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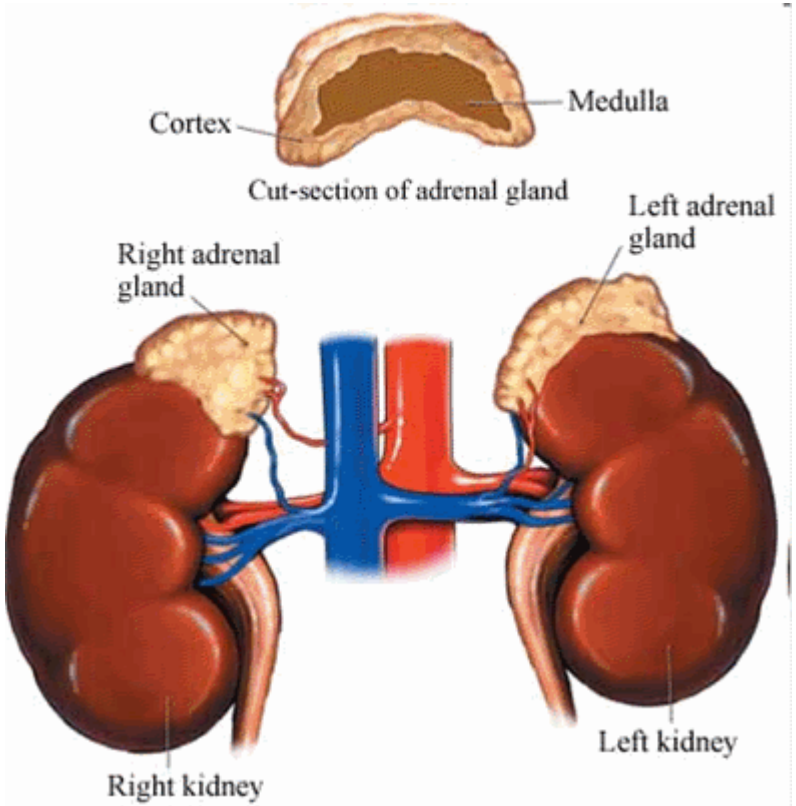
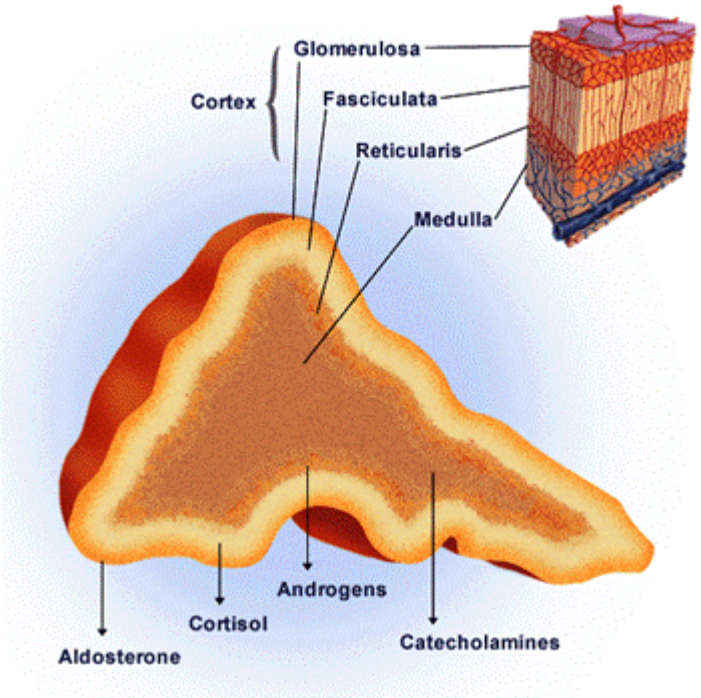
GLUCOCORTICOIDS

Department of Pharmacology MF MU

Suprarenal glands - anatomy





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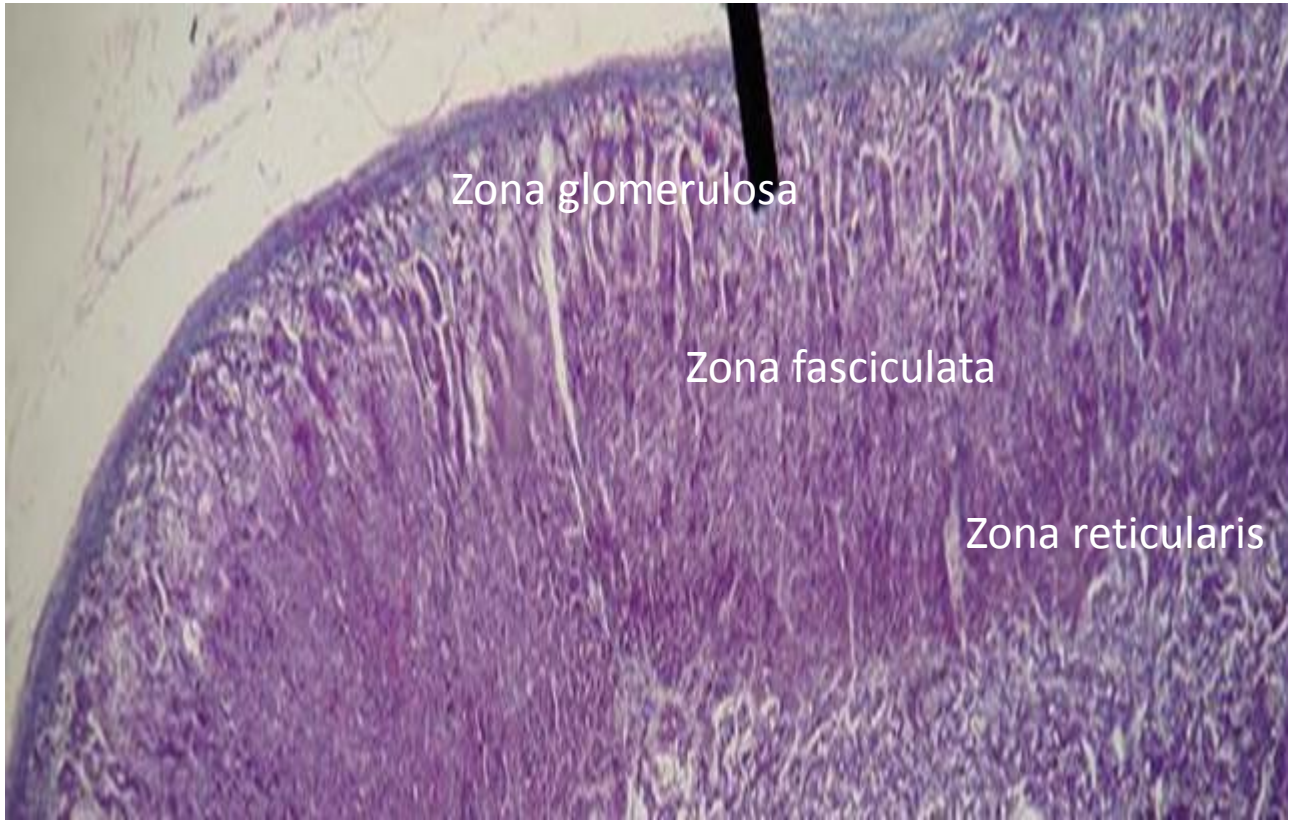
Adrenal cortex - physiology



- **Zona glomerulosa – mineralocorticoids production - aldosteron** 10 – 15% of tissue, controlled by ATII a K^+.
- **Zona fasciculata** 75% of tissue, controlled by ACTH, „stock“ of cholesterol, its releasing and transformation to **cortizol = main human glucocorticoid.**
- **Zona reticularis** 10 – 15 % of tissue – androgens, gestagens, cortisol production.

