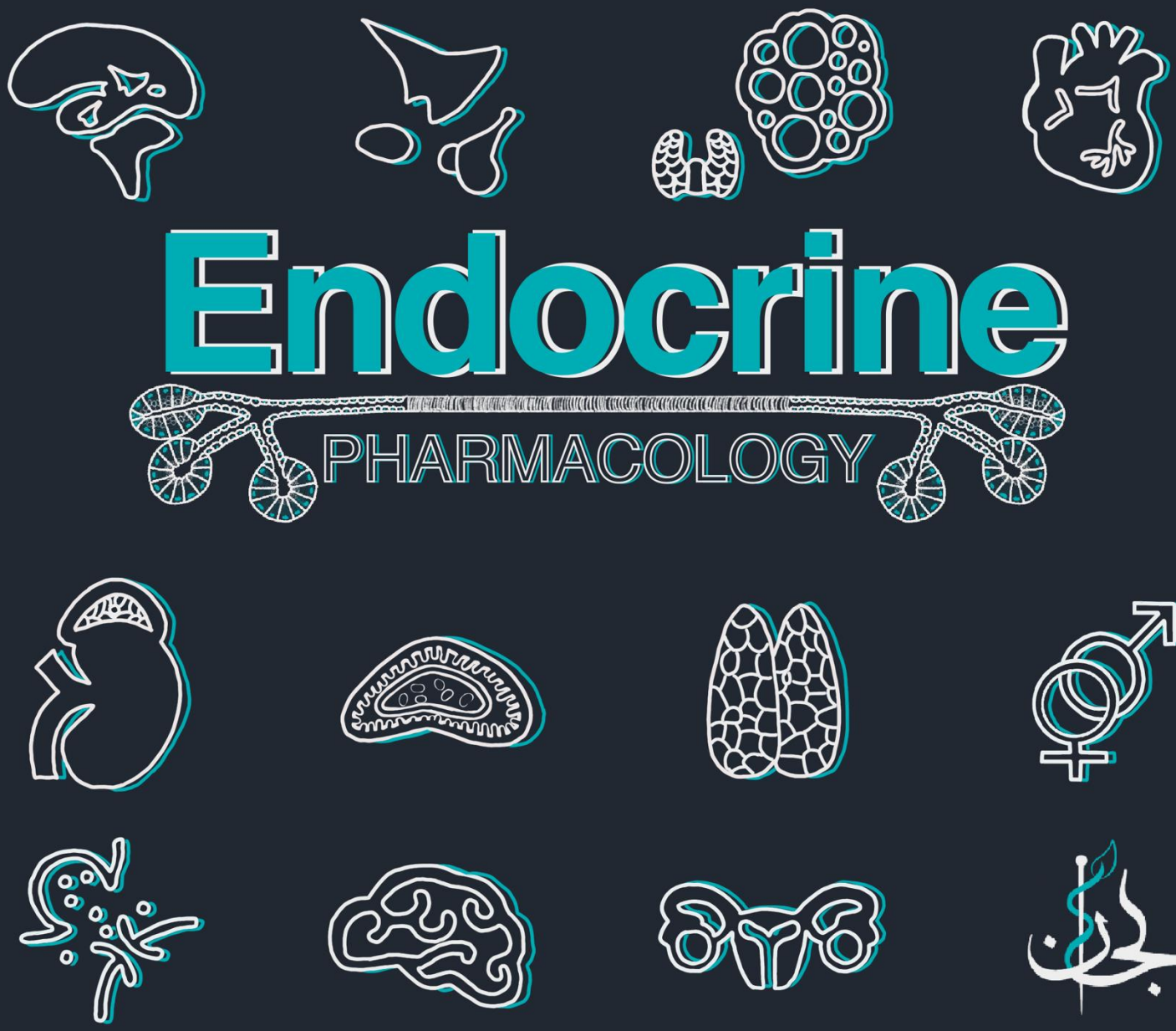


# Title: Sheet 6 – corticosteroids

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Science: Osama Alkaabneh
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Doctor: Manar Zraikat

This is the last lecture of pharmacology in the endocrine system. The doctor hadn't added much details to what is written in the slides, GOOD LUCK!

