

TETRACYCLINE

Presented by
Mr. Chaitanya Prasad Meher,
Asst.Prof.

Tetracyclines:

-a broad-spectrum antibiotics.

-It is commonly used to treat acne, infection, and other infections caused by bacteria.

-The first of these compounds was chlortetracycline followed by oxytetracycline and tetracycline.

Tetracyclines

Definition:

Tetracyclines are octahydro naphthacene derivatives which are bacteriostatic and broad spectrum antibiotics that kills certain infection-causing microorganisms and are used to treat wide variety of infections.

Introduction:

- . **Tetracyclins** isolated from ***Streptomyces***
- **Tetracyclines** are introduced **50** years ago as potent broad spectrum antibiotics.
- They are bio synthesized from acetic acid and propionic acid units in microorganisms.

- * Tetracyclines possess a wide spectrum of activity i.e. gram+ve and gram-ve bacteria.**
 - * They are mainly designed for oral route but parenteral and topical forms are available.**
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- At present, for many reasons such as toxicity, drug resistance, the development of more effectives, the uses of tetracyclines have been largely declined.**

Classification :

Based on

Duration of action :

Short acting(half-life 6-8hrs)

Tetracycline

Chlortetracycline

Oxytetracycline

Intermediate acting(half-life 12hrs)

Demeclocycline

Methacycline

Long acting(half-life is 16hrs)

Doxycycline

Minocycline

Tigecycline

According to source :

Naturally occurring

Tetracycline
Chlorotetracycline
Demeclocycline

Semi-synthetic

Doxycycline
Lymecycline
Meclocycline

Prodrugs:

Rolitetracline
Lymelicycline
Pipacycline
Guamecyclyne

SOURCES

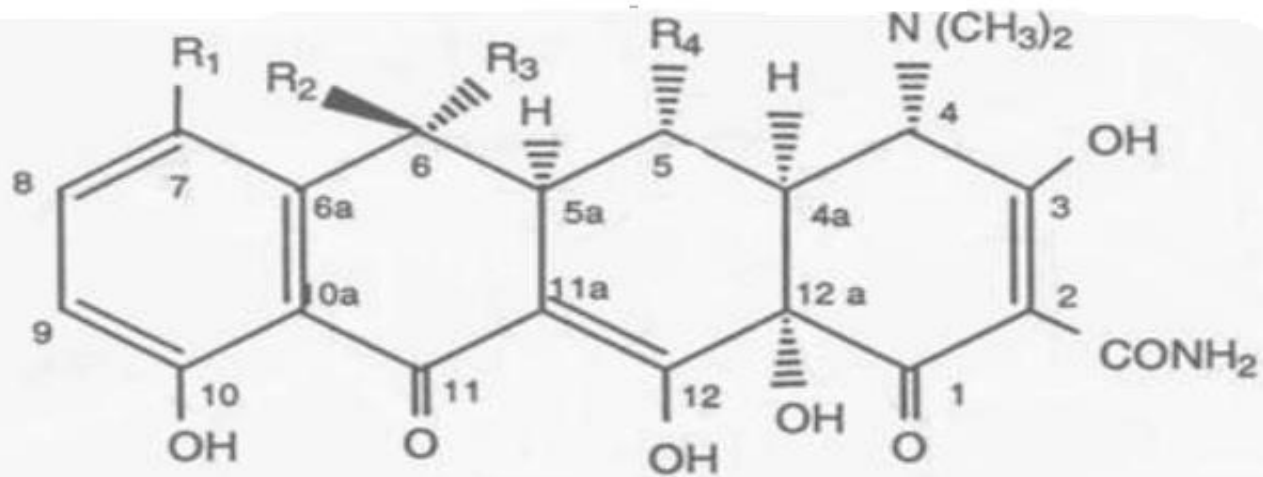
Tetracyclines are obtained from various species of *Streptomyces* bacteria by fermentation technology

Chlortetracyclin(aureomycin) – from *streptomyces aureofaciens*.

Oxytetracycline (Terramycin)– from *Streptomyces rimosus*.

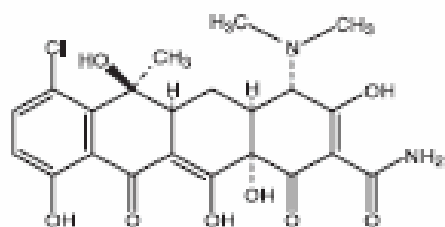
Chemistry

- The basic tetracycline structure consists of four benzene rings with various constituents on each ring.
- The crystalline bases are faintly yellow, odorless, slightly bitter compounds. They are only slightly soluble in water at pH 7 but they can form soluble sodium salts and hydrochloride.

