Addis Ababa University
College of Veterinary Medicine and Agriculture
Department of Biomedical Science

- **Module Title:** **Veterinary Pharmacology and Toxicology (Vetm - M3121)**
- **Course Title:** **Veterinary Pharmacology and Therapeutics II**
- **Course Code:** **Vetm3122**
- **Credit Hour:** **3 (5 ECTS)**
- **Students Year** **Year III DVM Students**
- **Semester** **II**
- **Academic Year:** **2019/2020 G.C**
- **Prerequisite** **Veterinary Pharmacology and Therapeutics I**
- **Instructors:** Dr. Getachew Tadesse* (DVM, MSc, PhD candidate; Assis. Professor)(50%)
  Mr. Takele Beyene (DAH, B.Pharm, MSc, Assistant Professor) (50%)
  *Course coordinator

I. Course Description

The course provides the opportunity to acquire the general principles of anti-infective agents. Upon the completion of this course students will be able to describe the general properties and principles of chemotherapy (antibacterial, antifungal, antiparasitic, antiviral and antineoplastic agents). The course will also make students to acquaint the basic theoretical knowledge in the selection and combination of the best drugs for prophylaxis and treatment of bacterial, parasitic, fungal, protozoal and viral infections.

II. Learning Outcomes

After the completion of the course, students would be able to:

- Describe variety of anti-infective drugs and their mechanism of action.
- Explain the nature of chemotherapeutic agents
- Describe the pharmacokinetics and dynamics of each group of drugs
- Discuss the interaction of one drug with the other
- Explain the adverse effect of each drugs
- Explain the effect of individual drugs on risk groups
- Explain the contra-indications of the drugs
- Distinguish the proper route of administration of each drug
- Identify, select and prescribe the appropriate drugs for the given infectious agents

III. Course Contents

Part I. Introduction to chemotherapy Week 1Dr. Getachew T

UNIT 1. Chemotherapy of Bacterial Diseases Week 1-6 Dr. Getachew T

General principle of antibacterial therapy,

Antiseptics and disinfectants,

Penicillins, Cephalosporins and other beta-lactams, Sulphonamides,

Aminoglycosides, Tetracycline, Macrolides, Chloramphenicol and Fluoroquinolones,

Miscellaneous Antibacterial agents (Polymyxins, Bacitracin, Vancomycin, Novobiocin, Nitrofurans, Nitroimidazoles)

UNIT 2. Antifungal Drugs Week 7 Dr. Getachew T

General principles of Antifungal therapy, Classification of Antifungal agents, Topical and systemic antifungal agents (Azole groups, Amphotericin B, Flucytosine, Griseofulvin and Nystatin)

UNIT 3. Anti-Viral Drugs Week 8 Dr. Getachew T

General principles of anti-viral therapy, Acyclovir, cidofovir, Lamivudine, Ganciclovir, Idoxuridine, Rimantadine, Vidarabine, Immunoglobulin, Interferons, and others.

UNIT 4. Antiparasitic Drugs Week 9-12 Mr. Takele B.

General principles of antiparasitic therapy,
Anthelmintics (Antinematodal, Antitrematodal and Anticestodal agents),
Insecticides (Ectoparasiticides),
Antiprotozoal agents

Unit 5. Antineoplastic Drugs Week 13-14 Mr. Takele B.

General principles of Cancer therapy, Common drugs used

Part II. Anti-inflammatory drugs and their mediators Week 15-16 Mr. Takele B.

IV. Resources to be used for teaching-learning

White board and markers, LCD projector and laptops, Animation Videos, Figures and tables

V. Instructional Methods

Interactive lecture using power point slides and overhead transparencies, Discussions using whiteboard and markers, Assignment, seminar paper, oral presentation.

VI. Evaluation Methods

Quizzes, tests and Assignments (individual)/presentation/attendance/discussion) =30%, Mid exam = 30%, Final exam = 40%

VII. Course Requirement

- Students required attending classes not less than 85% of the given time and 100% of the practical sessions, working the assigned assignments individually and submitting and presenting on time; and Read the assigned teaching materials

VIII. Exam Schedule and Grading

- Exam schedule will be based on the school schedule.
- Grading System is fixed as per the university's legislation.

IX. Reading Materials

1. Rock AH. 2007. Veterinary Pharmacology: A Practical guide for Veterinary Nurse. Butterworth Heinemann
2. Hardman, J.G., and Limbrid, L.E. 2006. Goodman and Gilmans the pharmacological basis of therapeutics. 11th ed. Mc Graw Hill, USA.
3. Bronder G.C and Pugh, D.M. 1991. Veterinary Applied pharmacology and therapeutics. 4nd ed. Baillier Tindall, London.
4. Frank, A. 1999. An Introduction to veterinary pharmacology 5th ed. Edinburgh, London.
5. Jones, L.M. 2004. Veterinary pharmacology & Therapeutics. Ames, Iowa, USA
6. Jones L.M., Booth N.H. and Donald L.E. 1998. Veterinary pharmacology and Therapeutics, 7th ed., Ames, Iowa state Univ. press, USA.

Chemotherapy of Parasitic Diseases (Antiparasitic Agents)

By
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Learning Objectives

At the end of this chapter you should be able to know:

- The General principles of antiparasitic therapy
- Identify the targets enzymes of parasites
- Know different antinematodal, antitrematodal, & anticestodal drugs with their MOA
- Understand the MOA of drugs used as insecticides
- Know commonly used antiprotozoal agents with their MOA

Overview

Parasites

- Organisms that live within, upon or at expense of another organism to survive
  - Include helminths, protozoa, scabies and pediculi
    - Endoparasites
    - Ectoparsites

- The economic importance of helminth infections in livestock has long been recognized

Helminthiasis

- Infestation with parasitic worms
- Some types of worms penetrate body tissues or produce larvae that migrate to blood, lymph, lungs, liver or other sites
- Anthelmintics (AHs) are used in all animal species and man.
- A significant part of the economic impact of parasitism in animal production is represented by the investment in control measures.
- A more complete understanding of the pharmacological properties of existing antiparasitic drugs should assist with more effient parasite control both in livestock and companion animals.

Factors responsible for therapeutic failure of AHs:

- Inadequate integration between management strategies and chemotherapy;
- Incorrect use of AHs drugs due to insufficient knowledge of their pharmacological features; and
- Insufficient understanding of the relationship between pharmacological properties and several host-related factors that could lead to modifiations of the PK behavior and to a decreased antiparasitic efficacy of the chosen drug.
- The availability of many compounds with a common mode of action and

Overview

Endoparasites

- live within the body of the host and cause internal parasite infections
- Helminths are divided into two major groups:
  - **Nematodes**: cylindrical, non-segmented worms commonly called *roundworms*
  - **Platyhelminths**: flattened worms that are subdivided into two groups-
    - ✓**Cestodes** (tapeworms) & **Trematodes** (flukes)

Ectoparasites

- live on the body surface of the host and cause external parasite infestations
  - Parasitic infestations of the skin

Overview

- **Protozoa**

· Single celled, usually contracted by:

  - ✓ oral-fecal route, contaminated water or bite of an insect.

· Include:

  - ◦ Coccidiosis
  - ◦ Babesiosis,
  - ◦ Trypanosomiasis
  - ◦ Toxoplasmosis
  - ◦ Trichomoniasis
  - ◦ Anaplasmosis
  - ◦ Giardiasis

General principles of antiparasitic therapy

- A rational approach to antiparasitic chemotherapy
  - requires comparative biochemical and physiologic investigations of host and parasite:
    - To discover differences in essential processes that will permit selective inhibition in the parasite and not in the host
- The parasite must have **defense mechanisms** in order to survive
  - To defend itself against immunologic attack, proteolytic digestion, etc,
- The great evolutionary distance between host and parasite
  - resulted in sufficient differences among individual enzymes or functional pathways to allow selective inhibition of the parasite.

Targets of chemotherapy

- Three major types of potential targets for chemotherapy of parasitic diseases:

1. **Unique essential enzymes** found only in the parasite;

2. **Similar enzymes found in both host and parasite** but indispensable only for the parasite; and

3. **Common biochemical functions found in both parasite and host** but with different pharmacologic properties.

1. Unique essential enzymes

Targets	Parasites	Inhibitors
Enzymes for dihydropteroate synthesis	Apicomplexa (plasmodium, toxoplasma, eimeria)	Sulfones and sulfonamides
Pyruvate:ferrodoxin oxidoreductase	Anaerobic protozoa (entamoeba, giardia, Trichomonas)	Nitroimidazoles
Pyruvate phosphate dikinase	Anaerobic protozoa	None
Nucleoside phosphotransferase	Flagellated protozoa	Allopurinol riboside and formycin B
Trypanothione reductase and peroxidase	Kinetoplastida	Nifurtimox

2. Indispensable enzymes

Targets	Parasites	Inhibitors
Purine phosphoribosyl transferase	Protozoa	Allopurinol
Lanosterol C-14 demethylase	*Leishmania* *Trypanosoma*	Azoles
Purine nucleoside kinase	*Trichomonas* *Entamoeba*	None
Ornithine decarboxylase	trypanosomes	Difluoromethylornithine
(S)Adenosylmethionine decarboxylase	trypanosomes	Diamidines
Glycolytic enzymes	Kinetoplastida	Glycerol plus Salicylhydroxamic acid Suramin

3. Common indispensable biochemical functions with different pharmacologic properties

Targets	Parasites	Inhibitors
Dihydrofolate reductase-thymidylate synthase bifunctional enzyme	Apicomplexa and Kinetoplastida	Pyrimethamine
Thiamine transporter	Coccidia	Amprolium
Mitochondrial electron transporter	Apicomplexa	4-OH-quinolines and 2-OH-naphthoquinones
Microtubules	Helminth	Benzimidazoles
Nervous synaptic transmission	Helminth and ectoparasite	Levamisole, piperazine, milbemycins, and avermectins

Antiparasitic Agents

- Anthelmintic Drugs
- Ectoparasiticides
- Antiprotozoals

Anthelmintic Drugs

Classification

- Antinematodal drugs
- Anticestodes
- Atitrematodes

Antinematodals

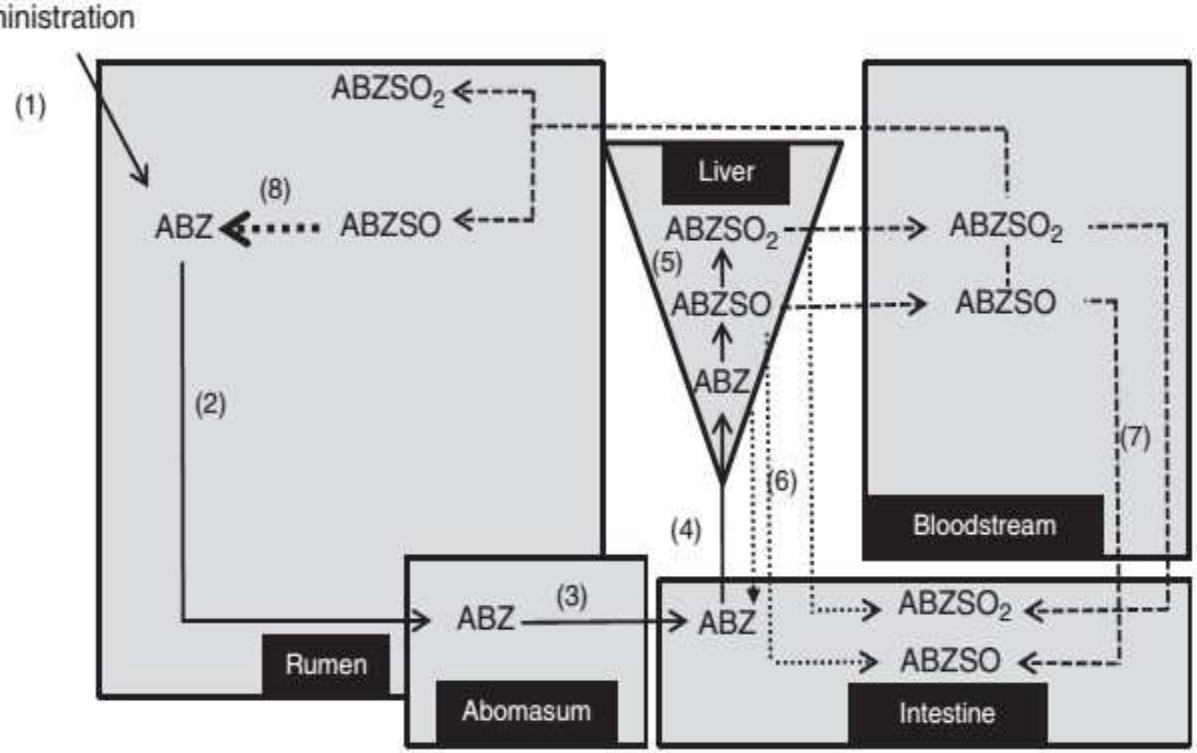
I. Benzimidazoles (BZD):

- Widely used in Vet and human medicine

- MOA:
  - Inhibit tubulin polymerization
  - Progressively deplete energy reserves and inhibit excretion of waste products and protective factors from parasite cells
  - work by interfering with energy metabolism of the worm

- Recognized by *–azole* ending in drug name
- Their AH activity depends on
  - its binding to β-tubulin,
  - their ability to reach high and sustained concentrations at the site

Fig. Schematic representation of the main PK features taking place after oral/intraruminal administration of BZ[



(1) Route of administration: only oral or intraruminal routes can be used for the sulfide compounds (ABZ, FBZ).
(2) Rumen: marked drug dilution. The rumen's reservoir effect is by drug adsorption to particulate digesta.
(3) Abomasum: the acidic pH facilitates drug particles dissolution and strong "ionic trapping" of the drug/metabolite at the abomasum.
(4) Small intestine: main drug absorption site.
(5) Liver: drug oxidative metabolism.
(6) Biliary system: drug excretion (unconjugated and conjugated metabolites), enterohepatic recycling.
(7) Bloodstream: metabolites distribution to different organs/tissues, including active secretion to gastrointestinal tract.
(8) Rumen: sulforeductive biotransformation by ruminal microflora.
ABZ, albendazole parent compound; ABZSO, albendazole sulfoxide; $ABZSO_2$, albendazole sulfone.

Benzimidazoles:

Albendazole

- A benzimidazole carbamate
- Formulated as a suspension or bolus for oral administration in cattle and sheep at the recommended dose of 7.5 & 5 mg/kg, respectively.
- A broad-spectrum oral anthelmintic: hydatidosis and cysticercosis, pinworm infection, ascariasis, trichuriasis, strongyloidiasis, and hookworms, cutaneous larva migrans
- It also used cyst excreted by Giardia infected calves (20 mg/kg once /3 days) and dogs (25 mg/kg 2x a day for 2 days.
- Effect better than Mebendazole.

