Methylxanthines

Methylxanthines actually came before the Beta-2 selective agonists

- **Theophylline.**
- **Aminophylline.**

Xanthine derivatives are tea, coffee, theophylline, aminiophylline, theobromine etc..

Remember that coffee and tea make your breathing relaxed, so they do bronchodilation

Were the mainstay treatment(60s-70s).

Oral and Intravenous.

CNS stimulants ← Their classification

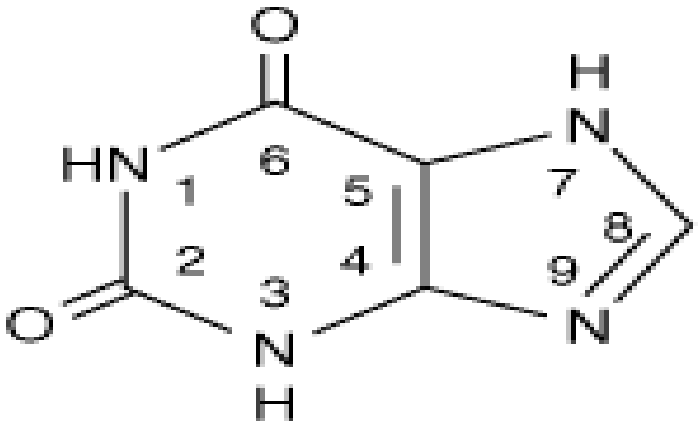
sinus tachycardia

Cardiovascular stimulants; arrhythmias.

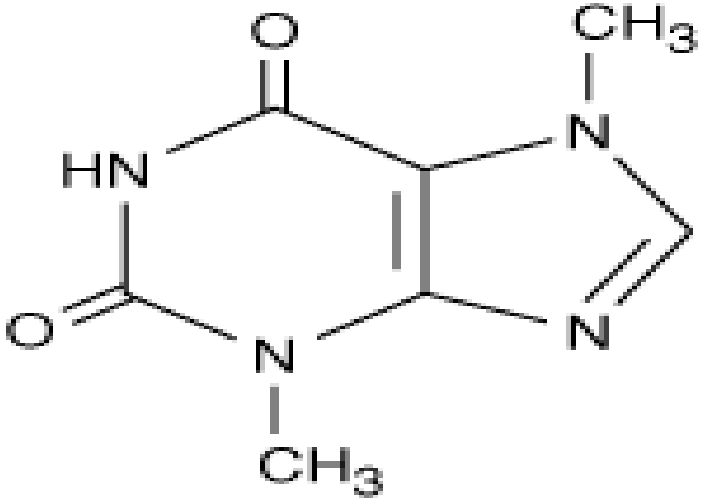
Nausea, GIT irritation, diarrhea.

These drugs were withdrawn because of their side effects (Toxicity), then they came back because they were found to have a low therapeutic index (nowadays it's easy to use them because we can measure the blood levels of these drugs)

