Poltava State Medical University

ANTI-INFLAMMATORY AND ANTI-ALLERGIC DRUGS

CONTENTS

1. Inflammation, pathogenesis, stages, and options for management
2. Glucocorticoids as steroidal anti-inflammatory and anti-allergic drugs
3. Non-steroidal anti-inflammatory drugs
4. Preparations for the treatment of rheumatoid diseases and gout
5. Non-steroidal anti-allergic drugs
6. Control tasks

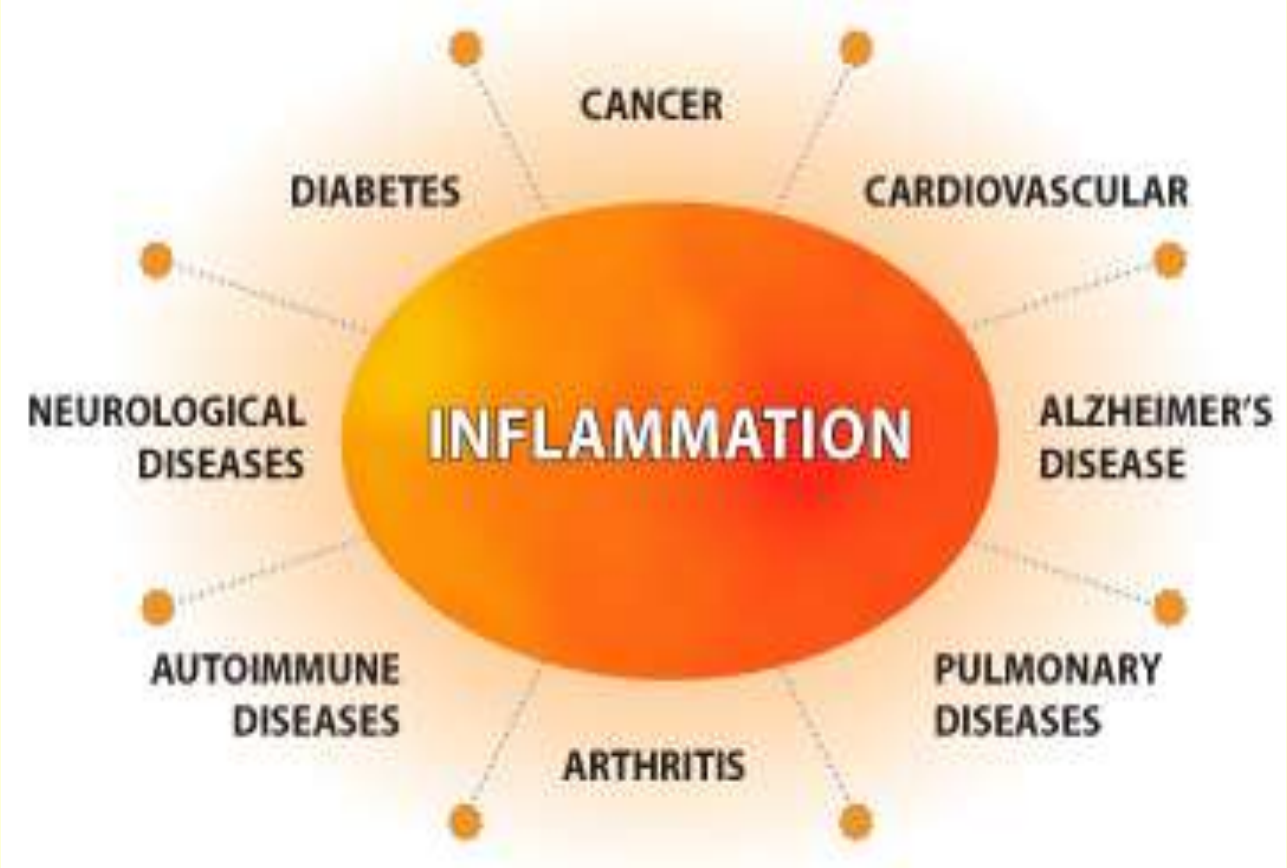
INFLAMMATION:
DEFINITION AND SIGNS

Inflammation is the body's natural response to an injury or infection.

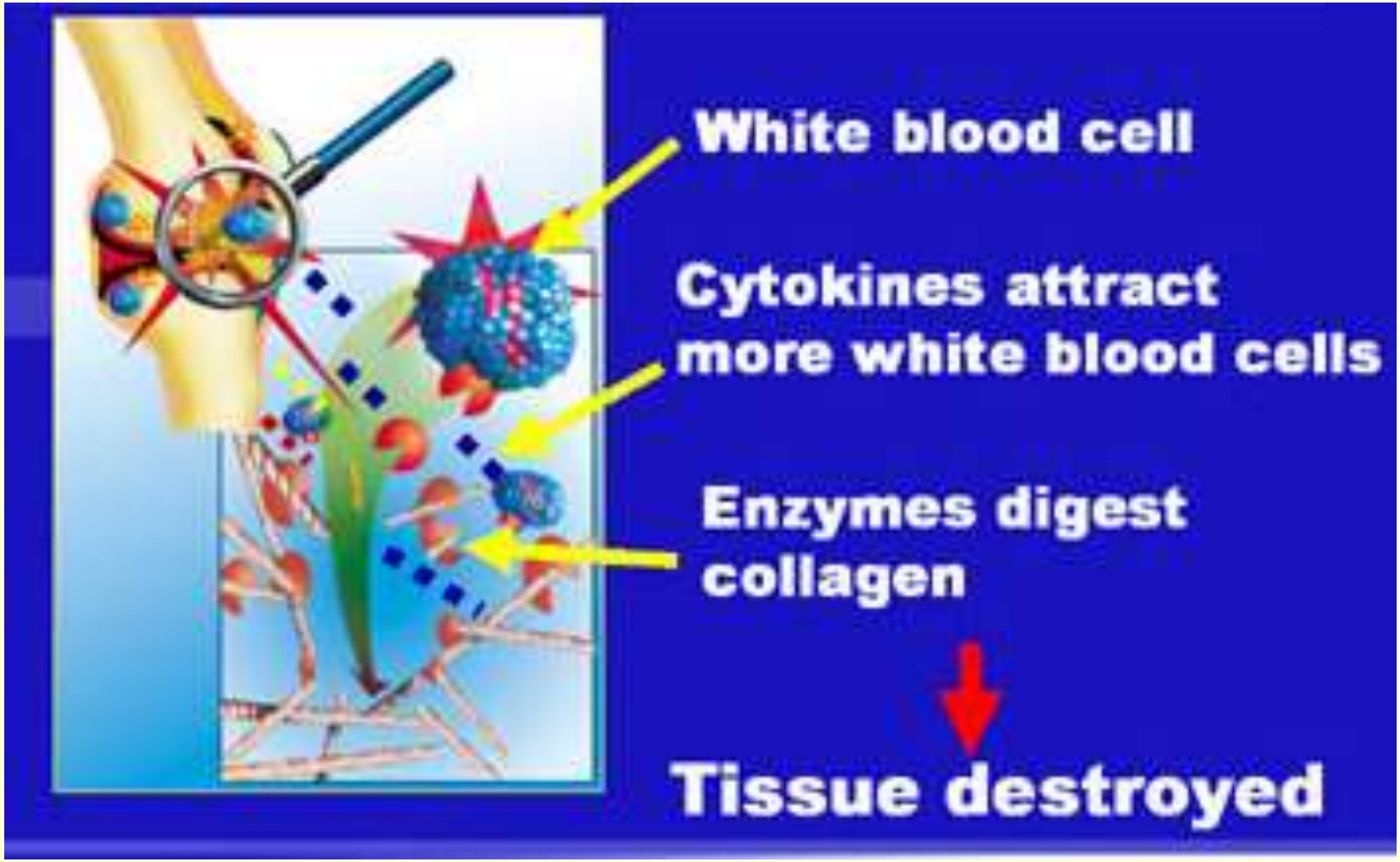
- Redness *Rubor*
- Swelling *Tumor*
- Heat *Calor*
- Pain *Dolor*
- Loss of function *Functio laesa*

INFLAMMATION

AS A LINK OF PATHOGENESIS OF OTHER DISEASES



INFLAMMATION



INFLAMMATION:
STAGES AND RESULTS

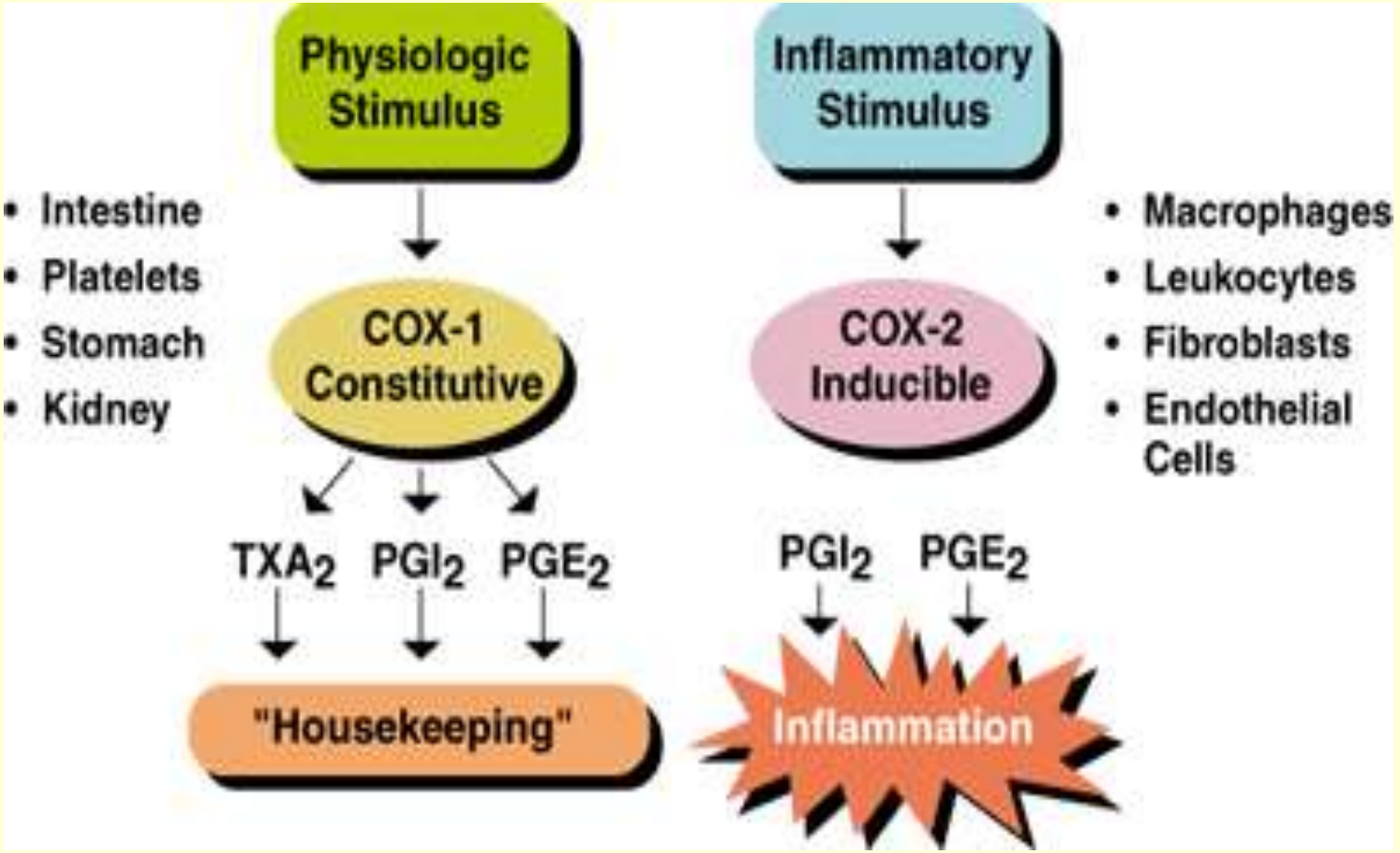
3 stages of inflammation:

- Alteration
- Exudation
- Proliferation

Results of acute inflammation:

- resolution
- fibrosis
- abscess formation
- chronic inflammation

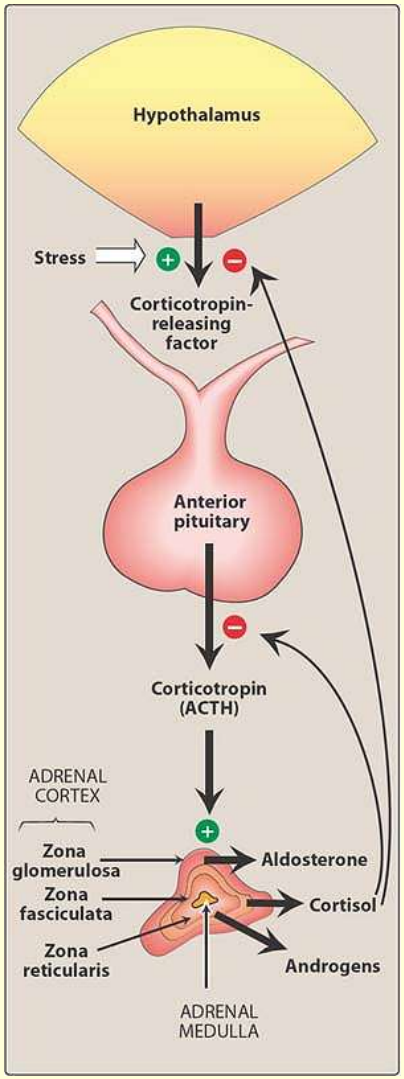
INFLAMMATION:
THE ROLE OF PROSTAGLANDINS



ANTI-INFLAMMATORY DRUGS

STEROIDAL ANTI-INFLAMMATORY DRUGS (SAIDs). GLUCOCORTICOIDS

ADRENAL STEROIDS (CORTICOSTEROIDS)



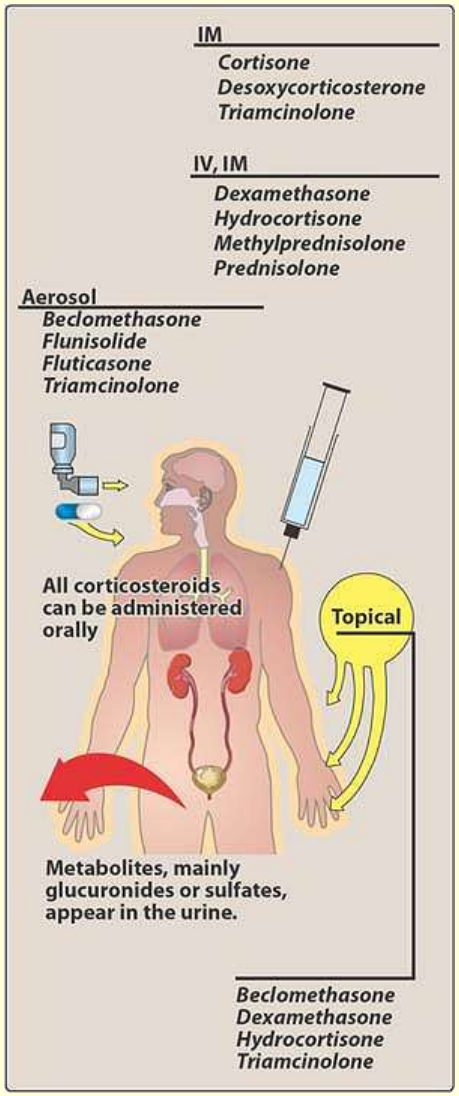
GLUCOCORTICOIDS:
MECHANISM OF ACTION

Glucocorticoids exert their effects by binding to intracellular cytoplastic receptors, **formation of complex hormone-receptor which moves to nucleus and interacts with genetic apparatus**

GLUCOCORTICOIDS:
CLASSIFICATION

1. Short-acting (8-12 hours)
– Hydrocortisone acetate
2. Intermediate-acting glucocorticoids (18-36 hours)
– Prednisolone
– Methylprednisolone
– Triamcinolone
3. Long-acting glucocorticoids (1-3 days)
– Dexamethasone
4. Topically active glucocorticoids
– Beclomethasone dipropionate
– Fluocinolone acetonide

GLUCOCORTICOIDS:
PHARMACOKINETICS



GLUCOCORTICOIDS:
ANTI-IMFLAMMATORY ACTION

***Main mechanisms* of anti-inflammatory action are:**

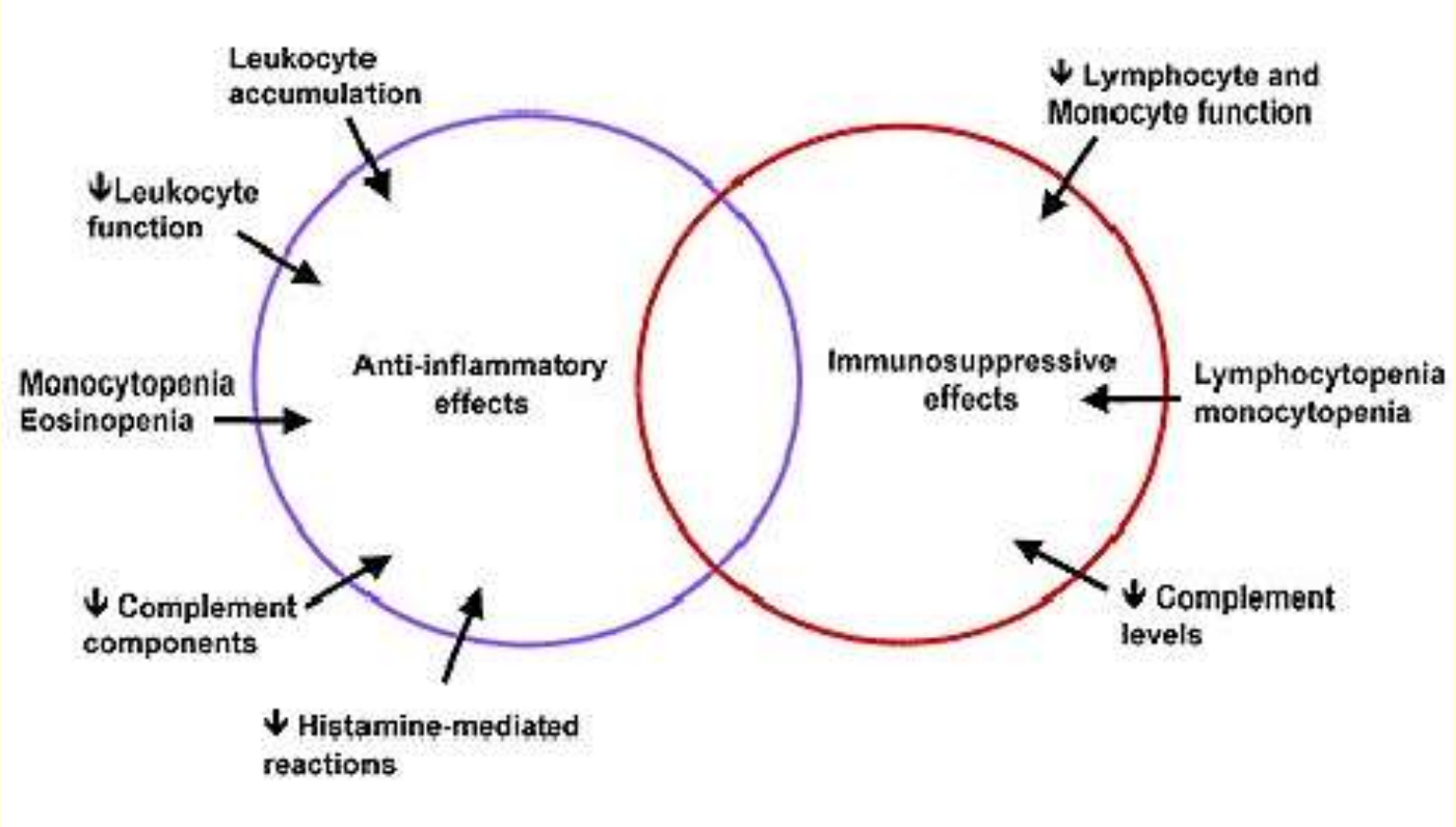
2. *Inhibition of PG and leukotriene synthesis*

- Inhibition of phospholipase A_2 production (through induction of lipocortin the synthesis of lipocortin, an enzyme the acts as an inhibitor of phospholipase A_2)
- Decreased Transcription of genes coding for cyclooxygenase 2

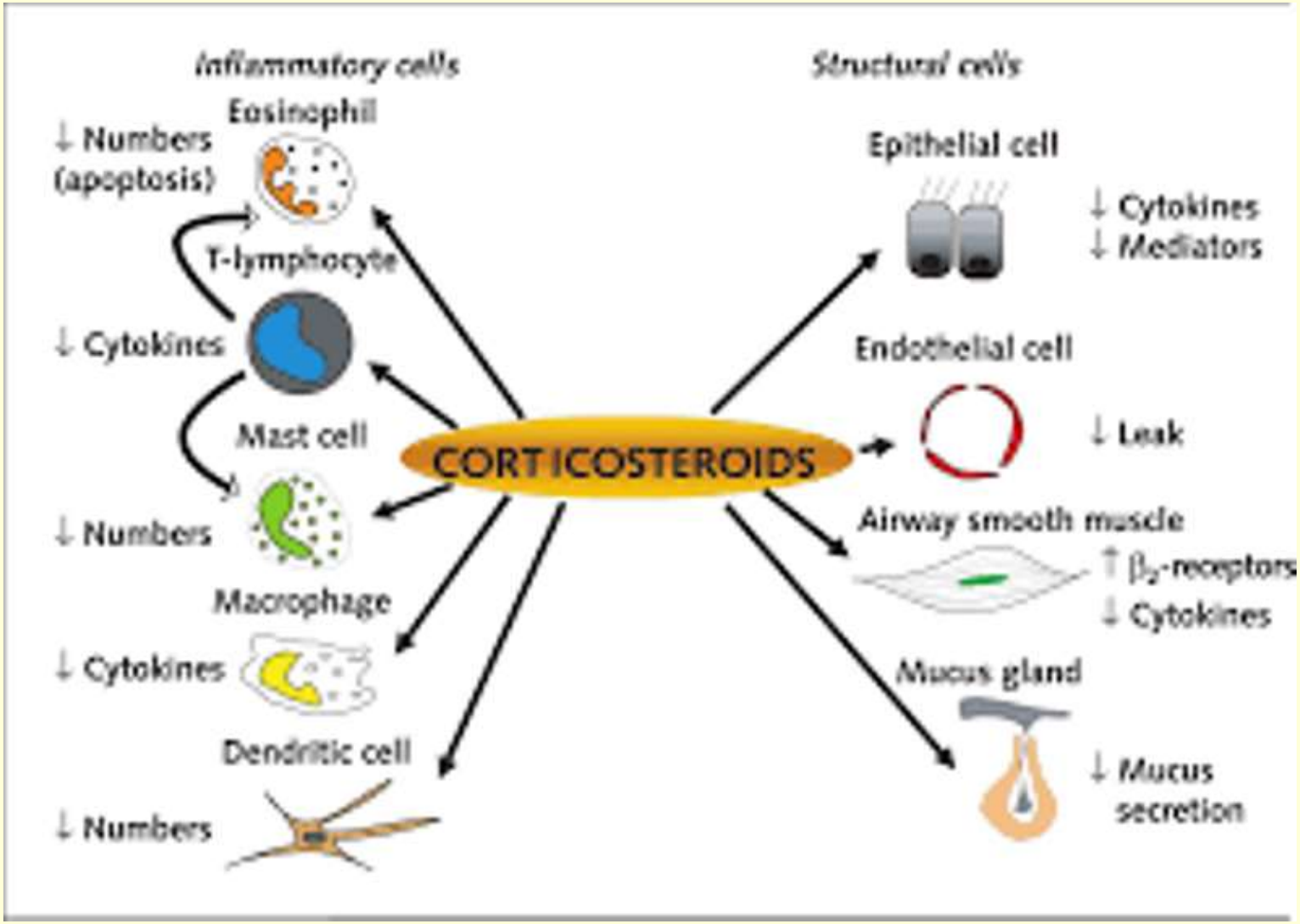
Additional Mechanisms:

Decrease in capillary permeability (due to inhibition of histamine release and kinin activity) and inhibition of the effects of complement system

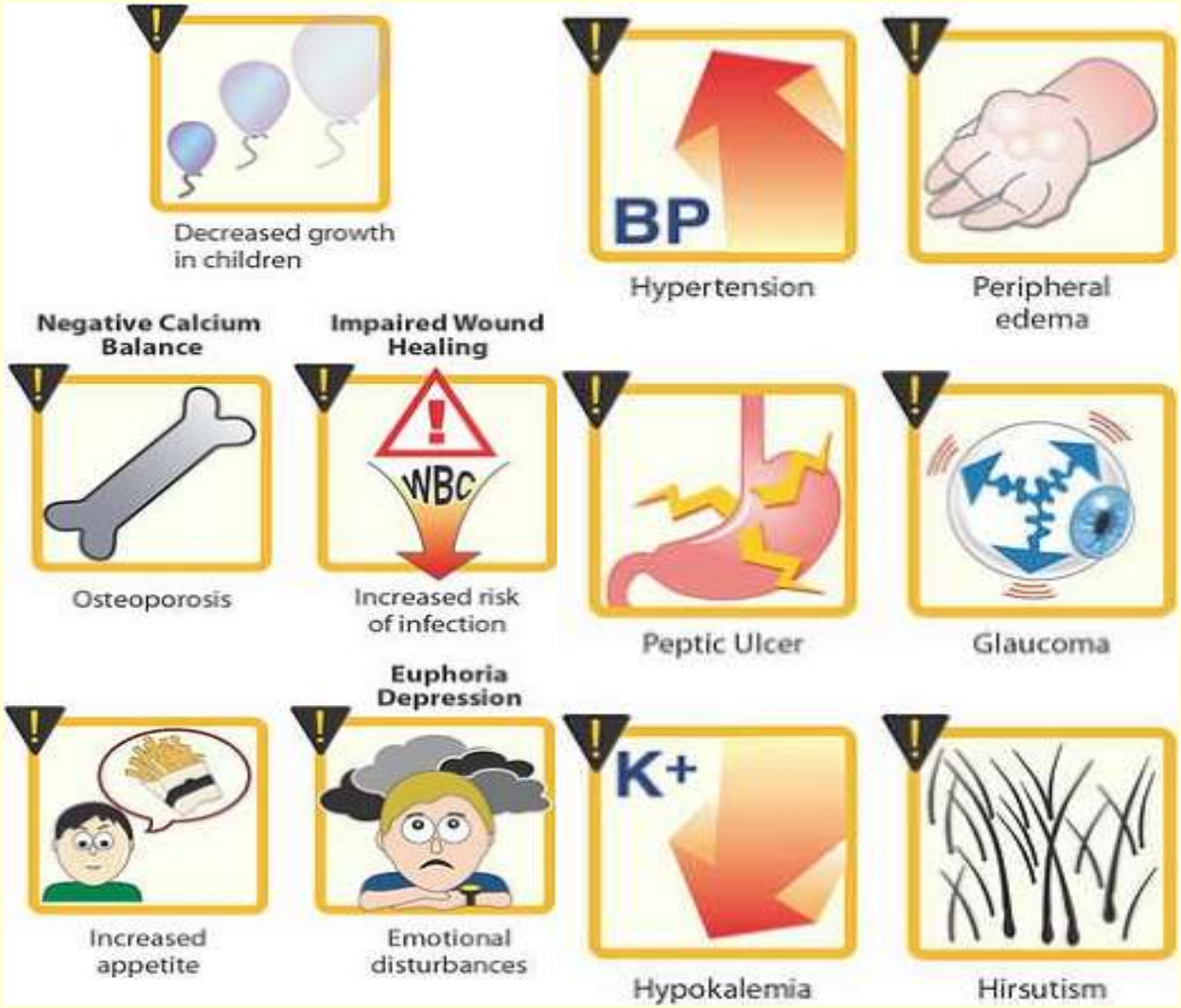
GLUCOCORTICOIDS:
RELATION BETWEEN THE ANTI-IMFLAMMATORY ACTION AND IMMUNE SUPPRESSION



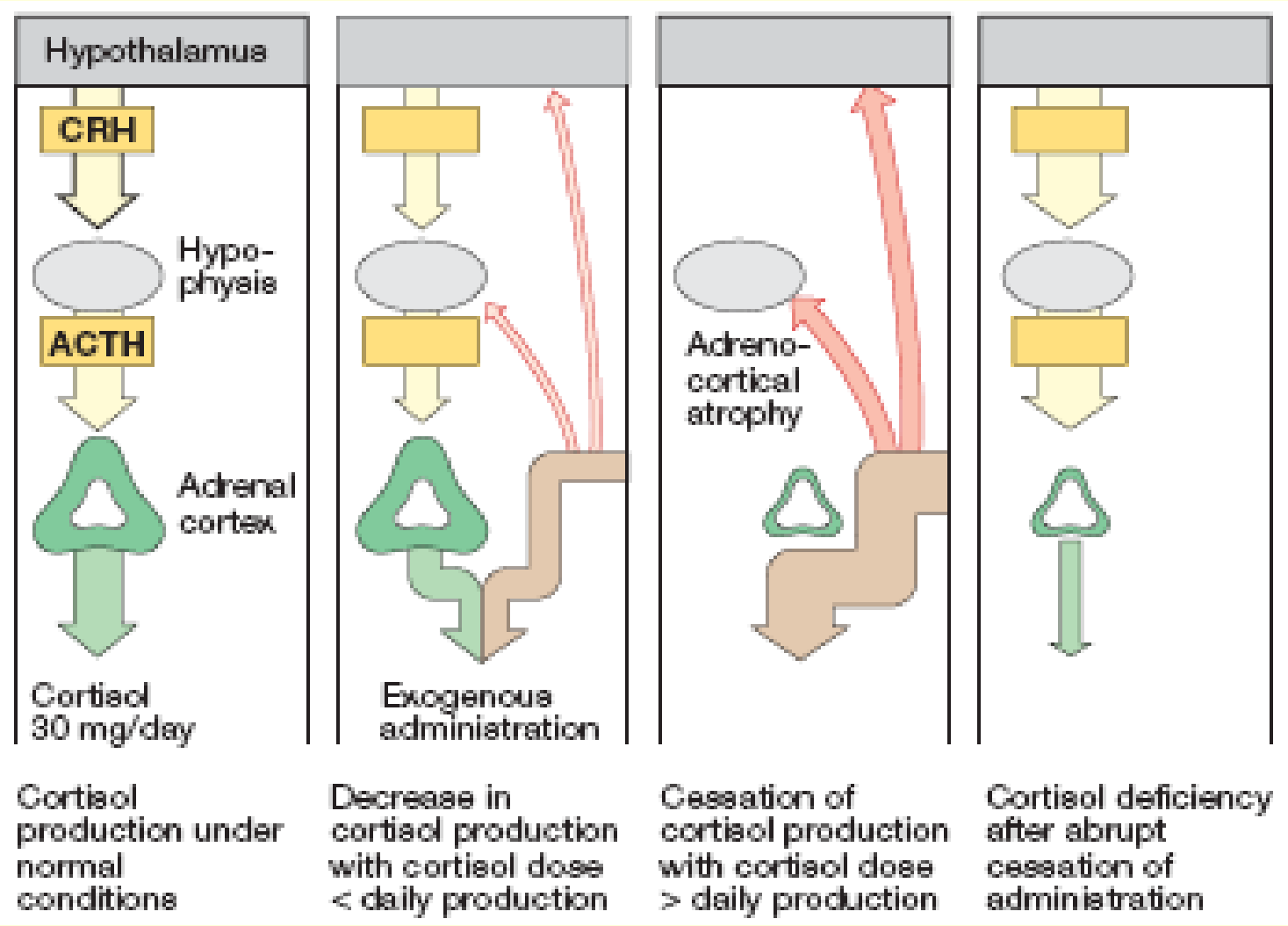
GLUCOCORTICOIDS:
ANTI-ALLERGIC ACTION IN BRONCHIAL ASTHMA



GLUCOCORTICOIDS:
SIDE EFFECTS



GLUCOCORTICOIDS:
WITHDROWAL SYNDROME



GLUCOCORTICOIDS:
PECULIARITIES OF PREPARATIONS

Hydrocortisone is used topically to treat allergic eye diseases, aseptic burns of the eyes or after eye surgeries; is applied in allergic skin diseases and administered in arthritis, arthrosis (into the joint), and bronchial asthma.

Prednisolone is a synthetic derivative of hydrocortisone; is more active (3-4 times) than hydrocortisone; is administered orally, IM, IV or applied topically in the form of ointment or eye drops

Dexametasone contains fluorine; is more active than hydrocortisone and prednisolone; has less side effects; is administered orally, IM, IV or applied topically in the form of ointment or eye drops; duration of anti-inflammation effect after the oral administration is 72 hrs.

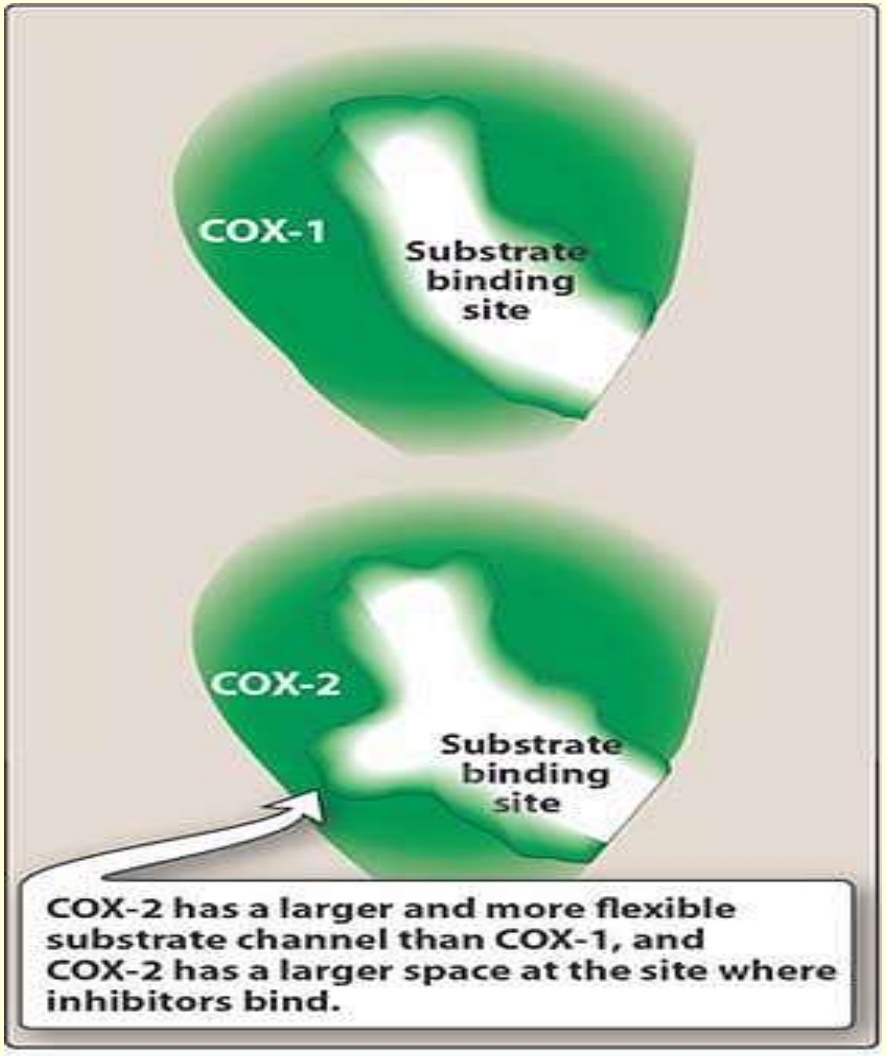
GLUCOCORTICOIDS:
PECULIARITIES OF PREPARATIONS

Triamcinilone (Kenalog) contains fluorine; has prolonged action; maximal effect is developed in 24-48 hrs and lasts during 6 weeks; is used to treat arthritis, arthrosis, joint lesions caused by collagenosis, rheumatism; is injected in the site of disease in psoriasis, neurodermitis; is not administered IV; has less side effects than other preparations

