Sulphonamides and Trimethoprim

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2020

Sulphonamides:

These are derivatives of sulphonamide radical (para amino benzene sulphonamide (sulphnilamide) to which other radicals are attached (Sulphonamides or sulpha drugs)

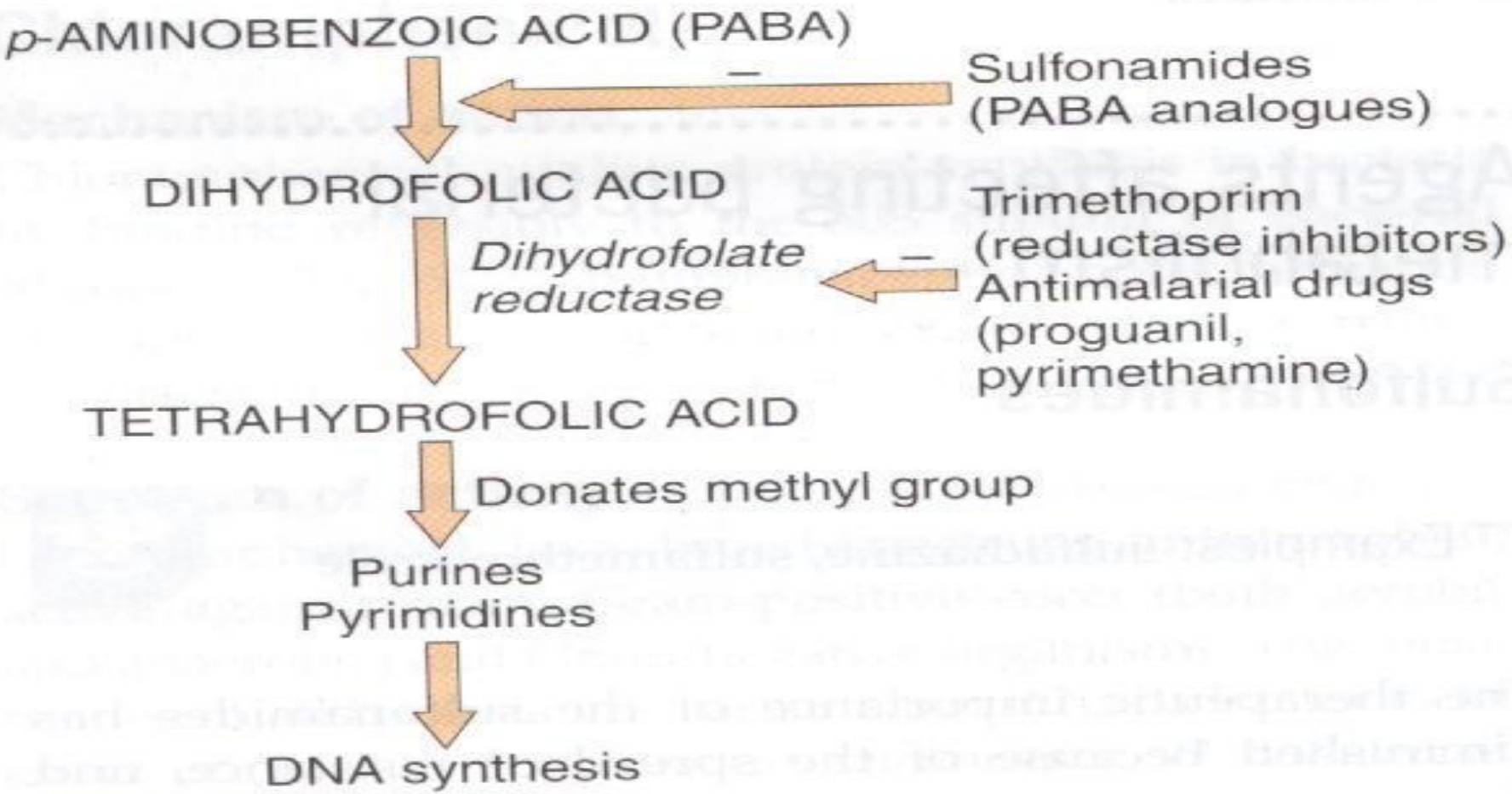
They have the same structure of para amino benzoic acid (PABA) needs for bacterial growth

All types of sulphonamides contain sulphonamide nucleus, so they have the same antibacterial mechanism of action, but they

Differ in their rate of solubility and pharmacokinetic and their anti-bacterial spectrum.