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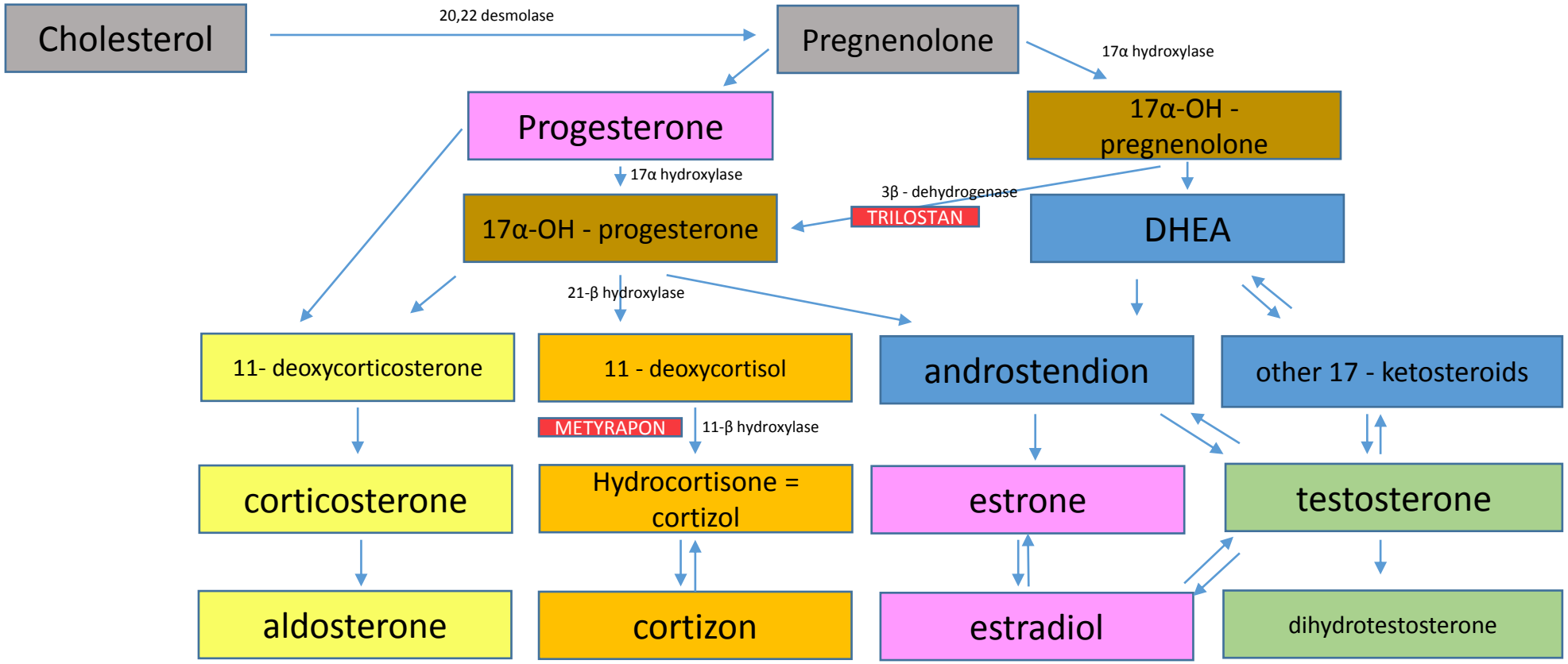
Steroid hormones biosynthesis - biochemistry



Precurzors

Intermediate products

Mineralocorticoids

Glucocorticoids

Estrogens

Androgens

17 ketosteroids

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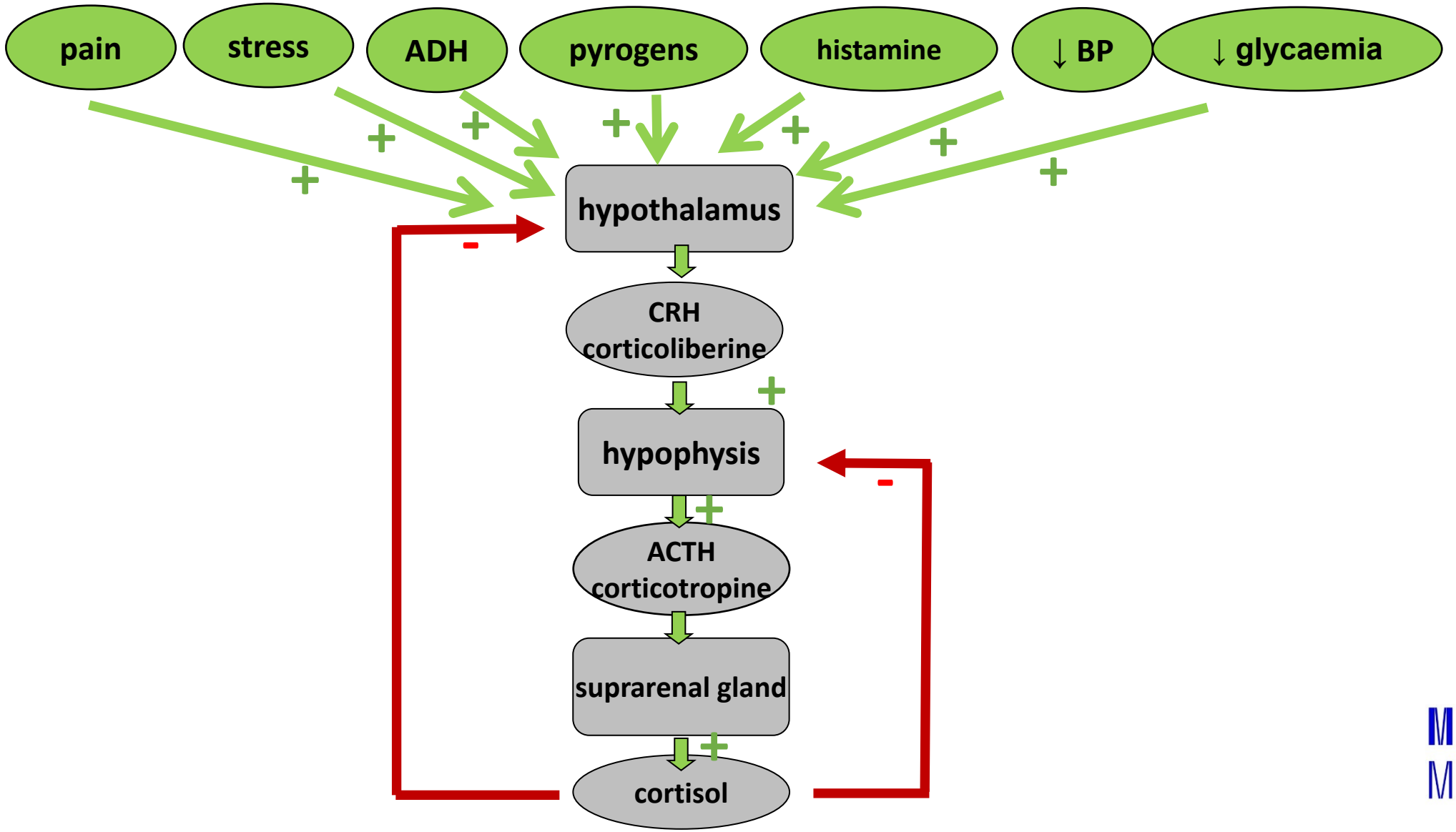
Glucocorticoids - regulation