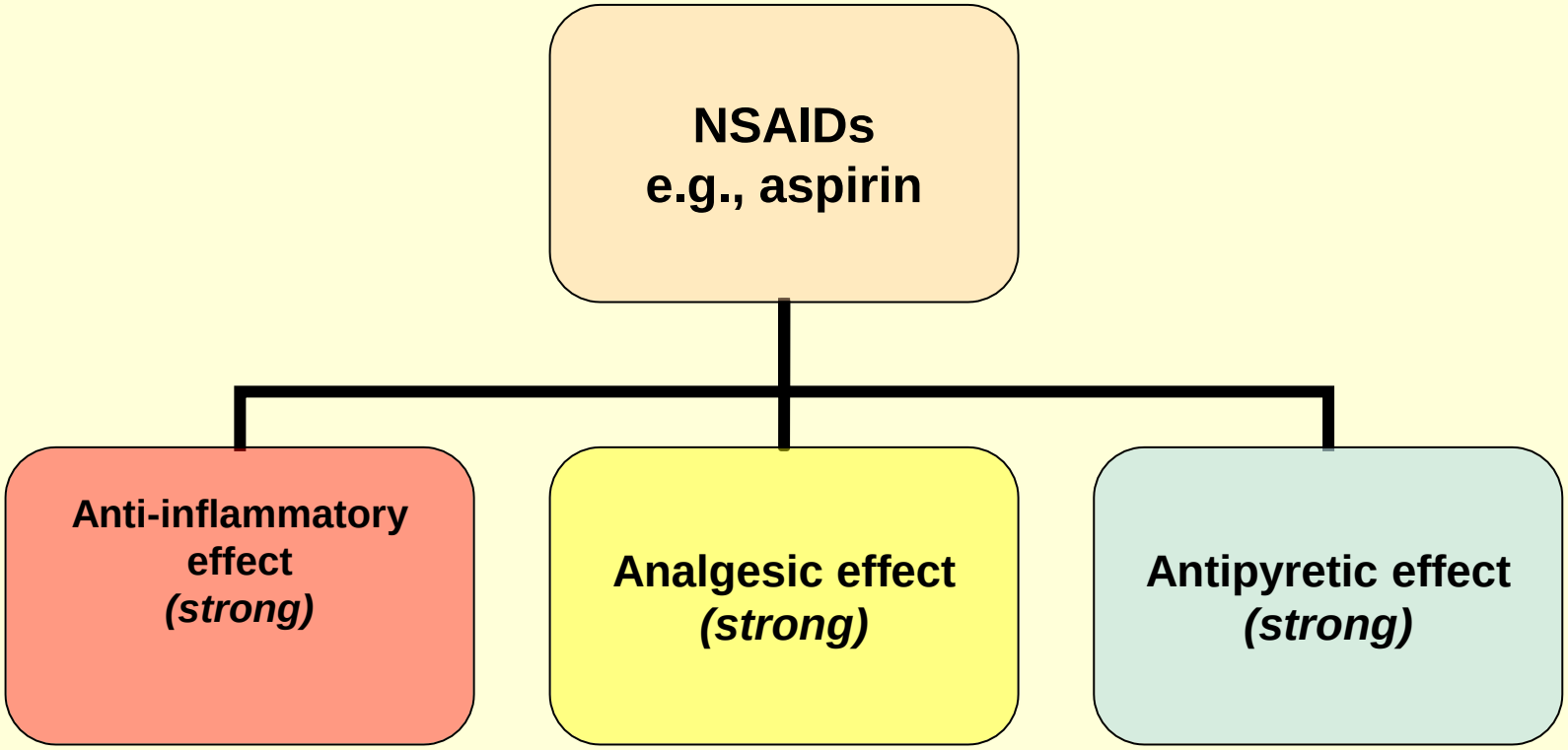
Fluocinolone acetonide (Flucinar) is a fluorine-containing preparation for topical application in dermatology; is used in the form of ointment, penetrates upper layer of epidermis and stays in the skin during 15 days; is indicated in allergic and inflammatory diseases of skin, and psoriasis

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

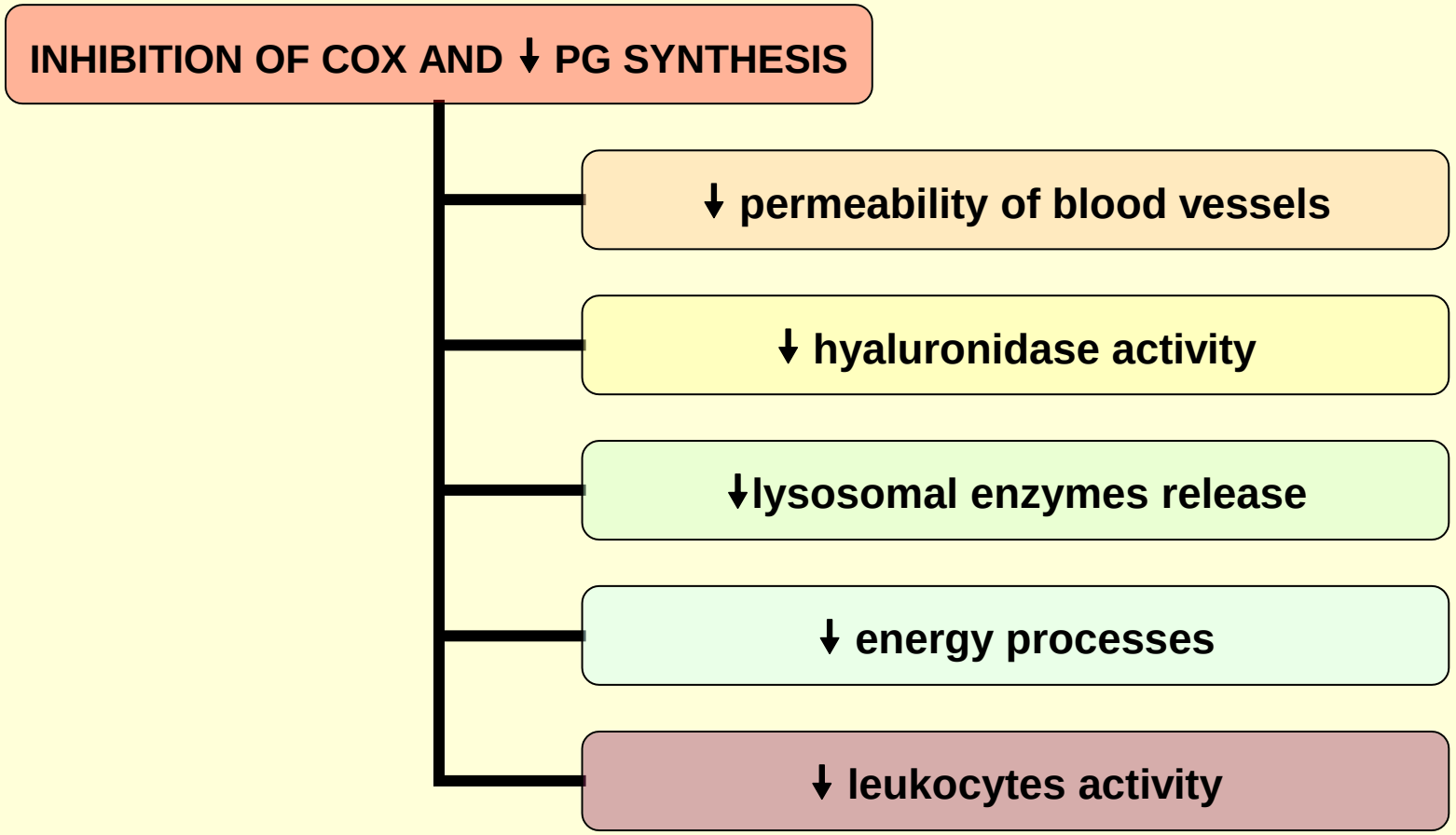
COX-1,2 AS A TARGET FOR NSAIDs



EFFECTS OF NSAIDs



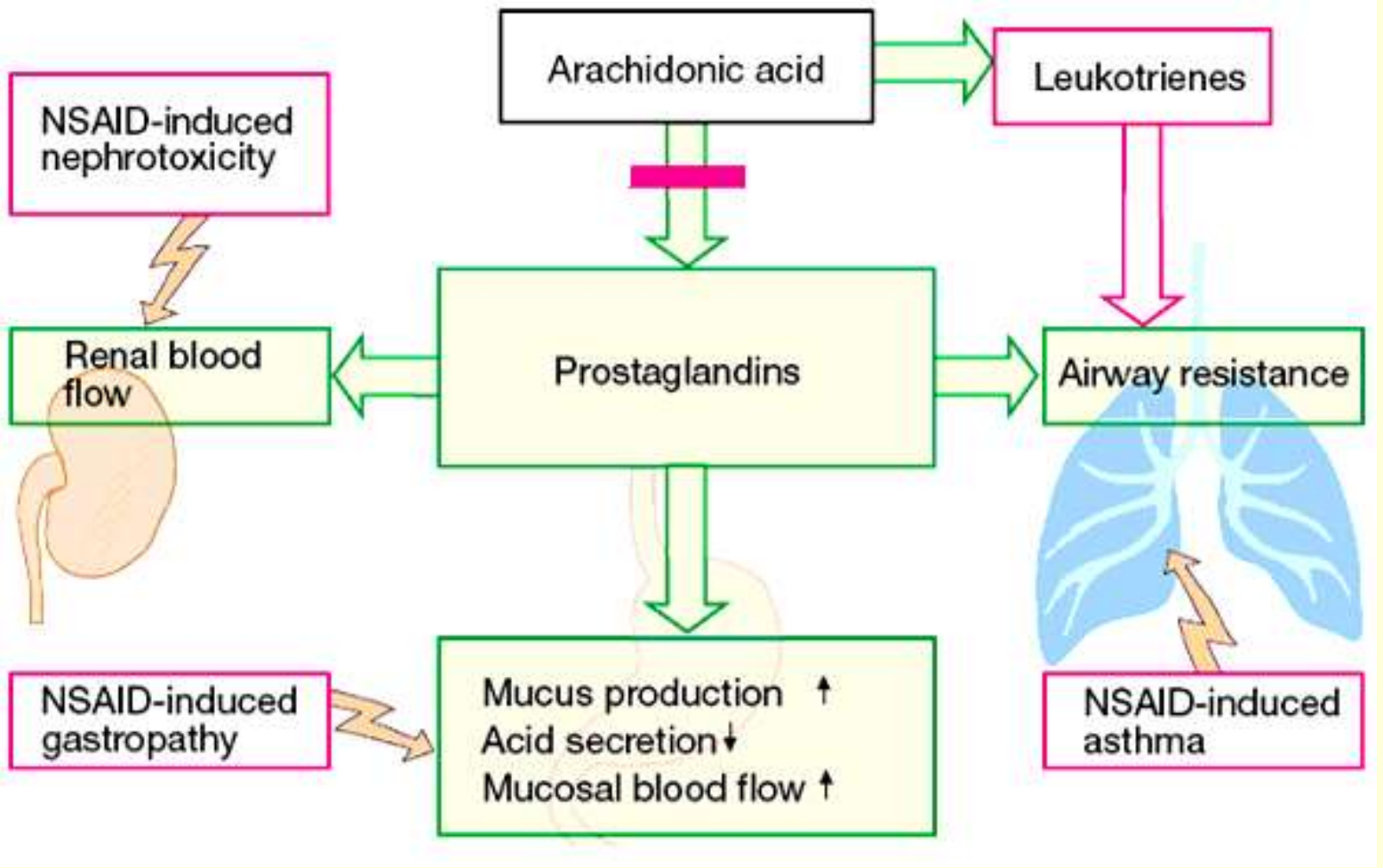
NSAIDs: DETAILS OF ANTI-INFLAMMATORY ACTION