They are hardly soluble in water and acids, but easily soluble in alkaline solutions as sodium hydroxide to for sodium soluble salts in water

The folic acid pathway:



Mechanism of action of the sulfonamides, trimethoprim and antimalarial drugs in the folic acid pathway.

Antibacterial spectrum

- (Inhibit growth of G +ve & G –ve bacteria): Chlamydia trachomatis. E. coli- , klebsiella, salmonella, Shigella & Enterobacteriaceae.

- Both humoral and cellular defense mechanisms of host are essential to eradicate infection.

Pharmacokinetics

- Absorption: (absorbable, non absorbable & topical)
- 70-100% of the absorbable from intestine
- Distribution: well distributed to all tissues and fluids including:-

Pleural, peritoneal synovial, CSF, ocular fluid and placenta.

- Bind to albumin.
- Metabolism: acetylated or glucuronited in the liver

Pharmacokinetics

1.Absorption:

Depend upon solubility, fat solubility

Degree of ionization and tendency of protein binding.

e.g. sulphacetamide is highly soluble

sulphadiazine is moderately soluble

sulphsuxidine is poorly soluble.

Absorbed from intestine (absorbed Sulpha) or via IM, IV, Sc injection.

The degree of absorption is also depended upon animal species

Cattle (slowly),dog, cat and man (rapid), horse (moderate).

2.Distribution:

sulphonamides are highly distributed in the body tissues and fluids, pass all barriers (as brain, cerebrospinal fluids and placenta.

Therefore some of them like sulphadiazine and sulphmerazine are used in cases of meningitis as they can diffuse to CSF

3. Protein binding tendency:

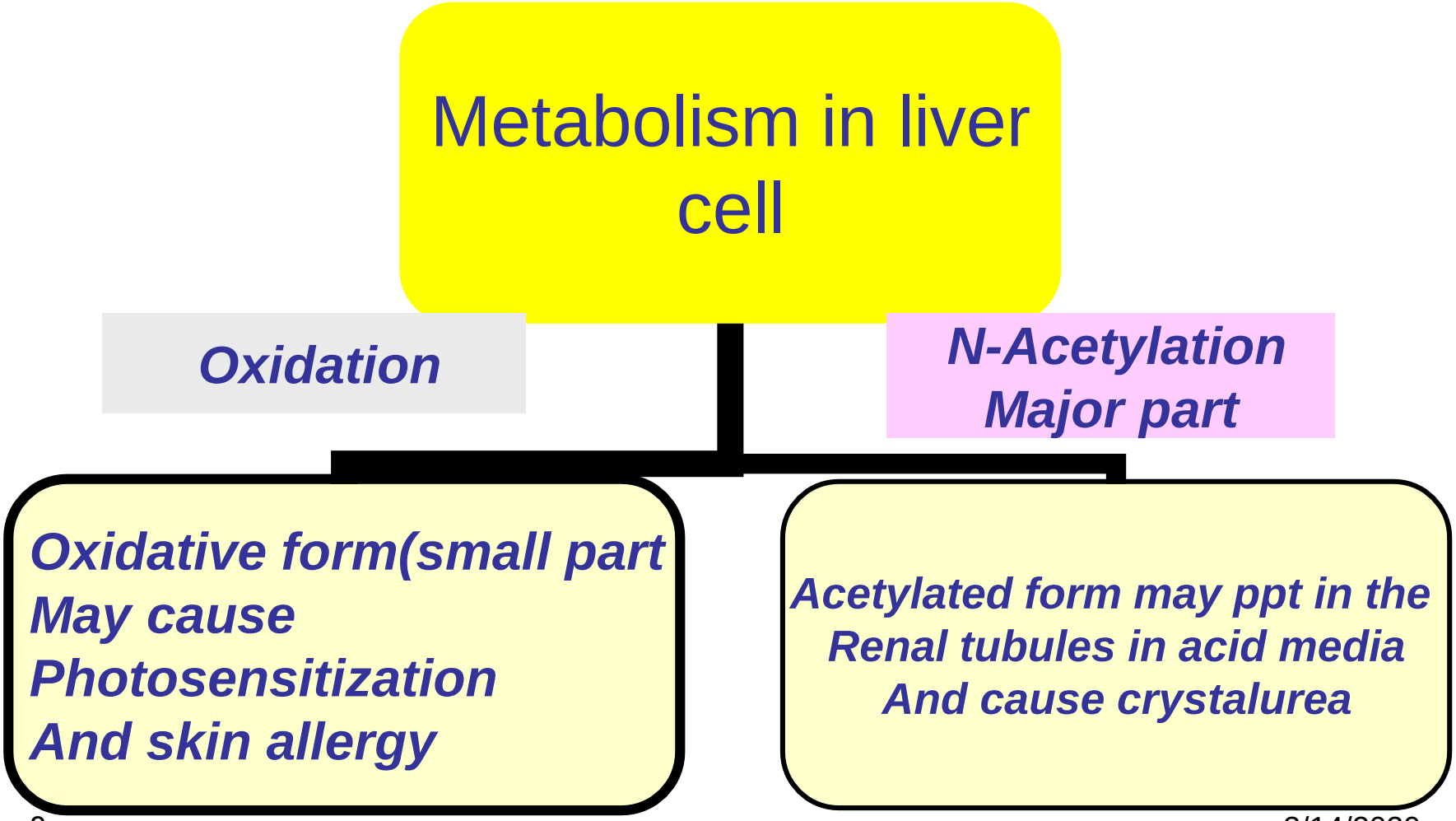
A part of sulphonamide can bind with plasma protein .this binding may either:

a). High tendency (firm) in which the active sulphonamide is released slowly and result in long activity (i.e. slowly excreted)

e.g. sulphadimethoxine and sulphamethoypyrizadine

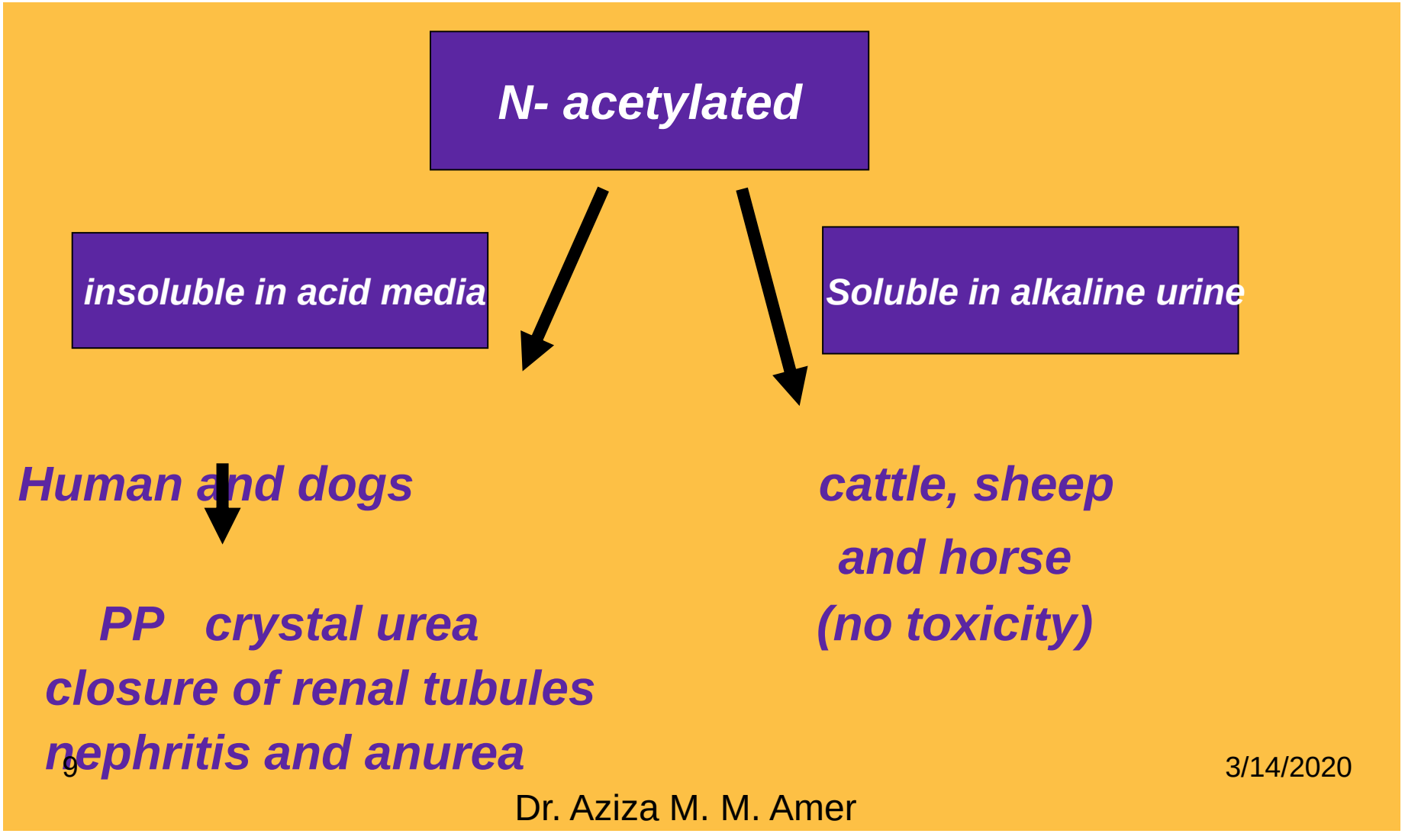
b.) Low tendency (loosely) in which active part is released rapidly producing short duration of action, e.g. sulphadimidine and sulphdiazine'