# Corticosteroids

•The steroidal nature of adrenocortical hormones was established in 1937, when Reichstein synthesized deoxycorticosterone.

•In humans, hydrocortisone (cortisol) is the main carbohydrate-regulating steroid, and aldosterone is the main electrolyte-regulating steroid.

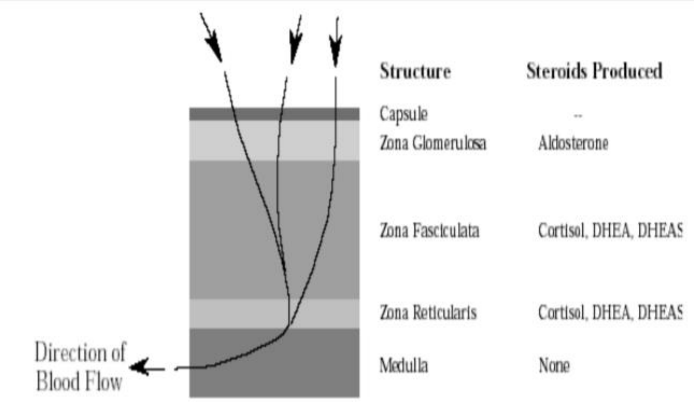
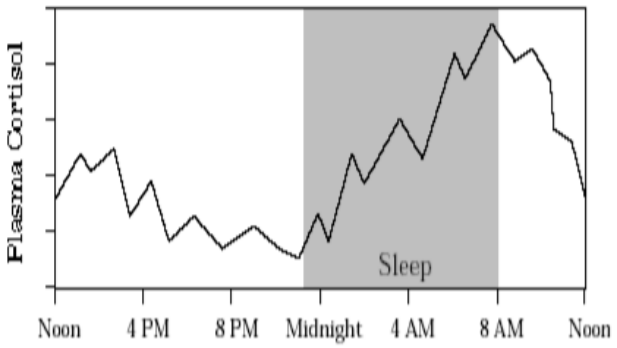


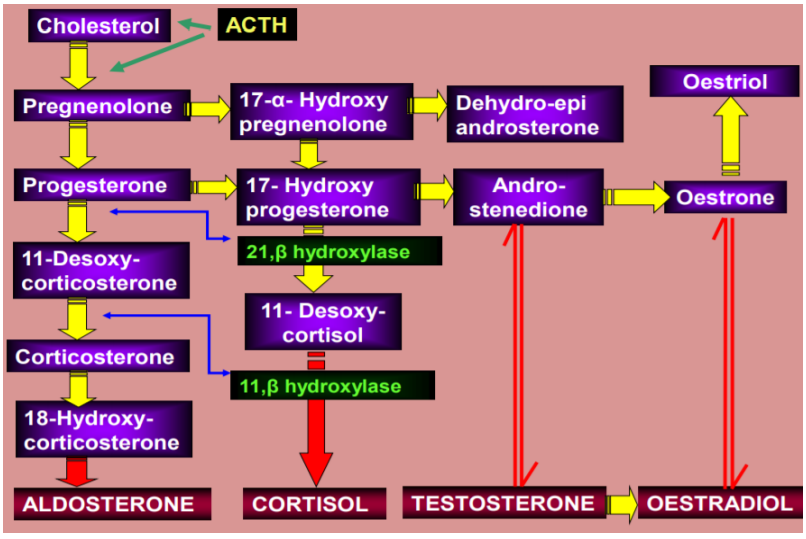
Figure 1. Cartoon of Adrenal Morphology.

•The mammalian adrenal cortex is divided into three concentric zones: the **zona glomerulosa, zona fasciculata, and zona reticularis**. Each of these zones secrete different set of hormones as seen in this picture.