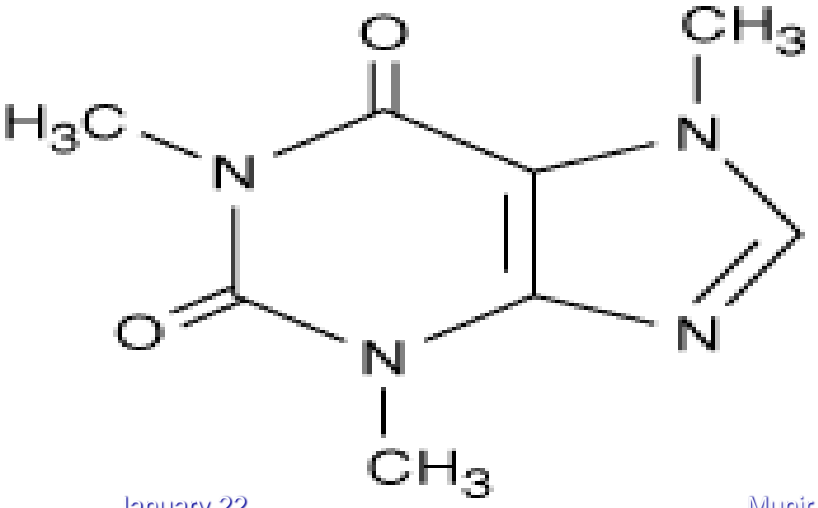
METHYLXANTHINE DRUGS



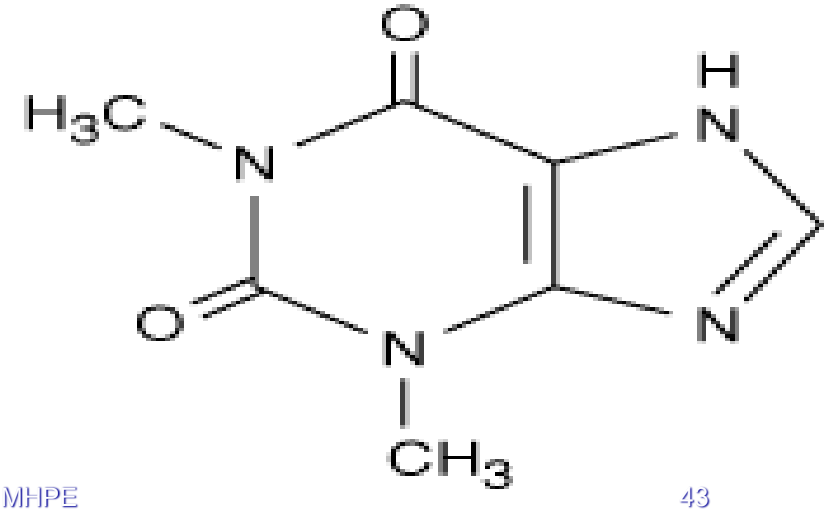
Xanthine



Theobromine



Caffeine



Theophylline

Mechanism of Action of Methylxanthines

- **Phosphodiesterase inhibition.**
- **Adenosine receptor antagonism .**
- **Antiinflammatory activity.**

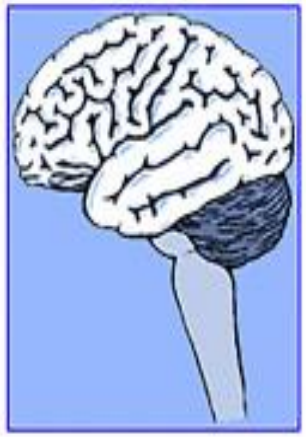
- Phosphodiesterase enzyme: it's the enzyme which breaks down cAMP
Recall that cAMP is important for dilatation and relaxation of smooth muscles.

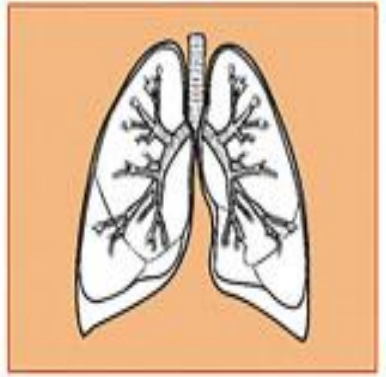
- Adenosine causes bronchoconstriction

Methylxanthines

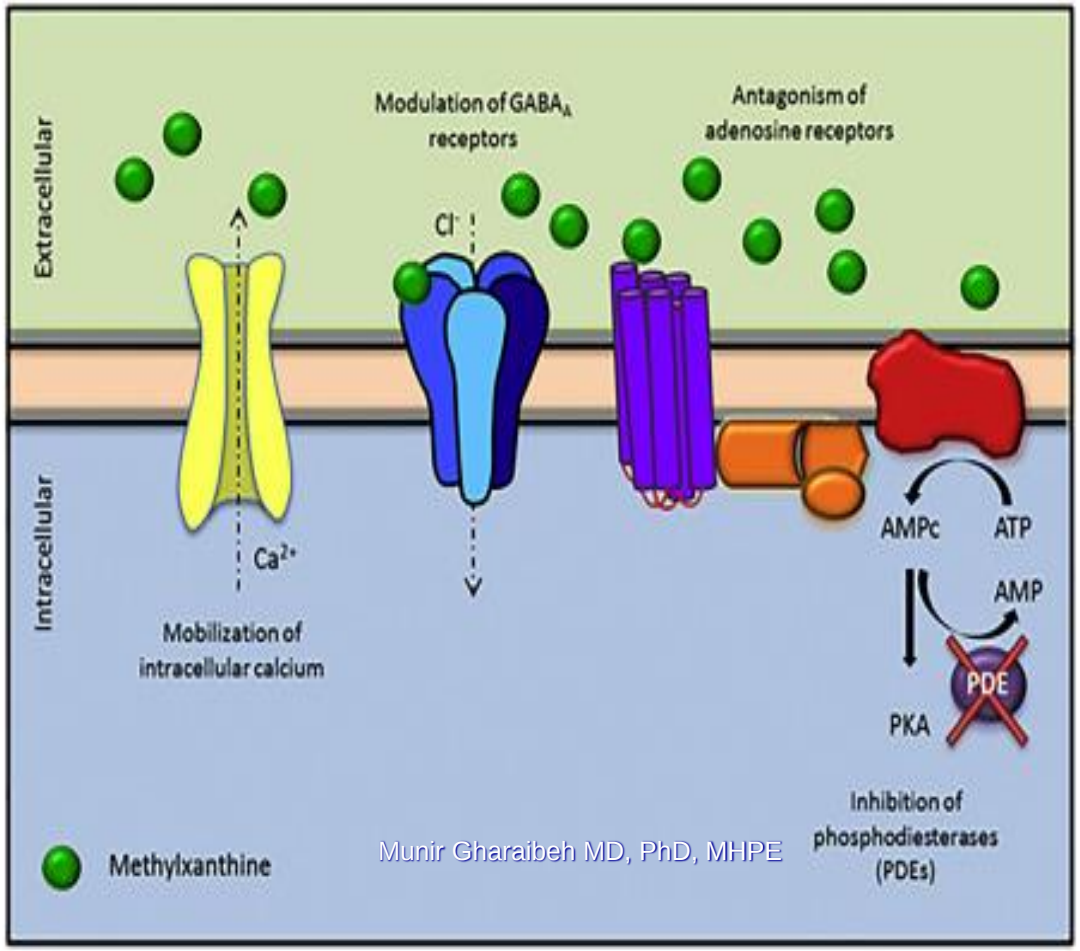
- Theophylline and its derivatives are most commonly used for the treatment of COPD and asthma.
- Caffeine, theophylline and theobromine are naturally occurring xanthine alkaloids which have qualitatively similar actions.