Benzimidazoles:

Mebendazole

- A synthetic benzimidazole
- has a wide spectrum of anthelmintic activity:
  - Pinworm, *Ascaris*, *Trichuris*, Hookworm, and Trichostrongylus, Other infections: intestinal capillariasis, trichinosis, taeniasis, strongyloidiasis, *et al.*
- Orally to horses (8.8mg/kg), sheep and goats (15 mg/kg), birds, dogs (22 mg/kg for 3 days), chicken
- a low incidence of adverse effects.
  - Only 10% is absorbed systemically
  - Absorption is increased with a fatty meal.
  - liver toxicity side effects

Benzimidazoles:

- **Fenbendazole**:
  - ✓Wide spectrum of activity; given for three consecutive days
  - ✓Oral administration in cattle, sheep, and goats at the recommended dose of 10 mg/kg (cattle) and 5 mg/kg (sheep, goats).
  - ✓indicated for the removal and control of tapeworms (heads and segments), abomasal and intestinal

Benzimidazoles:

- **Thiabendazole**:
  - ✓treatment and control of GI roundworms in horses, cattle, sheep, and goats, and the control of lungworms in sheep
  - ✓Dose: 66-110 mg/kg
  - ✓Usually used with piperazine to increase the efficacy against ascarids and immature *Oxyurus* spp.
  - ✓Ineffective against cestodes and treamtodes
  - ✓has antifungal and anti-inflammatory effects as well

- Others: Refer the textbook for Oxfendazole, flubendazole, netobim, recobendazole, Febantel, etc

Factors Affecting the Disposition Kinetics and Efficacy of BZD Anthelmintics

- ruminant esophageal groove closure
- reduced GI transit time
- the type of diet
- nutritional status and parasite infection

Antinematodals …cont'd

II. Imidazothiazoles

- Work by stimulating (agonist) the nematode's cholinergic nervous system, leading to paralysis of the parasite
- Effective against ascarids, Strongyles (Heamonchus, ostertagia, cooperia, nematodirus, etc), whipworms, and hookworms
- An example is **levamisole, tetramisole**

- **Levamisole**
  - A synthetic imidazothiazole derivative and the L isomer of D,L-tetramisole.
  - Highly effective in eradicating ascaris and trichostrongylus and moderately effective against species of hookworm.
  - Inhibiting succinic dehydrogenase → energy↓ → flaccid paralysis (interfer CHO metabolism)

Antinematodals …cont'd

- **Levamisole …(cont'd)**
- Effective against mature and immature forms of helminths within the intestinal tract but not against migratory stages in the tissues or against ova.
- Effective against both mature & immature larval stages of lung worms
- Dogs: GI nematodes and Diroflaricides
- Inhibition of cholinesterase (a depolarizing neuromuscular blocking agent) → spastic paralysis
- Rate of absorption differs with the route of adminstration.
  - Fast absorption via IM or SC

Antinematodals …cont'd

III. Tetrahydropyrimidines

- Mimic the action of ACh and cause paralysis of the worm
- Effective against ascarids, pinworms, strongyles, and hookworms
- Examples include pyrantel pamoate, pyrantel tartrate, and morantel tartrate

- **Pyrantel**

- A broad-spectrum anthelmintic, safe at dose of 7x
- Moderately effective against hookworms.
- Not effective in trichuriasis or strongyloidiasis.

- **Oxantel**, an analog of pyrantel, is effective against in trichuriasis; the two drugs have been combined for their broad-spectrum anthelmintic activity.

Antinematodals …cont'd

IV. Organophosphates

- Inhibit cholinesterase activity, causing ACh to remain active in the neuromuscular junction of the parasite= spastic paralysis
- Are neurotoxic to parasites; some cause neurologic side effects in the host
- Both endoparasitic and ectoparasitic activity
- Narrow range of safety; not for use in heartworm-positive dogs
- Effective against bots and a variety of nematodes
- Examples include **dichlorvos, coumarphos, haloxon, naphtalophos, trichlorfon**

Antinematodals …cont'd

V. Piperazine

- Belongs to the hetrocyclic group: phenothiazine
- Blockage of transmission at neuromuscular junction, producing flaccid paralysis (by blocking acetylcholine at the myoneural junction).
- It also blocks succinate production by the worm.
  - The parasites, paralyzed and depleted of energy, are expelled by peristalsis
- Effective only against ascarids (Toxocara, Toxascaris)
- No longer recommended for treatment of pinworm infection, because a 7-day course of treatment is required.
- Not useful in hookworm infection, trichuriasis, or strongyloidiasis

Antinematodals …cont'd

VI. Avermectins (macrocyclic lactones)

- Potentiation of Inhibitory NT (GABA).
- Bind to certain chloride channels (by binding to glutamate-gated chloride channel receptors) in the parasite nerve and muscle cells, causing paralysis and death of the parasite
- Prototype: **ivermectin**,
  - used for a wide variety of endo- and ectoparasites
  - May be combined with other antiparasitic agents to broaden its spectrum of activity
- Used for heartworm prevention
- Another example in this group:
  - moxidectin, abamectin, doramectin, milbemycin oxime, eprinomectin, selamectin

Resistance to nematicides

- Resistance appears when drugs are intensively used against parasites
- Nematodes develop cross-resistance to a mode of activity
- Once use of the anthelmintic class stops, reversion back to sensitivity is low
- Drugs should be rotated and the frequency of treatment should also be considered

Table: Summary of the main anthelmintic resistance mechanisms described in helminth parasites for the most important chemical families: macrocyclic lactones (ivermectin, moxidectin, etc.), benzimidazoles (albendazole, fenbendazole, etc.), and imidazothiazoles (levamisole)

	Macrocyclic lactones	Benzimidazoles	Imidazothiazoles
Pharmacodynamic based mechanisms	Mutations in GluCl receptor genes[a] Mutations in GABA receptor genes[b] Decreased GluCl receptor gene expression[c]	Mutations in isotype-1 β-tubulin genes[f]	Mutations in nACh receptor subunits genes[i] Different combinations of receptor subunits[j] Reduced/increased expression of nACh receptor subunit genes[k] Abbreviated isoforms of nACh receptor subunits genes[l]
Pharmacokinetic based mechanisms	P-GP overexpression[d] Reduced drug uptake[e]	P-GP overexpression[g] Detoxification[h] (enhanced oxidation and drug efflux)	P-GP overexpression[m]

GluCl, glutamate-gated chloride ion channel receptor; GABA, γ-aminobutyric acid receptor; nACh, nicotinic acetylcholine receptor; P-GP, P-glycoprotein.

[a]Mutations in *GluClα3* subunit gene in resistant *Cooperia oncophora* (Njue et al., 2004).

[b]Mutations in GABA receptor genes on a *Haemonchus contortus* isolate (Feng et al., 2002).

[c]Reduced expression levels of the GluCl receptor genes in *H. contortus* (Williamson et al., 2011), *C. oncophora*, and *Ostertagia ostertagi* (El-Abdellati et al., 2011). However, receptor gene changes appear not to be primarily involved in most cases of field resistance to macrocyclic lactones (Kotze et al., 2014).

[d]Increased drug efflux mediated by overexpression of P-GP (Williamson et al., 2011; Dicker et al., 2011; Janssen et al., 2013; De Graef et al., 2013).

[e]Changes to the anatomy and/or function of amphid sensory endings associated to reduced drug intake (Dent et al., 2000).

[f]Single nucleotide polymorphisms (SNPs) at position 200 (Kwa et al., 1994), 167 (Silvestre and Cabaret, 2002), and 198 (Ghisi et al., 2007) in the isotype-1 β-tubulin gene; SNPs at position 200 appears to be the most important regarding the BZD-resistance phenotype.

[g]Increased drug efflux mediated by overexpression of P-GP in *H. contortus* (Blackhall et al., 2008) and *Fasciola hepatica* (Alvarez et al., 2005).

[h]Increased triclabendazole detoxification in triclabendazole-resistant *F. hepatica* (Robinson et al., 2004; Alvarez et al., 2005).

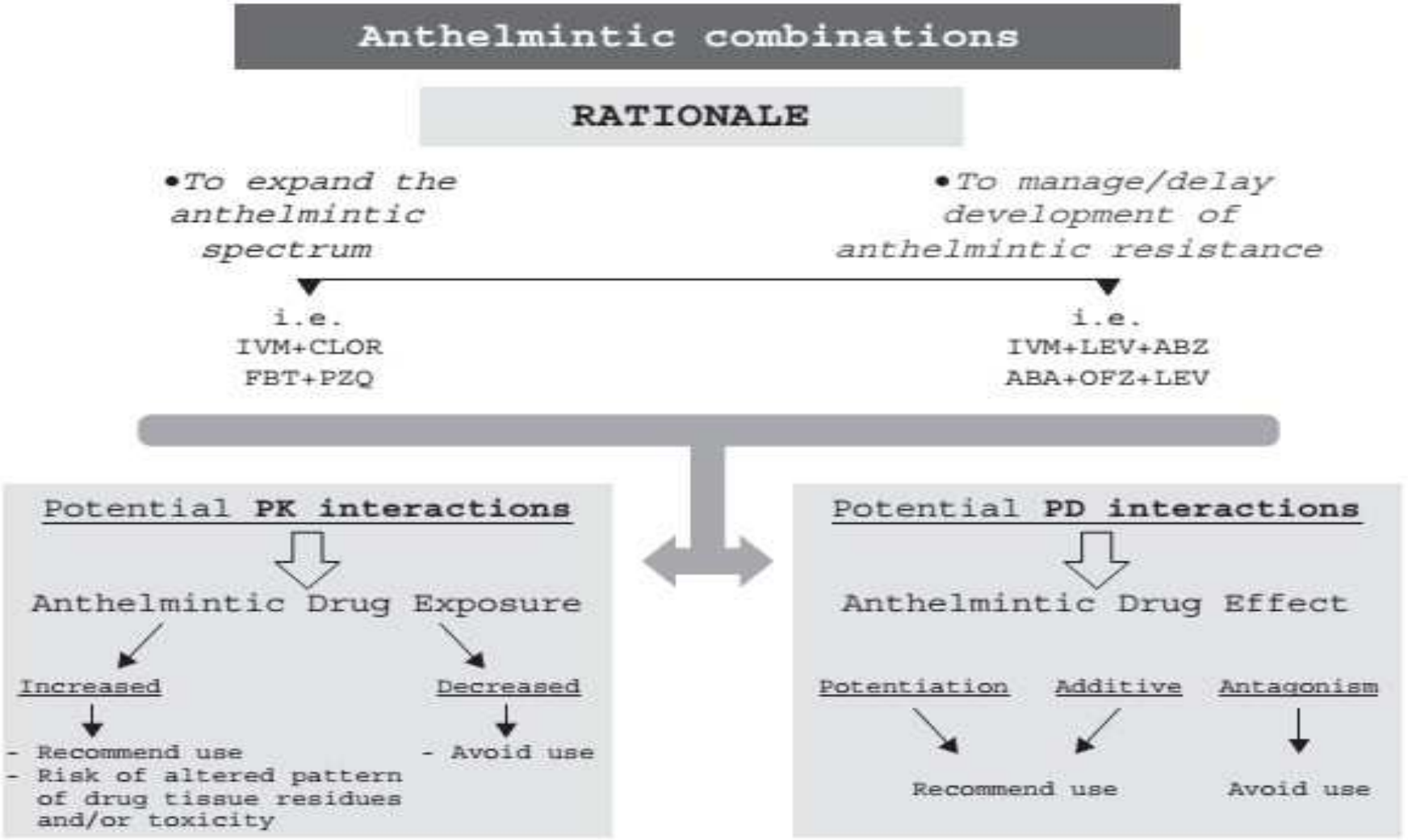
[i]Mutations in nACh receptor subunit gene observed in *Caenorhabditis elegans* (Fleming et al., 1997).

[j]Different combinations of receptor subunits give raise to receptors with different pharmacological properties (Kotze et al., 2014).

[k]Reduced/increased expression of several nACh receptor subunits genes (Kopp et al., 2009; Sarai et al., 2013; Sarai et al., 2014; Romine et al., 2014).

[l]Abbreviated isoform of a nACh receptor subunits (unc-63) in *H. contortus*, *Teladorsagia circumcincta*, and *Trichostrongylus colubriformis* (Neveu et al., 2010).

[m]Increased expression of several P-GP genes in levamisole-resistant *H. contortus* larvae (Sarai et al., 2014).



Combined use of anthelmintic drugs. Rationale and potential PK and PD drug to drug interactions. IVM, ivermectin, CLOR, clorsulon, FBT, febantel, PZQ, praziquantel,LEV, levamisole, ABZ, albendazole, ABA,abamectin, OFZ, oxfendazole.

Anticestodal agents

Praziquantel

- Works by increasing the cestode's cell membrane permeability (this disintegrates the worm's outer tissue covering)
- Works on adult stages of all cestode species (also used to eliminate fleas)
- Both human and veterinary use

Epsiprantel

- Causes disintegration of the cestode
- Effective against *Taenia* and *Dipylidium*, and also *Echinococcus*

Fenbendazole

- Covered previously

Anticestodals … cont'd

Niclosamide

- A salicylamide derivative
- nterference with glucose absorption, uncouplers of oxidative phosphorylation and stimulation of adenosine triphosphatase activity at mitochondrial level.
- Treatment of most tapeworm infection:
  - ruminants *Moniezia* spp. and *Thysanosoma* spp.
  - horses it may be used for the treatment of *Anoplocephala* spp.
- poor efficy against *Dipylidium* spp. and *E. granulosus*

Anticestodals … cont'd

- Clinical Uses
  - Given in the morning on an empty stomach.
  - The tablets *must be chewed thoroughly* and are then swallowed with water.
  - ➢Niclosamide can be used as an alternative drug for the treatment of *intestinal fluke* infections.

- Adverse Effects
  - Infrequent, mild and transitory.
  - Nausea, vomiting, diarrhea, and abdominal discomfort.

Anticestodals … cont'd

Bunamidine

- is a taeniacidal drug that disrupts the tapeworm's tegument and reduces glucose uptake. Consequently, subtegumental tissues are exposed and destroyed by the host digestive enzymes.

  Taenia spp., *Dipylidium* spp., *Mesocestoides* spp., and *Diphyllobothrium* spp. (oral treatment at 25–50 mg/kg). However, efficacy against *D. caninum* may be erratic.

- Effectiveness ranging from 85.9 to 98.8% (immature stages) and 100% (mature stages) of *E. granulosus* have been reported

Antitrematodals

- **Benzimidazoles**
  - **Albendazole, Netobimin**
    - ✓ Effective for all adult stages
  - **Triclabendizole**
    - ✓ Effective for all stages of immature and adult fluke

- **Salicylaniides (closantel, oxyclozanide, rafoxanide)**
  - ✓ **All stages, some nematodes & nasal bot fly**
  - ✓ **Proton ionophores**
  - ✓ **Uncouples oxidative phosphorylation**

Antitrematodal agents

Benzenesulfonamides (Clorsulon)

- Works by inhibiting the trematode's enzyme systems for energy production (the glycolytic pathway)

- Effective against adult *Fasciola hepatica*

Nitroxynil

- ✓ **Adult flukes**
- ✓ **Uncouples oxidative phosphorylation**

Phenoxyalkanes (Diamphenethide)

- ✓ Exceptionally effective against early immature flukes from 1 day to 6 weeks of age.

Praziquantel

Antifilariasis

- **Heartworm Disease**

- is caused by the filarial nematode *Dirofilaria immitis*

- Three stages of management of heartworm disease
  - ✓Preventing third-stage larvae from reaching maturity (preventative)
  - ✓Adulticide therapy
  - ✓Eradication of circulating microfilariae after infection

Antifilariasis ...cont'd

- Heartworm Disease
- **Preventing third-stage larvae from reaching maturity (preventative)**
  - Daily oral preventative
    - Diethylcarbamazine (DEC)
      - Given during mosquito season and two months after
      - Patient must be heartworm negative
  - Once-monthly oral preventatives
    - Ivermectin
    - Milbemycin
  - Once-monthly topical preventative
    - Selamectin

Antifilariasis ...cont'd

- **Adulticide therapy**
  - Melarsomine
    - A trivalent arsenical cpd, Given in the epaxial muscles
    - Less toxic than former drug (thiacetarsamide)
    - Side effects include nephrotoxicity and hepatotoxicity
    - Active against immature (>4-month-old) and adult heartworms in dogs

- **Eradication of circulating microfilariae after infection**
  - Ivermectin (given at higher dose as a microfilaricide)
  - Milbemycin
  - Levamisole (infrequently used)

Anti-filariasis ...cont'd

- Human lymphatic filariasis
- Epidemic in ------:
  - *Wuchereria bancrofti , Brugia malayi and B.timori*
- Parasitize in lymphatic system.

Rx: **Diethylcarbamazine**

- A synthetic piperazine derivative.
- Rapidly absorbed from the GIT;
- Immobilizes microfilariae (which results in their displacement in tissues) and alters their surface structure, making them more susceptible to destruction by host defense mechanisms.
- Adult parasites are killed more slowly.
- Against adult worms is unknown.