•This picture shows the **diurnal pattern of secreting Cortisol**, which is highest immediately before waking up in morning, and lowest in midnight.

•The adrenal gland synthesizes steroids from cholesterol. Cholesterol is transported into the mitochondria of steroidogenic tissue, where side chain cleavage is carried out producing different types of hormones as seen here:




•Different kinds are produced according to what enzymes acts on it.

•ACTH plays an important role in stimulating these processes.

## Synthetic Corticosteroids:

We use synthetic corticosteroids widely in clinical field.

Synthetic corticosteroids are produced by alerting the steroid molecule, but what is the ultimate aim of altering the steroid molecule? Two main goals:

***1- decrease sodium-retaining activity(water retaining and edema).***

***2- increase anti-inflammatory glucocorticoid activity***.

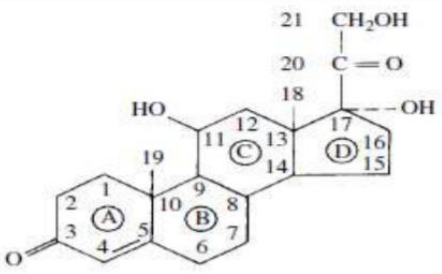
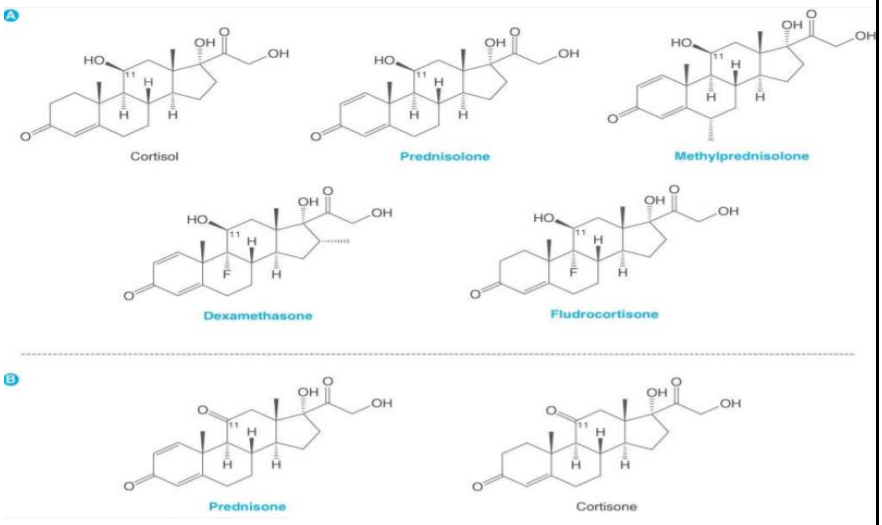


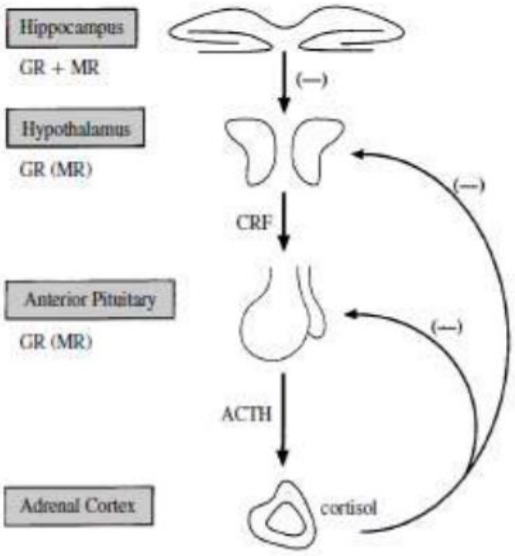

**FIGURE 60.4**
Basic corticosteroid nucleus.

## Glucocorticoid analogs:




This figure shows Cortisol, the **natural glucocorticoid**, and other synthetic corticosteroids produced by modifying cortisol at some carbons such as: Prednisolone, Dexamethasone…etc.