- ***Mechanism of action:***
  - Methylxanthines inhibits cyclic nucleotide phosphodiesterase (PDEs), thereby preventing conversion of cAMP and cGMP to 5'-AMP and 5'-GMP, respectively. Inhibition of PDEs will lead to an accumulation of intracellular cAMP and cGMP. Bronchodilataion, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells. Theophylline and related methylxanthines are relatively nonselective in the **PDE subtypes inhibitor**.
  - Theophylline is a competitive **antagonist at adenosine receptors**. Adenosine can cause bronchoconstriction in asthmatics and potentiate immunologically induced mediator release from human lung mast cells. Methylxanthines inhibits the adenosine action thereby casing bronchodilataion.





Central control of respiratory function



- Bronchodilatation
- Decrease pulmonary arterial pressure
- Increase the airway diameter

Problems with Methylxanthines

the optimal dose is very difficult to determine because of the low therapeutic index as we said before

- Optimal dosing is very difficult.
- Wide inter-individual variation in the rate of hepatic metabolism.
- Half life: 3-16 hours.
- Food and drug interactions (erythromycins and ciprofloxacin).
- Blood assay is a routine. Drug monitoring is important

Theophylline Returns

- **Resurgence of an old friend:**

  Use of low dose theophylline, with mean plasma level of 36.6 µmol/ml (6.7 µg/ml), significantly inhibits the Late Asthmatic Reaction (LAR) and airway inflammatory infiltration.

Anticholinergic Agents

- **Atropine:**

Can be inhaled, but; can cause systemic side effects.

Impairs mucociliary clearance leading to dryness, and consequently, impaired clearance of airway secretions.

Anticholinergic Agents

- **Ipratropium Bromide Inhaler:**

Poorly absorbed from respiratory mucosa.

Does not impair clearance of airway secretions.

Causes minimal cardiac or central effects.

Anticholinergic Agents

- **Ipratropium Bromide Inhaler:**
- Metered dose inhaler and as a solution for nebulization.
- Mainly for COPD, not for asthma, because of slow onset (10-15 minutes) and low potency.
  not used for emergency
- Might be very useful in special conditions(beta blocker- induced asthma, resistant attacks, cardiac patients)

Anti-inflammatory Agents and Alternative Therapy

- Coricosteroids.
- Inhibitors of Mast Cell Degranulation.
- Leukotriene Pathway Modifiers.
- Immunomodulatory Agents.

Corticosteroids(1950s)

- Inhibit the synthesis and release of many chemical mediators (histamine, PGs and cytokines).
- Suppress the inflammatory cell influx and process.
- Relax bronchial smooth muscle.
- Enhance beta-adrenergic responsiveness (upregulate β receptors).
- Increase synthesis of adrenergic mediators.
- Decrease quantity and viscosity of secretions.
- Inhibit IgE synthesis.
- Decrease microvascular permeability.

Corticosteroids

Highly lipophilic, enter the cytosole.

