# Endocrinology
# L:5


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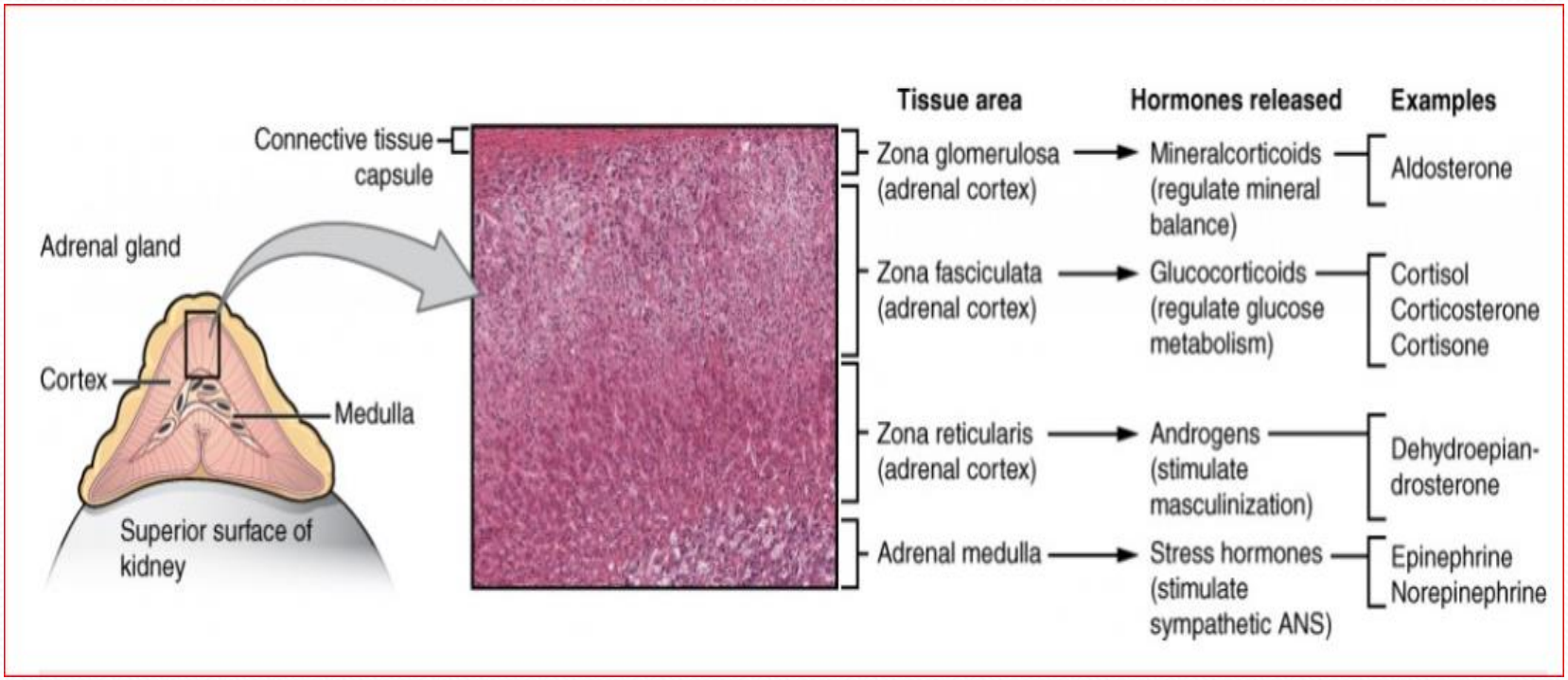
*13-12-2021*

# Adrenal Gland




- Steroid Excess
- Steroid Deficiency

# ADRENAL INSUFFICIENCY

- Adrenal insufficiency results from inadequate secretion of cortisol and/or aldosterone.
- It is potentially fatal and variable in its presentation.
- A high index of suspicion is therefore required in patients with unexplained fatigue, hyponatremia or hypotension.

- *John F. Kennedy, 1957.*

## Etiology

- The most common is ACTH deficiency (i.e. secondary adrenocortical failure), usually because of inappropriate withdrawal of chronic glucocorticoid therapy or a pituitary tumor .
- Congenital adrenal hyperplasias and Addison's disease (i.e. primary adrenocortical failure) are rare, but in areas where HIV/AIDS and tuberculosis are common, associated Addison's disease is increasing in prevalence.