Antiparasitic Agents
Ectoparasiticides

Ectoparasiticides

- Ectoparasites can be controlled using a variety of different drugs in a variety of different formulations:
  - Sprays
  - Dips
  - Pour-ons
  - Shampoos
  - Dusts or powders
  - Oral products
  - Spot-ons
  - Injectables

Ectoparasiticides

- Most these drugs are neurotoxins, exerting their effect on the nervous system of the target parasite.
- Can be grouped according to structure and MOA into:
  - **organochlorines, organophosphates and carbamates,**
  - **pyrethrins and pyrethroids,**
  - **avermectins and milbemycins,**
  - **Formamidines, insect growth regulators**

- Ectoparasite nervous system
  - ✓ acetylcholinesterase (AChE) inhibitors
  - ✓ Na+ channel blockers

Organochlorines

- withdrawn in many parts of the world due to concerns regarding environmental persistence.
- However, some compounds, including lindane (γ benzene hexachloride) and methoxychlor, are still used.
- 3 main groups:
  - ❑ Chlorinated ethane derivatives:
    - ✓ DDT (dichlorodiphenyltrichloroethane), DDE (dichlorodiphenyldichloroethane), and DDD (dicofol, methoxychlor);
  - ❑ Cyclodienes:
    - ✓ chlordane, aldrin, dieldrin, hepatochlor, endrin, and tozaphene; and
  - ❑ Hexachlorocyclohexanes:

Organochlorines

- Chlorinated ethanes
  - cause inhibition of sodium conductance along sensory and motor nerve fibers by holding sodium channels open, resulting in delayed repolarization of the axonal membrane
- cyclodienes
  - inhibition of GABA-stimulated Cl- flux in to the neuron and
  - interference with Ca2+ flux.
    - partial depolarization of the postsynaptic membrane and vulnerability to repeated discharge.
- Lindane:
  - ✓binds to the picrotoxin side of GABA receptors, resulting in an inhibition of GABA-dependent Cl- flux into the neuron

Organophosphates (OP)

- Inhibit the action of AChE at cholinergic synapses and at muscle endplates.
  - ✓accumulating ACh at the postsynaptic membrane, leading to neuromuscular paralysis
- Extremely toxic in animals and humans, causing an inhibition of AChE and other cholinesterases
- Topically used include:
  - Coumaphos, diazinon, dichlorvos, famphur, fenthion, malathion, trichlorfon, stirofos, phosmet, and propetamphos.
  - generally active against fly larvae, flies, lice, ticks, and mites on domestic livestock
  - Diazinon and propetamphos dip formulations for the control of psoroptic mange in sheep

Organophosphates

- **OP poisoning**
- Antidote:
  1. Atropine sulfate 0.1-1mg/kg Im
  2. Pralidoxime – break the bond between organophosphate and acetylcholine-estrase.
     - ✓Dose of 2-PAM: 20mg/kg, BID

Carbamates

- Closely related to OP
- Inhibit AChE activity but reversible

- Two main carbamate cpds used are:
  - carbaryl and propoxur.

    ➢ Carbaryl has low mammalian toxicity
- Efficacy: lice, ticks, keds and fleas

- Toxicosis:
  - antidote: atropine sulfate 0.1-1mg/kg.

Pyrethrins and Synthetic Pyrethroids

- MOA:
  - Interference with sodium channels of the parasite nerve axons, resulting in delayed repolarization, incoordination and convulsion and eventual paralysis
- Preparation:
  - ✓ Available as pour-on, spot-on, spray, and dip formulations
- Activity:
  - Activie against biting and nuisance flies, lice, and ticks on a domestic livestock.
  - Flumethrin and high cis-cypermethrin are also active against mange mites

Pyrethrins and Synthetic Pyrethroids

- Are lipophilic molecules
- Cross resistance with DDT present
- Provide excellent knockdown (rapid kill) but have poor residual activity due to instability
- Generally safe in mammals and birds but are highly toxic to fish and aquatic invertebrate
- common pyrethroids used include
  - bioallethrin, cypermethrin, deltamethrin, fenvalerate, flumethrin, lambdacyhalothrin, phenothrin, and permethrin

Macrocyclic Lactones
(Avermectins and Milbemycins)

- Activity
  - active against a wide range of nematodes and arthropods and, are often referred to as endectocides
- Preparation
  - Given PO, parenterally, or topically (as pour-ons)
- are highly lipophilic
- reduced absorption and bioavailability of ivermectin given PO in cattle
  - due to its metabolism in the rumen.
- Its affinity for fat explains their persistence in the body and the extended periods of protection afforded against internal and external parasites.

Macrocyclic Lactones

- MOA:

- Act on GABA neurotransmission in nematodes,
  - ✓ blocking interneuronal stimulation of EMN, leading to flaccid paralysis.
  - ✓by stimulating the release of GABA from nerve endings and by enhancing the binding of GABA to its receptor on the postsynaptic membrane (PSM) of an excitatory motor neuron(EMN) =results in an increased flow of Cl- ions into the cell, leading to hyperpolarization.
  - ✓ In mammals, GABA neurotransmission is confined to the CNS; the lack of effect of ivermectin on mammalian NS at therapeutic concentrations is probably because it does not readily cross BBB.

- Recent evidence: its effect through action on glutamate-gated Cl- ion conductance at the PSM or NMJ

Formamidines

- **Amitraz**
  - is the only formamidine used as an ectoparasiticide.

- MOA
  - act by inhibition of the enzyme monoamine oxidase (MAO) that metabolizes amine neurotransmitters in ticks and mites and
  - as an agonist at octopamine receptors
    - octopamine is thought to modify tonic contractions in parasite muscles.

❖results in accumulation of nor-epinephrine and serotonin and when the insect in contact with this drug they become quiescent (unable to move) finally die

Amitraz

- Amitraz has a relatively **wide safety margin** in mammals

- SE:
  - sedation- associated with an agonist activity of on α2 -receptors in mammalian species.

- available as a spray or dip for use against mites, lice, and ticks in domestic livestock.

- It is contraindicated in horses.

Insect Growth Regulators

- Do not kill the target parasite directly but interfere with growth and development.
- act mainly on immature parasite stages
  - not usually suitable for the rapid control of established adult parasite populations.
- Based on their mode of action, it can be divided into:
  - chitin synthesis inhibitors (benzoylphenyl ureas),
  - chitin inhibitors (triazine/pyrimidine derivatives), and
  - juvenile hormone analogs

US FDA approved Ectoparasiticides

Drug class	Approved species	Ectoparasite approved indications
Avermectins/milbemycins		
Ivermectin	Cats	Ear mites
	Beef cattle	Lice, mites, ticks, grubs
	Pigs	Lice, mites
Doramectin	Beef cattle	Lice, mites, ticks, grubs
	Pigs	Lice, mites
Pour-on eprinomectin	Dairy and beef cattle	Lice, mites, flies, grubs
Injectable eprinomectin	Beef only	Lice, mites, flies, grubs
Selamectin	Dogs	Fleas, mites, ticks
	Cats	Fleas, mites
Moxidectin	Dairy and beef cattle	Lice, mites, flies, grubs
Milbemycin	Cats	Ear mites
Organophosphates		
Fenthion	Beef cattle	Grubs, lice, flies
Famphur	Beef cattle	Grubs, lice, flies, ticks
Amitraz	Dogs	Mites
	Dairy and beef cattle	Lice, mites, ticks
	Swine	Louse, mites
Nitenpyram	Dogs and cats	Fleas
Lufenuron	Dogs and cats	Fleas

[a] Approved as of March 2015.

Resistance to Ectoparasiticides

- Resistance has been widely reported for many popular ectoparasiticides such the avermectins, pyrethroids, and OPs.
- Resistance also tends to occur where there is intensive use of antiparasitic drugs
- There is some concern that as the newer insecticides such as the neonicotinoids become more frequently and inappropriately used, resistance can potentially emerge. However, there is little or no evidence of fleas developing resistance to the increasing and popular
  use of imidacloprid.
- Mechanisms of resistance may be related to
  - ✓ decreased penetration,
  - ✓ increased detoxification enzyme activity, and
  - ✓ Decreased sensitivity of the target site.
  - ✓ Pyrethroid resistance amongst insects has been associated with

Antiparasitic Agents
Antiprotozoal Drugs

Objectives

- Know the name of drugs commonly used to treat protozoal diseases
- Understand the MOA of antiprotozoal drugs
- Identify the effectiveness of the drugs (prophylactic/curative use)

Antiprotozoals

- Anticoccidials
- Antibabesiosis
- Antitrypanosomosis
- Antitrichomoniasis
- Others (Reading assignment)
  - Antigiardiasis
  - Antiameobiasis

I. Anticoccidials

- *Coccidiosis*
  - is a protozoal infection that causes intestinal disorders
- Anticoccidial drugs are
  - coccidiostats (do not actually kill the parasite, so hygiene is crucial)
  - Sulfadimethoxine
    - Reduces the number of oocysts shed, thus reducing spread of disease
    - Thymidylate synthase inhibitor
  - Trimethoprim
    - DHFR inhibitor
- Others (work mainly by affecting the protozoan's metabolism)

Amprolium

- A structural analogue of thiamine (vitamin B1)
- Competitively inhibits thiamine utilization by the parasite.
  - Prolonged high dosages can cause thiamine deficiency in the host and excessive thiamine in the diet can reduce or reverse the anticoccidial activity of the drug
- Good activity against and used as a therapeutic agent
  - *E. tenella, E. acervulina* in poultry
- It has weak activity against E. maxima, E. mivati, *E. necatrix*, or *E. brunetti*.
- In cattle, amprolium has approval for the treatment and prevention of *E. bovis* and *E. zurnii* in cattle and calves
- Treatment of coccidiosis in dogs and cats

Anticoccidials…cont'd

Monensin:

- An ionophore, causing osmotic imbalance by interfering transport of ions
- Effective for all spps.
- Growth promotion effect in cattle
- Dose: 100-120ppm for chicken.

  16-33ppm for cattle (calf).

  11-33ppm for sheep
- Characteristics:
  - Lipid soluble, biodegradable (within the host / environment),
  - Act as contact, stomach, systemic poison mainly for equine

Anticoccidials…cont'd

Benzeacetonitrils

- Diclazuril-
- Coccidostatic agent
- used for chicken to treat E.maxima, E.burnetti, E.acervulina, given with feed1ppm
- highly potent drug (for toxoplasmosis, Neospora caninum and sarcocyst)

Benzyl purines

- Arprinocids
- used for poultry
- MOA: Inhibit DNA synthesis.
- Effective for all spps of emeria.
- Dose: 60ppm in feed

Carbanilides

Anticoccidials…cont'd

Guanidines- Robenidine

- Active against first generation schizont of E. tenella
- MOA:
  - ✓Inhibit DNA replication,
  - ✓Affect energy metabolism. i.e. oxidative phosphorylation.
  - ✓Used in prevention in chickens
- Dose: 33ppm.For theileriosis – In cattle
  - Parvaquone – Im, 20mg/kg stat dose
  - Buparuquone – Im, 2.5mg/kg
    - ✓1-2 times curative treatment in cattle

Ionophores

- MOA:
  - ✓Cause osmotic imbalance by interfering transport of ions

Drugs licensed for the treatment of coccidiosis in food animals

Species	Drug	Trade name	Regulatory information
Chickens	Roxarsone	Ren-O-Sal®, Roxarsone 10% Type A Medicated Article, combination products available	Not for use in laying hens; 5-day slaughter withdrawal for noncombination products, no longer marketed
	Decoquinate	Deccox® Type A Medicated Article, combination products available	Not for use in laying hens; no withdrawal necessary for noncombination products
	Clopidol	Cloyden 25®, combination products available	Not for use in laying hens; 5-day slaughter withdrawal for noncombination products
	Robenidine	Robenz®, combination products available	Not for use in laying hens; 5-day slaughter withdrawal for noncombination products
	Amprolium	Amprol 25%, CORID 25% Type A Medicated Article, combination products available	No withdrawal necessary for noncombination products
	Dinitolmide	Zoamix®	Not for use in laying hens; no withdrawal necessary
	Nicarbazin	Nicarbazin, combination products available	Not for use in laying hens; 4-day slaughter withdrawal for noncombination products
	Halofuginone	Stenerol®, combination products available	Not for use in laying hens; 4-day slaughter withdrawal for noncombination products
	Lasalocid	Avatec®, combination products available	Not for use in laying hens; no withdrawal necessary for noncombination products
	Maduramicin	Cygro®	Not for use in laying hens; 5-day slaughter withdrawal for noncombination products
	Monensin	Coban®, combination products available	Not for use in laying hens; no withdrawal necessary
	Narasin	Monteban®, combination products available	Not for use in laying hens; no withdrawal necessary
	Semduramicin	Aviax®, combination products available	Not for use in laying hens; no withdrawal necessary for noncombination products
	Salinomycin	Bio–Cox®, Sacox®	Not for use in laying hens; no withdrawal necessary
	Diclazuril	Clinacox®, combination products available	Not for use in laying hens; no withdrawal necessary for noncombination products
	Ormetoprim/ sulfadimethoxine	Rofenaid®, combination products available	Not for use in laying hens; 5-day slaughter withdrawal for noncombination products
	Sulfamethazine	Sulmet® Drinking Water Solution	Not for use in laying hens; 10-day slaughter withdrawal for noncombination products

Drugs licensed for the treatment of coccidiosis in food animals

Species	Drug	Trade name	Regulatory information
Cattle	Decoquinate	Deccox® Type A Medicated Article, combination products available	Not for use in lactating dairy cattle; approved for preruminating calves; no withdrawal necessary for noncombination products
	Amprolium	Amprol 25%, CORID 25% Type A Medicated Article, combination products available	Not for use in preruminating calves; 1-day slaughter withdrawal
	Sulfamethazine	Sulmet® Oblets, Sulfamethazine sustained release bolus	Not for use in lactating dairy cattle; 8 to 10-day slaughter withdrawal for individual products
	Sulfaquinoxaline	Sulfa-nox Liquid	Not for use in lactating dairy cattle; 10-day slaughter withdrawal for noncombination products
Sheep	Decoquinate	Deccox® Type A Medicated Article, combination products available	Not for use in lactating sheep; no withdrawal necessary for noncombination products
	Lasalocid	Bovatec®, numerous others and combination products available	Not for use in breeding animals; no withdrawal necessary for noncombination products
Goats	Decoquinate	Deccox® Type A Medicated Article, combination products available	Not for use in lactating goats; no withdrawal necessary for noncombination products
	Monensin	Rumensin®	Not for use in lactating goats; no withdrawal necessary
Swine	Toltrazuril	Baycox®	Extralabel drug use, contact regulatory agencies for withdrawal times
Rabbits	Diclazuril	Clinicox®	Extralabel drug use, contact regulatory agencies for withdrawal times
	Lasalocid	Avatec/Bovatec®, numerous others and combination products available	No withdrawal necessary for noncombination products

II. Anti-Babesiosis

- Blood protozoan *Babesia sp.* is transmitted by ticks
  - Tick prevention

- Urea complex drugs are commonly used
  - Amicarbalid isothionate
  - Imidocarp dipropionate
  - Quinoronium sulfate
  - Diminazene diaceturate
  - Pentamidine

Antibabesial drugs

Amicarbalid isothionate

- MOA: Inhibition of DNA replication –
  - Not completely remove the parasite but help to develop preimmunity. So the animals carry the parasite through out the life.
- Effective against bovine babesiosis
  - Route: Sc, Im, Iv, Dose: 5-10mg/kg

Imidocarb dipropionate = Imizol

- Diamidine of the carbanalide series of antiprotozoal
- MOA:
  - inhibit cellular repair and replication of babesia
- Dose: 1-2mg/kg horse, 2-4mg/kg dogs
- more effective against bovine babesiosis (but *B. canis* than B. gibsoni), B caballi (equine),

Antibabesial drugs

Quinorunium sulfate

- ® acaprin, acapron, babesan

- ✓ Curative drug.
- ✓ Dose:
  - 0.3-0.5mg/kg horses,
  - 0.5mg/kg cattle, sheep and pig,
  - 0.25mg/kg dogs.
- ✓ Route: SC.