- **Bind to cytosolic receptors.**
- **The drug-receptor complex enters the nucleus.**
- **Decrease transcription of genes coding for pro inflammatory cytokines.**
- **Take several hours to days to work.**

Corticosteroids

- Short term systemic use in severe refractory attacks.
- Long term use for ”Steroid Dependant” asthma.

We start with a high dose, then we decrease it.
In some patients, you cannot reduce the dose; as bronchial asthma comes back after stopping the treatment .
This patient is called "Steroid Dependent", and usually continues on a small dose like 5mg of prednisolone

Corticosteroids

- **Systemic Use:**

  Oral or injectable

  (Cortisone, Prednisolone, Dexamethasone)

- **Inhalation:**

Aerosol treatment is the most effective way to avoid the systemic adverse effects

(Beclomethasone, Triamcinolone, Flunisolide, Budesonide, Fluticasone).

Corticosteroids

- **Local Side Effects:**

Hoarseness of voice (dysphonia), sore throat and cough.

Candida infection.

So, before taking corticosteroids, you should give Beta-2 agonist which helps stop coughing

- **Systemic Side Effects:**

Osteoporosis, cataract, glaucoma, growth retardation, adrenal suppression, CNS effects and behavioral disturbances, increased susceptibility to infections, and teratogenicity.

Adrenal suppression happens when the patient has been on corticosteroids for a long time, then they stop taking it suddenly.
Taking corticosteroids for a long time causes suppression of ACTH (adrenocorticotropic hormone), so we should reduce the dose gradually to avoid causing adrenal suppression.

Inhibitors of Mast Cell Degranulation

Recall that Ag-Ab reaction occurs on the mast cells, and it causes the breakdown of mast cells releasing Histamine. Histamine is a bronchoconstrictor.

- **Cromolyn Na and Nedocromil Na:**

Inhibit the release of inflammatory mediators from mast cells (*Mast Cell Stabilizers*).

Prophylactic for mild to moderate asthma.

Regular use (4 times daily).

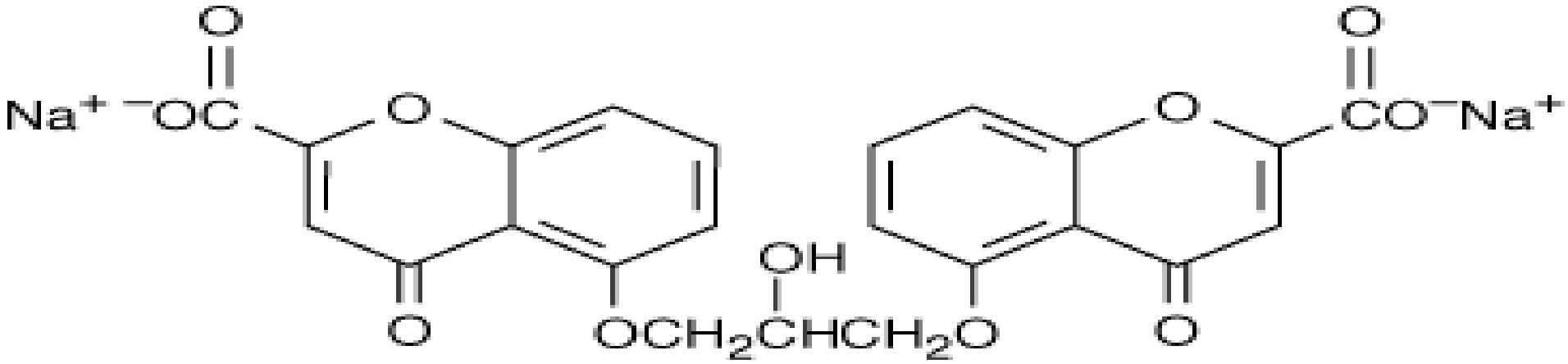
Not for acute asthma.

Phosphorylates a cell membrane protein, so, mediator release is inhibited despite antigen-IgE interaction.