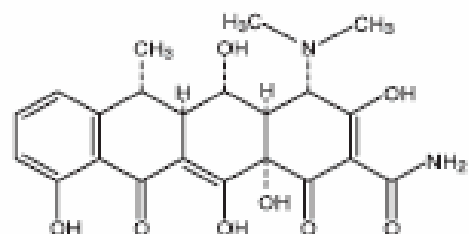


Name	R ₁	R ₂	R ₃	R ₄
Tetracyclines	H	OH	CH ₃	H
Chlortetracycline	Cl	OH	CH ₃	H
Oxytetracycline	H	OH	CH ₃	OH
Demeclocycline	Cl	OH	H	H
Methacycline	H	CH ₂	-	OH
Doxycycline	H	CH ₃	H	OH
Minocycline	N(CH ₃) ₂	H	H	H
Meclocycline	Cl	CH ₂	-	OH

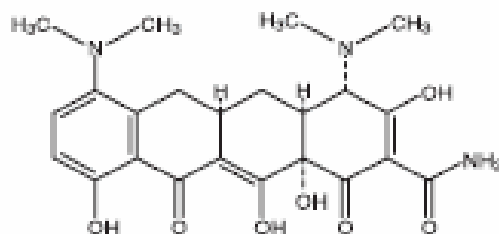
Chlortetracycline



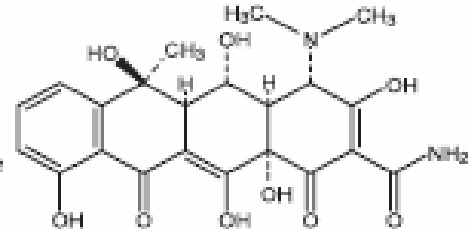
Doxycycline



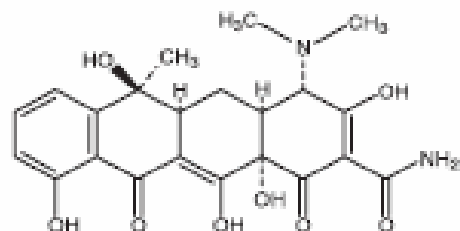
Minocycline



Oxytetracycline

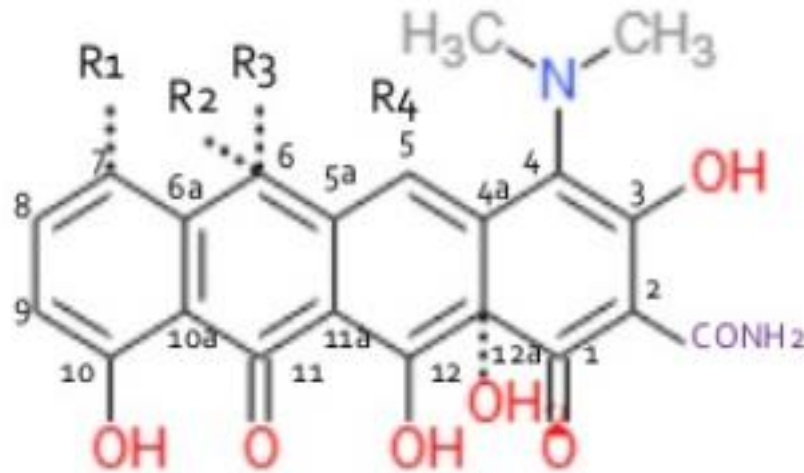


Tetracycline

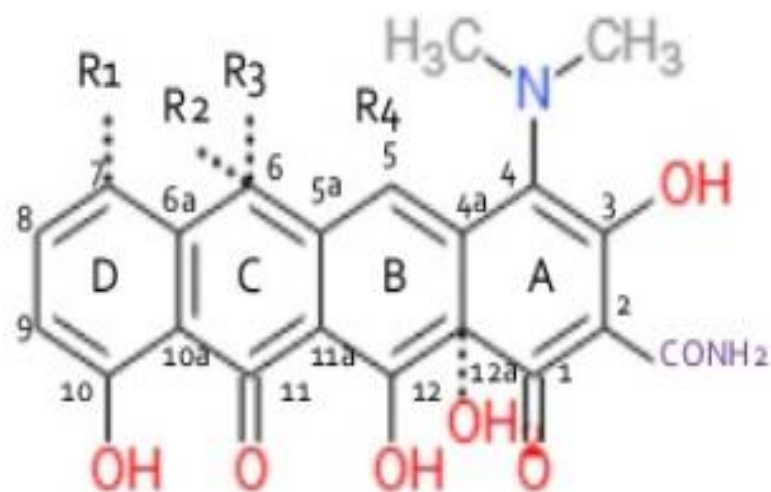


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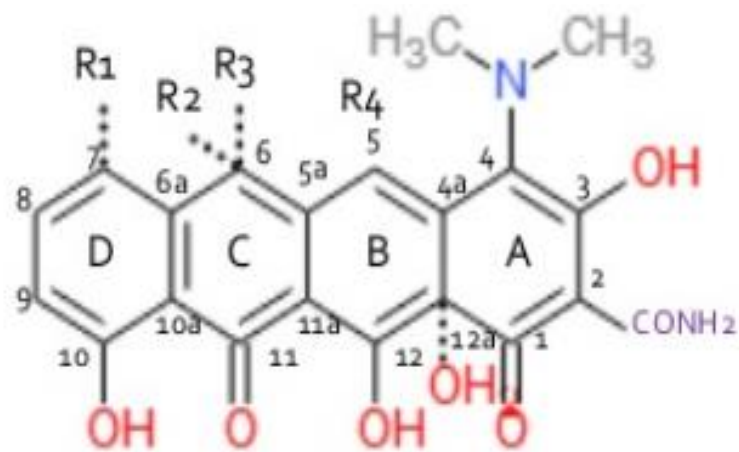
Structure activity relationship



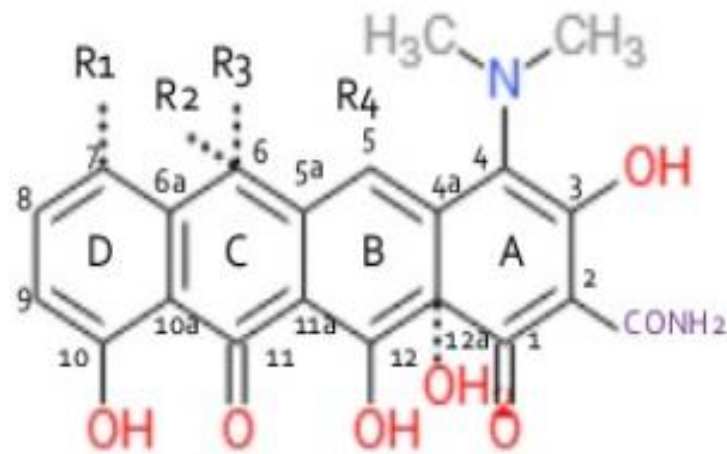