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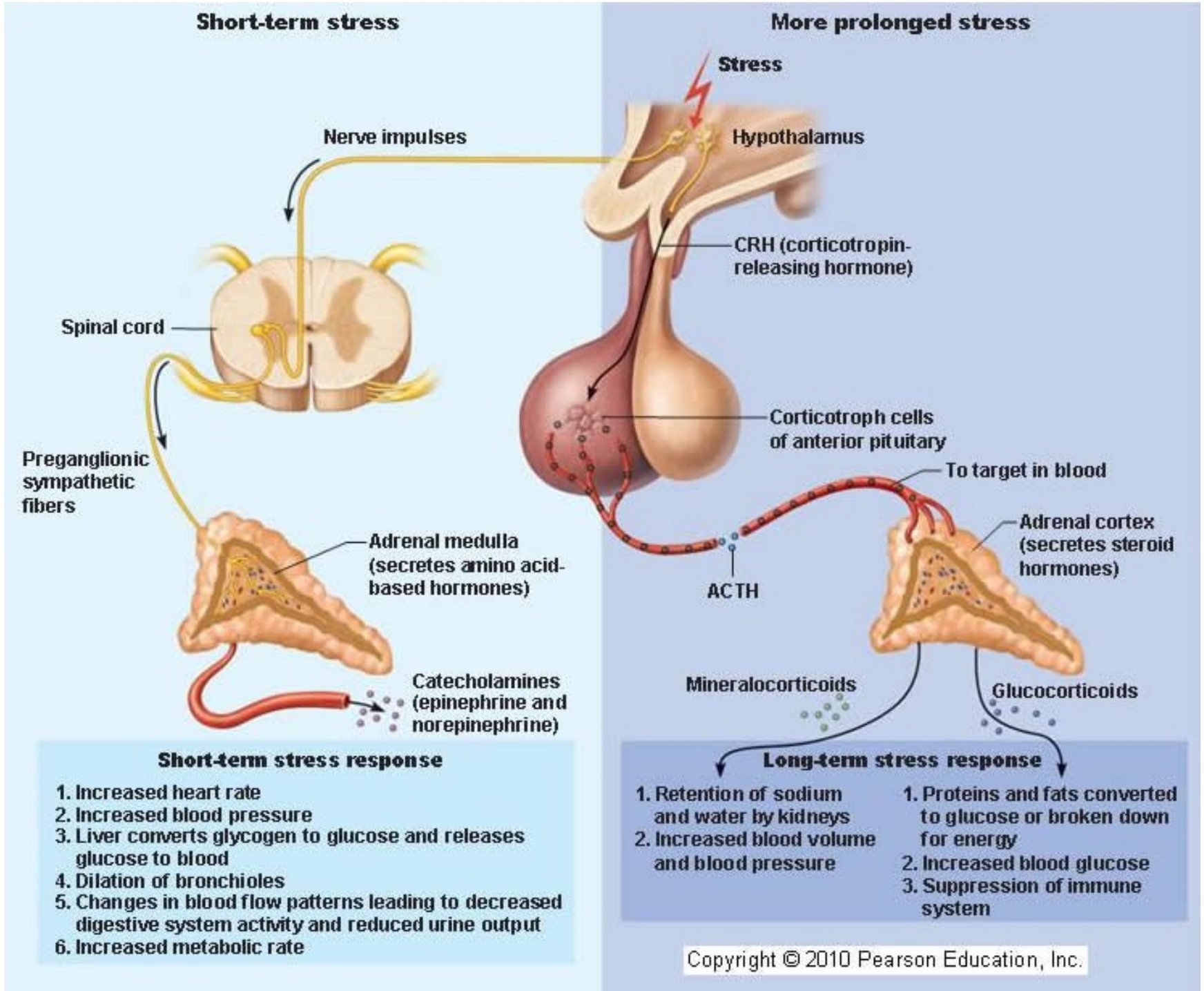
Short-term stress
More prolonged stress
Stress
Nerve impulses
Hypothalamus
CRH (corticotropin-releasing hormone)
Spinal cord
Corticotroph cells of anterior pituitary
Preganglionic sympathetic fibers
To target in blood
Adrenal cortex (secretes steroid hormones)
Adrenal medulla (secretes amino acid-based hormones)
ACTH
Catecholamines (epinephrine and norepinephrine)
Mineralocorticoids
Glucocorticoids
Short-term stress response
1. Increased heart rate
2. Increased blood pressure
3. Liver converts glycogen to glucose and releases glucose to blood
4. Dilation of bronchioles
5. Changes in blood flow patterns leading to decreased digestive system activity and reduced urine output
6. Increased metabolic rate
Long-term stress response
1. Retention of sodium and water by kidneys
2. Increased blood volume and blood pressure
1. Proteins and fats converted to glucose or broken down for energy
2. Increased blood glucose
3. Suppression of immune system
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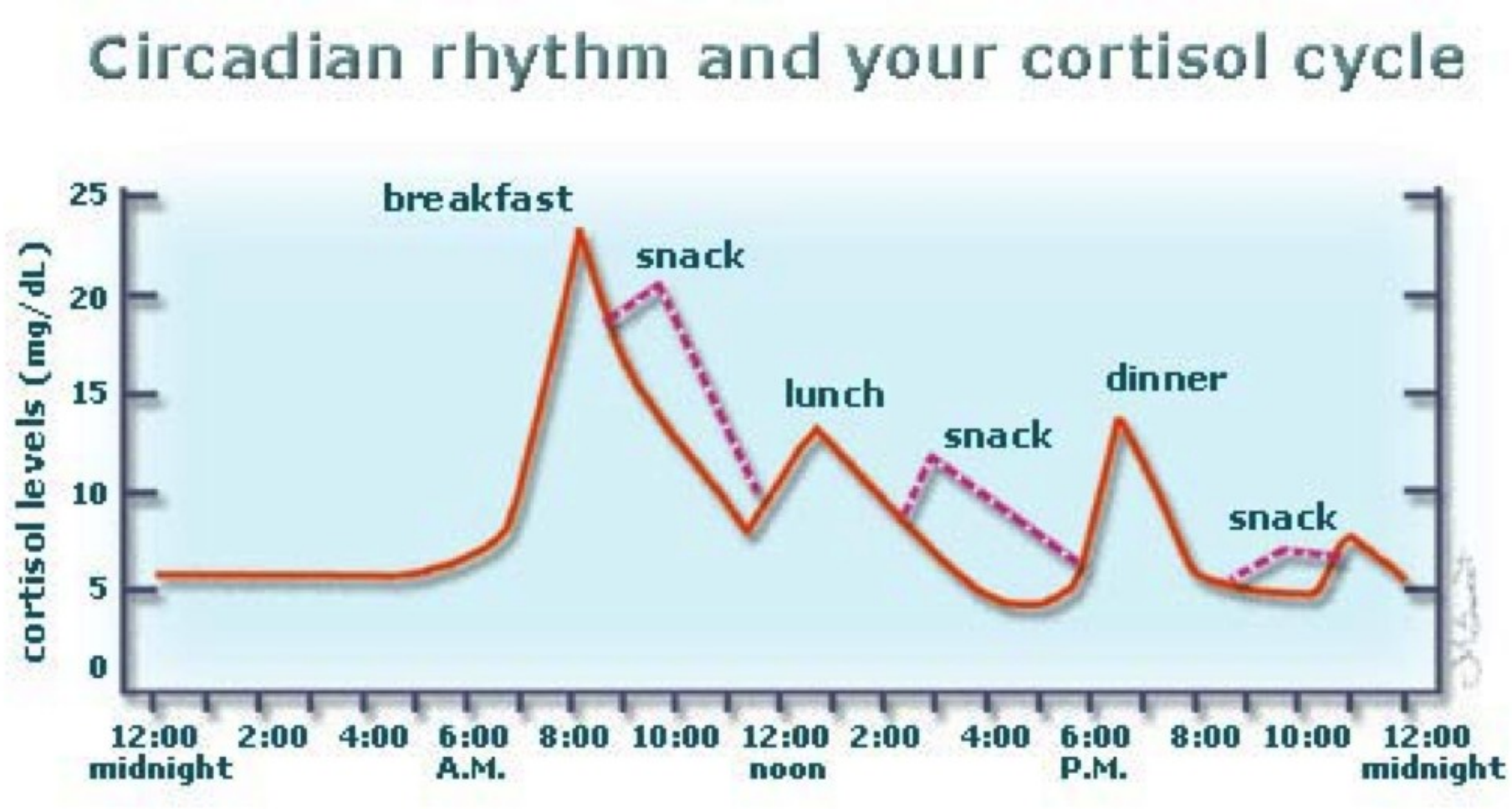
Endogenous and exogenous cortisol secretion