## Clinical assessment

- In Addison's disease, either glucocorticoid or mineralocorticoid deficiency may come first, but eventually all patients fail to secrete both classes of corticosteroid

# CAUSES OF ADRENOCORTICAL INSUFFICIENCY

## ❖ Primary (↑ACTH): Common causes include

- Autoimmune
- Sporadic
- Polyglandular syndromes
- Tuberculosis
- HIV/AIDS
- Metastatic carcinoma
- Bilateral adrenalectomy

## ❖ Secondary (↓ACTH)

- Withdrawal of suppressive glucocorticoid therapy
- Hypothalamic or pituitary disease

## ❖ Rare causes

- Lymphoma
- Intra-adrenal haemorrhage (Waterhouse-Friedrichsen syndrome following meningococcal septicaemia-)
- Amyloidosis
- Haemochromatosis
- Corticosteroid biosynthetic enzyme defects
- Congenital adrenal hyperplasias
- Drugs
- Aminoglutethimide, metyrapone, ketoconazole, etomidate etc.

# What other disease has a strong association with Addison disease?

- Addison's disease is also often associated with other autoimmune disorders such as autoimmune thyroid disease, premature ovarian failure, type I diabetes mellitus, vitiligo, alopecia and coeliac disease

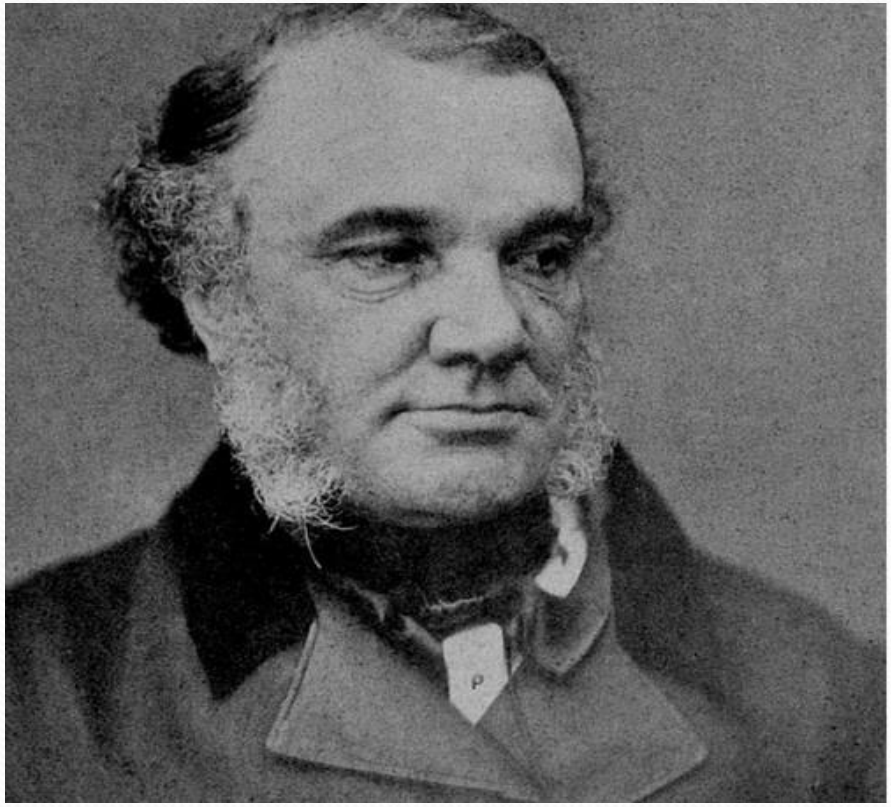
A cluster of diseases known as

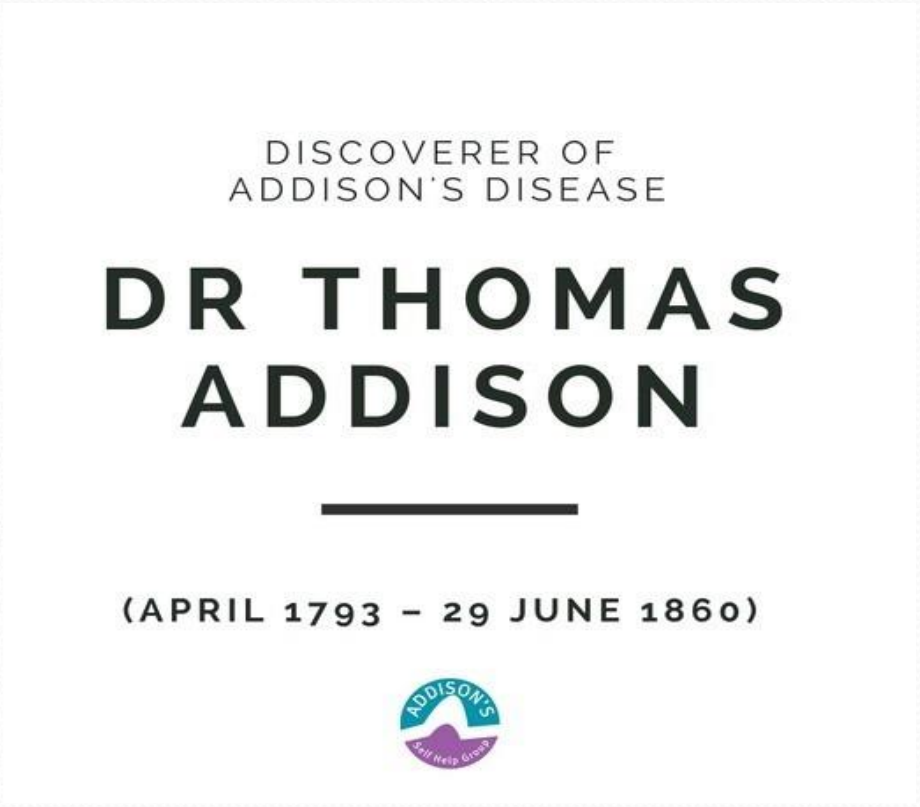
## Autoimmune polyendocrine syndrome type II

- 50% of patients with Addison's disease have an associated autoimmune disease with the most common being thyroid disease

# Addison's disease

In 1855, the English physician Thomas Addison first described the clinical features of the disease,





# Addison's disease

- Primary adrenal insufficiency is due to impairment of the adrenal glands. 80% are due to an autoimmune disease .
- Patients may present with chronic features and/or in acute circulatory shock.