- All derivatives containing less than four rings are inactive
- Substitution at 1,2,3,4,10,11,11a, and 12 represent hydrophilic property that cannot be charged drastically.
- Replacement of amide at c-2 with aldehyde or nitrile abolishes activity



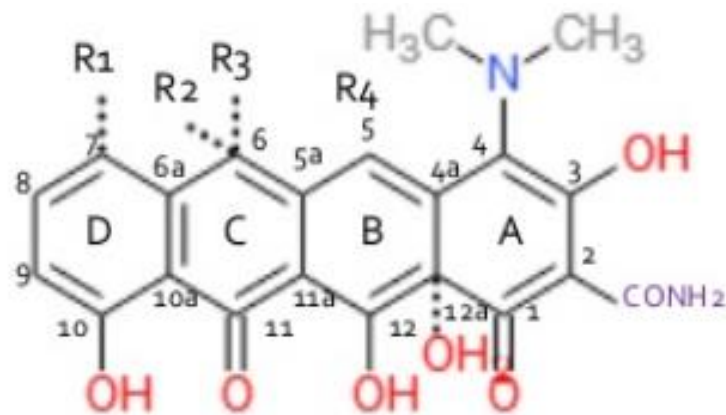
- A slight modification of ring A can be done without much loss of activity
- Aromatisation of ring C gives in hydro tetracycline which is less active than natural one.



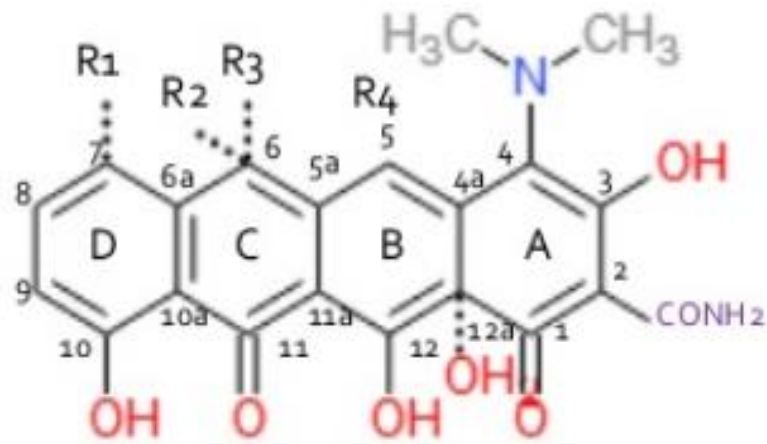
- The hydrophobic part of the molecule from C-5 to C-9 may be altered in various ways:
 - modifications at C-6 and C-7 in particular afford products having greater chemical stability.
 - increased antibiotic activity and more favourable pharmacokinetics