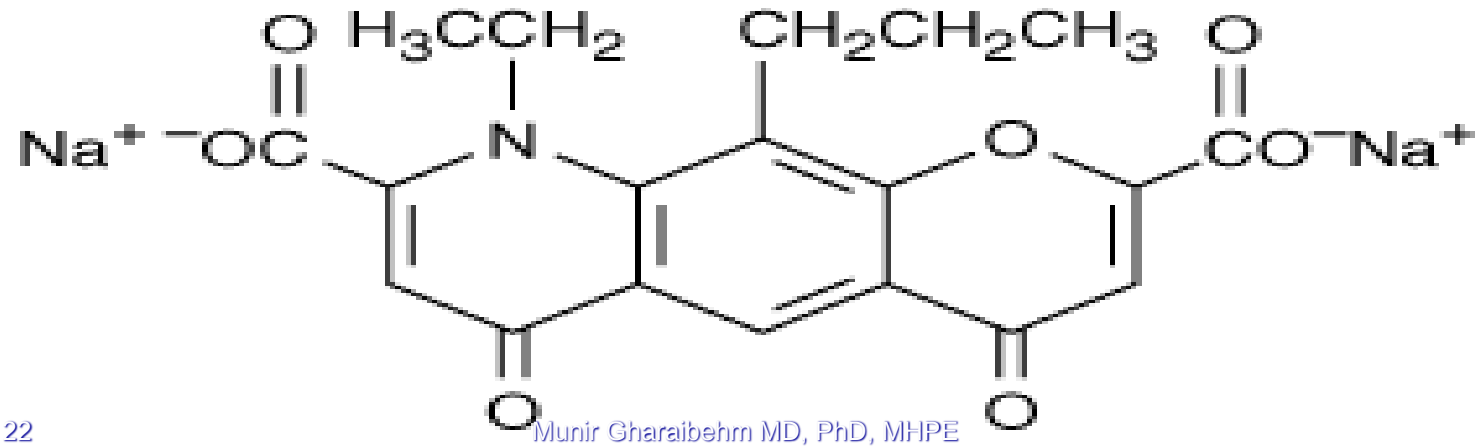
Might decrease Ca++.

Might decrease neural pathways, plasma exudation and inflammation in general.

Complete absence of side effects.



Cromolyn sodium



Nedocromil sodium

Leukotrienes

- Synthesized by mast cells and eosinophils.
- They are 1000-fold more potent than histamine in stimulating airway smooth muscle constriction.
- They also promote microvascular leakage, mucus secretion and eosinophil chemotaxis.
- Pathway augmented by COX inhibitors (i.e. NSAIDs)

Leukotriene Pathway Modifiers

- 3-5% of adults with asthma, have “aspirin sensitivity’.
- This reaction is not an allergic response, can be induced by many different chemicals (tetrazine, FDC Color #5), and does not involve IgE antibody response.
- Patients produce high levels of cysteinyl leukotrienes in response to COX inhibitors, probably by shunting of arachidonic acid into leukotriene pathway.
- Abnormality of the promotor region of the gene for LTC4 synthase, leading to overexpression of the enzyme leading to increased conversion of LTA4 to LTC4.

it's just due to shunting.

Leukotriene Pathway Modifiers

- **Inhibitors of 5-Lipoxygenase enzyme:**

Zileuton: for acute and chronic treatment, 4 times daily, hepatotoxic.

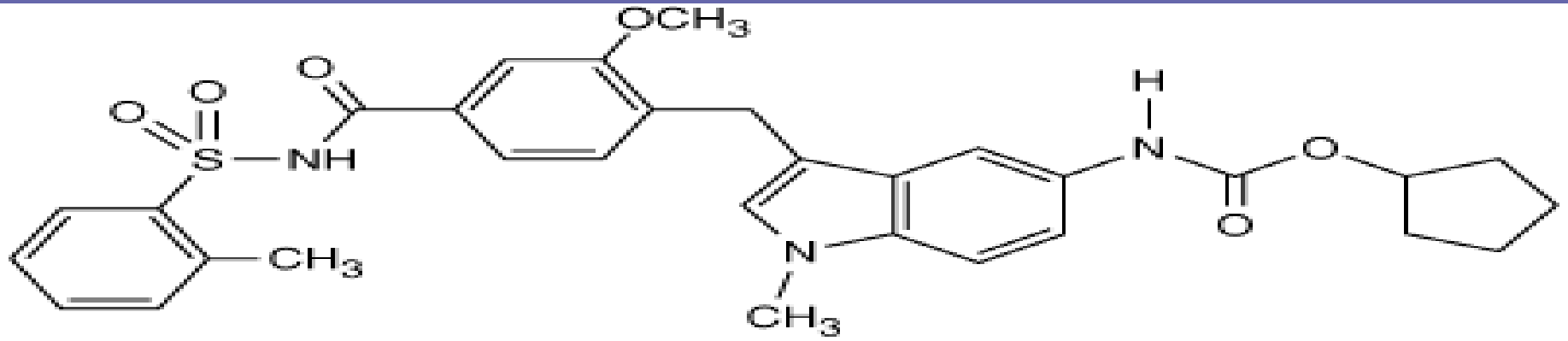
- **Antagonists of Cysteinyl Leukotriene Receptors:**

Montelukast.