Resting – 20 – 25 mg/24 hours

Stress: 10 times higher

Maximum: 6 – 8 hours a.m.

Exogenous corticoids usage – endogenous secretion downturn

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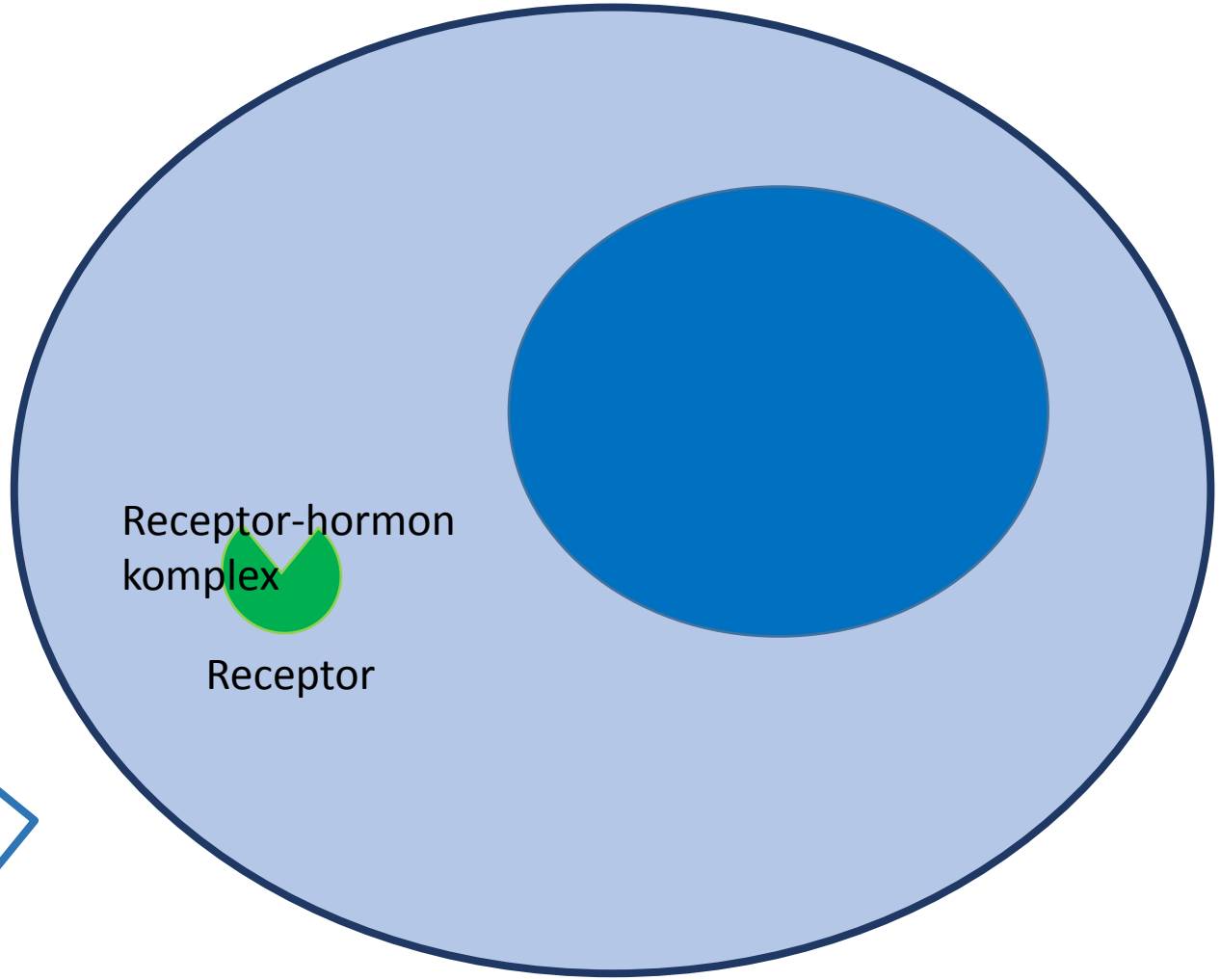
Mechanism of action in cellular level → **Specific**