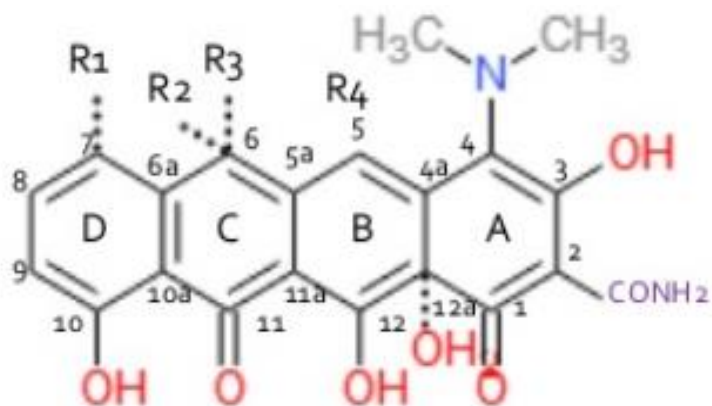
- Dehydrogenation to form a double bond between C-5a and C-11a **markedly decreases activity**
- Polar substituents at C-5 and C-6 contribute **decreased lipid versus water solubility to the tetracycline**



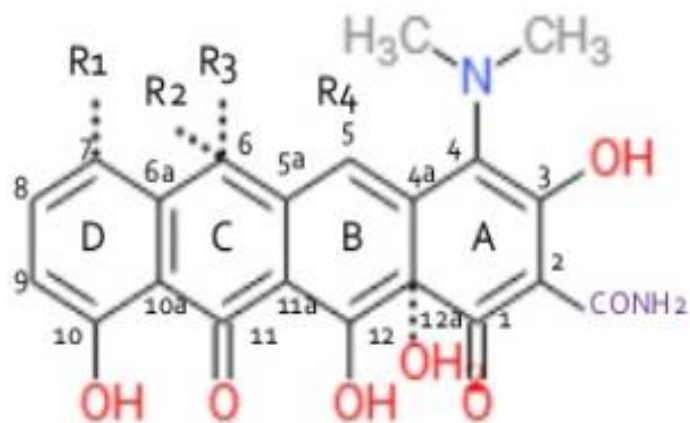
- Retention of the configuration of the asymmetric centres C-4, C-4a and C-12a is essential, whereas the configurations at C-5, C-5a and C-6 may be altered:
- 1) The amide hydrogen may be replaced with a methyl group, but larger groups have a deleterious effect except for those which are eliminated spontaneously in water .



2) The dimethyl amino group may be replaced by a primary amino group without loss of *in vitro* activity but all other changes so far lead to decreased bacteriostatic action .