## Negative feedback mechanism:




The role of the hypothalamic–pituitary axis in the regulation of adrenocortical hormone synthesis and release.
The major physiological stimulus for the synthesis and release of glucocorticoids is corticotropin (ACTH) secreted from the anterior pituitary gland.

(ACTH is an indicator of stress)

## ***Pharmacological Actions:***

- The pharmacological actions of steroids are generally an extension of their physiological effects.
- Glucocorticoids (e.g., prednisolone) are used to **suppress inflammation**, **allergy** and **immune responses**.
- Anti-inflammatory therapy is used in many illnesses (e.g., Rheumatoid arthritis, ulcerative colitis, BA, eye and skin inflammations).
- Glucocorticoids are used also in **Tissue transplantation and lymphopoiesis** (leukemias and lymphomas).
- Striking improvements can be obtained, but we need to take its **severe adverse effects** in consideration.
- For most clinical purposes, synthetic glucocorticoids are used because **they have a higher affinity for the receptor**, are less activated and **have little or no salt-retaining properties** thus decreasing Edema that might happen sometimes.

Let's take some examples about synthetic glucocorticoids and their clinical uses:

• ***Hydrocortisone (cortisone)*** can be used:

1-**orally** for replacement therapy (when cortisol is deficient).

2-**IV** for allergic shock and asthma.

3- **Topically** (ointment) for eczema.

4-**enemas** for ulcerative colitis.

• ***Prednisolone*** is the most widely used drug given **orally** in **inflammation and allergic diseases.**

• ***Betamethasone and dexamethasone***: they are very potent. They have **no salt-retaining properties**; thus, very useful for **high-dose therapies** (e.g., cerebral edemas).

• ***Beclomethasone, dipropionate, budesonide***: they **pass membranes poorly**, thus, they are more active when applied **topically** (severe eczema for local anti-inflammatory effects) than orally. Also, can be used in **asthma, (as aerosol**).

• **Triamcinolone**: used for **severe asthma and for local joint inflammation** (intra-articular injection).

## ***ACTIONS OF THE CORTICOSTEROIDS***

### *Carbohydrate, Protein, and Fat Metabolism*

• The glucocorticoids **increase blood glucose** and **liver glycogen** levels by stimulating **gluconeogenesis**.

• The source of this augmented (great) carbohydrate production is **protein**.

• The protein catabolic actions of the glucocorticoids result in a negative nitrogen balance.

• The **inhibition of protein synthesis** by glucocorticoids brings about a **transfer of amino acids from muscle and bone to liver, where amino acids are converted to glucose.**

### *Electrolyte and Water Metabolism*

•Another major function of the adrenal cortex is the regulation of water and electrolyte metabolism.

•The steroid-binding specificity of mineralocorticoid and glucocorticoid receptors overlaps in the **distal cortical cells and collecting tubules**, **so that glucocorticoids may mediate mineralocorticoid-like effects .Mineralocorticoid can increase the rate of sodium reabsorption and potassium excretion several fold**.

•This will occur **physiologically** in response to sodium or volume depletion or both. The primary site of this effect is the **distal tubule**.

***REMEMBER THAT SYNTHETIC steroids have less salt-retaining activity than natural steroids, to avoid hypertension. ***

### *Cardiovascular Function*

•Glucocorticoids **directly stimulate cardiac output** and **potentiate the responses of vascular smooth muscle to the pressor effects of catecholamines and other vasoconstrictor agents**.

•The presence of **steroid receptors on vascular smooth muscle suggests a direct effect on vasomotor activity**. Thus, corticosteroids appear to play an important role in the regulation of blood pressure by modulating vascular smooth muscle tone.