NSAIDs:
COMMON INDICATIONS

Arthritis
Arthosis
Rheumatism
Collagenosis
Miositis
Radiculitis
Trauma of soft tissues and joints
Control of pain associated with inflammation

NSAIDs:
GROUP-SPECIFIC SIDE-EFFECTS



NSAIDs: CLASSIFICATION

On chemical structure

1. Salicylate
   – Acetylsalicylic acid (Aspirin)
2. Pyrazoles
   – Metamizole (Analginum)
   – Phenylbutazone (Butadionum)
3. Fenamates
   – Mefenamic acid
4. Indolacetic acid derivatives
   – Indomethacin
5. Phenylacetic acid derivatives
   – Diclofenac-sodium
6. Propionic acid derivatives
   – Ibuprofen
7. Para-aminophenol derivatives
   – Paracetamol (Acetominophen)
8. Oxicams
   – Piroxicam
   – Meloxicam (Movalis)
9. Coxibs
   – Celecoxib

On mode of action

A. Non-selective inhibitors of COX-1 and COX-2

1. Mainly with peripheral action
   – Acetylsalicylic acid
   – Phenylbutazone
   – Metamizole
   – Mefenamic acid
   – Indometacin
   – Diclofenac-sodium
   – Ibuprofen
   – Piroxicam
2. Mainly with central action
   – Paracetamol

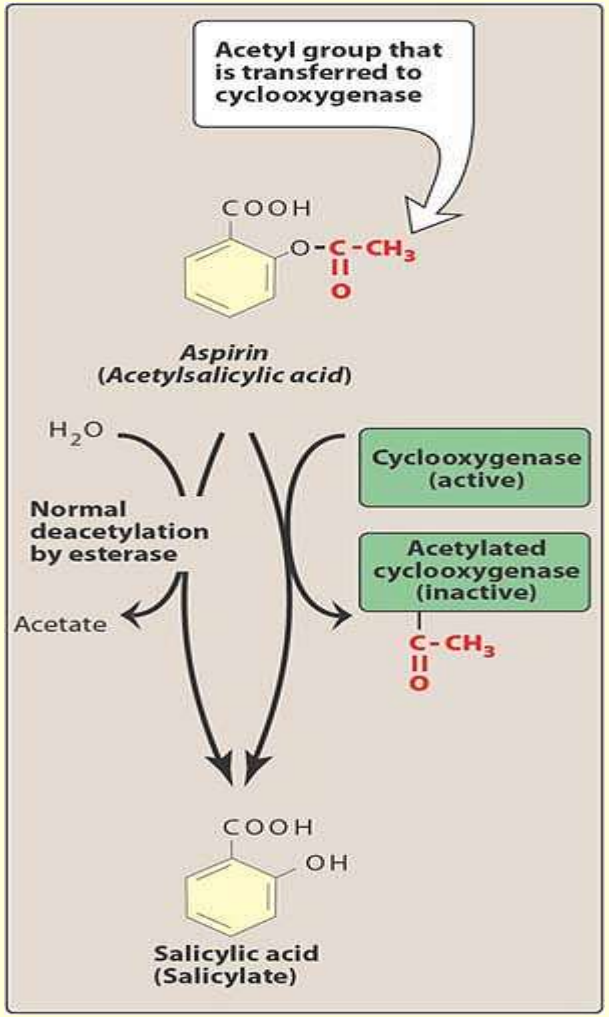
B. Selective inhibitors of COX-2

   – Meloxicam
   – Celecoxib.

ACETYLSALICYLIC ACID (ASPIRIN): PHARMACOKINETICS

- is taken orally, sometimes IM, IV (Acelysin)
- is absorbed in the stomach and small intestine by passive diffusion
- binds with albumins in blood plasma
- crosses the blood-brain barrier and placenta
- displays maximal concentration in the blood within 2 hrs after the administration
- concentrates in the adrenal glands, liver, heart, and lungs
- is metabolized in the liver where salicylate is converted to water-soluble conjugates
- is excreted with urine
- acts during 4-6 hrs; has duration of anti-platelet action of 7 days
- at normal low dose 600 mg/day has a half-life of 3,5 hrs; at anti-inflammatory doses (>4 g/day) has a half-life of 15 hrs or more due to saturation of hepatic metabolic pathway.

ACETYLSALICYLIC ACID (ASPIRIN): MECHANISM OF ACTION



ACETYLSALICYLIC ACID (ASPIRIN): PHARMACODYNAMICS

- anti-inflammatory action (a decrease in exudation)
- anti-pyrexia (a decrease in high body temperature)
- analgesia (a decrease in intermediate and weak pain)
- anti-platelet action (an irreversible decrease in platelet aggregation)
- anti-gout action (an increase in output of urates)
- stimulation of respiration (at therapeutic doses, aspirin increases alveolar ventilation; at high doses, it works directly on respiratory center resulting in hyperventilation and respiratory alkalosis)
- dilation of blood vessels (in higher doses)
- stimulation of synthesis of glucocorticoids (in higher doses)
- an increase in secretion and excretion of bile
- changes in pH of blood (in higher doses)
- hypoglycemia (in higher doses).

ACETYLSALICYLIC ACID (ASPIRIN): INDICATIONS

- Rheumatism
- Fever
- Arthritis
- Headache, toothache, myalgia, neuralgia
- Gout
- Prophylaxis of re-thrombosis, myocardial infarction, or stroke
- Thombophlebitis
- Prevention of colorectal cancer

ACETYLSALICYLIC ACID (ASPIRIN): SIDE EFFECTS AND CONTRAINDICATIONS

SIDE EFFECTS

1 Allergy
2. Skin rash
3. Spasm of bronchi
4. Gastric ulceration
5. Vertigo
6. Thrombocytopenia
7. Hypocoagulation, bleeding
8. A decrease in renal blood flow, retention of sodium and water
8. Disturbances in normal development of pregnancy, prolonged labor, bleeding tendency in mother and infant,
9. Reye's syndrome in children (hepatitis and cerebral edema).

CONTRAINDICATIONS

1. Allergy to salicylates
2. Ulcerative disease of the stomach and duodenum
3. Ulcerative colitis
4. Bleeding
5. Bronchial asthma
6. Inhibition of hemopoiesis
7. Hepatic and renal impairment
8. Pregnancy.

NSAIDs:
PECULIARITIES OF PREPARATIONS

INDOMETHACIN

- Is an indolacetic acid derivative
- is one of the most active non-narcotic analgesics, ***belongs to NSAIDs***
- anti-inflammation is the strongest effect: it inhibits exudation as well as proliferation
- exceeds aspirin in the anti-inflammation, analgesia and anti-pyrexia
- routs of administration: oral, rectal, topical; maximal concentration 2 hrs after oral administration; half-life is 2-3 hrs.; is metabolized in the liver; 2/3 is excreted with urine and 1/3 – with bile
- indications: rheumatism, collagenosis, arthritis, gout, glomerulonephritis, trauma of joints and soft tissues, thrombophlebitis, tendovaginitis, myositis, myalgia, neuralgia (topically in the form of ointment)
- side effects: headache, vertigo, dormancy, depression, pain in the epigastric area, ulcer of stomach, nausea, decrease in appetite, gastro-intestinal bleeding, skin rash, leucopenia, aplastic anemia, disturbances in renal function, acute pancreatitis, hepatitis and jaundice
- contraindications: ulcerative disease, bronchial asthma, infections, pregnancy, lactation, epilepsy, Parkinson’s disease, psychic disorders, anemia

NSAIDs:
PECULIARITIES OF PREPARATIONS

DICLOFENAC-SODIUM

- is a phenylacetyc acid dervative
- anti-inflammation is the strongest effect
- ***belongs to NSAIDs***, exceeds aspirin and indomethacin
- routs of administration: oral, IM, topical (gel, ointment)
- maximal concentration in plasma 1-2 hr after oral administration; 96% of preparation binds to proteins in blood plasma; concentration in synovial liquid exceeds the same in blood in 5 times; half-life in synovial liquid (8 hrs) is more than the same in blood (3 hrs); is excreted with urine and bile
- indications are similar to indications to application of indomethacin; is approved for long-term use in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondilitis
- is less toxic than indomethacin, but may cause loss of appetite, pain in epigastric area, meteorism, constipation, diarrhea, rarely ulceration in stomach, gastro-intestinal bleeding, headache, drowsiness, thrombocytopenia, nasal bleeding, microhematuria, allergy, skin rash

NSAIDs:
PECULIARITIES OF PREPARATIONS

IBUPROFEN

- is a propionic acid derivative
- is active anti-inflammatory and analgesic agent, ***belongs to NSAIDs***
- has high effectiveness for treatment of joint diseases
- routs of administration: oral, topical (gel, ointment)
- indications: arthritis, osteoarthrosis, joint form of rheumatism, bursitis, tendovaginitis, trauma of joints and soft tissues
- is untoxic; has minimal influence on gastric mucosa
- may be used in pregnant women

PIROXICAM

- is a preparation from oxicams
- has a strong durative anti-inflammatory action, ***belongs to NSAIDs***
- is taken orally once a day; half-life is 40-45 hrs, so is administered once a day; is metabolized in liver and excreted with urine in the form of glucuronides
- indications: rheumatism, rheumatoid arthritis, ankylosing spondilitis, osteoarthritids, acute gout
- side effects: gastric ulceration, skin rash, influence on blood formation, toxic action on CNS

