to hypercalcaemia and are commonly summed up as ‘bones, stones, abdominal groans and psychic moans’.

***Bone:***

* Osteitis fibrosa cystic (brown tumor), due to excess PTH

***Renal:***

* Formation of calcium-containing renal stones
* Nephrocalcinosis

***Gastrointestinal:***

* Peptic ulcer
* Pancreatitis
* Vomiting
* Abdominal pain

***Neuromuscular:***

* Generalized weakness

***Psychiatric:***

* Depression
* Impaired memory
* Emotional lability

**Secondary hyperparathyroidism (and renal osteodystrophy)**

This most commonly arises in the setting of renal failure or vitamin D deficiency. In renal failure, there is loss of calcium and reduced synthesis of 1, 25-dihydroxy vitamin D₁ leading to hypocalcaemia and secondary hyperparathyroidism and there is retention of phosphate, which also induces secondary hyperparathyroidism. The result is hyperplasia of the parathyroid glands and skeletal changes comprising a mixture of osteitis fibrosa cystica (due to increased PTH-dependent osteoclastic resorption of bone) and osteomalacia (due to lack of vitamin D). The skeletal changes are referred to as renal osteodystrophy.

**Hypoparathyroidism**

The most common causes of hypoparathyroidism are:

* Surgical removal or ablation of the parathyroid glands during thyroidectomy
* Congenital absence of all of the parathyroid glands (di George syndrome)
* Autoimmune destruction of the glands

The clinical manifestations, which are due to hypocalcaemia are:

* Increased neuromuscular excitability – this is manifest by the Chvostek sign (tapping along, the course of the facial nerve causes the facial muscles to twitch), Trousseau sign (occlusion of the arteries in the forearm by inflating a blood pressure cuff induces carpal spasm), perioral paraesthesia, and if severely hypocalcaemic, overt tetany.

**Lecture 5 pathology of the adrenal gland and its disorders.**

**The Adrenal Gland**

*Learning objectives:*

* Understand the structure and its function of the adrenal glands
* Know the common disorders that can affect the adrenal medulla
* Know the disorders that can cause hypo or hyperfunction of adrenal cortex.

**Structure of the Adrenal Gland**

The adrenal glands are located in the retroperitoneum, superomedial to the kidneys. Each is composed of two totally separate functional units: the central medulla and the peripheral cortex (Figure 52).

***The Adrenal Medulla***

The adrenal medulla, which is derived from the embryonic neural crest, is part of the sympathetic nervous system. It consists of neuroendocrine cells (chromaffin cells) and sympathetic nerve endings. The main function of the chromaffin cells is to synthesize and secrete the catecholamines, adrenaline and noradrenaline. The adrenal medulla is the main source of endogenous adrenaline.

The most significant disorders arising from the adrenal medulla are neoplasms, which include phaeochromocytomas (most common), neuroblastomas and ganglioneuromas.

***Phaechromocytoma***

This is functioning tumor derived from the chromaffin cells of the adrenal medulla, and is classified as a paraganglioma. Overproduction of cathecholamines produces hypertension (which may be intermittent) associated with headaches, sweating, palpitations, pallor, anxiety and nausea. The presence of a phaeochromocytoma should be suspected in any young hypertensive patient and, although rare, is one of the curable causes of hypertension. Around 10-20% of these tumors are associated with familial syndromes such as multiple endocrine neoplasia (MEN) syndrome, von-Hippel-Lindau disease, von Recklinghausen’s disease, tuberous sclerosis, and Sturge-Weber syndrome. About half of these familial cases are bilateral. The diagnosis of phaeochromocytoma is based on estimating the urinary excretion of the catecholamine metabolite vanillylmandelic acid (VMA), which is at least doubled when the tumor is present.

***The Adrenal Cortex***

The adult cortex constitutes the peripheral 80% of the adrenal gland. The adrenal cortex is derived from mesoderm and synthesises and secretes the three main classes of steroid hormones: mineralocorticoids, glucocorticoids and sex steroids. There are three functional zones of the adrenal cortex:

* Zona glomerulosa (10%) which lies beneath the capsule and secrets mineralocorticoids
* Zona fasciculate (80%)
* Zona reticularis (10%), which corresponds to the middle and inner zones of the adrenal cortex and secretes glucocorticoids and sex steroids.

Glucocorticoids

These hormones have important effects on a wide range of tissues and organs. The effects include:

* Increased blood sugar
* Increased protein breakdown
* Increased fat loss from the extremities, but fat accumulation in the trunk, neck and face
* Effects on the immune system bone, kidneys, CNS, circulatory system, other endocrine glands and connective tissue.