- With a chronic presentation, initial symptoms are often misdiagnosed (e.g. as chronic fatigue syndrome or depression).
- Adrenocortical insufficiency should also be considered in patients with hyponatraemia, even in the absence of symptoms).
- Features of an acute adrenal crisis include circulatory shock with severe hypotension, hyponatremia, hyperkaliemia and, in some instances, hypoglycaemia and hypercalcaemia.
- Muscle cramps, nausea, vomiting, diarrhea and unexplained fever may be present.
- The crisis is often precipitated by intercurrent disease, surgery or infection.
- Vitiligo occurs in 10-20% of patients with autoimmune Addison's disease .

# Clinical features

- Weight loss, Malaise, Weakness, Anorexia, Nausea ,Vomiting, diarrhea,
- dizziness and symptoms of orthostatic hypotension (assessing the patient for postural hypotension is a very sensitive test for adrenal insufficiency). Shock,
- Pigmentation : Mucous membranes, Palmar creases
- Sun-exposed areas Pressure areas, e.g. elbows, knees ,, knuckles, Conjunctivae, Recent scars,
- loss of libido
- Hypoglycaemia,Hyponatraemia ,Hypercalcaemia and Hyperkalaemia

# Investigations

- Assessment of glucocorticoids
- Random plasma cortisol is usually low in patients with adrenal insufficiency, but it may be within the normal range yet inappropriately low for a seriously ill patient.
- Random measurement of plasma cortisol not so sensitive in the diagnosis, unless the value is high, i.e. > 460 nmol/l l

# Addison's disease: Investigations

## ❖ ACTH STIMULATION TEST

- Used for diagnosis of primary or secondary adrenal insufficiency
- ( short Synacthen test ) : Dose: 250 µg ACTH1-24 (Synacthen) by i.m. injection at any time of day