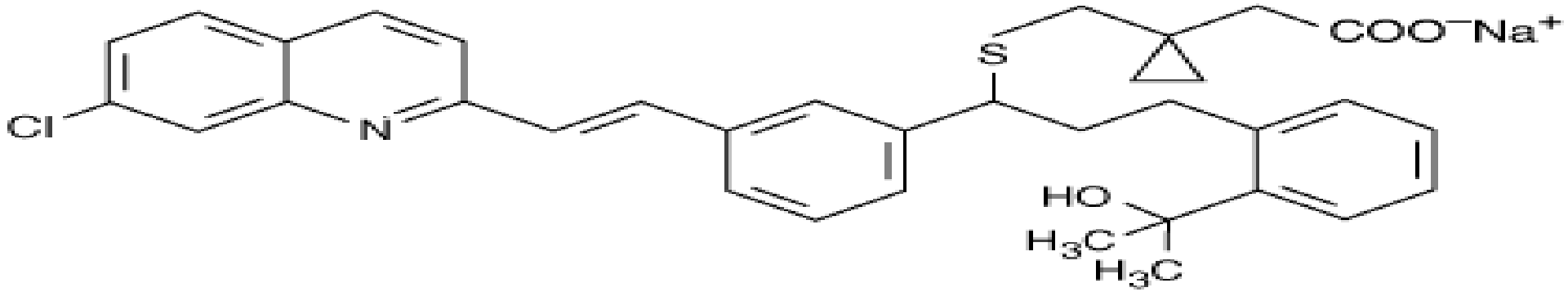
Zafirlukast.

Some patients improve, others do not (**Churg-Strauss Syndrome.**

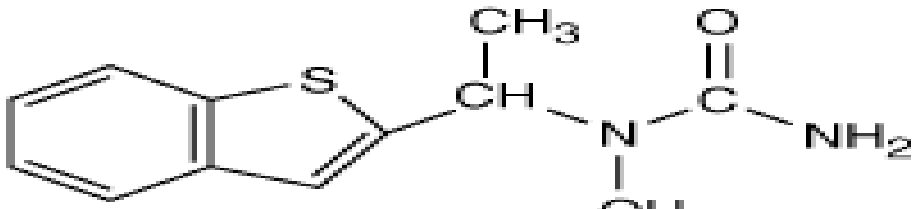
Leukotriene Pathway Inhibitors



Zafirlukast



Montelukast



Zileuton

Leukotriene Pathway Modifiers

- **Churg-Strauss Syndrome:**

Rare reaction in newly treated asthmatic patients.

Severe inflammatory reaction, pulmonary infiltration, neuropathy, skin rash, and cardiomyopathy.

A common finding is systemic vasculitis with eosinophilic infiltration and granuloma formation.

Could also be due to unmasking of vasculitis after steroid withdrawal.