NSAIDs:
PECULIARITIES OF PREPARATIONS

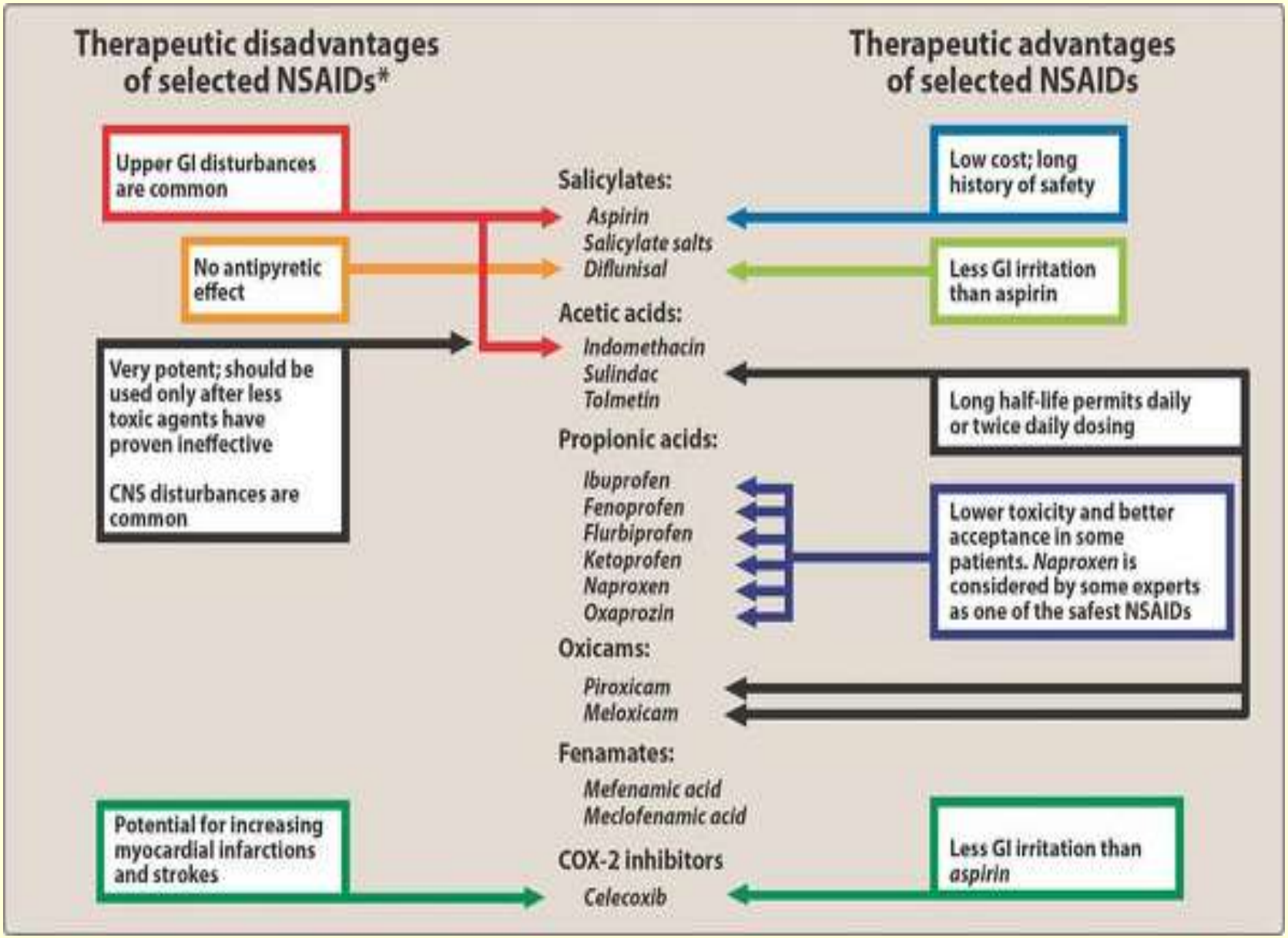
MELOXICAM (MOVALIS)

- Is a drug from oxicams
- ***is selective inhibitor of COX-2; NSAID***; does not influence on platelet aggregation and gastric mucosa
- has mainly peripheral action
- routs of administration: oral, IM
- is absorbed in the GI tract; maximal concentration is developed 1 hr after IM injection; stable concentration in plasma is observed 3-5 days after the start of treatment; concentration in synovial fluid is more than the same in plasma; half-elimination is 20 hrs, is excreted with urine and bile
- indications: arthritis, arthrosis, spondilitis, rheumatoid arthritis
- side effects: dyspepsia, gastric ulceration, gastro-intestinal bleeding, hepatic and hematological disturbances, skin rash, headache (in 0,1-1% of patients)
- contraindications: hypersensitivity to salicylates and other non-steroid anti-inflammatory drugs; under the physician's supervision in the cases of gastro-intestinal diseases, heart failure, cirrhosis of the liver, chronic renal diseases

NSAIDs:
PECULIARITIES OF PREPARATIONS

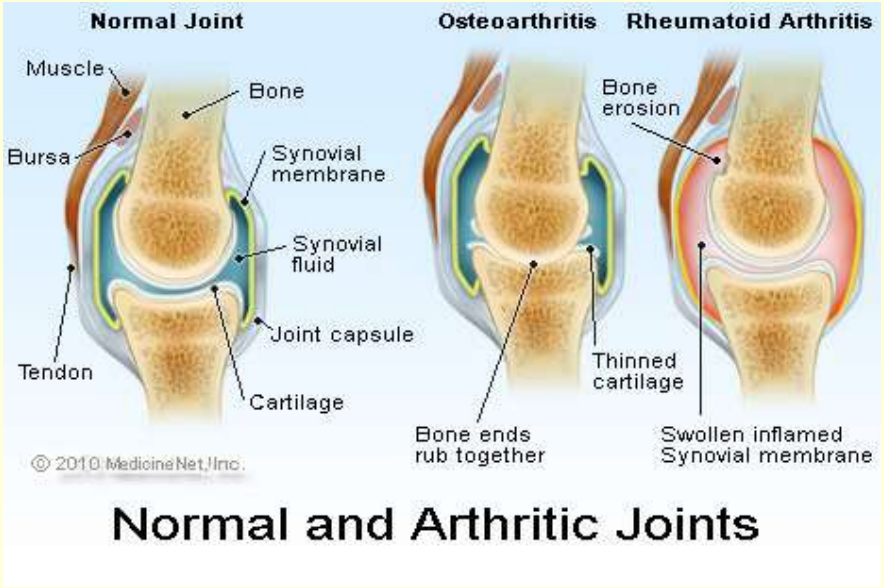
CELECOXIB

- belongs to the group of coxibs
- is a ***selective inhibitor of COX-2; NSAID***; acts in the site of inflammation
- does not influence platelet aggregation as well as gastric mucosa
- is taken orally
- is absorbed in the GI tract; maximal concentration in plasma is observed 2-3 hrs after administration; 97% of preparation is bound with plasma proteins, half-life is 8-12 hrs; stable concentration is observed 5 days after the start of treatment; penetrates blood-brain barrier and placenta
- indications: rheumatoid arthritis, osteoarthrosis
- side effects: pain in the epigastrium, dyspepsia; very rarely: gastritis, stomatitis, ulcer of the stomach, dysphagia, gastro-intestinal bleeding, headache, vertigo, insomnia, depression, increase in intracranial pressure, hypertension, tachycardia etc.
- contraindications: acute gastric ulcer, hypersensitivity to NSAIDs

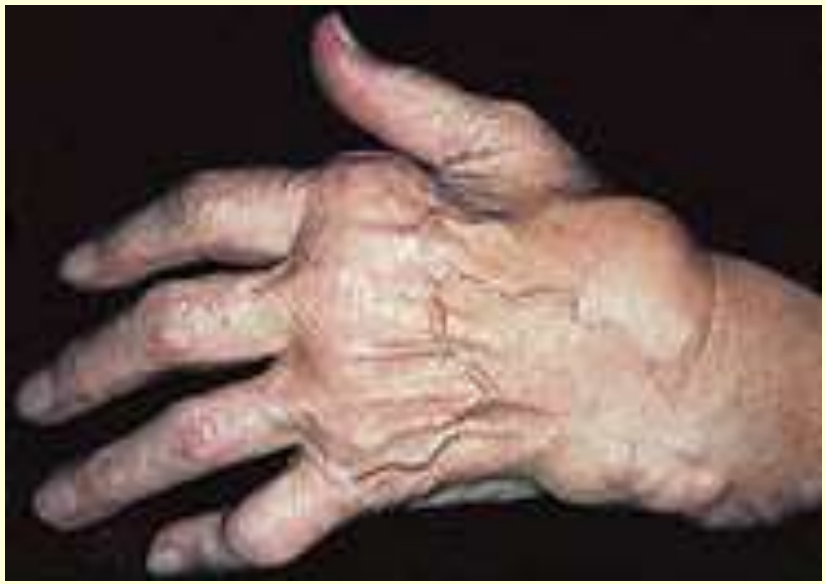

Therapeutic disadvantages of selected NSAIDs*
Therapeutic advantages of selected NSAIDs
Upper GI disturbances are common
No antipyretic effect
Very potent; should be used only after less toxic agents have proven ineffective
CNS disturbances are common
Potential for increasing myocardial infarctions and strokes
Salicylates:
Aspirin
Salicylate salts
Diflunisal
Acetic acids:
Indomethacin
Sulindac
Tolmetin
Propionic acids:
Ibuprofen
Fenoprofen
Flurbiprofen
Ketoprofen
Naproxen
Oxaprozin
Oxicams:
Piroxicam
Meloxicam
Fenamates:
Mefenamic acid
Meclofenamic acid
COX-2 inhibitors
Celecoxib
Low cost; long history of safety
Less GI irritation than aspirin
Long half-life permits daily or twice daily dosing
Lower toxicity and better acceptance in some patients. Naproxen is considered by some experts as one of the safest NSAIDs
Less GI irritation than aspirin