## ❖ Blood samples

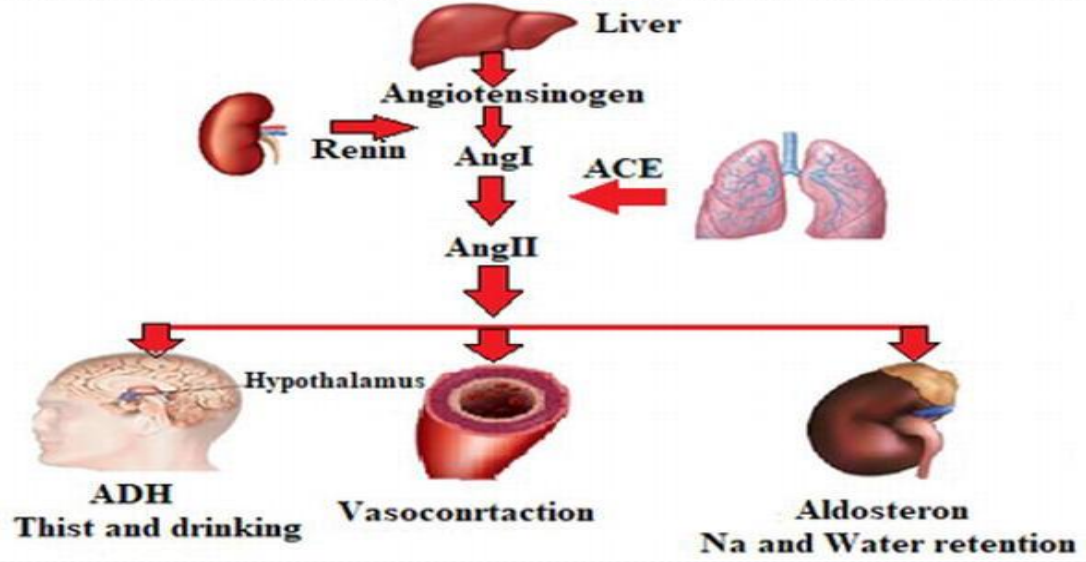
- . 0 and 30 minutes for plasma cortisol
- 0 .0 minutes also for ACTH ,if Addison's disease is being considered (i.e. patient not known to have pituitary disease or to be taking exogenous glucocorticoids)

## • Results

- Normal subjects plasma cortisol > 460 nmol/l either at baseline or at 30 minutes
- More useful is the short ACTH stimulation test ( short Synacthen test) .Cortisol levels fail to increase in response to exogenous ACTH in patients with primary or secondary adrenal insufficiency. These can be distinguished by measurement of ACTH (which is low in ACTH deficiency and high in Addison's disease).
- If an ACTH assay is unavailable, then **a long ACTH** stimulation test can be used (1 mg depot ACTH i.m. daily for 3 days); in secondary adrenal insufficiency there is a progressive increase in plasma cortisol with repeated ACTH administration, whereas in Addison's disease cortisol remains less **than 700 nmol/l** at **8 hours after the last injection .**

# Assessment of mineralocorticoids

- Assess -Plasma electrolyte measurements are insufficient to a mineralocorticoid secretion in patients with suspected Addison's disease.
- Hyponatremia occurs in both aldosterone and cortisol deficiency.
- Hyperkaliemia is common, but not universal, in aldosterone deficiency.
- Plasma renin activity and aldosterone should be measured in the supine position.
- In mineralocorticoid deficiency, plasma renin activity is high, with plasma aldosterone being either low or in the lower part of the normal range



# Adrenal Crisis: Rapid Approach

- In acute adrenal crisis, where treatment should not be delayed in order to do the tests, a blood sample for a random plasma cortisol level should be drawn prior to starting hydrocortisone replacement.
- ❖ Other tests performed in the diagnosis of Addison disease include the following:
- Comprehensive metabolic panel
- Complete blood cell (CBC) count
- Thyroid-stimulating hormone (TSH) levels
- Autoantibody testing: Thyroid and/or adrenal autoantibodies may be present
- Prolactin testing: Modest hyperprolactinemia has been reported in cases of Addison disease and also in secondary adrenocortical insufficiency