The most important glucocorticoid is cortisol. The synthesis and secretion of glucocorticoids is under negative feedback control by ACTH, which is by synthesized by the anterior pituitary.

***Mineralocorticoids***

Aldosterone is the most important mineralocorticoid. Its function is to maintain intravascular volume. When intravascular volume is decreased, aldosterone acts on renal tubules to increase the reabsorption of sodium and elimination of potassium and hydrogen ions. The retention of sodium leads to retention of water and consequent restoration of the intravascular volume. The synthesis and secretion of the mineralocorticoids is controlled by the renin-angiotensin system and not the pituitary (See Figure I).

***Sex steroids***

The sex steroids are involved in the development of the male and female sexual characteristics. Most of the body’s sex steroids are synthesized in the gonads, but the adrenal sex steroids usually have a role in the development of some sexual characteristics.

***Adrenocortical hyperfunction (hyperadrenalism)***

The clinical syndromes of cortical hyperfunction are due to excess production of one of the adrenal steroid. Cushing’s syndrome is due to excess glucocorticoids, Conn’s syndrome is due to excess mineralocorticoids and adrenogenital syndromes result from excess sex steroids.

Renin substrate in bloodstream Low renal perfusion pressure

Renin release Low Na⁺

Angiotensin I

Angiotensin – converting enzyme

Angiotensin II

Stimulation of adrenal cortex by Angiotensin II

Aldosterone

Conservation of Na⁺ and H₂O

Loss of K⁺

Renal perfusion pressure and Na⁺ levels restored

**Figure I.**

***Cushing’s syndrome***

There are four main causes of excess circulating glucocorticoids. The commonest is administration of exogenous glucocorticoids. The three remaining causes are related to the overproduction of endogenous glucocorticoids as follows:

* Excess production of ACTH from the anterior pituitary
* Oversecretion of cortisol by an adrenal neoplasm
* Secretion of ectopic ACTH

**Excess production of ACTH by the anterior pituitary**

Overproduction of ACTH by an adenoma results in bilateral adrenocortical hyperplasia and hypercortisolism. This from of Cushing’s syndrome is known as Cushing’s disease. Removal of the pituitary tumor is the treatment of choice. Removal of the adrenals is not advocated because this may result in the development of the Nelsons syndrome, which is characterised by marked enlargement of the pituitary adenoma, high ACTH levels and skin pigmentation (due to the overproduction of melanocyte-stimulating hormone (MSH), which, as well as ACTH, is a cleavage product of POMC.

**Oversecretion of cortisol by an adrenal neoplasm (ACTH-independent Cushing’s syndrome)** Adrenal adenomas, carcinomas and cortical hyperplasia may cause autonomous production of cortisol independent of ACTH levels. If the neoplasm is unilateral, the uninvolved adrenal gland undergoes atrophy because of suppression of ACTH.

**Production of ectopic ACTH** Certain non-pituitary tumors, such as small cell carcinoma of the lung, may secrete ectopic ACTH, producing Cushing’s syndrome.

**Clinical features of Cushing’s syndrome**

A wide range of clinical features, which together are termed Cushing’s syndrome, result from oversecretion of cortisol, including:

* Moon face
* Buffalo hump
* Hypertension
* Hair thinning
* Central obesity
* Osteoporosis
* Hirsutism
* Abdominal striae
* Hyperglycaemia
* Acne
* Proximal muscle intolerance
* Plethora
* Wasting and weakness
* Tendency to infections
* Menstrual abnormalities

***Diagnosis of Cushing’s syndrome***

Diagnosis of Cushing’s syndrome depends on finding raised circulating or urinary cortisol levels. Establishing the cause of Cushing’s syndrome depends on the performance of two tests:

* Levels of serum ACTH
* Low with adrenal neoplasms
* High with pituitary adenomas and ectopic ACTH production
* Measurement of urinary cortisol excretion after administration of high dose dexamethasone (a potent steroid). This is called the high dose dexamethasone suppression test.
* Low with pituitary adenomas
* High with ectopic ACTH

***Primary hyperaldosteronism (Conn’s syndrome)***

In this condition, excess mineralocorticoid production due to a lesion in the adrenal cortex. The commonest cause is an adenoma of the zona glomerulosa, although bilateral adrenal hyperplasia is sometimes responsible. High levels of aldosterone lead to excessive retention of sodium and water, excessive loss of potassium and a metabolic alkalosis. The hypokalaemia may lead to muscular weakness, cardiac, arrhythmias, paraestheia and tetany. Diagnosis depends on finding raised levels of circulating aldosterone and low levels of renin (if the renin levels are raised, then the hyperaldosteronism is secondary to raised renin levels is known as secondary hyperaldosteronism). Adrenal adenomas can be surgically excised, whereas adrenal hyperplasia can be managed medically.