4-Metabolism (Biotransformation)

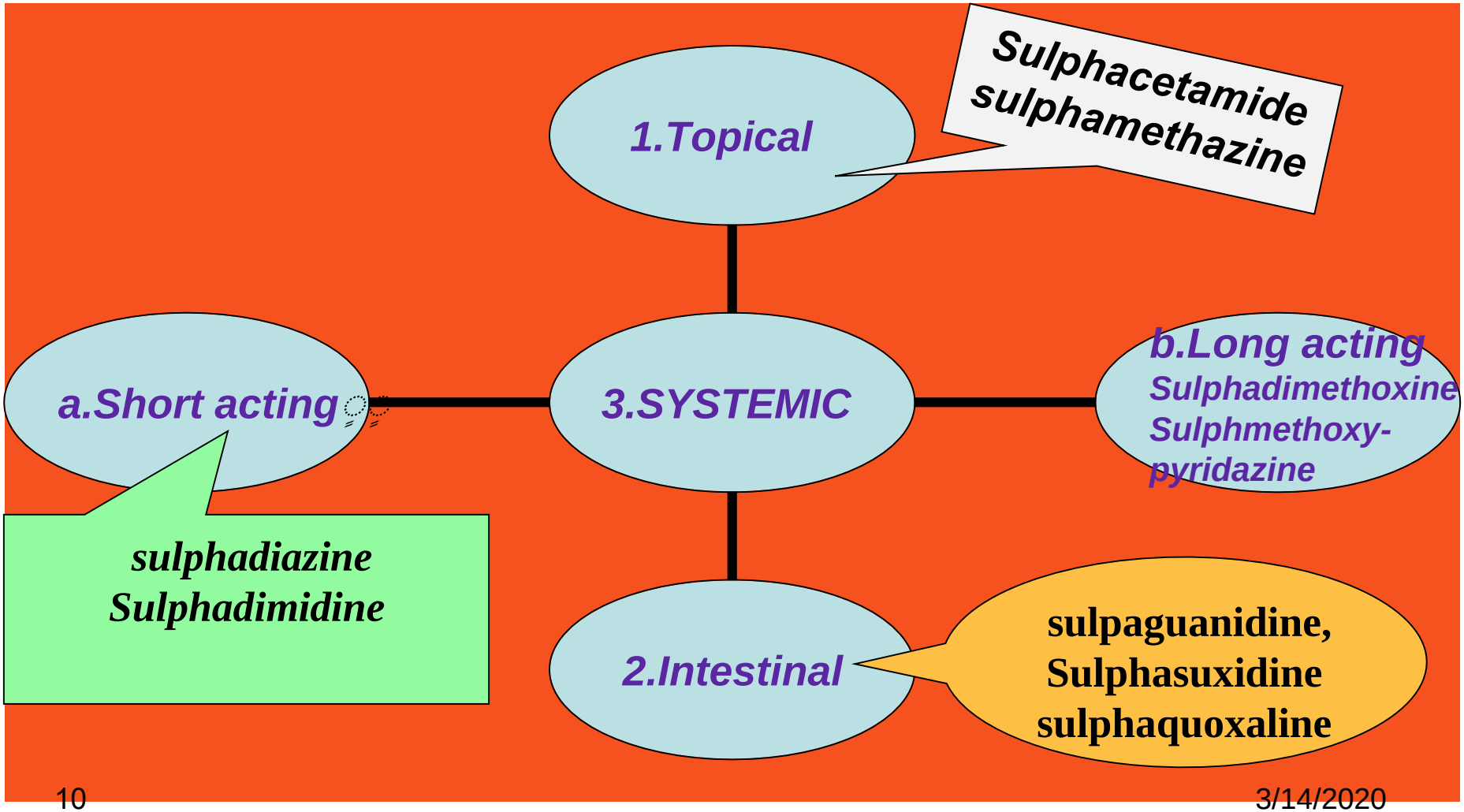


5-Excretion:

Excretion mostly via urine, partly via milk, bile and saliva They are excreted in free and acetylated forms.



Classification of sulphonamides



1. Topical

They are applied on skin and mucous membrane to treat infected wounds, ulcers, burns, conjunctivitis etc….They are used in the form of ointments, solutions or eye drops.

e. g sulphacetamide, sulphamethazine (topical sulphonamides)

They are rarely used as they are irritants, retard healing and weakened by the presence of Pus.

Sulphacetamide is less irritant so used for eye infections in form of eye drops 10 – 20%.

2.Intestinal (enteric, gut active or poorly absorbed) sulphonamides

They are poorly absorbed from intestine and stay long time in the intestinal wall.

They are used commonly for treating scours (diarrhea), bacillary dysentery intestinal coccidiosis, ulcerative Colitis.

suphaguanidine	***calf-scour, salmonellosis coccidiosis***