III. Anti-trypanosomial drugs

- **Isomethamedium = ®**samorin
- MOA:
  - inhibit cell division and growth of parasite.
- Active against *T. vivax* and *T. congolense, T.evansi*
- Have prophylactic effect for 6 month.
- Dose: 0.5mg/kg, 1-2mg/kg in resistant areas.

Anti-trypanosomial drugs

- **Quinapyramines** ®=Antrycide
  - Quinapramine chloride – as prophylaxis –
  - Quinapramine sulfate – curative drug
- Effective –
  - T.congolense, T.vivax, T.equiperdium, T.evansi
  - For all, but mainly used in equine and camel
- Dose: prophylaxis: 0.025mg/kg of 10%.
  - Therapeutic: 3-5mg/kg s/c

Anti-trypanosomial drugs

Suramin:

- curative drug
- MOA:
  - Inhibit cell division
- Active for
  - *T.evansi, T.bruci, T.equiperdum*
  - but not for *T.vivax* and *T. congolense*
- Dose: 7-12mg/kg of 10%,
- best drug for dourine,
- used in horse and camel

Individual assignment

- Briefly discuss about drugs commonly used to control (prevention & treatment) bovine trypanosomiasis in Ethiopia
  - Detail mechanisms of action
  - Level of Resistance development
  - Mechanism of how resistance developed by trypanosomes

Date of submission: 14th week of the semester

Via email: takele.beyene@aau.edu.et

IV. Anti-trichomoniasis Drugs

- Trichomoniasis
  - Vaginal infection caused by *Trichomonas*
- Contracted sexually
- Treat both sexes
- Rx:
    - Metronidazole
    - Acetarsol

Others

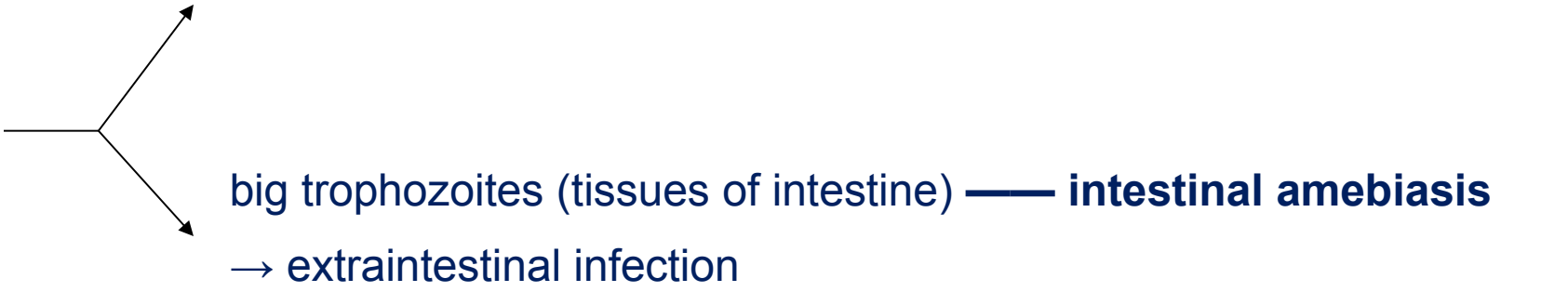
Antigiardiosis

- *Giardiosis* is a protozoal disease caused by the parasite *Giardia*
  - Antiprotozoal drugs
    - Metronidazole
      - (enters the protozoal cell and interferes with its ability to function and replicate)
    - Fenbendazole (covered previously)
    - Albendazole (covered previously)
  - Vaccines for human
    - On development

Anti-amebiasis

- Amebiasis
- is infection with *Entamoeba spp.*
- is transmitted through GIT
- Ameba has two stages of development:
  - cyst and trophozoite.

Cysts → small intestine → little trophozoites (ileocecum)



Anti-amebiasis

- **Metronidazole, Tindazole**

- A nitroimidazole antibacterial and antiprotozoal agent.
- The nitro group of metronidazole is chemically reduced in anaerobic bacteria and sensitive protozoans.
- Reactive reduction products appear to be responsible for antimicrobial activity.

Pharmacological Effects and Clinical Uses

1. Anti-amebiasis:
   - ✓ kills trophozoites but not cysts.
   - ✓ Treatment of all tissue infections.
   - ✓ No effect against luminal parasites
2. Anti-trichomoniasis:
3. Anti-giardiasis

Anti-amebiasis

- **Emetine**, an alkaloid derived from ipecac, and
- **dehydroemetine**, a synthetic analog,
  - are effective against tissue trophozoites
  - kills *E histolytic* trophozoites of histolytic tissues but no effection against luminal trophozoites.
  - used to treat amebic dysentery for the minimum period because of toxicity.
  - Occasionally as alternative therapies for amebic liver abscess

- MOA
  - Inhibiting peptidyl-tRNA transposition → inhibiting elongation of peptide chain → inhibiting protein synthesis → interfering cleavage and breeding of trophozoites
    - low selection → also inhibiting protein synthesis of eukaryocyte.
    - Toxicity increase with length of therapy

Anti-amebiasis

Diloxanide

- is a dichloroacetamide derivative.
- Effective against luminal amebicide but is not active against tissue trophozoites.
- The unabsorbed diloxanide in the gut is the active antiamebic substance.
- It is used with a tissue amebicide: metronidazole.

Anti-ameobiasis

- **Paromomycin**
  - Aminoglycoside antibiotic.
  - Not significantly absorbed from the GIT.
  - Only as a luminal amebicide effect
  - inhibiting protein synthesis → kill trophozoites;
  - inhibiting symbiosis flora → indirectly inhibiting ameba protozoa.
- **Chloroquine**
  - ✓ reaches high liver concentrations → treatment of amebic liver abscess.
  - ✓ Not effective for intestinal or other extrahepatic amebiasis.

Summary of drugs used to treat selected protozoal diseases in animals

Protozoal disease	Protozoa	Species	Drug class	Drug and dosing regimen
Giardiasis	*Giardia duodenalis, G. intestinalis, G. lambia*	Dogs	Nitroimidazoles	Metronidazole: 12–15 mg/kg PO q12h for 8 days Tinidazole: 15 mg/kg PO q12h
			Benzimidazoles	Albendazole: 25 mg/kg q12h for 2 days Fenbendazole: 50 mg/kg q24h for 3 days Febantel, pyrantel, and praziquantal: febantel (26.8–35.2 mg/kg), pyrantel (26.8–35.2 mg/kg), praziquantel (5.4–7 mg/kg) PO q24h for 1–3 days
		Cats	Nitroimidazoles	Metronidazole: 22–25 mg/kg PO q12h for 5–7 days Tinidazole: 15 mg/kg PO q24h Secnidazole: 30 mg/kg PO q24h
			Benzimidazoles	Fenbendazole: 50 mg/kg q24h for 5 days Febantel, pyrantel, and praziquantal: febantel (56.5 mg/kg), pyrantel (11.3 mg/kg), and praziquantel (37.8 mg/kg) PO q24h for 5 days
		Horses	Nitroimidazoles	Metronidazole: 5 mg/kg PO q8h for 10 days
		Cattle	Benzimidazoles	Albendazole: 20 mg/kg PO q24h for 3 days Fenbendazole: 5–20 mg/kg PO q24h for 3 days
			Aminoglycosides	Paromomycin: 75 mg/kg PO q24h for 5 days
Trichomoniasis	*Tritrichomonas foetus, Pentatrichomonas hominis, Trichomonas gallinae*	Cats	Nitroimidazoles	Tinidazole: 30 mg/kg PO q24h for 14 days Ronidazole: 30 mg/kg PO q24h for 14 days
		Cattle	Nitroimidazoles	Metronidazole: 75 mg/kg IV q12h for 3 doses[a]
		Pigeons	Nitroimidazoles	Metronidazole: 40–60 mg/kg orally once a day for 5 days Ronidazole: 5 mg/kg orally once a day for 14 days Carnidazole: 20 mg/kg orally once
Trypanosomiasis	*Trypanosomas cruzi*	Dogs	Nitroimidazoles Nitrofurans	Benznidazole: 5–7 mg/kg PO q24h for 2 months Nifurtimox: 2–7 mg/kg PO q6h for 3–5 months
		Cattle	Diamidene derivatives	Diminazene diaceturate: 3.5–7 mg/kg IM
Babesiosis	*Babesia divergens,*	Dogs	Tetracyclines	Doxycycline: 10 mg/kg PO q12h for 11 days (*B. canis*) Doxycycline (7–10 mg/kg, q12h) in combination with enrofloxacin (2–2.5 mg/kg, q12h) and metronidazole (5–15 mg/kg, q12h) for a duration of 6 weeks (*B. gibsoni*)

Protozoal disease	Protozoa	Species	Drug class	Drug and dosing regimen
	B. equi, B. caballi, B. bigemini, B. canis		Hydroxyquinolones and naphthoquinones	Atovaquone: 13.3 mg/kg PO q8h combine with azithromycin 10 mg/kg PO q24h for 10 consecutive days (*B. gibsoni*)
			Diamidene derivatives	Diminazene diaceturate: 3.5–5 mg/kg BW IM (*B. canis*); 3.5 mg/kg q12h for 2 treatments (*B. gibsoni*) Pentamidine isethionate: 16.5 mg/kg IM on 2 consecutive days Phenamidine isethionate: 15–20 mg/kg SC q24h for 2 days (*B. gibsoni*); 8–13 mg/kg SC once (*B. canis*) Imidocarb dipropionate: 7.5 mg/kg SC (*B. canis*); 3.5 mg/kg diminazene followed by 6 mg/kg imidocarb on the following day (*B. canis*)
		Horses	Tetracyclines	Chlortetracycline: 0.5–2.6 mg/kg IV q24h for 6 days (*B. equi*)
			Diamidene derivatives	Diminazene diaceturate: 3–5 mg/kg IM q12h for 2 treatments (*B. caballi*); 6–12 mg/kg IM (*B. equi*); 0.5 mg/kg IM (*B. bigemina*) Phenamidine isethionate: 8.8 mg/kg IM q12h for 2 treatments Amicarbalide: 8.8 mg/kg IM q12h for 2 treatments (*B. caballi*) Imidocarb dipropionate: 1–2 mg/kg IM q12h for 2 treatments (*B. caballi*); 4 mg/kg IM q72h for 4 treatments (*B. equi*)
		Cattle	Tetracyclines	Oxytetracycline: 20 mg/kg IM every 4 days for 3 weeks (*B. divergens*)
			Diamidene derivatives	Diminazene diaceturate: 3–5 mg/kg IM (*B. bigemina* and *B. bovis*) Pentamidine isethionate: 0.5–2 mg/kg SC Phenamidine isethionate: 8–13 mg/kg IM q12h for 2 treatments Amicarbalide: 5–10 mg/kg IM Imidocarb dipropionate: 1–3 mg/kg IM or SC

(*continued*)

Protozoal disease	Protozoa	Species	Drug class	Drug and dosing regimen
Cryptosporidiosis	*Cryptosporidium parvum*	Cats	Aminoglycosides	Paromomycin: 165 mg/kg PO q12h for 5 days[b]
			Nitrothiazole derivatives	Nitazoxanide: 75 mg/kg PO once
		Cattle	Aminoglycosides	Paromomycin: 12.5–50 mg/kg PO q24h for 12 days
			Azalides	Azithromycin: 1500–2000 mg/calf/day PO for 7 days
			Nitrothiazole derivatives	Nitazoxanide: 1.5 g suspended in water and given orally q12h
			Alkaloids	Halofuginone: 100 µg/kg BW PO q24h for 7 days
		Goats	Aminoglycosides	Paromomycin: 50 mg/kg PO q12h for 10 days
Leishmaniasis	*Leishmania donovani, L. infantum, L. chagasi*	Dogs	Pentavalent antimonials	Sodium stibogluconate: 30–50 mg/kg pentavalent antimony IV or SC q24h for 3–4 weeks
				Meglumine antimonate: 100 mg/kg IV or SC q24h for 3–6 weeks or 75 mg/kg SC q12h in combination with allopurinol at 15 mg/kg PO q12h
				Liposomal meglumine antimonate: 9.8 mg/kg IM or SC q24h
Hepatozoonosis	*Hepatozoon americanum*	Dogs	Aminoglycosides	Paromomycin: 20–40 mg/kg IM q24h for 15–30 days
			Hydroxyquinolones and naphthoquinones	Decoquinate: feed additive (27.2 grams/pound or 59.8 grams/kg of premix) added to moist dog food at 0.5–1.0 tablespoons per 10 kg BW twice a day
			Triazene derivatives	Toltrazuril: 5–10 mg/kg PO q12h for 5–10 days
			DHFR/TS[c] inhibitors	Trimethoprim–sulfadiazine: 15 mg/kg PO q12h combined with clindamycin 10 mg/kg PO q8h and pyrimethamine 0.25 mg/kg PO q12h for 14 days[d]
			Diamidene derivatives	Imidocarb dipropionate: 5–6 mg/kg BW SQ or IM every 2 weeks until gamonts are no longer present in blood smears
Cytauxzoonosis	Cytauxzoon felis	Cats	Diamidene derivatives	Imidocarb dipropionate: 3.5 mg/kg BW IM once then repeat 7 days later
			Hydroxyquinolones and naphthoquinones	Atovaquone: 15 mg/kg PO q8h combine with azithromycin 10 mg/kg PO q24h for 10 consecutive days
Theileriosis	*Theileria parva*	Cattle	Hydroxyquinolones and naphthoquinones	Parvaquone: 20 mg/kg IM once
				Buparvaquone: 2.5 mg/kg IM 1–2 times
			Alkaloids	Halofuginone: 1–2 mg/kg PO once

Protozoal disease	Protozoa	Species	Drug class	Drug and dosing regimen
Equine Protozoal Myelitis	*Sarcocystis neurona*	Horses	Triazene derivatives	Diclazuril: 0.5–1 mg/kg PO q24h for 28 days, or 0.5 mg/kg PO, once every 3–4 days. Toltrazuril: 5 mg/kg PO q24h for 28 days Ponazuril: 15 mg/kg PO loading dose; 5 mg/kg PO q24h for 28 days
			DHFR/TS inhibitors	Pyrimethamine: 1 mg/kg PO q24h combined with sulfadiazine 20–30 mg/kg PO q12h for 30 days after clinical signs plateau
			Nitrothiazole derivatives	Nitazoxanide: 11.36 mg/lb (25 mg/kg) PO q24h for the first 5 days, followed by 22.72 mg/lb PO q24h for 23 days
			Hydroxyquinolones and naphthoquinones	Decoquinate: 0.5 mg/kg PO q24h combined with levamisole 1 mg/kg PO q24h for 10 days
Neosporosis	*Neospora caninum*	Dogs	DHFR/TS inhibitors	Pyrimethamine: 0.25–0.5 mg/kg PO q12h combined with sulfadiazine 30 mg/kg PO q12h for 2–4 weeks
			Lincosamides	Clindamycin: 12.5–18.5 mg/kg PO q12h for 2–4 weeks
		Cattle	Triazene derivatives	Ponazuril: 20 mg/kg PO q24h for 6 days
Toxoplasmosis	*Toxoplasma gondii*	Dogs	DHFR/TS inhibitors	Pyrimethamine: 0.25–0.5 mg/kg PO q12h combined with sulfadiazine 30 mg/kg PO q12h for 2–4 weeks
			Lincosamides	Clindamycin: 3–13 mg/kg PO or IM q8h for 2 weeks or 10–20 mg/kg PO or IM q12h for 2 weeks
		Cats	DHFR/TS inhibitors	Pyrimethamine: 0.25–0.5 mg/kg PO q12h combined with sulfadiazine 30 mg/kg PO q12h for 2–4 weeks
			Lincosamides	Clindamycin: 10–12 mg/kg PO q12h for 4 weeks or 12.5–25 mg/kg IM q12h for 4 weeks

Protozoal disease	Protozoa	Species	Drug class	Drug and dosing regimen
Sarcocystis	*Sarcocystis spp.*	Dogs	Hydroxyquinolones and naphthoquinones	Decoquinate: 10–20 mg/kg PO q12h
Coccidiosis	*Eimeria sp., Isospora sp.*	Dogs	DHFR/TS inhibitors	Ormetoprim/sulfadimethoxine: 11 mg/kg ormetoprim combined with 55 mg/kg sulfadimethoxine PO for up to 23 days Trimethoprim/sulfadiazine: 5–10 mg/kg trimethoprim combined with 25–50 mg/kg sulfadiazine PO q24h for 6 days to dogs over 4 kg; dogs under 4 kg BW are given half this dosage for 6 days
			Thiamidine derivatives	Amprolium: 100–200 mg total PO q24h for 7–12 days; in drinking water (sole source) at 30 ml (9.6% solution)/gal for up to 10 days; in food at 250–300 mg (20% powder) q24h for 7–10 days
			Sulfonamides	Sulfadimethoxine: 55 mg/kg PO q24h for 1 day, then 27.5 mg/kg PO q24h for 14–20 days
			Triazine derivatives	Toltrazuril: 9 mg/kg BW PO once Ponazuril: 50 mg/kg BW PO q24h for 3 days
		Cats	Sulfonamides	Sulfadimethoxine: 55 mg/kg PO q24h for 1 day, then 27.5 mg/kg PO q24h for 14–20 days
			DHFR/TS inhibitors	Trimethoprim/sulfadiazine: 5–10 mg/kg trimethoprim combined with 25–50 mg/kg sulfadiazine PO q24h for 6 days to cats over 4 kg; cats under 4 kg BW are given half this dosage for 6 days.
			Thiamidine derivatives	Amprolium: 110–220 mg/kg PO q24h for 7–12 days; in drinking water (sole source) at 1.5 tsp (9.6% solution)/gal for up to 10 days; 150 mg/kg PO combined with sulfadimethoxine at 25 mg/kg PO q24h for 14 days.
			Triazine derivatives	Toltrazuril: 18 mg/kg BW PO once Ponazuril: 50 mg/kg BW PO q24h for 3 days

[a]The use of nitroimidazoles in food-producing animals is strictly prohibited by the US FDA. Cattle receiving metronidazole should never enter the food chain.
[b]See text for discussion of toxicity.
[c]Dihydrofolate reductase/thyamidine synthase inhibitors.
[d]Regimen should be followed up with decoquinate therapy.