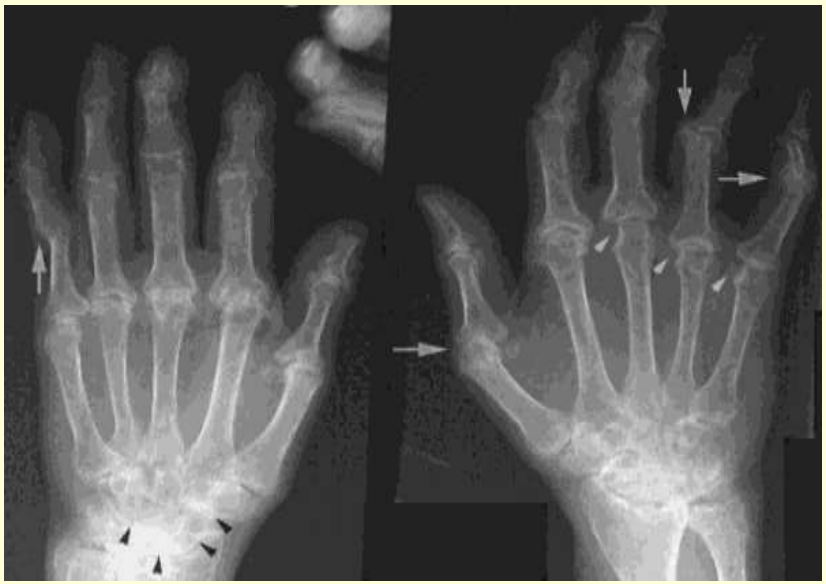
PREPARATIONS FOR THE TREATMENT OF RHEUMATOID DISEASES AND GOUT

RHEUMATOID DISEASE



Normal and Arthritic Joints



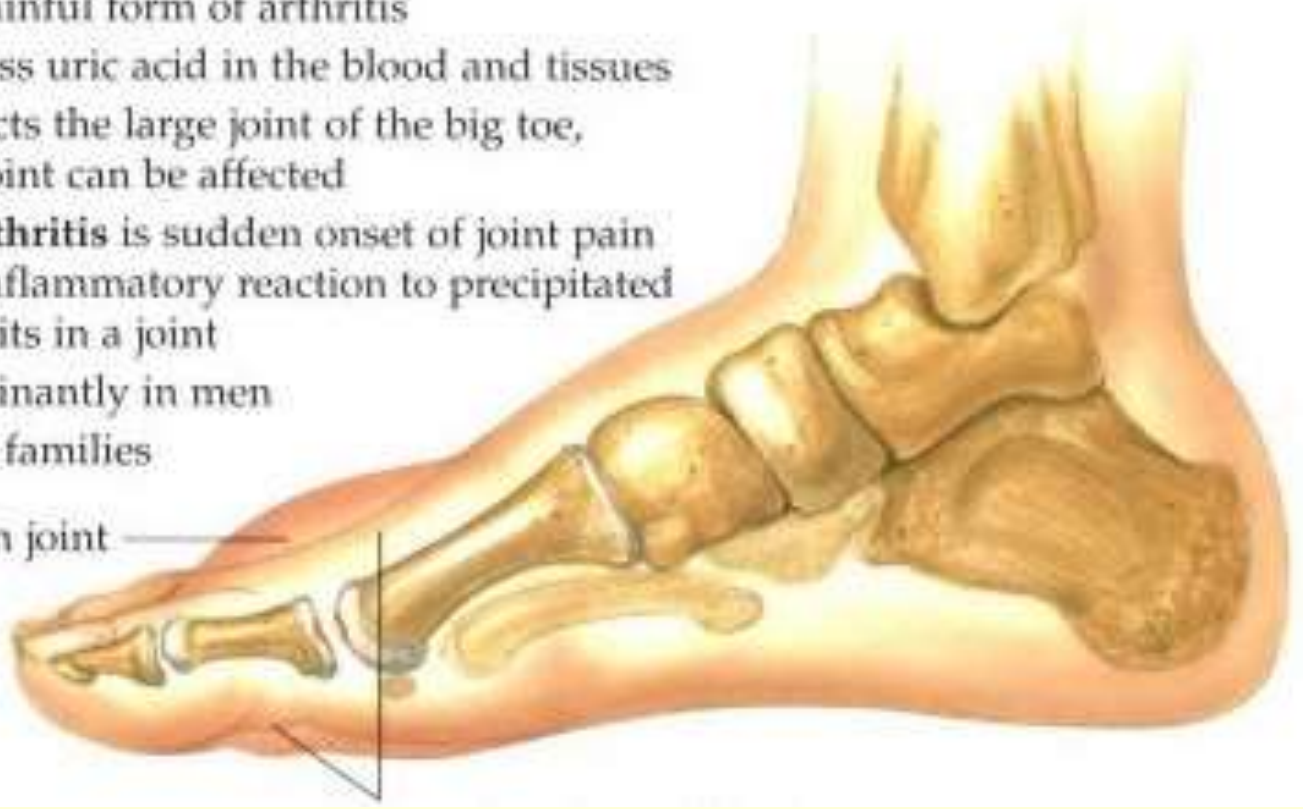


DRUGS FOR RHEUMATOID DISEASES

- ***Disease-modifying antirheumatic drugs (DMARD)*** are the primary treatment for rheumatoid arthritis
- The most commonly used agent is ***methotrexate*** with other frequently used agents including ***sulfasalazine and leflunomide.***
- ***Sodium aurothiomalate (Gold) and cyclosporin*** are less commonly used due to adverse effects
- ***Biological agents*** should generally only be used if methotrexate and other conventional agents are not effective. These agents include: tumor necrosis factor alpha (TNFα) blockers such as infliximab; interleukin 1 blockers such as anakinra, monoclonal antibodies against B cells such as rituximab, T cell costimulation blocker such as abatacept among others.
- Anti-inflammatory agents (***NSAIDs***)
- ***COX-2 inhibitors***, such as celecoxib, and NSAIDs are equally effective.
- ***Glucocorticoids*** can be used in the short term for flare-ups, while waiting for slow-onset drugs to take effect. Injection of glucocorticoids into individual joints is also effective

GOUT

- Presents as a painful form of arthritis
- Caused by excess uric acid in the blood and tissues
- Frequently affects the large joint of the big toe, although any joint can be affected
- **Acute gouty arthritis** is sudden onset of joint pain caused by an inflammatory reaction to precipitated uric acid deposits in a joint
- Occurs predominantly in men
- Tends to run in families



PHARMACOLOGICAL MANAGEMENT OF GOUT

- treatment of the gout attack with colchicine, indomethacin, phenylbutazone, glucocorticoids
- prophylaxis of gout attacks with diet low in purines, uricostatics, uricosurics.

ANTI-GOUT DRUGS:
CLASSIFICATION

A. Uricostatics (They decrease urate production)

– Allopurinol

B. Uricosurics (They promote renal excretion of uric acid)

1. Drugs inhibiting reabsorption of ureic acid

– Probenecid

– Aethamidum

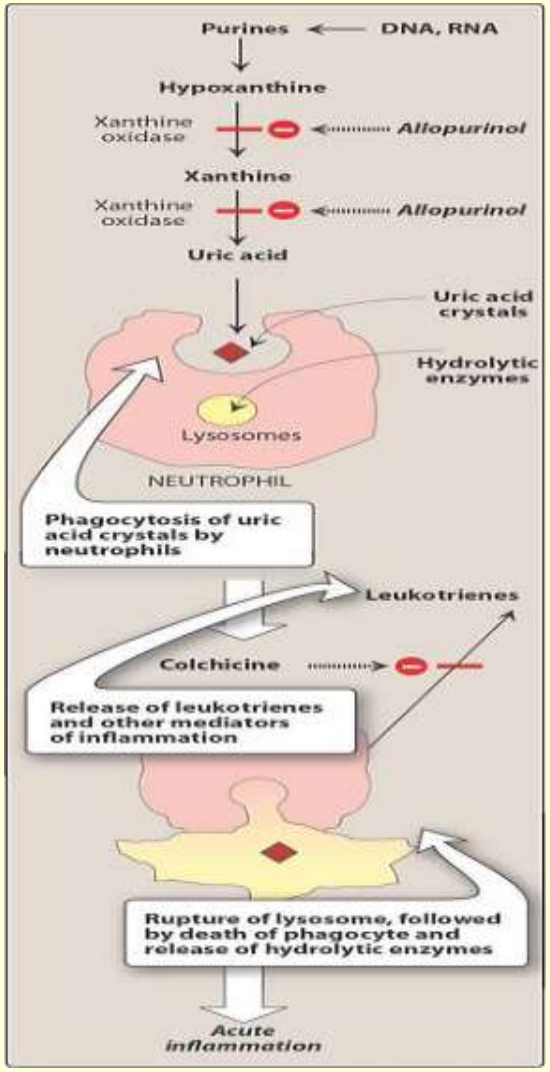
2. Drugs increasing the solubility of urates

– Urodanum

3. Drugs decreasing forming of urate concrements

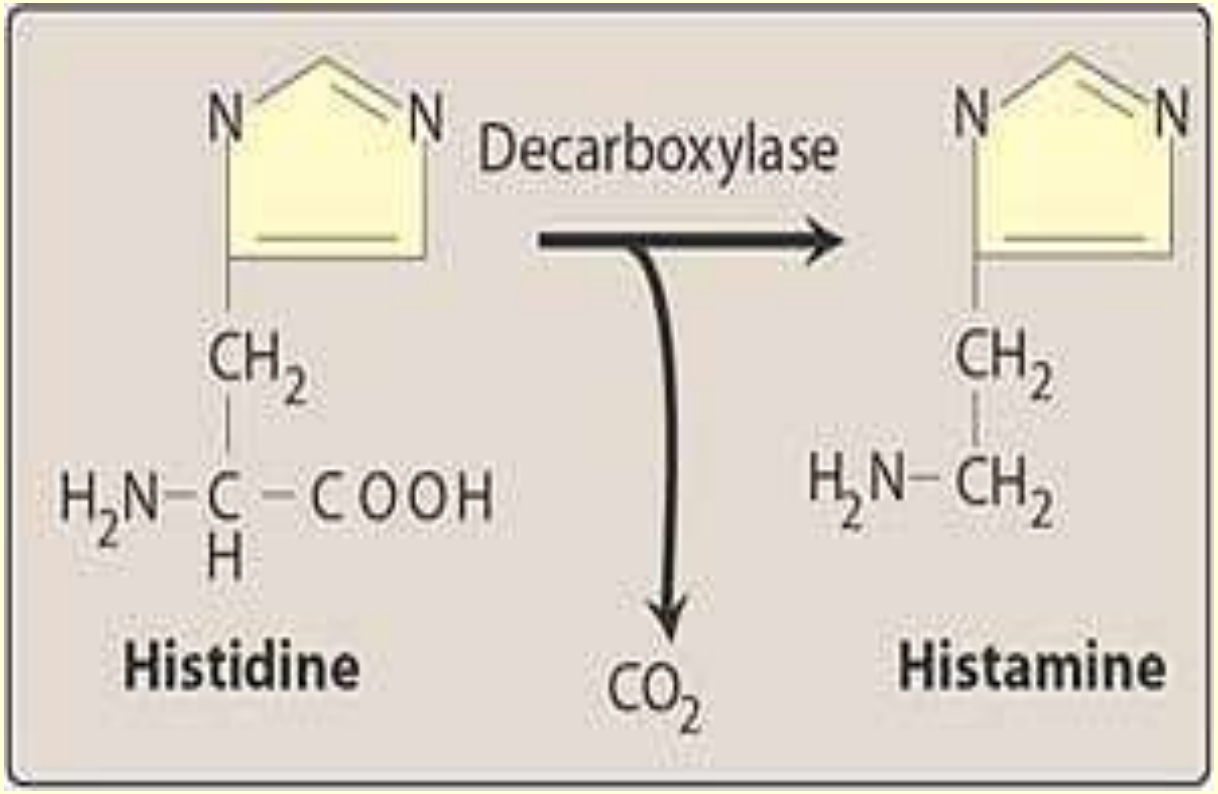
– Urolesanum.

MECHANISM OF ACTION OF ANTI-GOUT DRUGS



NON-STEROIDAL ANTI-ALLERGIC DRUGS

SYNTHESIS OF HISTAMINE



HISTAMINE'S EFFECTS

H_1 Receptors

EXOCRINE EXCRETION

Increased production of nasal and bronchial mucus, resulting in respiratory symptoms.

BRONCHIAL SMOOTH MUSCLE

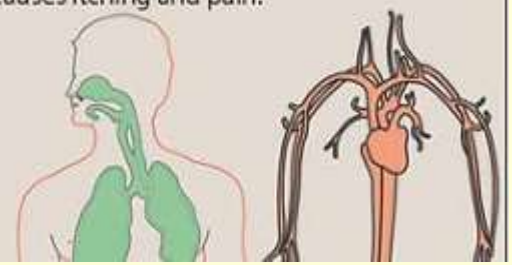
Constriction of bronchioles results in symptoms of asthma and decreased lung capacity.

INTESTINAL SMOOTH MUSCLE

Constriction results in intestinal cramps and diarrhea.

SENSORY NERVE ENDINGS

Causes itching and pain.



H_1 and H_2 Receptors

CARDIOVASCULAR SYSTEM

Lowers systemic blood pressure by reducing peripheral resistance. Causes positive chronotropism (mediated by H_2 receptors) and a positive inotropism (mediated by both H_1 and H_2 receptors).

SKIN

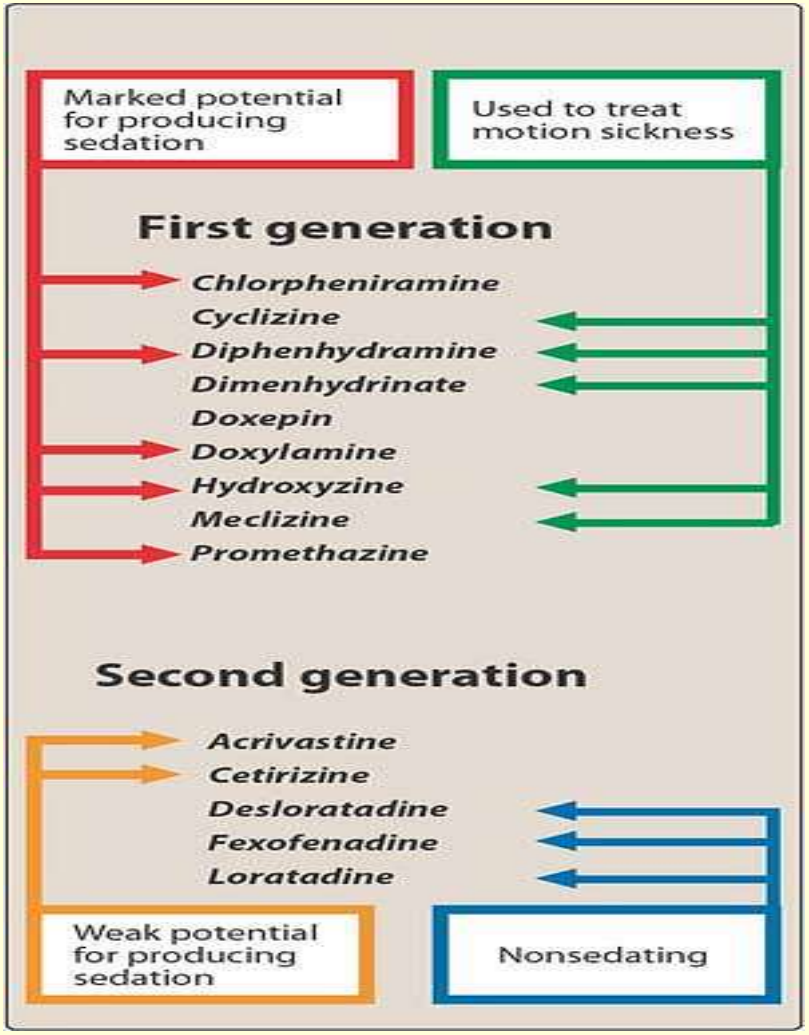
Dilation and increased permeability of the capillaries results in leakage of proteins and fluid into the tissues. In the skin, this results in the classic "triple response": wheal formation, reddening due to local vasodilation, and flare ("halo").