Sulphaqunoxaline	***cocidiosis, colienteritis, salmonellosis when added to drinking water.***

3-Systemic sulphonamides

1. Short acting sulphonamides

They are rapidly absorbed from GIT or site of injection and rapidly excreted (low protein biding tendency)

They must be given every 6 -8 hours.

in cases of acute infections like pneumonia, tonsillitis, meningitis, Mastitis, metritis, septicemia, Calf-scour, foel cholera, hepatic Coccidiosis, urinar infections e.g. sulphadimidine, Sulphadiazine ,sulphasomidine, sulphfurazone

2.Long acting sulphonamides:

They are rapidly absorbed from GIT or site of injection and slowly excreted via urine (high binding tendency with plasma protein)

They are given orally every 12 – 24 hours for treating acute and chronic infections in combination with trimethoprim e.g. Sulphadimethoxine Sulphmethoxypyradazine.

Potentiation of Sulphonamides

Trimethoprim

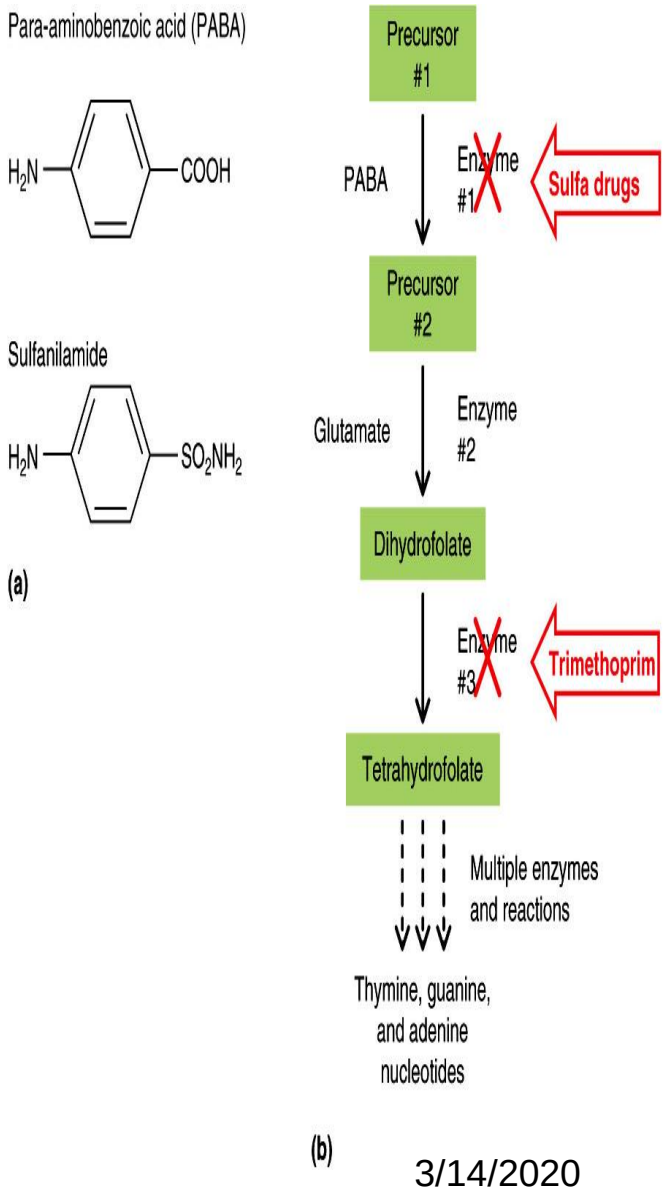
(Bacteriostatic – Broad Spectrum)