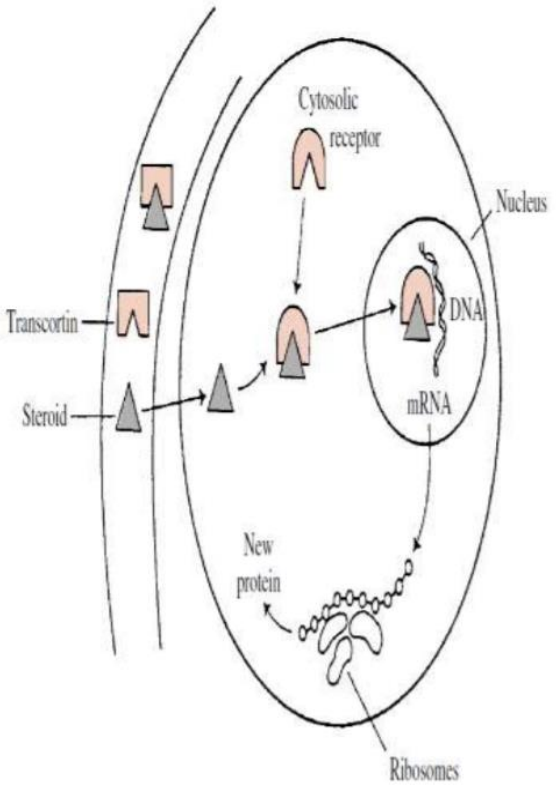
## ***Mechanism of action***

1-Steroids transported by **transcortin** enter the target cell by diffusion and then form a complex with its cytosolic receptor protein.

2-Glucocorticoids bind to **cytoplasmic glucocorticoid receptors** containing two subunits of the heat shock protein that belong to the 90-kDa family.

3-**The heat shock protein dissociates**, allowing rapid nuclear translocation of the receptor–steroid complex.

4- Within the nucleus, the glucocorticoid receptor induces gene transcription by binding to specific sequences on DNA called **glucocorticoid response elements** in the promoter– enhancer regions of responsive genes. Resulting in production of proteins such as: ***Lipocortin***.




What do these products (e.g., lipocortin) do?

We need to know that metabolites of arachidonic acid, including prostaglandins (PG), thromboxanes, and leukotrienes, are considered strong candidates as **mediators of the inflammatory process**. So, we need to ***block*** their production.

### ****The mechanism****

**1-**Steroids may exert a primary effect at the inflammatory site by inducing the synthesis of a group of proteins called **lipocortins**.

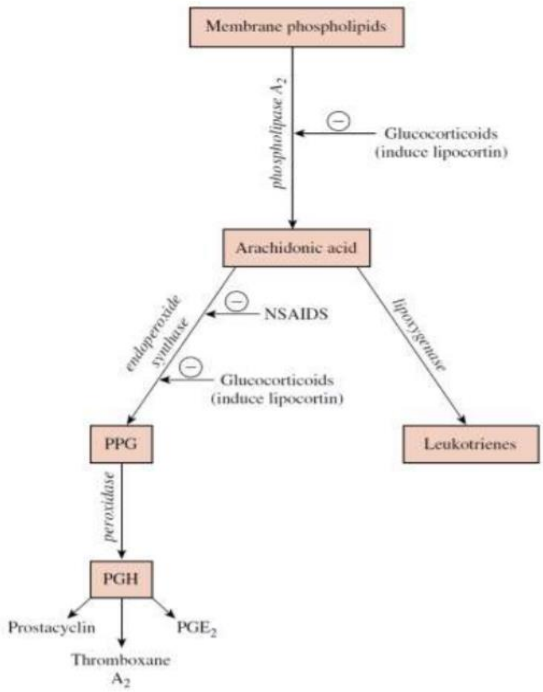



**FIGURE 60.6**
Possible site or sites of action of glucocorticoids on prostanoid production.

These proteins (lipocortins) suppress the activation of phospholipase A2, so decreasing the release of arachidonic acid and the production of proinflammatory effect.