Reading materials

Textbook

- Rivire JE and Papich MG (2018): Veterinary Pharmacology and therapeutics 10th ed.

OR

- Rivire JE and Papich MG (2016): Veterinary Pharmacology and therapeutics 9th ed.

ANTI-CANCER Agents

By
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Learning Objectives

- At the end of this lecture you should be able to:

1. Know the characteristics of cancer cells,
2. the MOA of the classes of anticancer drugs
3. Mechanisms of resistance to anticancer drugs
4. Define the term Multidrug Resistance
5. Know the advantages of combination chemotherapy,

Overview

- Cancer or Neoplasm is a disease in which there is uncontrolled multiplication and spread within the body of abnormal forms of the body's own cells.
- Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called **tumor**
- **Cancer occurs after normal cells have been transformed into neoplastic cells through alteration of their genetic material and the abnormal expression of certain genes.**
- **Neoplastic cells usually exhibit chromosomal abnormalities and the loss of their differentiated properties.**
- **These changes lead to uncontrolled cell division and**

CHARACTERISTICS OF CANCER CELLS

- There are four characteristics that distinguish them from normal cell.
  - Uncontrolled proliferation / Hyperplasia
  - Dedifferentiation and loss of function
  - Invasiveness- attacking adjacent tissue
  - Metastasis
- different rates of cellular drug uptake and increased cellular

FORMS OF CANCER

1. **BENIGN TUMOR**

   A tumor that stops growing by itself, does not invade other tissues and does not metastasize.

2. **MALIGNANT TUMOR**

   A tumor that starts growing itself and invade the other tissues and metastasize

CAUSES OF CANCER

1. CHEMICAL CARCINOGENS

- ✓ Tobacco, benzene, formalin, etc.

2. IONIZING RADIATIONS

- ✓ Ultra-voilet radiations, Sun Radiations

3. VIRAL & BACTERIAL INFECTIONS

- ✓ Papilloma virus
- ✓ Hepatitis B & C virus

4. HORMONAL IMBALANCE

- Hyperestrogenic state

5. IMMUNE SYSTEM DYSFUNCTION

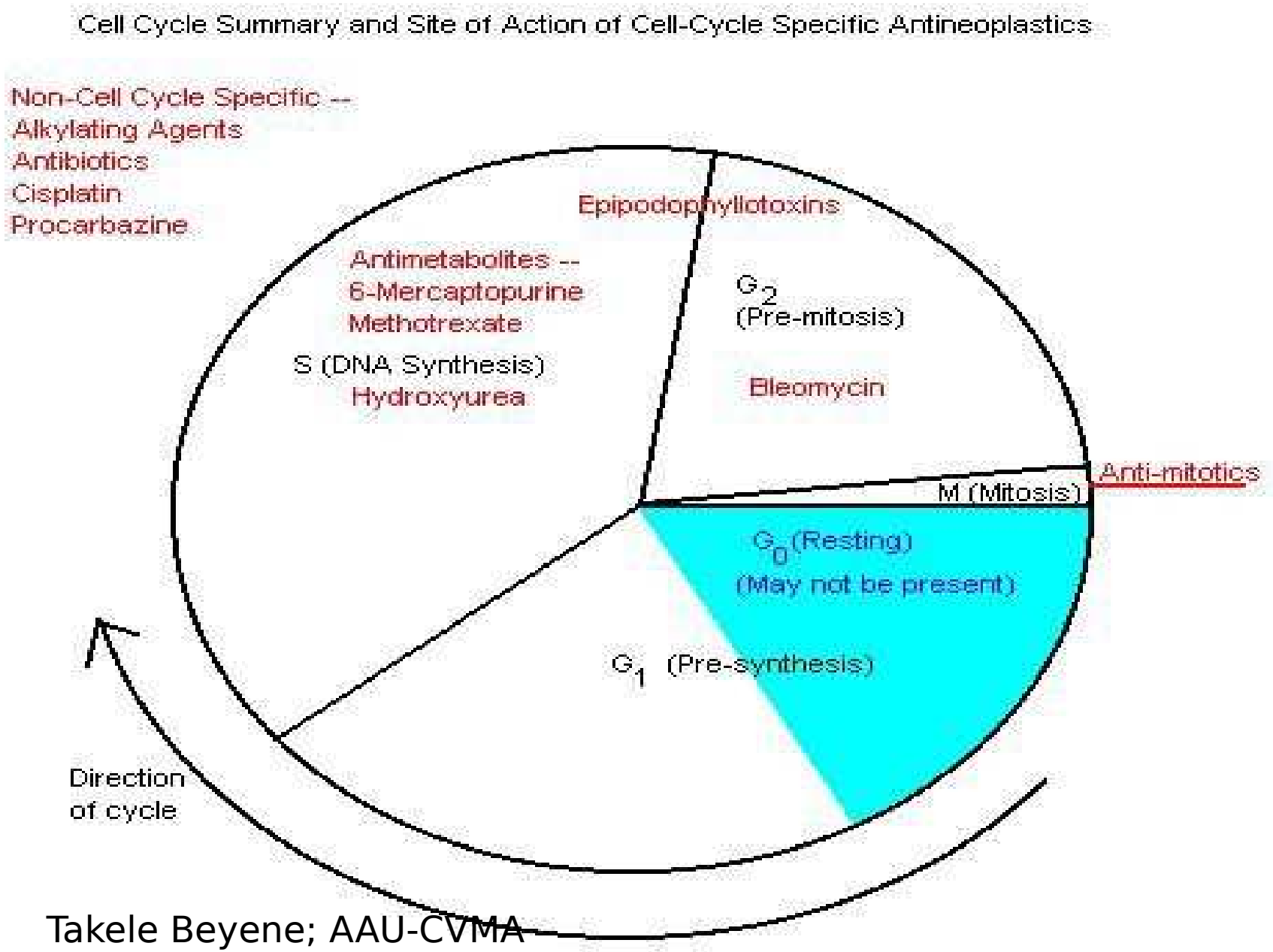
- Immunideficiency
- IgA deficiency

6. HERIDITY

- Mutation in genes BRCA 1 & BRCA 2

CELL CYCLE

- This starts with the cell ‘gearing up’ for division by synthesizing the components necessary for DNA replication.
- The **five phases** of the cell cycle:
  - G1: enzymes needed for DNA synthesis are produced
  - S: DNA synthesis and replication
  - G2: RNA and protein synthesis
  - M: mitosis phase
  - G0: resting phase(cell are not dividing but re-enter the cycle)
- Two checkpoints, one between G1 & S and



GENESIS OF CANCER CELL

- A normal cell turns into a cancer cell because of a mutation in its DNA, which can be inherited or acquired.

- Two main categories of **genetic change which lead to cancer**:

1. The inactivation of tumor suppressor genes
2. The activation of proto-oncogenes to

Advances in Cancer Chemotherapy

- **Treatment options of cancer:**
  - Surgery: before 1955
  - Radiotherapy: 1955~1965
  - Chemotherapy: after 1965
  - Immunotherapy and Gene therapy

- **The treatment of a patient with cancer may aim to:**

CLASSIFICATION

I. ALKYLATING AGENTS

A. Nitrogen Mustards: Cyclophosphamide

B. Alkyl Sulfonates: Busulfan

C. Nitrosoureas: Carmustine , Lomustine, Streptozocin

D. Ethylenimines

E. Triazenes: Dacarbazine

II. ANTI-METABOLITE

A. Folate Antagonist

- Methotrexate

III. ANTIBIOTICS

A. Anthracyclines

- Doxorubicin, Daunorubicin, Idarubicin

B. Bleomycins

C. Mitomycin

D. Dactinomycin

IV. PLANT-DERIVED PRODUCTS

A. Vinca Alkaloids: Vincristine, Vinblastine

B. Epipodophyllotoxins: Etoposide, Teniposide

C. Taxanes: Paclitaxel

V. ENZYMES

A. L-Asparaginase

VI. HORMONAL AGENTS

A. Glucocorticoids

B. Estrogens/Anti-estrogen

- Tamoxifen, Estramustine phosphate

C. Androgens/Anti-androgens: Flutamide

D. Progestins

E. LH-RH Antagonist: Buserelin, Lueprolide

F. Octreotide acetate

VIII. IMMUNOMODULATING AGENTS

A. Levamisole

B. Interferons: Interferon alfa

C. Interleukins: Aldesleukin

PHASE SPECIFIC DRUGS

CELL CYCLE SPECIFIC	CELL CYCLE NON SPECIFIC
S Phase: Cytosine arabinoside, 6-MP,MTX,5-Fu	Alkylating agents
M Phase: Vincristine, Vinblastine, Paclitaxel, Taxol, Taxotere	Antibiotics
G2 Phase: Bleomycin	Nitrosoureas
G1 Phase: 5-Fu	Cisplatin, Procarbazine

Mode of Action

ALKYLATING AGENTS

- The agents form reactive molecular species that alkylate nucleophilic groups on DNA bases, particularly the N-7 position of guanine.
- This leads to cross-linking of bases, abnormal base pairing, and DNA strand breakage.

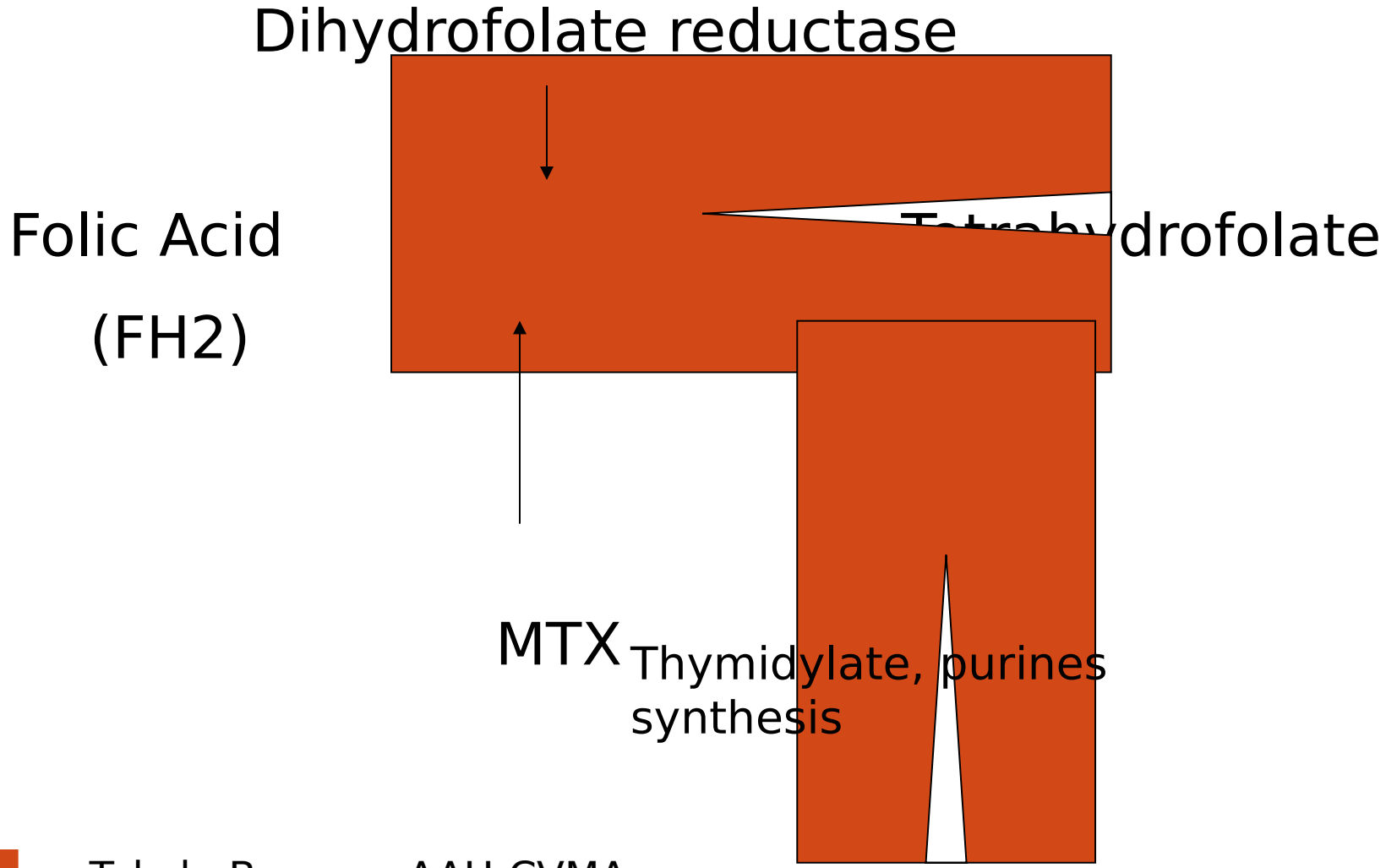
ANTI-METABOLITES

1. FOLATE ANTAGONIST:

- These agents competitively inhibits the binding of folic acid to the enzyme **dihydrofolate reductase** and thus catalyzes the formation of tetrahydrofolate.

- Tetrahydrofolate in turn converted to N5, N10 methylenetetrahydrofolate which is essential co-factor for the synthesis of thymidylate, purines, methionine and glycine.