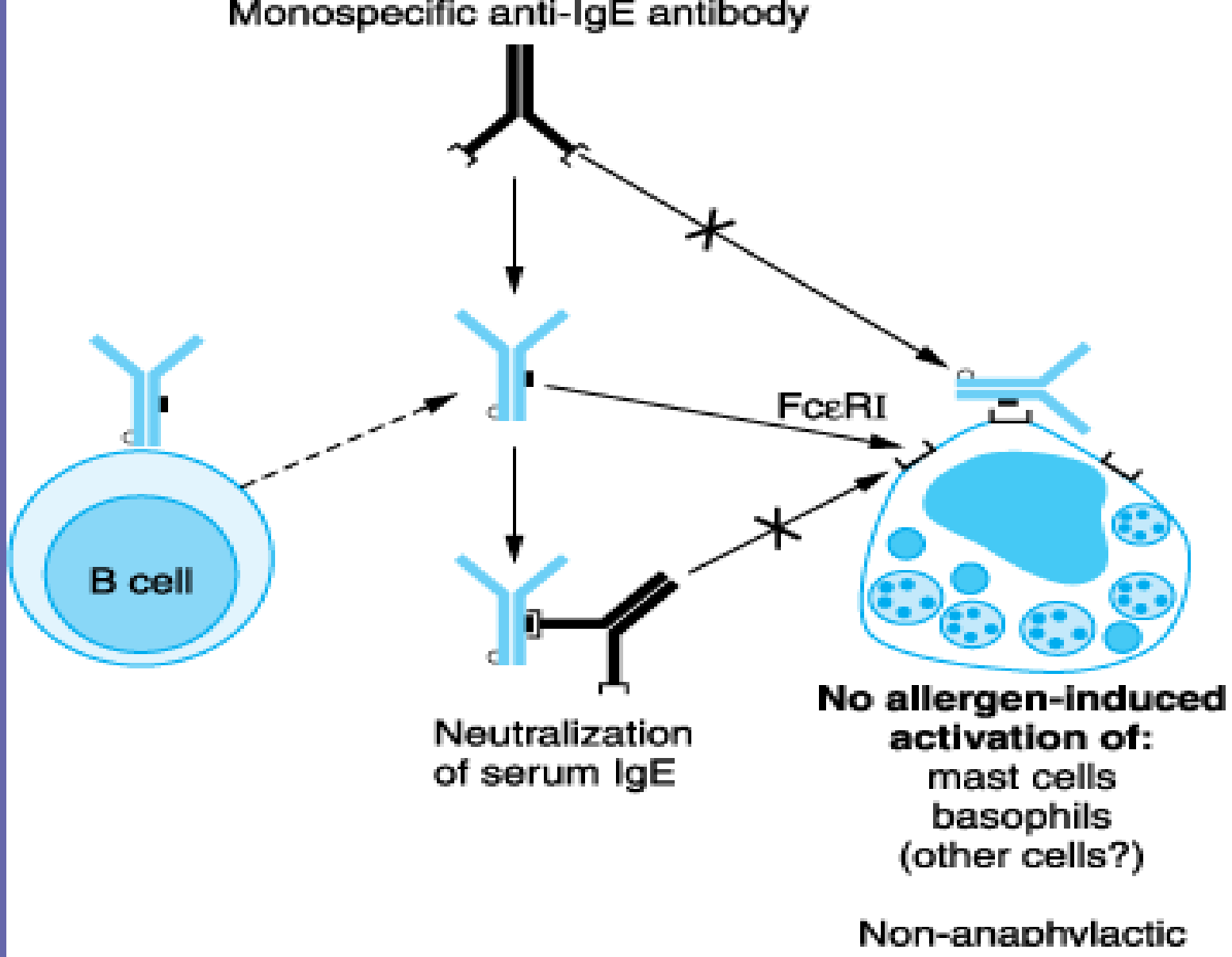
Montelukast / Beta agonist study

- ↓ percent of patients needing systemic use of corticosteroids by 39%
- ↓ in nighttime awakenings
- ↓ percent of patients having asthma attacks by 37%
- ↓ need for beta-agonists by 21%

Immunomodulating Biotherapeutics

Omalizumab:

- It is a humanized monoclonal anti-IgE antibody raised in mice.
- Not recognized as foreign by human immune system.
- Targeted against the portion of IgE that binds to its receptors (FC-R1 and FC-R2 receptors) on mast cells and other inflammatory cells.
- IgE-anti-IgE complexes are cleared from the blood without deposition in the kidneys or joints.
- Given as IV or SC injection every 2-4 weeks.



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Immunomodulating Biotherapeutics

- **Monoclonal antibodies directed against cytokines (IL-4, IL-5, and IL-13), antagonists of cell adhesion molecules, protease inhibitors, and immunomodulators aimed at shifting CD4 lymphocytes from the TH2 to the TH1 phenotype or at selective inhibition of the subset of TH2 lymphocytes directed against particular antigens.**

General Therapy of Asthma

- **Oxygen.**
- **Hydration: Oral or Intravenous.**
- **Expectorants.**
- **Antimicrobials.**

Possible Future Therapies

- There is evidence that asthma may be aggravated—or even caused—by chronic airway infection with *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*. This may explain the reports of benefit from treatment with macrolide antibiotics (erythromycins) and, if confirmed, would stimulate the development of new diagnostic methods and antimicrobial therapies.

Probiotic

- Feeding *Lactobacillus caseii* to infants born to allergic parents reduced the rate of allergic dermatitis at age 2 years, offers reason for hope.

Status Asthmaticus

- Life threatening exacerbation of asthma symptoms that is unresponsive to standard therapy, preceded by rapid increase in the daily use of bronchodilator drugs.
- Provocative factor usually present.
- Needs aggressive treatment in the hospital.