Glucocorticoid



Receptor in cytoplasma – slower efekt

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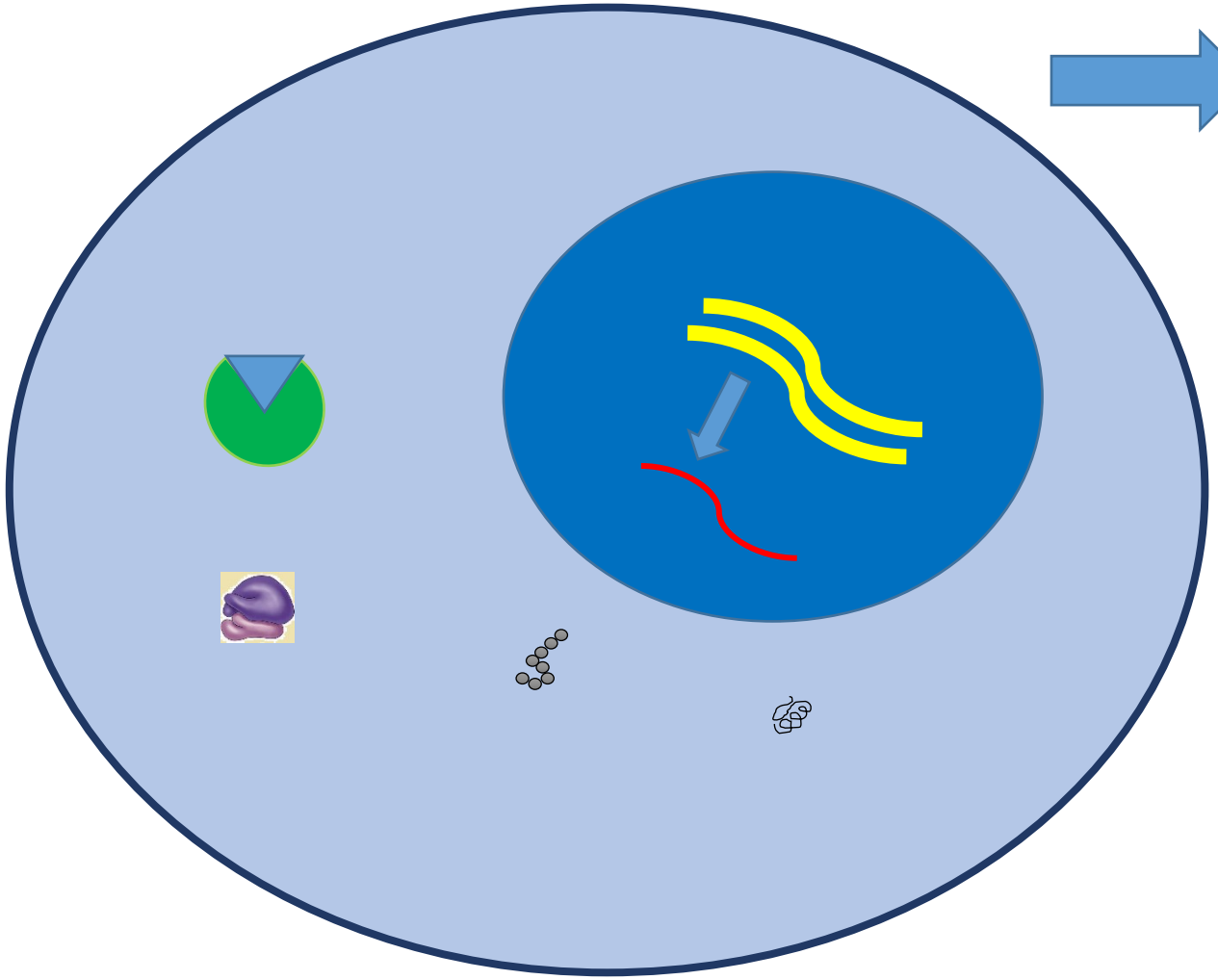
Mechanism of action in cellular level → **Specific**



Change of proteosynthesis

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Glucocorticoids

- influence sugar, fat and protein **metabolism**
- have **anti-inflammatory** and **anti-allergic** effect
- have **immunosuppressive** effect (in many branches – in next slides)
- have **antiproliferative** effect

- hydrocortisone (cortisol)

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GCs and sugar, fat and protein metabolism

reduced glucose uptake and reduced glucose utilisation in the cell

Proteolysis, tissue proteins = aminoacids
decomposition of tissue proteins
catabolism

↑ gluconeogenesis
(glucose formation from non sugar residues)

Fats: ↑ lipolysis, facilitation of lipid absorption, fat redistribution

↑ glycaemia

Connective tissue
muscle atrophy

fibroblasts growth stopping
↓osteoblasts, ↑osteoclasts
↓collagen synthesis
↓Ca resorption from intestine, kidneys (osteoporosis)

↑ of insulin secretion

↑ storage of glycogen in the liver

lipogenesis support, lipolysis inhibition
fat deposition, redistribution,
↑glycerol, aminoacids in blood

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Other effects

CNS: Euphoria / psychotic disorder after high doses / depression
GIT: Increasing formation of HCl and pepsin in the stomach

BLOOD: ↑ Tro, Ery, circul. ↓lymfocytes, ↓eosinofils

LUNGS: ↑ formation of pulmonary surfactant

HCl – hydrochloric acid

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GCs and congenital developmental defects
GK and ions

Permissive effect to:
- Development of organs of the fetus
- Development and maturation of intestinal enzymes
- Increases the synthesis of surfactant in the lungs of the fetus
- Suppresses bone growth

Ions
- Decreased calcemia
- Increased potassium loss
- Sodium and chloride retention

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Regulatory effects

- **Negative feedback on the hypothalamus and the anterior lobe of the pituitary gland**
  reduced release of endogenous glucocorticoids

- **Vasotropic** - GCs - vasoconstriction, decrease of permeability of vessels, suppression of edema

- **At cell level:**
  in place of acute inflammation: decrease in migration and leucocyte activity
  in place of chronic inflammation: decrease proliferation of blood vessels and fibrosis
  In place of lymphoid tissue: decrease B and T lymphocyte expansion

- **Towards the mediators of inflammation and immunological reaction:**
  Decrease of cytokine production and activity, decreased synthesis of PGs