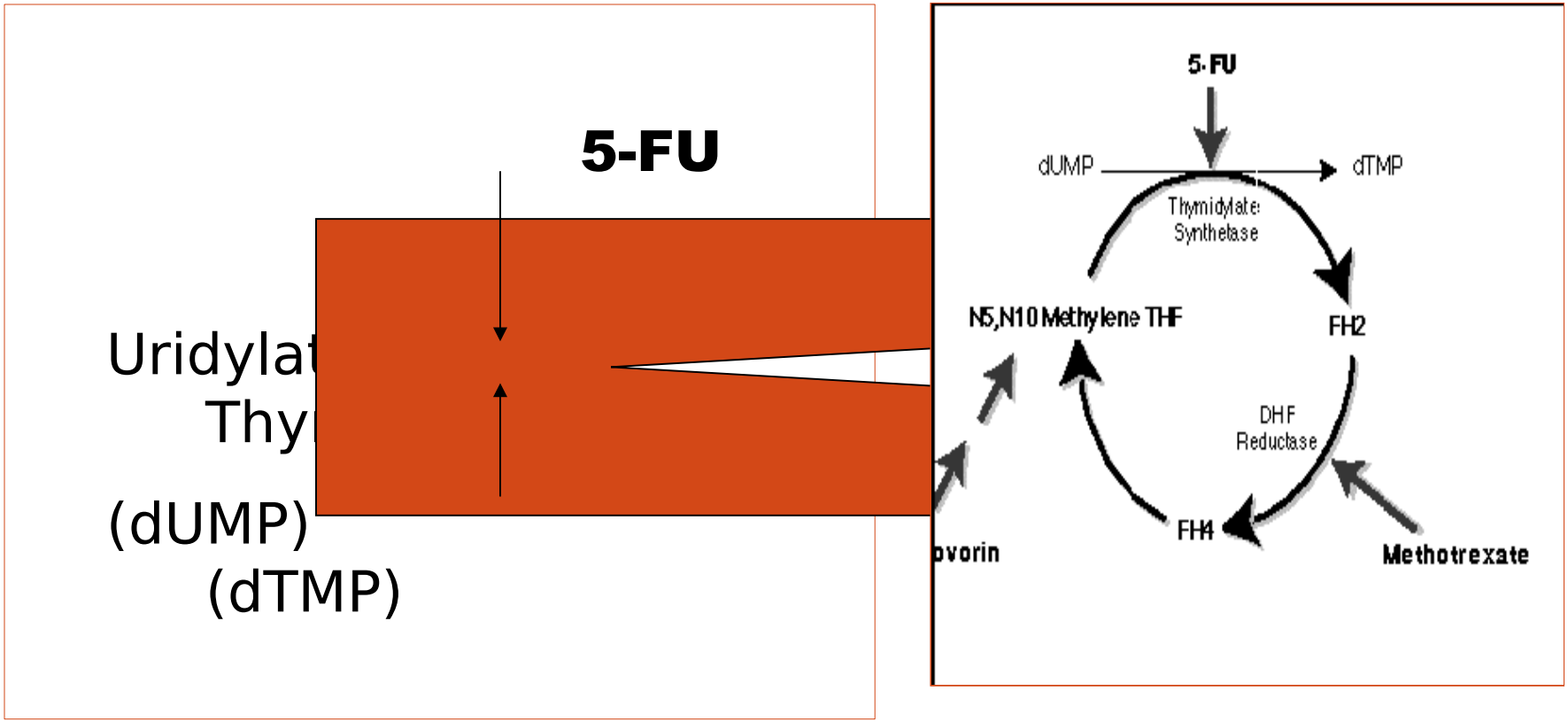
ANTI-METABOLITES---



ANTI-METABOLITES----

2. PYRIMIDINE ANALOGUES

- **The active metabolite that inhibit DNA synthesis is the deoxyribonucleotides 5-fluoro-2-deoxyuridine 5-phosphate.**



Thymidylate synthetase

ANTIBIOTICS

- It binds to DNA and inhibit the synthesis of both DNA & RNA.
- Its cytotoxic action is mediated by Topoisomerase II.
- The drug interplace in the DNA and stablize the **DNA topoisomerase II**
  - (the enzyme that prevent the DNA molecule to become enlarge during mitotic segregation during replication of the DNA helix)

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ANTI-MITOTIC (PLANT DERIVED)

- They have ability to bind specifically to tubulin and block its ability to polymerize with tubulin into microtubules.
- Cell division is arrested in metaphase.
- Cells blocked in mitosis undergo changes characteristic of apoptosis.

ENZYMES

- **L-asparaginase** catalyzes the hydrolysis of L-Asparagine to aspartic acid & ammonia.
- It also hydrolyze L-glutamic acid.
- Tumor cell are **deficient of enzyme asparagine synthetase** & cannot synthesize asparagine.
- **Depletion of this asparagine &**

HORMONAL AGENTS

- Estrogens act by binding to cytoplasmic protein receptor.
- The hormone-receptor complex is translocated into nucleus & induces the synthesis of rRNA & mRNA at specific site on the DNA of the target cell.
- **Tamoxifen** binds to estrogen receptors within the cell & competes with endogenous estrogen.

Conventional Chemotherapy

- **Problems**:

1) Lack of selectivity → many toxic side effects!

– Supportive therapies

• Nausea- antiemetics

• Myelosuppression- hematopoietic growth factors, bone marrow transplant, antibiotics

2) Resistance → tumor cells do not die in response to anticancer drugs

Why is there no cure for cancer?

- **Resistance**
- **Metastasis**
- **Tumor heterogeneity**
- **Cancer stem cells**

MECHANISM OF DRUG RESISTANCE

1. Increased DNA repair
2. Formation of trapping agents
3. Changes in target enzymes
4. Decreased activation of Pro-drugs
5. Inactivation of anti-cancer drugs
6. Decreased drug accumulation

Multidrug Resistance (MDR)

- Many patients that receive chemotherapy developed MDR → common cause of chemotherapy failure:
  - Cells exposed to a single drug develop resistance to a broad range of cytotoxic agents
  - Majority of tumors develop MDR through over-expression of the drug efflux pump P-glycoprotein→ Actively pumps out drugs of tumor cell

- Drugs that develop resistance:
  - vinca alkaloids, anthracyclines, taxol, epipodophyllotoxins

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Combination Chemotherapy

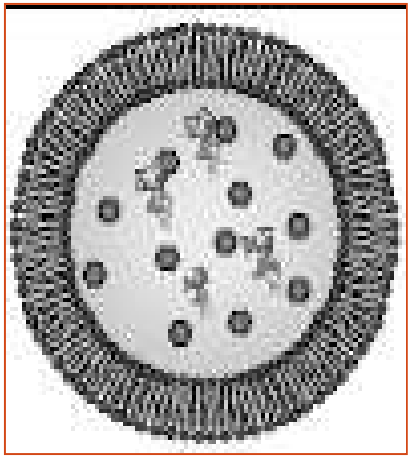
- Drug resistance can be circumvented by combination chemotherapy
- Select drugs with:

1) proven efficacy against tumor type when used alone
2) different mechanism of action (complementary)
3) non-overlapping toxicities

- Synergy

Drug Delivery: Liposomes

- A strategy to improve already existing therapies



1. Improves drug properties

– solubility

– increases drug circulation time (degradation)

– improves accumulation at tumor sites

2. Reduce toxicity

SIDE EFFECTS

1. Bone Marrow Suppression
   - Decreased WBC's & Platelets count
2. Gastrointestinal
   - Nausea & Vomiting, Anorexia, Alterations in taste perception, Mucositis, Stomatitis, dysphagia, esophagitis
3. Allopecia
4. Phlebitis
5. Nephrotoxicity
6. Hepatotoxicity
13. Cardiotoxicity
14. Pulmonary Toxicity

Summary Points

- Anticancer drugs target rapidly growing cells (normal and cancer)
- Most drugs either damage DNA or inhibit DNA synthesis or mitosis
- Resistance to chemotherapy can arise due to increased expression of p-glycoprotein, a drug efflux pump
- Existing drugs may be improved (made less

Have we met our Learning Objectives?

1. Know the characteristics of cancer cells,
2. the MOA of the classes of anticancer drugs
3. Mechanisms of resistance to anticancer drugs
4. Define the term Multidrug Resistance
5. Know the advantages of combination chemotherapy,
6. Identify adverse drug reactions of antineoplastic drugs

Reading materials

Textbook

- Rivire JE and Papich MG (2018): Veterinary Pharmacology and therapeutics 10th ed.

OR

- Rivire JE and Papich MG (2016): Veterinary Pharmacology and therapeutics 9th ed.

You can send your questions to:

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Anti-Inflammatory Drugs (AIDs)

Learning Objectives

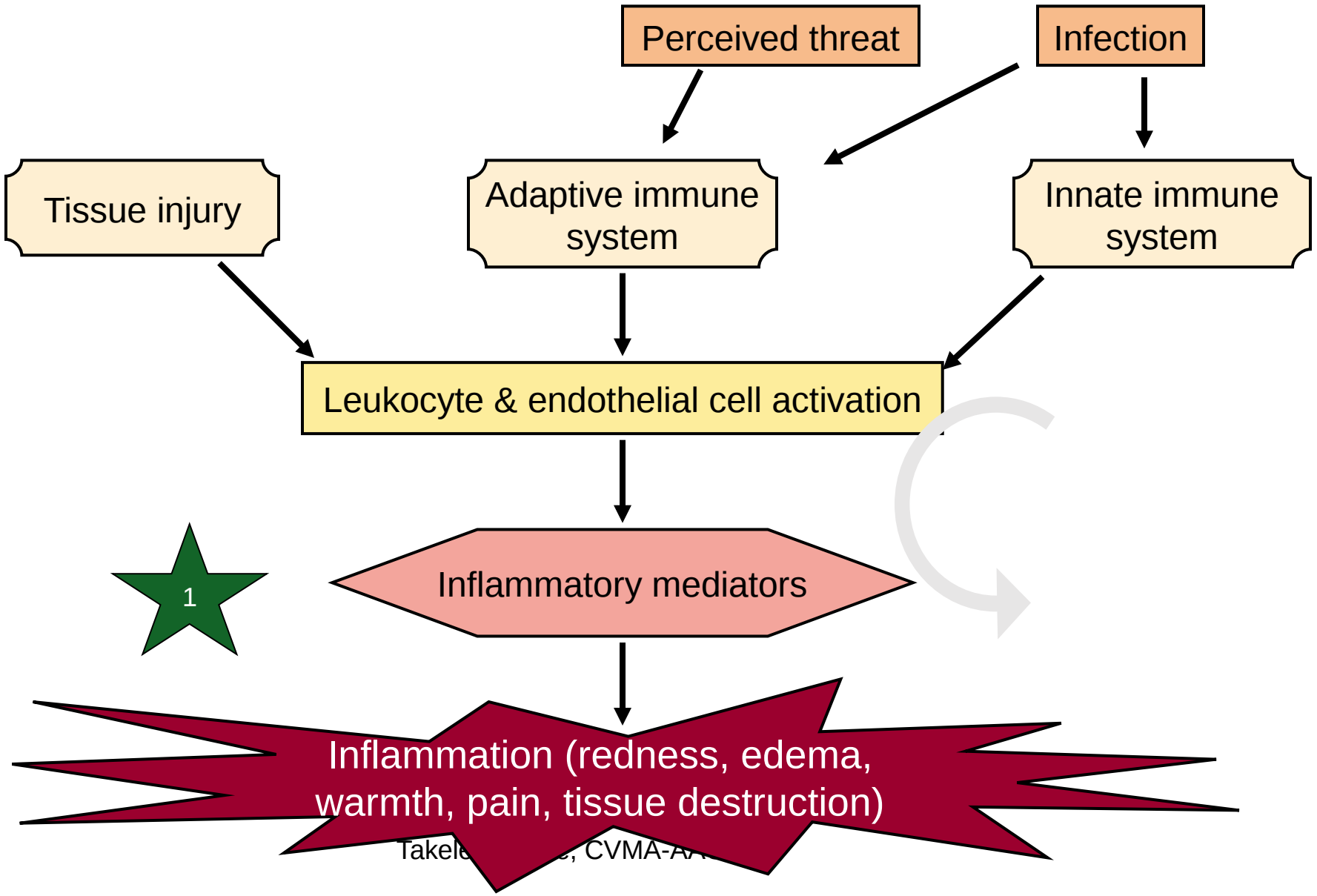
- Understand the inflammatory cascades
- Know inflammation mediators
- Know drugs commonly used in VM to treat inflammation
- Know SEs associated with AIDs

Overview

What is Inflammation?

- is a useful and normal process that consists of a series of events, including:
  - ✓ vascular changes and
  - ✓ release of chemicals that help to destroy harmful agents at the injury site and repair damaged tissue
- Vasodilation increases permeability of blood vessels in the early phase
- Accumulation of leukocytes, reduced blood flow, chemical release (histamine, prostaglandin, and bradykinin) and tissue damage in cellular phase

The Inflammatory Cascade

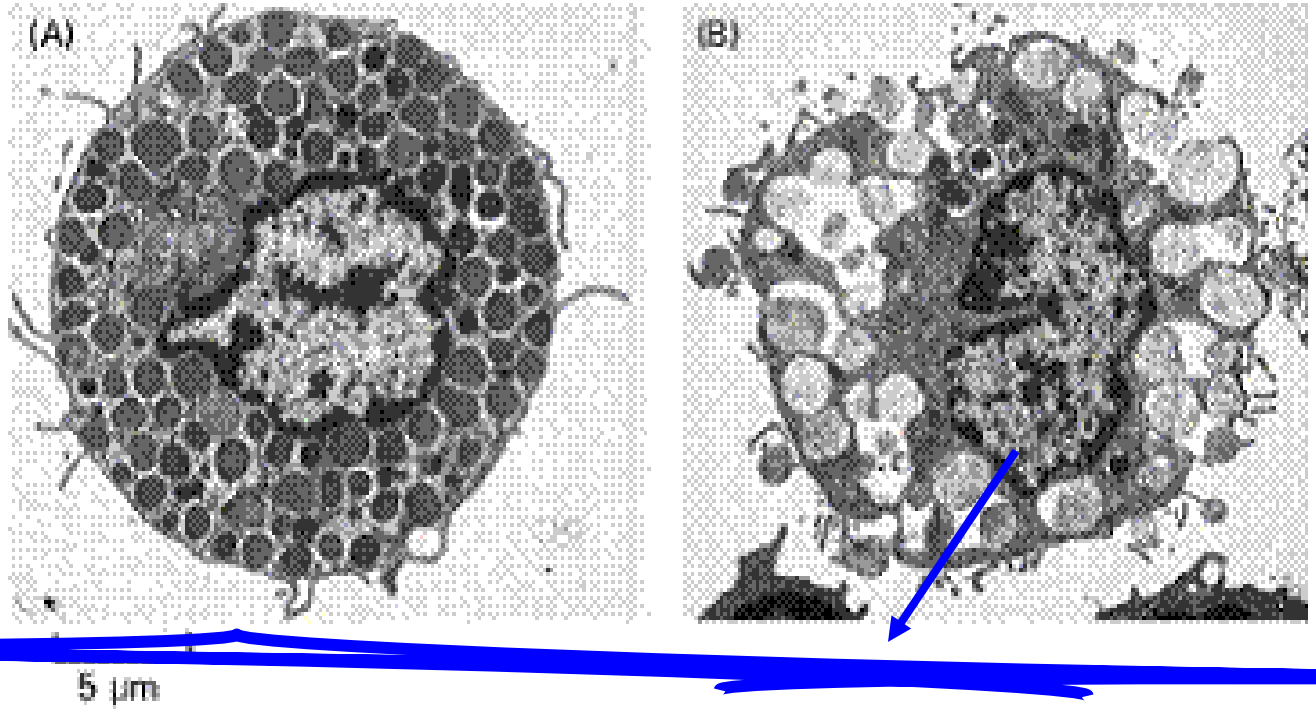


Chemical Mediators

- Numerous chemical involve to increase leakage of blood and fluid:
  - Histamines
  - Prostaglandins
  - Kinins