# Other tests to establish the cause of Addison's disease

- In patients with elevated ACTH, further tests are required to establish the cause of Addison's disease.
- In those who have autoimmune adrenal failure, antibodies can often be measured against steroid-secreting cells (adrenal and gonad), thyroid antigens, pancreatic β cells and parietal cells. Thyroid function tests, full blood count (to screen for pernicious anemia), plasma calcium, glucose and tests of gonadal function should be performed.
- Tuberculosis causes adrenal calcification, visible on plain X-ray or ultrasound scan. A chest X-ray and early morning urine for culture should also be taken.
- An HIV test may be appropriate if risk factors for infection are present.
- Imaging of the adrenals by CT or MRI to identify metastatic malignancy may also be appropriate

- *Polyglandular Autoimmune Syndrome : rare disorder , autosomal recessive inheritance , include : (Autoimmune adrenal insufficiency, Hypoparathyroidism, Chronic mucocutaneous candidiasis*

# Adrenal Insufficiency management

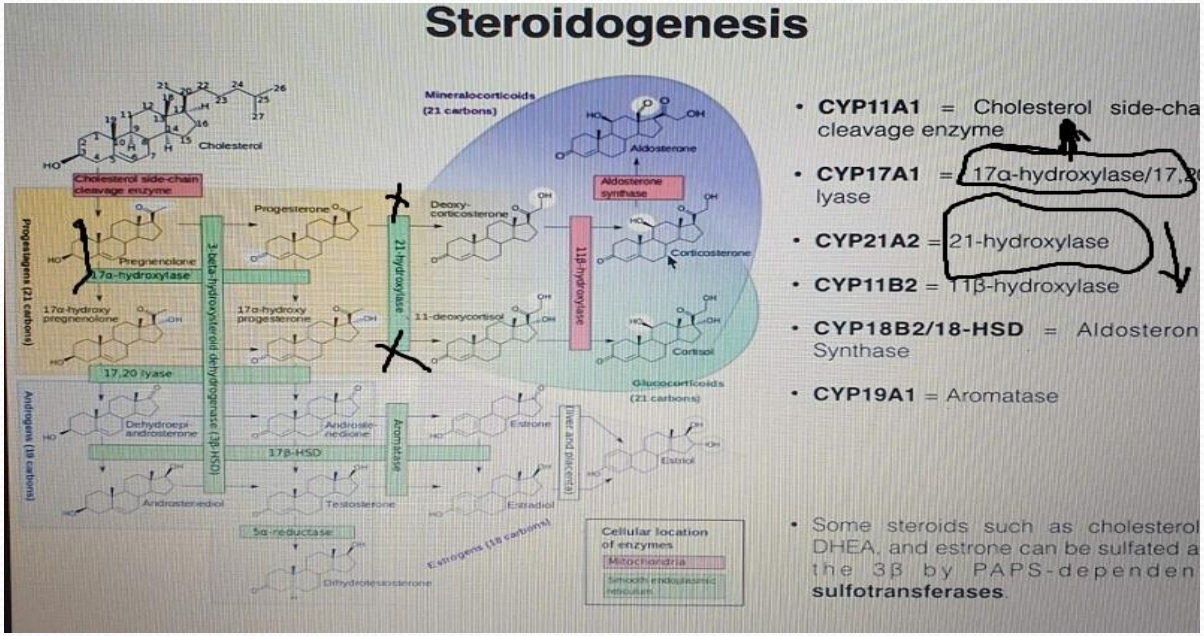
- Patients with adrenocortical insufficiency always need glucocorticoid replacement therapy and usually, but not always, mineralocorticoid.
- Glucocorticoid replacement
- Cortisol (hydrocortisone) is the drug of choice
- Cortisol should be given by mouth, 15 mg on waking and 5 mg at 1800 hrs. The dose may need to be adjusted for the individual patient,. Excess weight gain usually indicates over-replacement, whilst persistent lethargy or hyperpigmentation may be due to an inadequate dose.
- Measurement of plasma cortisol levels is unhelpful, because the dynamic interaction between cortisol and glucocorticoid receptors is not predicted by measurements such as the maximum or minimum plasma cortisol level after each dose.
- These are physiological replacement doses which should not cause Cushingoid side-effects .
- An adrenal crisis is a medical emergency and requires intravenous hydrocortisone succinate 100 mg and intravenous fluid (normal saline and 10% dextrose for hypoglycaemia).
- Parenteral hydrocortisone should be continued (100 mg i.m. 6-hourly) until gastrointestinal symptoms subside before starting oral therapy.
- The precipitating cause should be identified. and, if possible, treated