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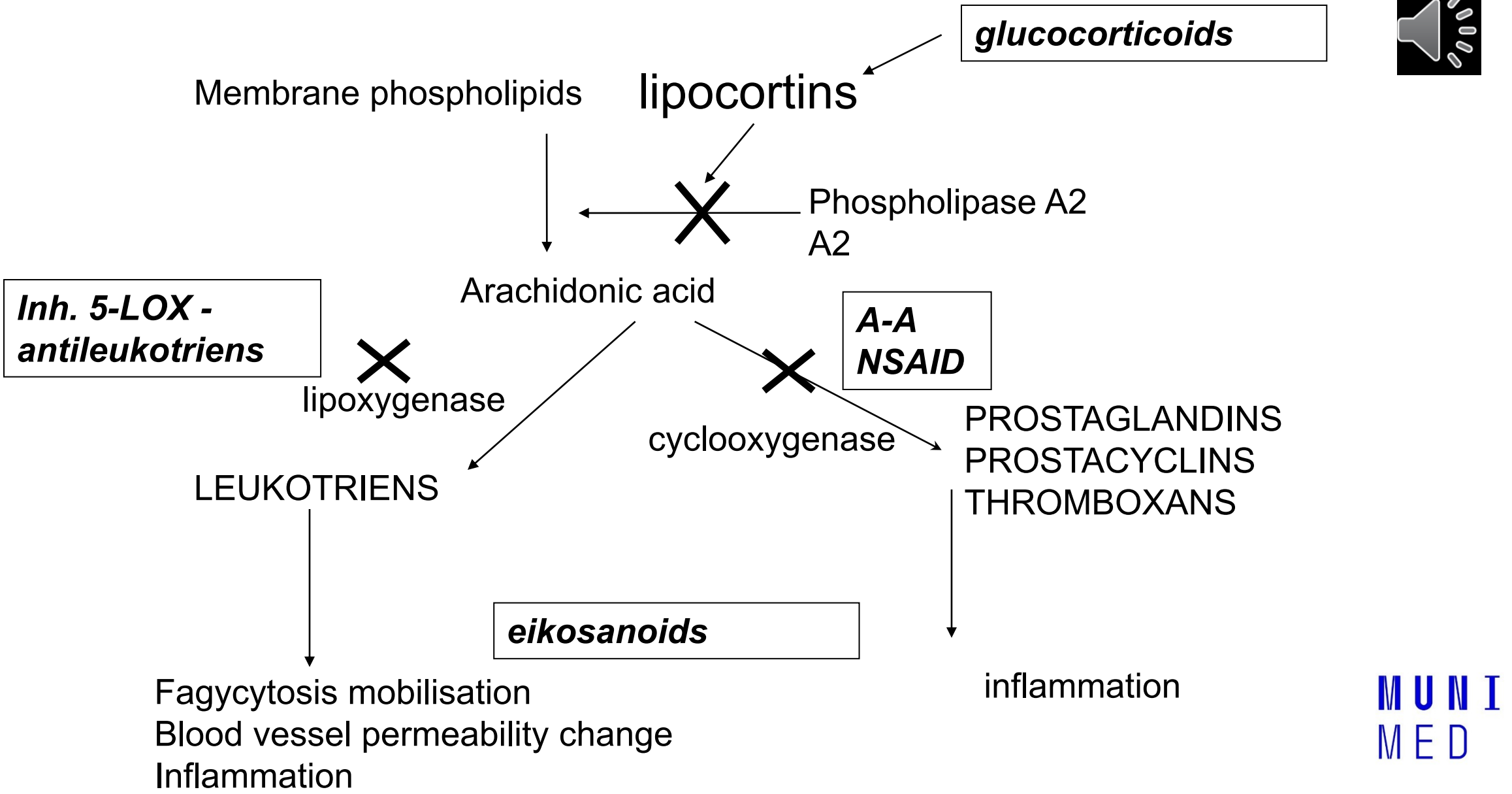
Anti-inflammatory – cascade inhibition of AA



Anti-inflammatory effect

- AA cascade inhibition
- Migration and leucocyte function disruption
- Antibody production reduction

All types of inflammation regardless of origin!

(aseptic, viral, bacterial, parasitic….)

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Immunosupressive effect

Inhibition of antigen recognition

Inhibition of the effector phase of the immune response (cell lysis)

- **! CAUTION:**
- **Inhibition CELL MEDIATED immunity**
- **ANTIBODY immunity is affected significantly less and in GSc higher doses**

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Anti-inflammatory effect

- Decreased histamine release from basophils

- Inhibition of the formation of inflammatory mediators and allergic reactions (cytokines, complement components, kallikrein ...)

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Anti- proliferative effect

Block cell cycle

Induction of differentiation

GCs - lymphocyte disintegration (acute and chronic lymphocytic leukemia, lymphomas, myelomas)

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Effect and equipotent doses of CSs

Substance	Equip.dose	Anti infl. effect	Mineral. effect
Cortisol	20 mg	1	1
Cortisone	25 mg	0,8	0,8
Prednisone	5 mg	4	0,8
Prednisolone	5 mg	4	0
Methylpredn.	4 mg	5	0
Triamcinolone	4 mg	5-10	0
Dexamethasone	0,75 mg	25	0
Bethametasone	0,6 mg	25	0
Fludrocortisone	-	10	125

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Systemically administered GCs

- 1-4 times efficient than cortisol
  - **prednisolone, prednisone**
  - **hydrocortisone**

Short term acting

- 5-15times efficient than cortisol
  - **methylprednisolone (Solu-Medrol)**
  - **triamcinolone**
  - paramethasone
  - fluprednisolone

Medium term acting

- approx 30times efficient than cortisol
  - bethametasone
  - **dexamethasone**

Long term acting

(stronger axis supressior

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Glucocorticoids therapeutical regimen types

Short term application of high doses

A) single (2-4 g methylprednisolone)
Polytraumatas, septic, toxic shock
Hydrocortisone 30 mg / kg

B) repeated (methylprednisolone, hydrocortisone, dexamethasone)
Anaphyl. shock, status asthmaticus, hypoglycemic coma ...
Duration up to 48 hours
Exceptionally up to 7 days

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Glucocorticoids therapeutical regimen types

C) Pulse therapy

Short-term infusions for several days
Originally in transplant rejection
Today predominantly in immune-mediated diseases resistant to standard therapy

D) Prolonged therapy

In most branches
Primarily for anti-inflammatory and immunosuppressive effects
Dosage and length depends on the current status of the patient
Strength differences, duration and frequency of adverse effects
No hydrocortisone with respect to mineralocorticoid activity

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Supression of endogenous glucocorticoid production

- Acute inadequacy when suddenly discontinuing higher doses

- Prevention = complete therapy by gradual dose reduction

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Glucocorticoids – adverse events