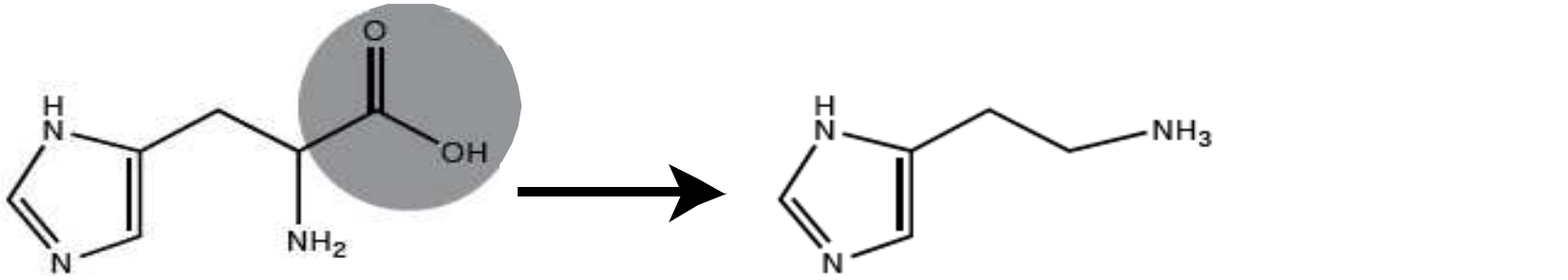
IgE-Mediated Mast Cell Degranulation

Resting Mast Cell **Activated Mast Cell**



Histamine
Proteases
Heparin

Histamine



Histidine

Histidine decarboxylase

Histamine

Cimetidine, ranitidine

H_1 receptor

↑***vascular permeability***
venule vasodilation
pruritus

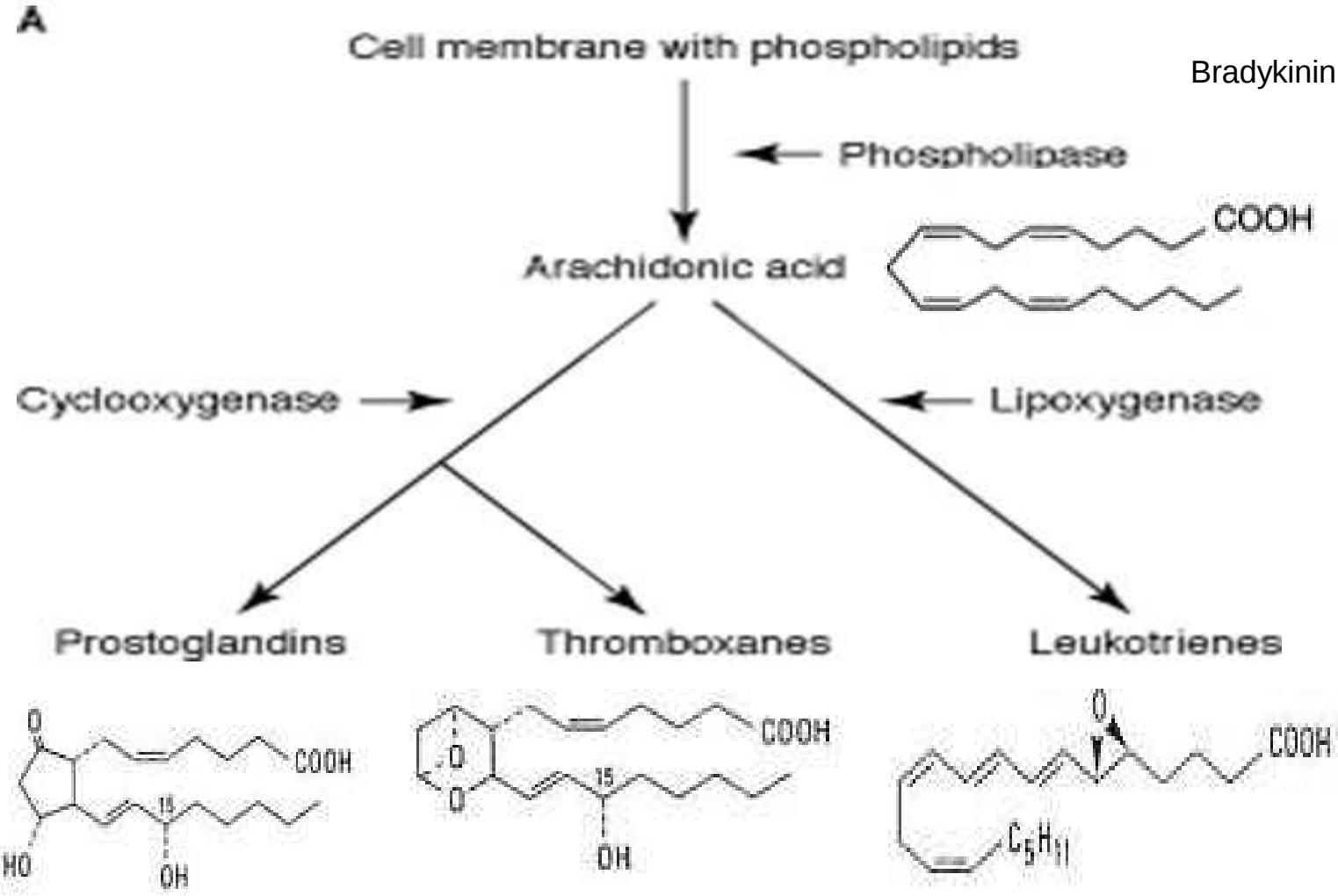
H_2 receptor

↑ ***gastric acid secretion***

Prostaglandins

- Found in almost every tissue and body fluid
- Causes:
  - Increase VD at low levels
  - Increase vascular permeability and pain producing activity of other substances

Eicosanoids

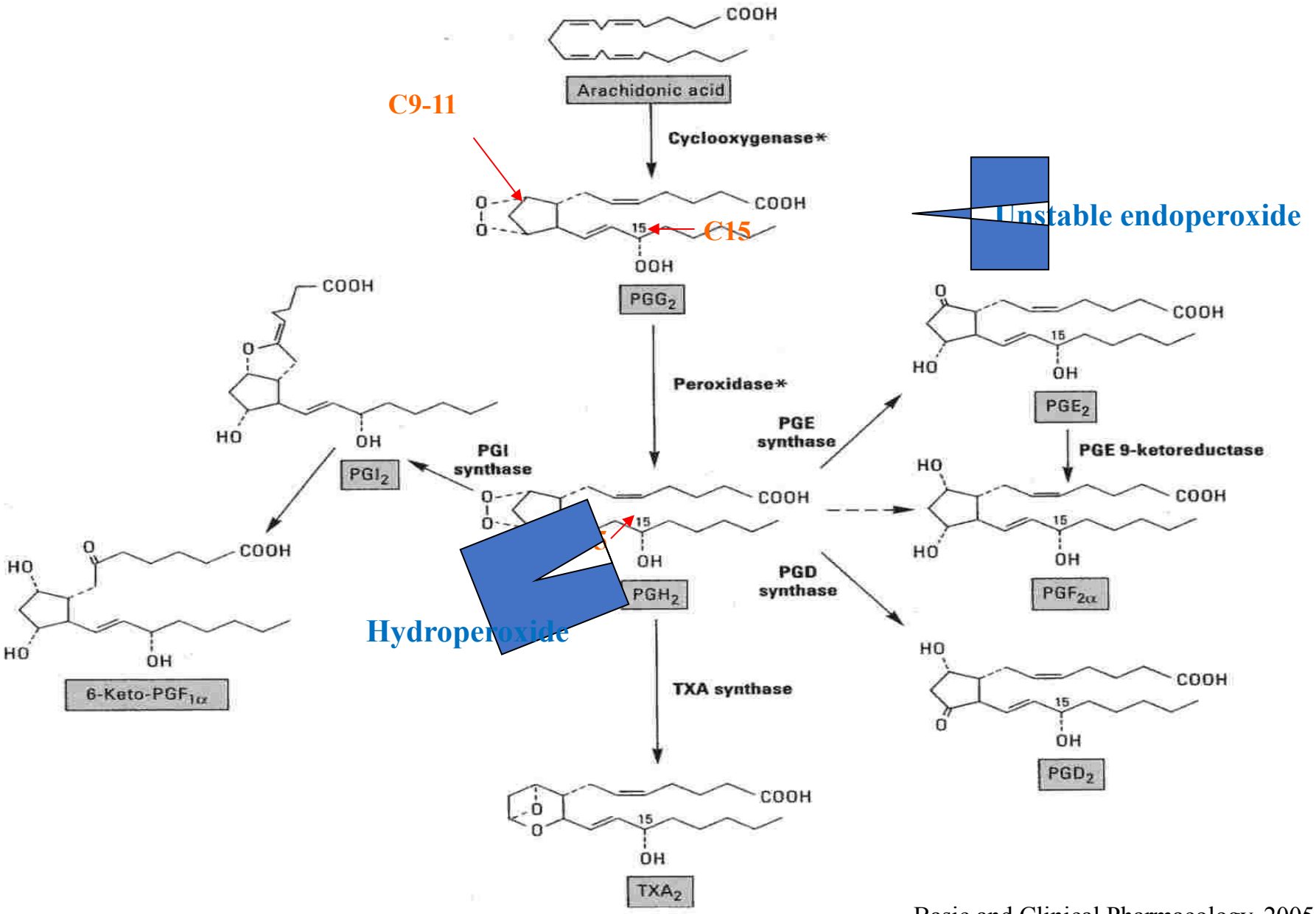


Bradykinin

- **PGD2, PGF2 , PGI2**
- **TXA2**

LTC4, LTD4, LTE4

Cyclooxygenase Pathway



Basic and Clinical Pharmacology, 2005

Anti-Inflammatory Drugs

A. **Steroidal AIDs**
B. **Non-steroidal AIDs**
C. **Anti-histamines**

A- Steroidal Anti-inflammatory Agents

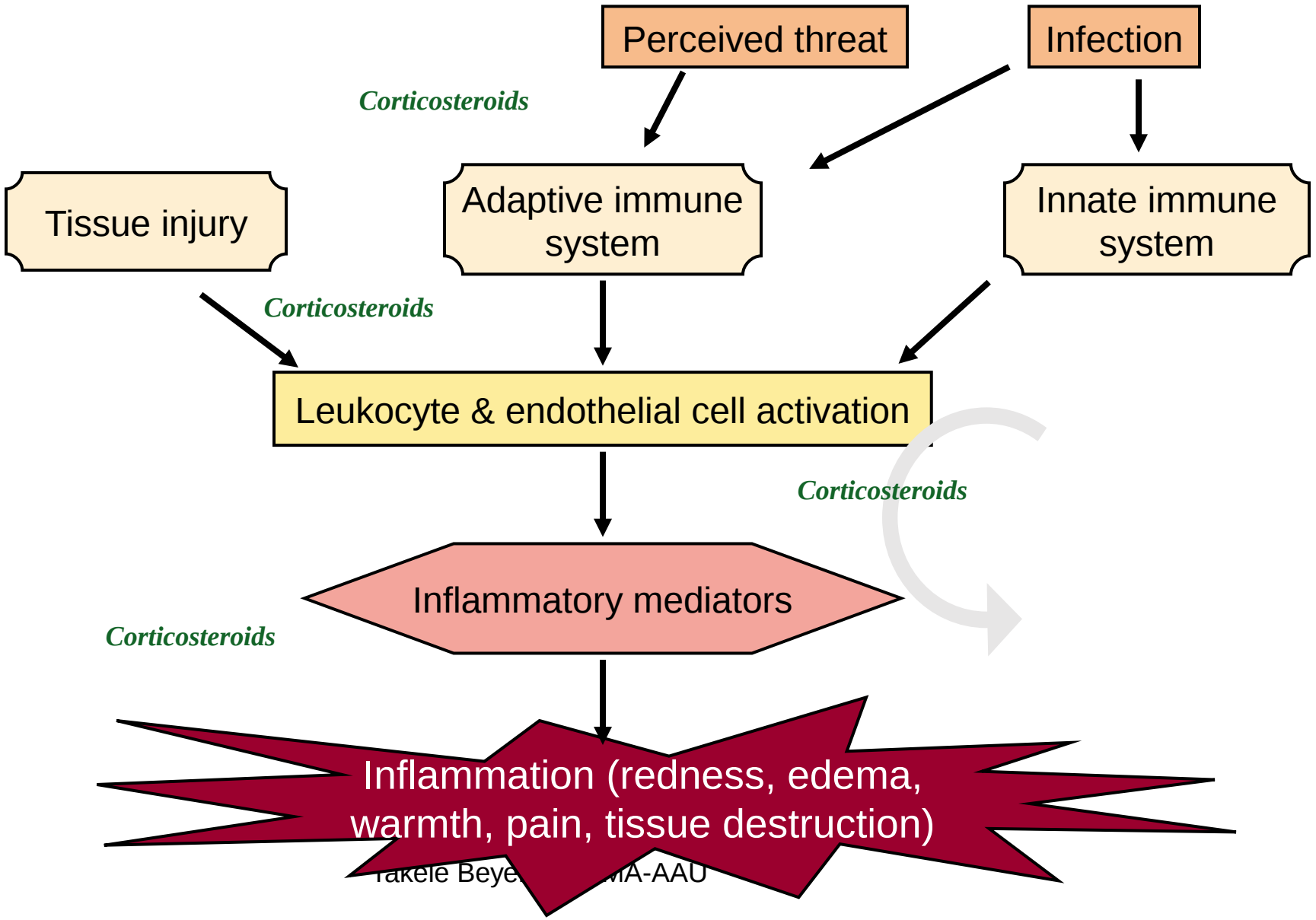
Corticosteroids

- are hormones produced by the adrenal cortex
- Two groups of corticosteroids used in veterinary medicine:
  - Glucocorticoids
  - Mineralocorticoids

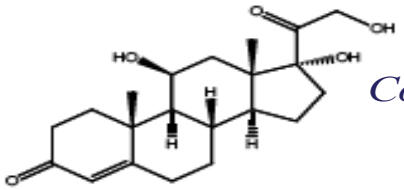
Glucocorticoids

- Naturally occurring glucocorticoids: cortisol (=hydrocortisone)
- Have anti-inflammatory effects due to their inhibition of phospholipase (PLA2)
- Raise the concentration of liver glycogen and increase blood glucose levels

The Mighty Corticosteroids



Glucocorticoids Regulate Transcription



Cortisol

MOA

Cortisol

Cortisol
GR

NUCLEUS

↑ transcription (eg, lipocortin)
or
↓transcription (IL-1, IL-2, TNF-α, IF-γ)