# Mineralocorticoid replacement

- Aldosterone is not readily available and **fludrocortisone** (i.e. 9α-fluoro-hydrocortisone) is the **mineralocorticoid** used.
- The usual dose is 0.05-**0.1** mg daily. Adequacy of replacement can be assessed objectively by measurement of **blood pressure**, plasma **electrolytes** and plasma **renin** activity .
- In adrenal crisis, however, **rapid replacement** of **sodium** deficiency is more important than administration of **fludrocortisone**. Intravenous saline should be **infused** as required to **normalise hemodynamic** indices.
- In severe **hyponatraemia (< 125** mmol/l) caution should be exercised to avoid too rapid normalisation, which risks **pontine demyelination**


# CONGENITAL ADRENAL HYPERPLASIA

- Congenital adrenal hyperplasia (CAH) refers to a group of genetic disorders that affect the adrenal glands,
- The adrenal glands produce important hormones, including: Cortisol, Aldosterone and sex hormone (androgen , estrogen) from cholesterol
- Defects in the cortisol biosynthetic pathway result in insufficiency of hormones 'distal' to the block, with impaired negative feedback and increased ACTH secretion.
- ACTH then stimulates the production of steroids 'proximal' to the enzyme block. This produces adrenal hyperplasia and a combination of clinical features that depend on the severity and site of the defect in biosynthesis.
- All of these enzyme abnormalities are inherited as autosomal recessive traits



# CONGENITAL ADRENAL HYPERPLASIA

- Etiology and clinical features

  The most common enzyme defect is **21-hydroxylase deficiency**. This results in impaired synthesis of cortisol and aldosterone and accumulation of **17OH-progesterone,** which is then diverted to form adrenal **androgens.**

- One-third of cases this defect is **severe and presents in infancy** with features of **glucocorticoid** and **mineralocorticoid deficiency** and **androgen** excess (i.e. **ambiguous genitalia** in **girls**).
- Other two-thirds, mineralocorticoid secretion is adequate, but there may be features of cortisol insufficiency and/or ACTH and androgen excess (including precocious pseudopuberty.
- Sometimes the mildest enzyme defects are not apparent until adult life, when females may present with amenorrhea and/or hirsutism. This is called 'non-classical' or 'late-onset' congenital adrenal hyperplasia .
- Both 17-hydroxylase and 11β-hydroxylase deficiency may produce hypertension due to excess production of 11-deoxycorticosterone, a mineralocorticoid

# CONGENITAL ADRENAL HYPERPLASIA

## ❖Investigations

- High levels of plasma 17OH-progesterone are found in 21-hydroxylase deficiency. In late-onset cases this may only be demonstrated after ACTH administration.
- To avoid salt-wasting crises in infancy, 17OH-progesterone can be routinely measured in heel prick blood spot samples taken from all infants in the first week of life.
- In siblings of affected children, antenatal genetic diagnosis can be made by amniocentesis or chorionic villus sampling. This allows prevention of virilisation of affected female fetuses by administration of dexamethasone to the mother.

# Congenital adrenal hyperplasia (CAH) :

## Management

- The aim is to replace deficient corticosteroids, and also suppress ACTH and hence adrenal androgen production.
- In contrast with glucocorticoid replacement therapy in other forms of cortisol deficiency, it is usual to give 'reverse' treatment, i.e. a larger dose of a long-acting synthetic glucocorticoid just before going to bed to suppress the early morning ACTH peak, and a smaller dose in the morning.
- In children, growth velocity is the most useful measurement since either under- or over-replacement with glucocorticoids suppresses growth.
- In adults, clinical features (menstrual cycle, hirsutism, weight gain, blood pressure) and biochemical profiles (plasma renin activity and 17OH-progesterone levels) provide a guide .
- Patients with late-onset 21-hydroxylase deficiency may not require corticosteroid replacement. If hirsutism is the main problem, anti-androgen therapy may be just as effective.

## By conclusion

- CAH is an inherited disorder that results in low levels of cortisol and high levels of male hormones, causing development of male characteristics in females, and early puberty in both boys and girls.