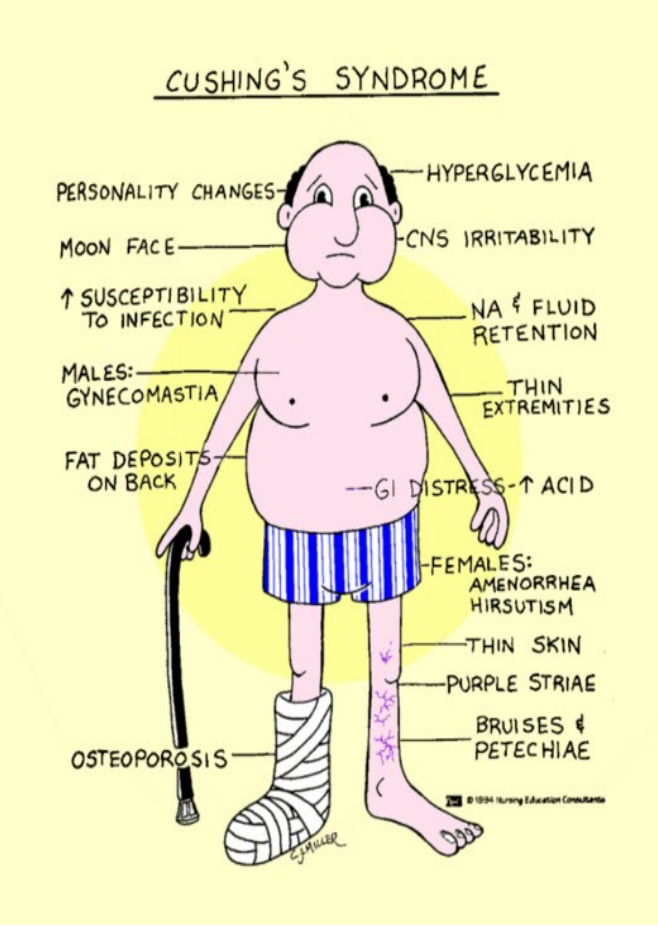
Hyperglycemia, steroidal diabetes

Muscle weakness, myopathy, atrophy

Psychotropic effects
Insomnia, motor agitation, vertigo, euphoria, depression
Psychic habit

GIT
Exacerbation of gastric ulcer
Intestinal perforation, acute pancreatitis

CVS
- HT, atherosclerosis, cardiomyopathy, ↑ coagulopathy, arrhythmia



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Glucocorticoids – adverse events

Eye
Induction of glaucoma (↑ intraocular pressure)
Corneal ulceration in keratitis herpetica

Endocrine
Growth inhibition in children (therapy longer than 6 months)
Amenorrhea, potency and libido decrease

Skin
atrophy
Intradermal bleeding
Acne, hirsutism

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Glucocorticoids – interactions

Prednisone reduces the plasma levels of salicylates and oral anticoagulants.

The effect of prednisone is reduced by barbiturates, phenytoin, rifampicin.

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Routes of administration

- p.o.
- i.v.
- i.m.
- s.c.
- inhalatory

- ointment/cream
- eye/nose drops
- intraarticularly

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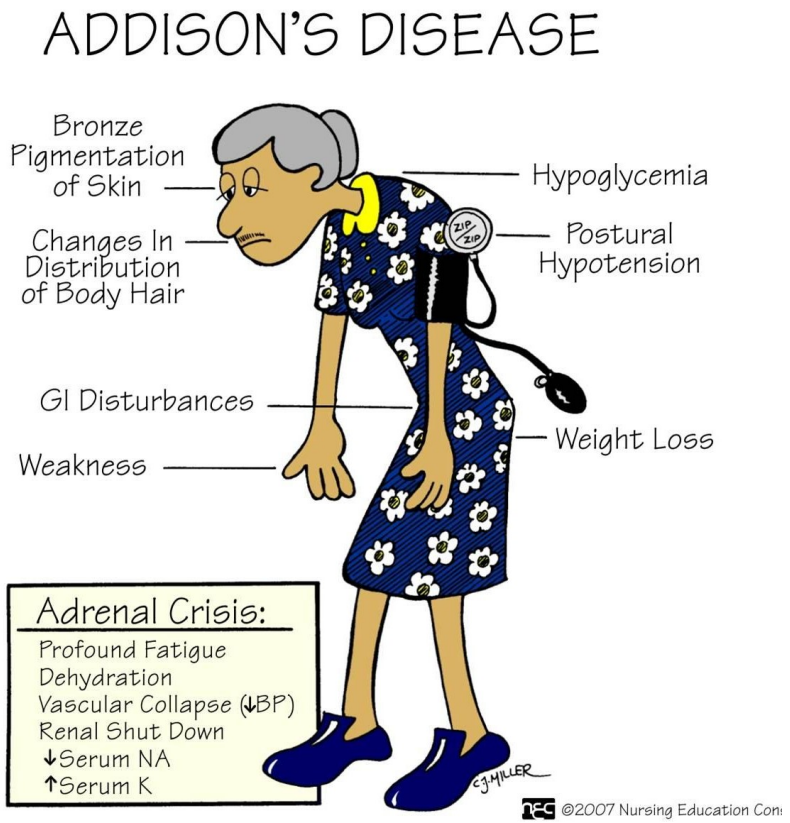
Therapeutic indications

PHYSIOLOGICAL (low) DOSES

- insufficiency: kortisol + fludrocortison (mineralokortikoid)
- I: Addison's disease



Therapeutic indications

Higher doses

- Diseases of connective tissue, rheumatological diseases and collagenoses (RA, SLE, SS, DM…)
- Severe forms of allergic reactions
- Non-infectious inflammatory diseases of the eye
- Severe skin disorders
- Haematological diseases
- Malignant diseases
- Conditions after organ transplantation
- Inflammatory gastrointestinal disease
- Non-inflammatory respiratory disorders
- Immunalternative disease in neurology

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Corticoids in clinical practice

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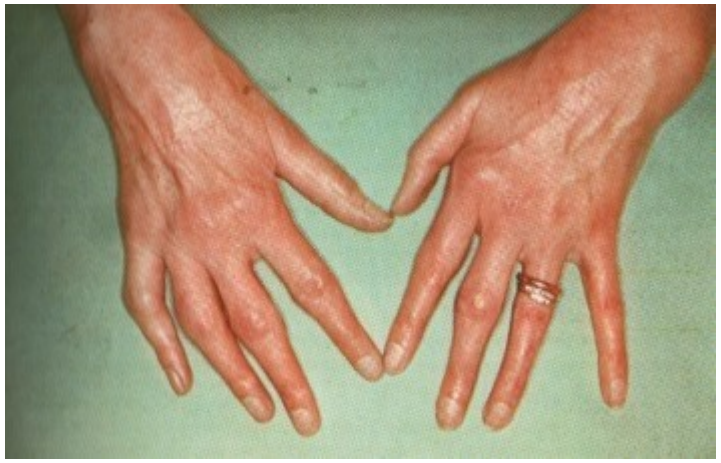
Rheumatoid arthritis



Glucocorticoids are used during periods of acute symptoms disease.

to bridge the period until the onset of effect DMD (MTX).

Recent studies, however, show that small doses of glucocorticoids have

modifying effect and slowdown the X-ray progression of the disease.