Status Asthmaticus isn't like acute asthma,
Acute attack of asthma is usually relieved (or might be relieved with difficulty) and responds very quickly to routine treatment. But if Asthma keeps recurring again and again, this condition is called Status Asthmaticus

Status Asthmaticus

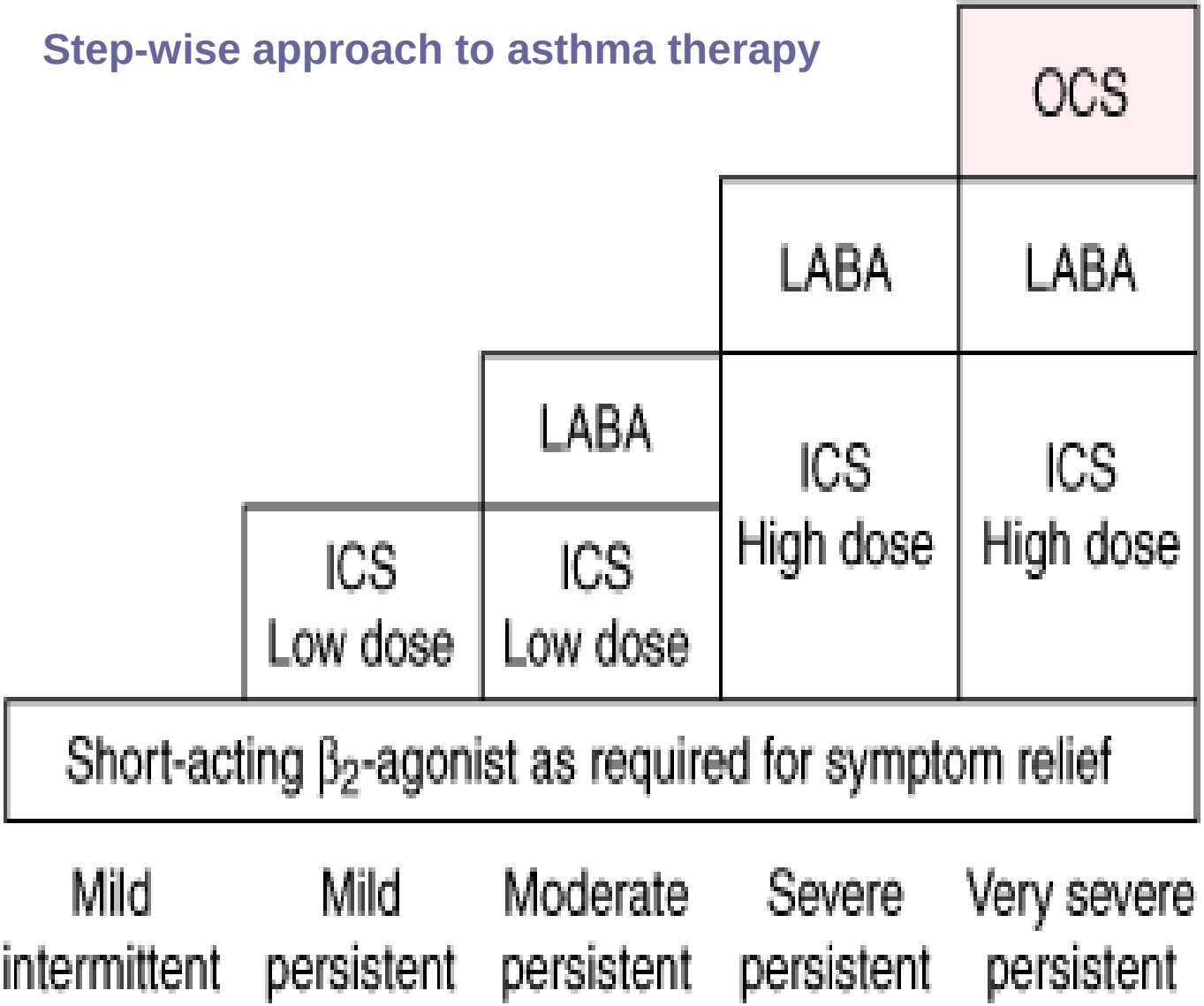
- Oxygen.
- Inhaled short acting β2 agonists.
- Oral or Parenteral corticosteroids.
- Subcutaneous β2 agonists.
- Inhaled ipratropium maybe effective in some patients.
- Epinephrin by subcutaneous injection.

Goal: No deaths on your watch

No patients should die of an acute episode of bronchoconstriction (an asthma attack) at any time, any place.

- **Aerosol therapy is available with hand held devices that operate on batteries.**
- **Even more immediate beta-agonist therapy via an “Epi-pen” is readily available.**

Step-wise approach to asthma therapy



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Conclusion

One day, in the future, doctors will know their patient's genetic make-up and response to drugs such that they will be truly able to individualize their patient's therapy on the basis of fact – not guesswork or trial by error.

For now, they should individualize their patient's therapy by therapeutic trial using the lowest dose that works and drugs in rational combinations.