- Inhibits folic acid production

- **Interfere with the synthesis of tetrahydrofolic acid from dihydrofolate by competing the dihydrofolate reductase enzyme.**

  - Often used synergistically with sulfonamide

  - Most common mechanism of resistance is plasmid encoded alternative enzyme
    - Genes encoding resistant to sulfonamide and trimethoprim are often carried on same plasmid



Antibacterial Spectrum

- Sulfonamide-diaminopyrimidine combinations are active against gram-negative and gram-positive organisms,
- including *Actinomyces* , *Bordetella* , *Clostridium*, *Corynebacterium* , *Fusobacterium* , *Haemophilus* , *Klebsiella* , *Pasteurella* , *Proteus* , *Salmonella*, *Shigella* , and *Campylobacter* spp , as well as *Escherichia coli* , streptococci, and staphylococci. Some streptococcal strains are only moderately sensitive, as are *Brucella* , *Erysipelothrix* , *Nocardia* , and *Moraxella* spp .
- The antibacterial spectrum does not include *Pseudomonas* or *Mycobacterium* spp.

Pharmacokinetic Features

Trimethoprim is rapidly absorbed after administration PO (plasma levels peak in ~2-4 hr.)

Trimethoprim diffuses extensively into tissues and body fluids.

Tissue concentrations are often higher than the corresponding plasma levels, especially in lungs, liver, and kidneys.

About 30-60% of trimethoprim is bound to plasma proteins.

The extent of metabolic transformation of trimethoprim has not yet been established, although there is a suggestion that hepatic biotransformation can be extensive, at least in ruminants.

Trimethoprim is largely excreted in the urine by glomerular filtration and tubular secretion.

Sulpha + trimethoprim

- **Bactericidal and Broad-Spectrum**
- **Synergistic combination, by sequential mode of action**
- **Broad spectrum act on gram+ and Gram- bacteria, mycoplasma, coccidia……..**

- **Uses:**
- It is used for treatment of infections caused by organism's sensitive to sulfadiazine and/or trimethoprim as:
  - Coccidiosis in chicken
  - gastrointestinal tract infection such as bacterial diarrhea - respiratory tract infection
  - treatment of omphalitis in baby chicks

Bacterial Resistance

1.Natural Resistance:

Some bacteria do not require folic acid for growth and multiplication and are naturally resistant to sulphonamides

2. Acquired resistance:

Sensitive bacteria to sulphonamides become resistant when given in repeated small doses. This is due to :

a. Ability of bacteria to destroy small amounts of sulphonamides

b. bacteria can form folic acid reductase enzyme which prevents the uptake of sulphonamides

Toxicity of sulphonamides

1. Acute :

Result due to administration of large toxic dose of sulphonamides

Symptoms:

nausea, temporary blindness, hemolytic anemia, skin rashes.

2.chronic toxicity (prolonged administration)

a. Precipitation of acetylated form, occur in human and dogs but not herbivores (alkaline urine) .treatment by Administration of large amount of water and alkalinizes.

b. Inhibition of intestinal flora Which are responsible for Synthesis of Vit. B complex (diarrhea, vomition, debility Treatment: administration of Vitamins B-complex Toxicity in laying hens causes Lowering of egg production and Thinning of egg shell.

Thank you

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