Prednisone at doses up to 10 mg daily or every other day. Only

Exceptionally, it is necessary to take higher doses, and it is only

In the case of very active disease, extra-articular symptoms, it s better to start therapy with GK pulse therapy.

Biological treatment is currently the most effective RA treatment and, in a number of cases, it can decisively slow down or stop the progression of the disease:

Chimeric monoclonal antibody against TNF-alpha infliximab,

Fully human monoclonal antibody against TNF-alpha-adalimumab

Soluble receptor for TNF-alpha etanercept

Monoclonal chimeric anti-CD20 molecule – rituximab

CTLA4 molecule linked to a modified Fc portion of human IgG1 - abatacept

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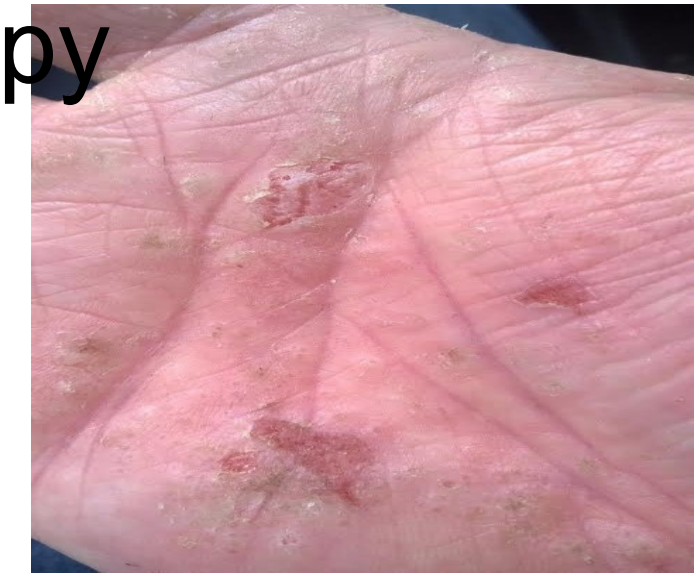
Skin diseases
Eczema dyshidroticum, before therapy



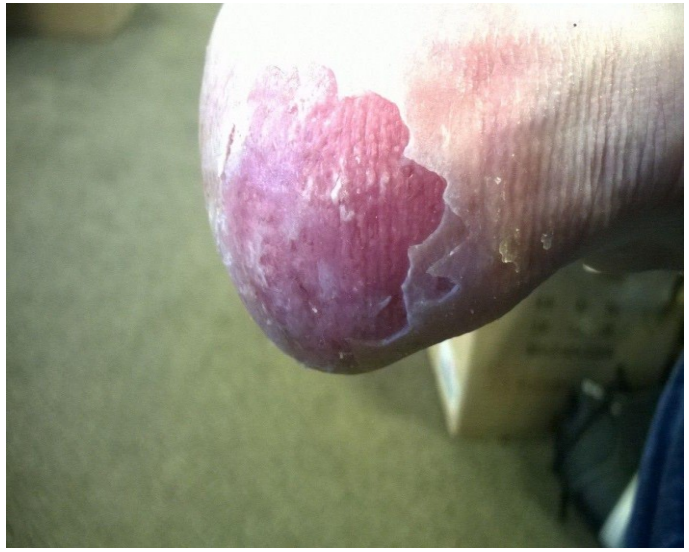
Hand-foot syndrom

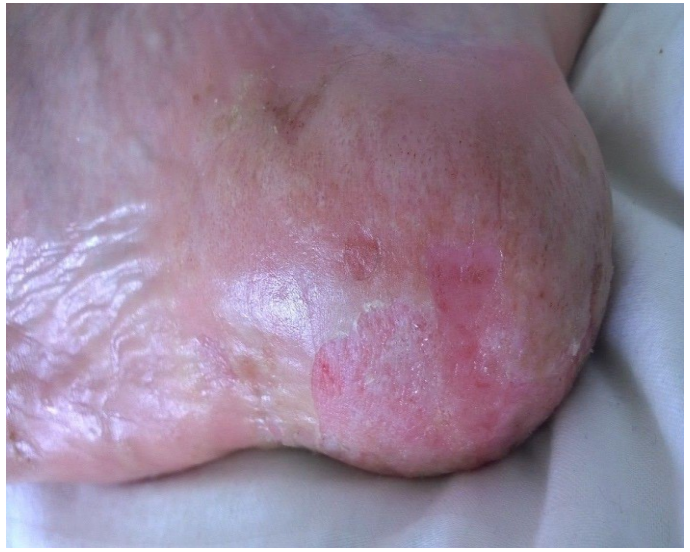
Man 35 years old

2 – 3 years of hands eczema, after 1 year added hands eczema

Status of treatment with local corticosteroids for 2 years

Extreme impact on quality of life!





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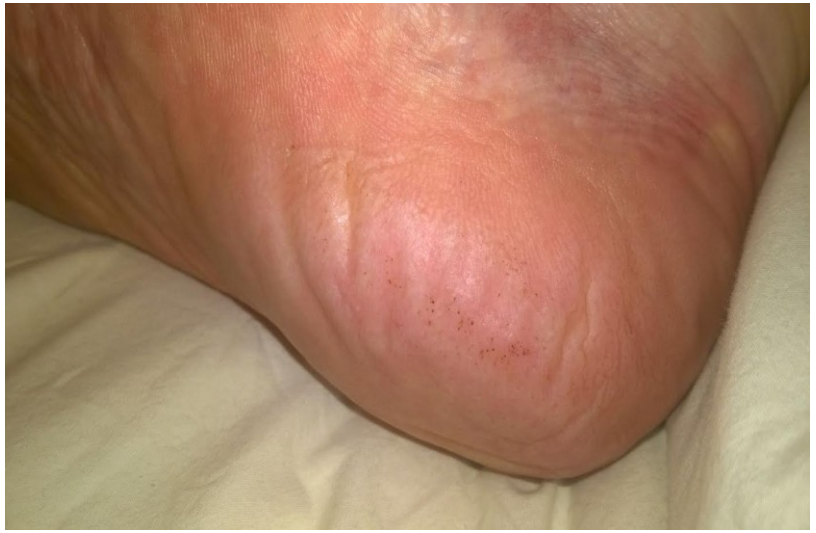
Skin diseases
Eczema dyshidroticum, after therapy



Prednison 50 mg / daily – 1 month

Proton pump inhibitors

Effect after 1 week of systemic therapy, but:

Severe AE:

- Sleep disturbances
- Depression
- Hypertension

  (repeatedly 160/110)

withadrawal

Next strategy?

Immunosupressants?

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Inhalation GCs in asthma treatment

- The most effective preventative antiasthmatics
- Improve pulmonary function, reduce bronchial hyperreactivity, reduce exacerbations, improve quality of life
- Beclomethasone dipropionate, budesonide, fluticasone propionate
- Inhaled corticosteroids have a better safety profile than oral
- Fixed combination - fluticasone + salmeterol (Seretide Discus)

  - budesonide + formoterol (Symbicort Turbuha

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