H_2 Receptors

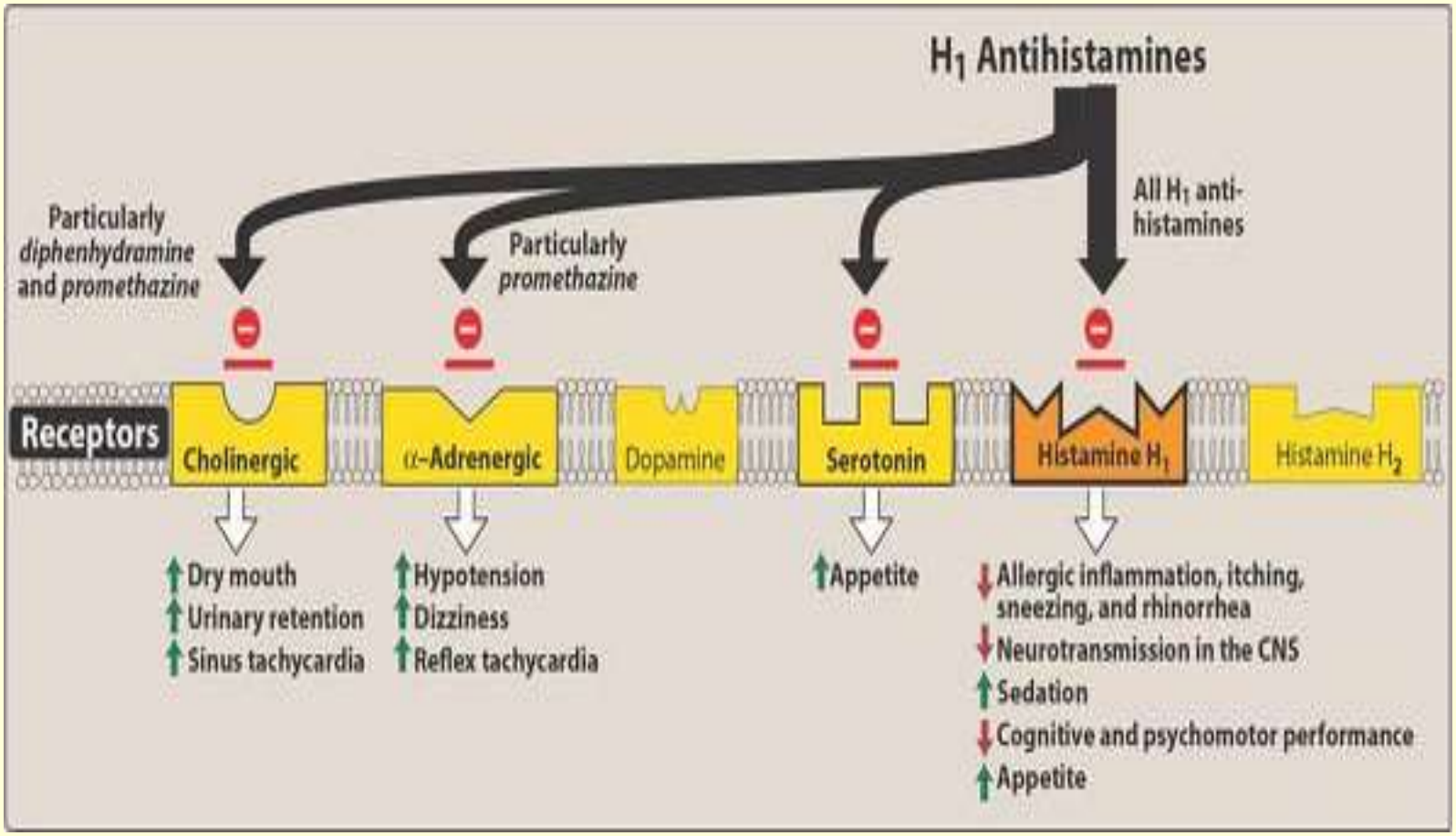
Stomach

Stimulation of gastric hydrochloric acid secretion.

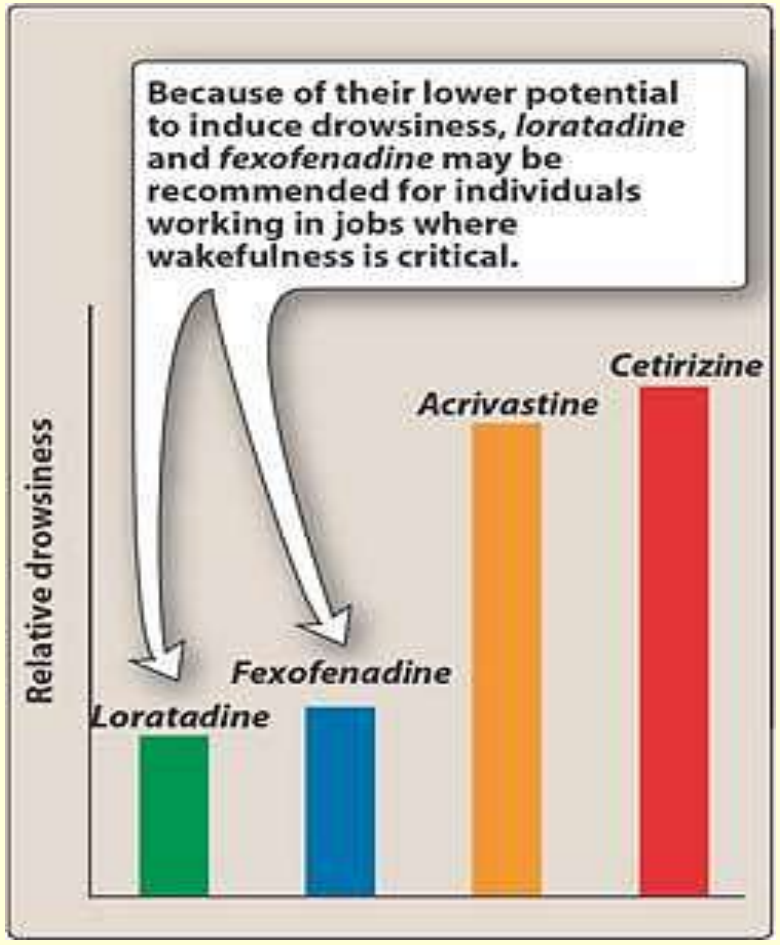
CLASSIFICATION OF H1-HISTAMINE RECEPTOR BLOCKERS



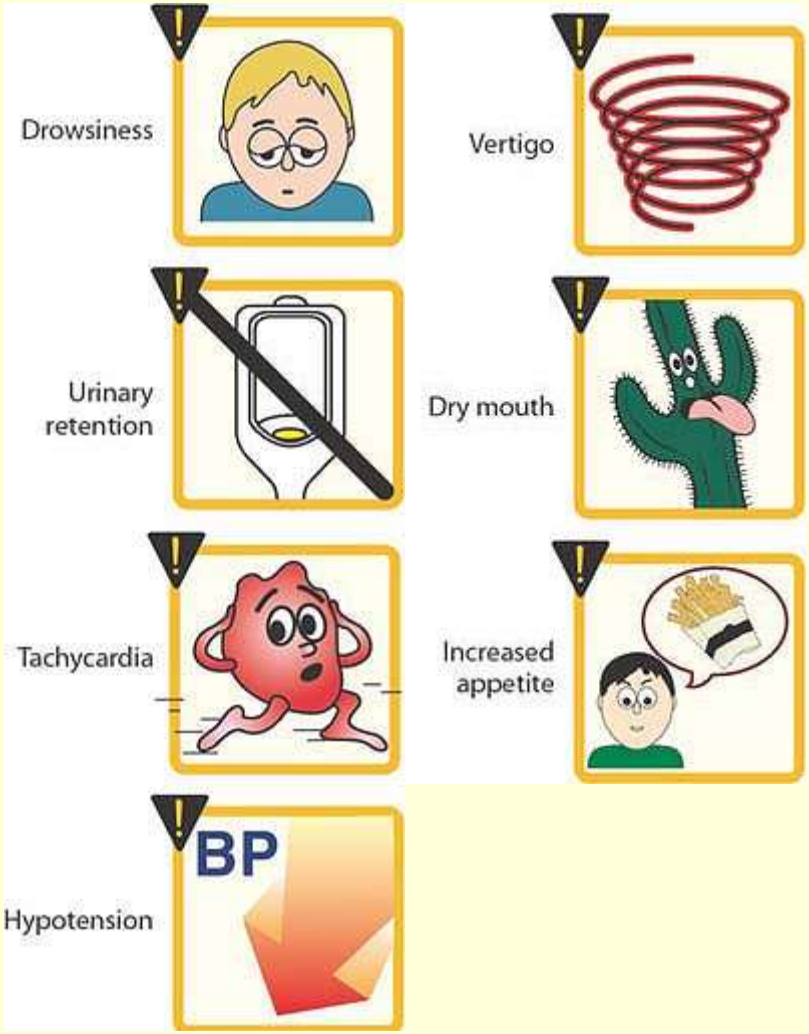
MECHANISM OF ACTION OF H1-ANTIHISTAMINES



DAY-TIME ANTIHISTAMINES



SIDE EFFECTS OF H1-ANTIHISTAMINES



CONTROL TASKS

- A 62-years-old man has been suffering from coxitis for a long time. A doctor prescribed him a new NSAID celecoxib. It improved the patient's state. What is the advantage of this drug?

A. Selective blockade of COX -2

B. Depression of choline esterase

C. Depression of phosphodiesterase

D. Activation of adenylate cyclase

E.Activation of phosphodiesterase

(A)

- Allergic dermatitis produces itching, hypostasis, reddening, and insomnia. What drug is expedient for prescribing to the patient?

A. Phenobarbitalum

B. Nitrazepamum

C. Dimedrolum

D. Chlorali hydras

E. Natrii oxybutyras (C)

CONTROL TASKS

- A woman appealed to a doctor with a complaint of pain in her knee joint. The diagnosis is: Acute arthritis. What drug from cortico-steroids group can be administered into the joint?

A. Progesterone

B. Desoxycorticosterone

C. Ergocalciferol

D. Hydrocortisone

E. Diclofenac-sodium. (D)

- Because of a long-term use of anti-inflammatory drug osteoporosis, ulcer of the stomach, edema, an increase of blood pressure, and hypokalemia have developed. What drug has been applied?

A. Prednisolonum

B. Digoxinum

C. Hypothiazidum

D. Indometacinum

E. Reserpinum (A)

CONTROL TASKS

- A second generation antihistamine drug is a derivative of piperidine, taken once a day. It has no M-anticholinergic and adrenergic blocking effect. It shows anti-allergenic, anti-exudative, and antipruritic action. What drug is this?

A. Retinoli acetas

B. Loratadinum

C. Dimedrolum.

D. Diazolinum

E. Suprastinum (B)

- It is necessary to prescribe non-steroidal anti-inflammatory drug from the group of salicylates to a patient with rheumatism. This drug is:

A. Indomethacin

B. Diclofenac sodium

C. Acetylsalicylic acid

D. Dexketoprofen

E. Nimesulide. (C)

THE END

Thank you for attention!