***Hypersecretion of the sex steroids***

Disorders of sexual differentiation are known collectively as an adrenogenital syndromes. There are two main causes of hypersecretion of sex steroids:

* Adrenocortical neoplasms
* Congenital enzyme deficiency in the pathways od steroid synthesis

***Adrenocortical neoplasm***

Adenomas or carcinomas of the adrenal cortex may secrete sex steroids (usually androgens). The effect of these androgens is to cause masculinization in females and precocious puberty in pre-pubertal males.

***Congenital enzyme defects***

There is a small group of rare congenital disorders characterised by a deficiency, or total lack, of a particular enzyme involved in the synthesis of steroids. The commonest of these disorders is 21-hydroxylase deficiency. This enzyme is necessary for the synthesis of cortisol and aldosterone. Its absence leads to low levels of cortisol and consequent elevated levels of ACTH resulting in bilateral adrenocortical hyperplasia. The underproduction of mineralocorticoids is life-threatening. Androgens are over-secreted because they are syntehsised before the metabolic block, resulting in masculinization in females and precocious puberty in males.

***Adrenocortical hypofunction (adrenocortical insufficiency)***

Adrenocortical insufficiency may be due to primary adrenal disease (primary adrenocortical insufficiency) or secondary to decreased stimulation of the adrenals due to a deficiency in ACTH (secondary adrenocortical insufficiency). Insufficiency may be acute or chronic, depending on the speed of onset of the symptoms. The symptoms and signs of adrenocortical hypofunction are related to deficiencies in both mineralocorticoids and glucocorticoids.

***Acute adrenocortical insufficiency***

Acute primary adrenocortical insufficiency ca occur in several circumstances:

* Patients with chronic adrecortical insufficiency may have an acute insufficiency crisis if an event occurs that requires an increased output of steroid hormones by the adrenals
* Patient on long-term steroid treatment have suppressed adrenal glands, which are unable to respond adequately if an event occurs that requires an increased output of steroid hormones, or if the steroid treatment is withdrawn too rapidly.
* Destruction of the adrenal glands by hemorrhage, which can be complicate bacterial (e.g. meningococcal) and septicaemia (Waterhouse-Friderichsen syndrome) and disseminated intravascular coagulation and can occur in neonates following a prolonged or difficult delivery.

Affected patients develop hypovolaemic shock due to mineralocorticoid deficiency and hypoglycaemia due to lack of glucocorticoids.

***Primary chronic adrecortical insufficiency (Addison’s disease)***

Addison’s disease is caused by any destructive process in the adrenal cortex. Previously the commonest cause was tuberculosis of the adrenal cortex, but nowadays autoimmune destruction of the adrenal cortex is a commoner. Affected patients may have autoimmune disease mat other sites (e.g. diabetes, thyroiditis, pernicious anemia). The resultant deficiency of mineralocorticoids and glucocorticoids leads to:

* Weakness and fatigue
* Anorexia, nausea, vomiting and weight loss
* Hypotension and dehydration
* Hyperpigmentation of the skin (due to excess melanocyte stimulating hormone (MSH) at pressure points and on sun-exposed skin
* Hyponatraemia, hyperkalaemia and hypoglycaemia

Serum ACTH levels are high. The condition is potentially life-threatening if steroids are not administered. Patients with Addison’s disease may also develop an acute addisonian crisis if exposed to any stress requiring an increased output of steroids by the adrenals (e.g. infection), with development of acute insufficiency.

To diagnose Addison’s disease, ACTH stimulation tests (synacthen tests) should be performed (Figure 2). Synacthen is a synthetic ACTH analogue and in normal individual, administration of Synacthen causes a serum cortisol levels to rise. In the short Synacthen test, a rise in serum cortisol levels excludes Addison’s disease. If there is no cortisol levels, then the patient has either primary or secondary adrenocortical insufficiency and the long Synacthen test should then be performed to establish the diagnosis.

Secondary adrenocortical insufficiency

This refers to the under reproduction of adrenal steroids due to under secretion of ACTH by the pituitary. There are two main causes:

* Primary lesions of the pituitary
* Hypothalamic-pituitary-adrenal suppression as a result of long-term steroid therapy

There is resultant deficiency of cortisol and sex steroids, but the aldosterone levels are normal, therefore the skin pigmentation and electrolyte disturbances typical of Addison’s disease are not seen. Also, unlike the situation in Addison’s disease, serum ACTH levels are low. Performance of the long Synacthen test will establish diagnosis.