IP
HSP
GR
HSP

Cortisol Cortisol
GR GR

GRE

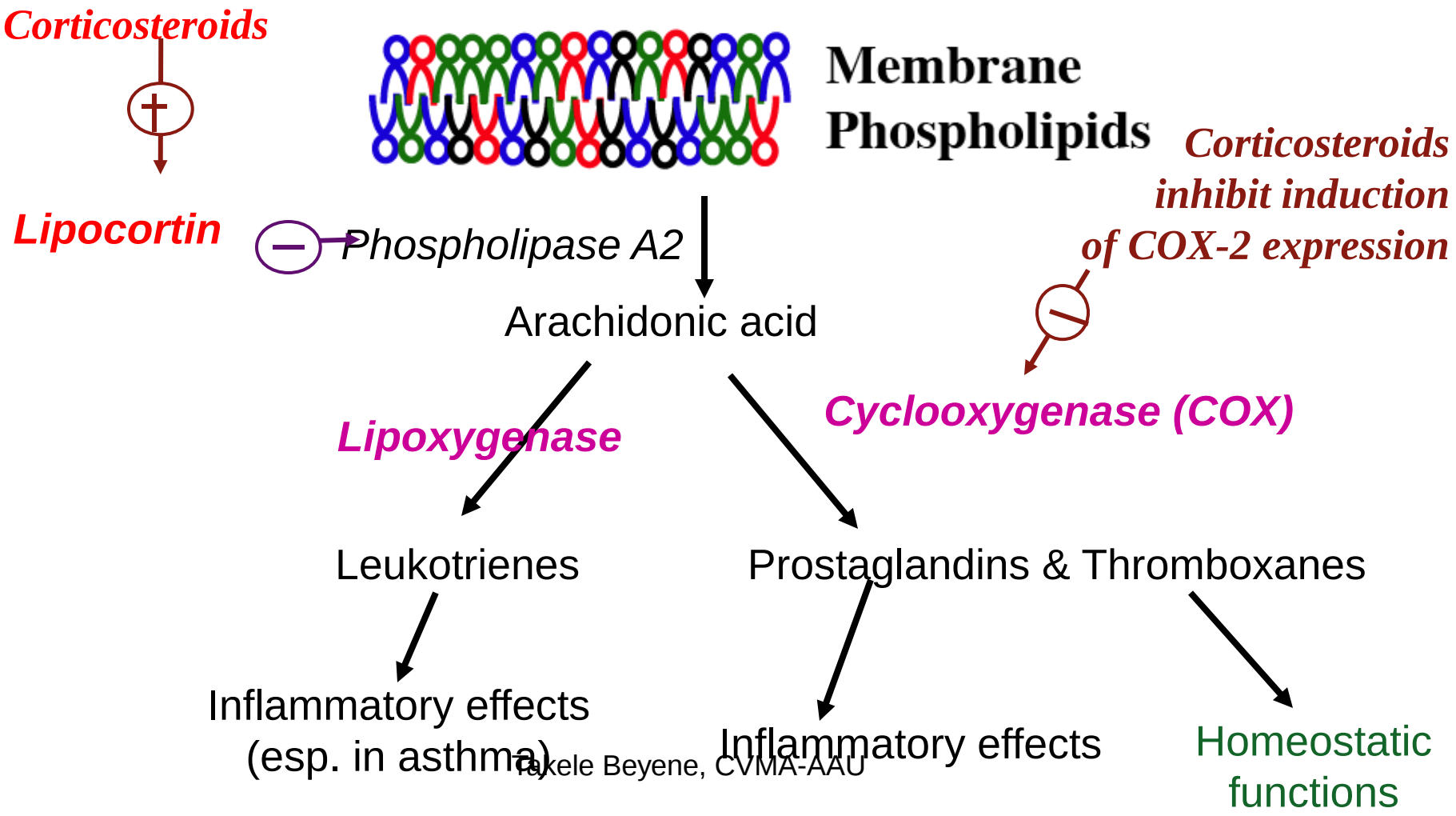
mRN A

mRN A

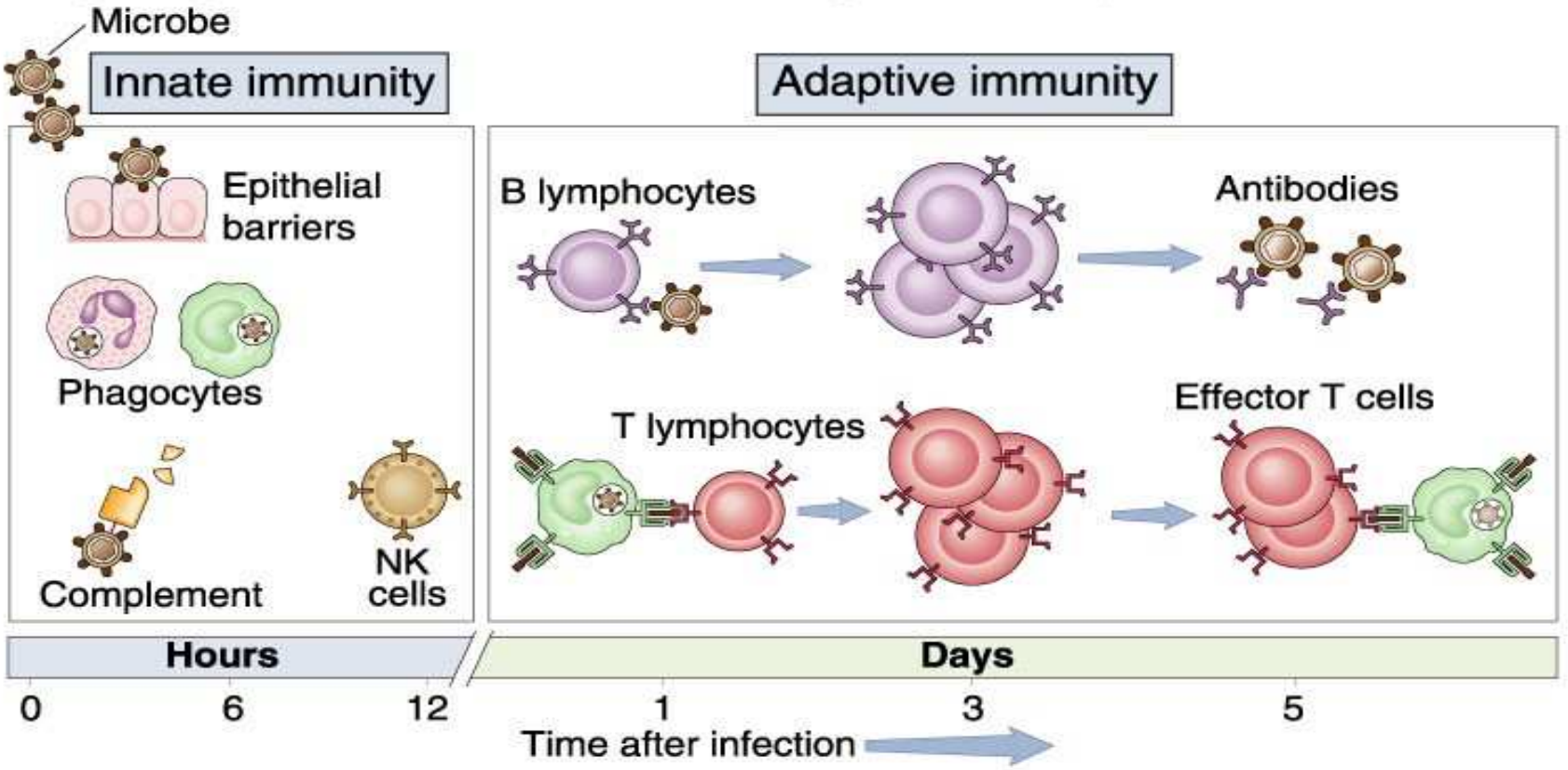
Proteins

GR- glucocorticoid receptor; HSP- heat shock protein; IP- immunophilin; GRE-- glucocorticoid receptor element; IL-intrleukin; TNF-tissue necrosis factor; IF-interferon

Corticosteroids Inhibit Eicosanoid Production

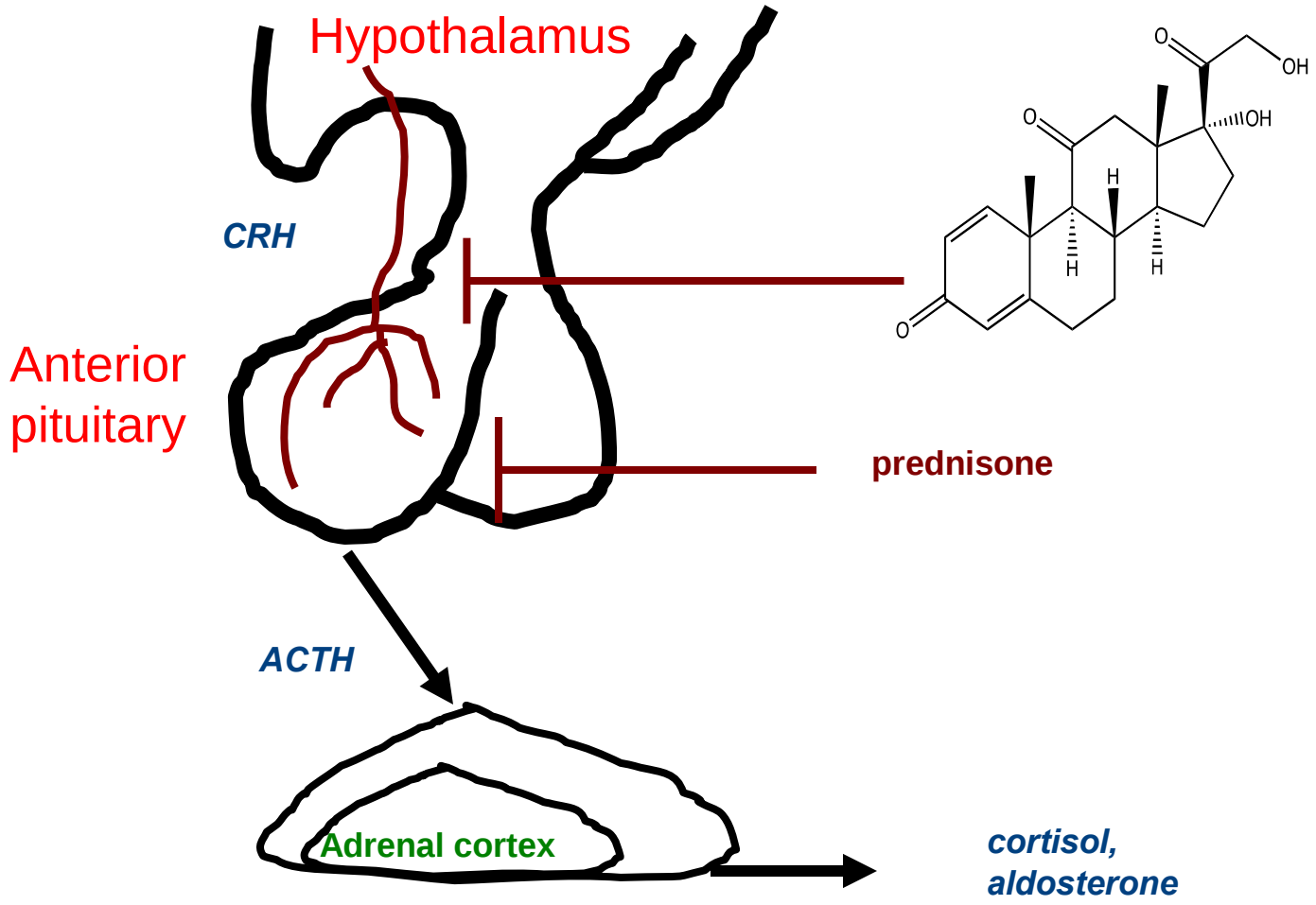


Glucocorticoids Are Powerful Immuno-suppressants



- ***Corticosteroids affect immune function, although less inhibition of humoral arm than cell-mediated arm;***
- ***also induce apoptosis in rapidly-dividing leukocytes***

Adrenal Suppression with Chronic Systemic use of Glucocorticoids



- Long term use will inhibit body's glucocorticoid activity and the body's ability to produce this substance naturally

Glucocorticoids

- May be categorized as
  - Short-acting (duration of action < 12 hours)
    - Cortisone and hydrocortisone
  - Intermediate-acting (duration of action 12–36 hours)
    - Prednisone, prednisolone, prednisolone sodium succinate, methylprednisolone,
  - Long-acting (duration of action > 36 hours)
    - Dexamethasone, betamethasone

- May be given orally, parenterally, or topically

Glucocorticoid clinical Use

- **Benefits**:
  - ✓ Reduce inflammation and pain
  - ✓ Relieve pruritus
  - ✓ Reduce scarring by delaying wound healing
  - ✓ Reduce tissue damage
  - ✓ Organ rejection reaction

- **Drawbacks**:
  - ✓ Delay wound healing
  - ✓ Increase risk of infection
  - ✓ May cause GI ulceration and bleeding
  - ✓ Increase the risk of corneal ulceration if corneal damage exists
  - ✓ May induce abortion in some species

Toxicity of Chronic Systemic Glucocorticoids

Cushing's syndrome

- Fat redistribution
- Hypertension
- Glucose intolerance
- Osteoporosis (prevent with bisphosphonates)
- Cataracts
- Gastric ulcers (prevent with omeprazole, misoprostol)
- Impaired wound healing
- Risk of infection
- CNS effects, including psychosis
- Growth inhibition in young

B- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

They are divided into:

A-Salicylate (*e.g. aspirin*) and,
B-Non-salicylate (*e.g. ibuprofen*).

NSAIDs

- NSAIDs work by inhibiting cyclooxygenase:
  - Cox-1 is involved with the stomach and kidneys
  - Cox-2 is involved with inflammation
- NSAIDs are also referred to as *prostaglandin inhibitors*
- NSAIDs have fewer side effects than glucocorticoids
- Side effects include:
  - GI ulceration and bleeding and
  - bone marrow suppression

Types of NSAIDs

- **Salicylates**
  - Potent inhibitors of PG synthesis

    E.g. Aspirin ***(acetylsalicylic acid)***
  - Side effects include gastrointestinal problems

- **Aspirin**

- Not veterinary licensed

A-Antipyretic action:

- Rapidly effective in febrile patient through central effect due to inhibited PGE2 synthesis from hypothalamus in response to pyrogens.

B-Anti-inflammatory effects:

- Due to inhibition of PG synthesis.

C-Analgesic effects:

-Effective for low-to-moderate pain (*musculoskeletal*)

Mechanism of pain relief:

Types of NSAIDs…cont'd

- **Pyrazolone derivatives**
  - Inhibit PG synthesis
  - **Phenylbutazone**
  - an analgesic, antipyretic, and anti-inflammatory
  - Used in equine medicine for musculoskeletal pain

- **Propionic acid derivatives** (the *–fen* drugs)
  - Block both cyclooxygenase and lipoxygenase
  - Carprofen- cats & dogs do not tolerate long term t/t
  - Ibuprofen- used in dogs (approved for human)

Types of NSAIDs…cont'd

- **Flunixin meglumine**
  - Inhibits COX
  - Used in cattle and horses for musculoskeletal and colic (visceral) pain
  - Is a potent analgesic, antipyretic, and anti-inflammatory
  - Toxicity: GI upset, limits its use in dogs to 2-3 days.

- Paracetamol
  - Cats lack glucuronyl transferase enzyme, required to metabolize the drug.
  - Antipyretic & analgesic with poor anti-infilammatory

Types of NSAIDs…cont'd

- **Cox-2 selective inhibitors**
  - Inhibit cyclooxygenase-2 without interfering with the protective cyclooxygenase-1
  - E.g. **deracoxib** and **meloxicam**
  - Meloxicam is eliminated as glucuronide conjugates (cats have a deficiency of bilirubin-glucuronoside glucuronsyl transferese enzyme)
  - Side effect include anorexia, vomiting, and lethargy

- **Dual-pathway NSAIDs**
  - Block arachidonic acid cycle (both cyclooxygenase and lipoxygenase pathways)
  - Are analgesics and anti-inflammatories
  - E.g. tepoxalin, which is a rapidly disintegrating tablet used

C. H1 Histamine Antagonists

Prototype	Properties	Clinical Uses
Loratadine (Claritin) Fexofenadine (Allegra)	Low affinity for muscarinic receptors, doesn't cross BBB	Allergic reactions
Diphenhydramine (Benadryl)	Muscarinic antagonist, crosses BBB	Allergic reactions, dystonic rxn to dopamine blockers, OTC sleep aid, antiemetic

However, in the case of severe hypersensitivity reactions, including anaphylaxis, drugs of choice are: Epinephrine (need 1 vasoconstriction and 2 bronchodilator) and corticosteroids!

Summary

- GC may help to disseminate infectious microorganisms
- Use caution when giving high dose of GC to pregnant animals
- Use alternate-day dosing at the lowest possible doses to prevent iatrogenic Cushing's disease
- Taper animals off GC to prevent iatrogenic Addison's disease.

Eicosanoids As Drugs

(Additional info)

Drug Name	Analog of	Clinical Use
Epoprostenol	PGI2	Pulmonary hypertension
Dinoprostone	PGE2	Medical abortion, relax uterine cervix in preparation for induction of labor
Misoprostol	PGE1	Peptic ulcer, medical abortion
Alprostadil	PGE1	Maintain a patent (open) ductus arteriosus in neonates with certain cardiac malformations until emergency surgery; erectile dysfunction
Carboprost	PGF2	Labor induction (parturition), luteolysis, abortion
Latanoprost	PGF2	Glaucoma

Have we met our objectives?

- What are you understood about inflammatory cascades?
- What are the inflammation mediators?
- What are drugs commonly used in vet. Medicine to treat inflammation?
- Describe the MOA of GC
- What are the SEs associated with AIDs?

Reading materials

Textbook

- Rivire JE and Papich MG (2018): Veterinary Pharmacology and therapeutics 10th ed.

OR

- Rivire JE and Papich MG (2016): Veterinary Pharmacology and therapeutics 9th ed.

THANK YOU