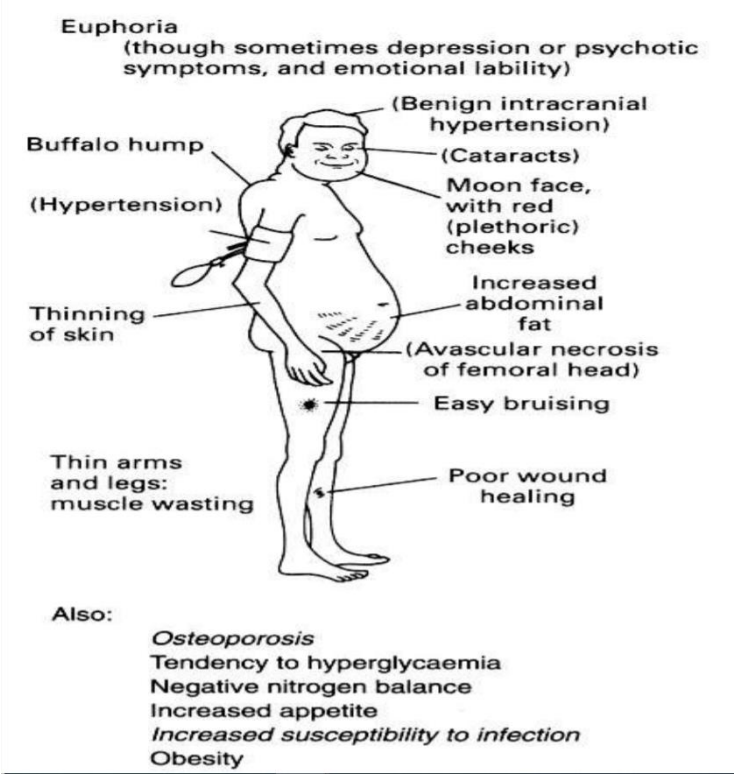
**2-**Another possible glucocorticoid-sensitive step is the PG endoperoxide H synthase (or cyclooxygenase) (COX) mediated conversion of arachidonate to PG endoperoxides. Blocking this step also prevents the formation of PG.

## ***Steroids adverse effects***

This figure is very important, and here is some notes about it:

1-Euohoria: psychiatric effect of using steroids mainly due to Oral or IV administered steroids rather than topical.

2- moon face, buffalo hump, cataracts, easy bruising and increased abdominal fat can be seen also.




## ***THERAPEUTIC USES OF STEROID HORMONES***

### ***1-Replacement Therapy in Adrenal insufficiency*:**

•Adrenal insufficiency may result from:

1- hypofunction of the adrenal cortex (**primary adrenal insufficiency, Addison's disease**, ACTH levels are **high** -due to feedback- so we might have **hyperpigmentation**-remember that ACTH contains MSH fragment-)

or

2- From a malfunctioning of the hypothalamic–pituitary system (**secondary adrenal insufficiency**, ACTH levels are **low**).

•In treating primary adrenal insufficiency, one should administer sufficient cortisol to **diminish hyperpigmentation and abolish postural hypotension****; which are the cardinal signs of **Addison's disease**.

**Remember that cortisol **up—regulates alpha1 receptors** on **arterioles** increasing their sensitivity to the vasoconstrictor effect of norepinephrine.

***2-Inflammatory States:***

•Glucocorticoids possess a wide range of effects on virtually every phase and component of the inflammatory and immune responses.

•They have assumed a major role in the treatment of *a wide spectrum of diseases with an inflammatory or immune-mediated component*.

•***Rheumatoid arthritis*** is the original condition for which anti-inflammatory steroids were used.

•**Intraarticular glucocorticoid injections** have proven to be *efficacious*, particularly in **children**.

***However,***

•The detrimental effects of glucocorticoids on **growth** are **significant for children** with active arthritis, even more than its effect on adults.

So, we say that:

•**steroids offer symptomatic relief** from this disorder by abolishing the swelling, redness, pain, and effusions.

***But they do not cure*** Progressive deterioration of joint structures **and the disease process may be exacerbated after steroid therapy is terminated.**

So, we need to properly calculate the dose we need specially in children.

***GOOD LUCK MATES***