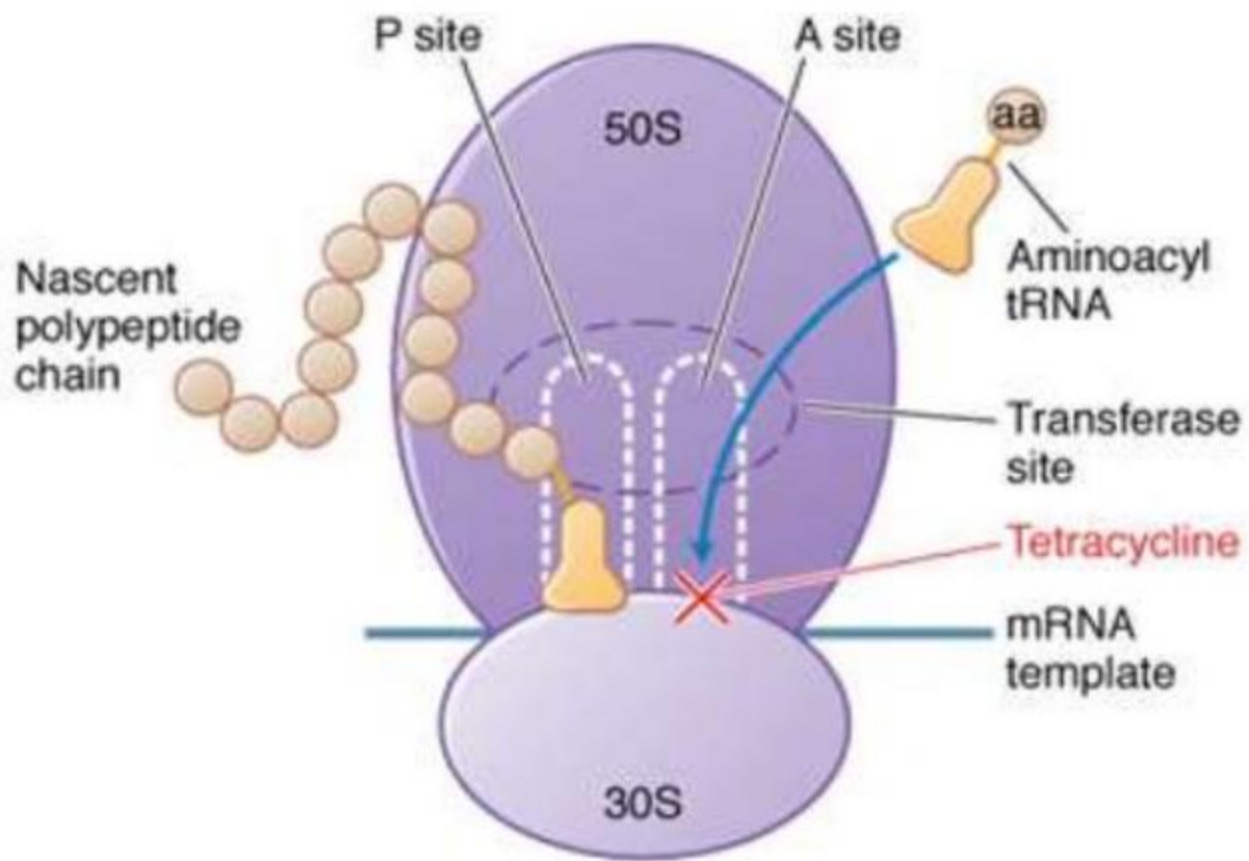
- Mono alkylation of amide group result in loss of activity
- Presence of electron withdrawing group (Cl⁻ or Na⁺) and electron donating group (dimethylamine) at c7 increaes activity.

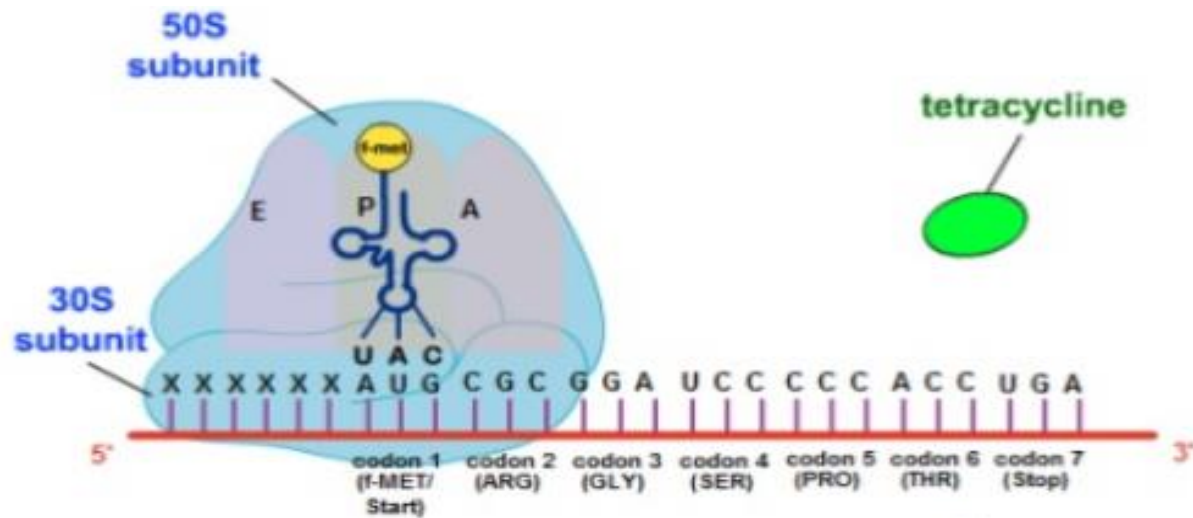


- Epimerization at C-5a gives or dehydrogenation and double bond formation between 5a and 11a markedly decreases activity.
- Alkyl substitution at c-11a leads to inactive compound because inolisable β -diketone at c-11a and 12 is essential for activity.

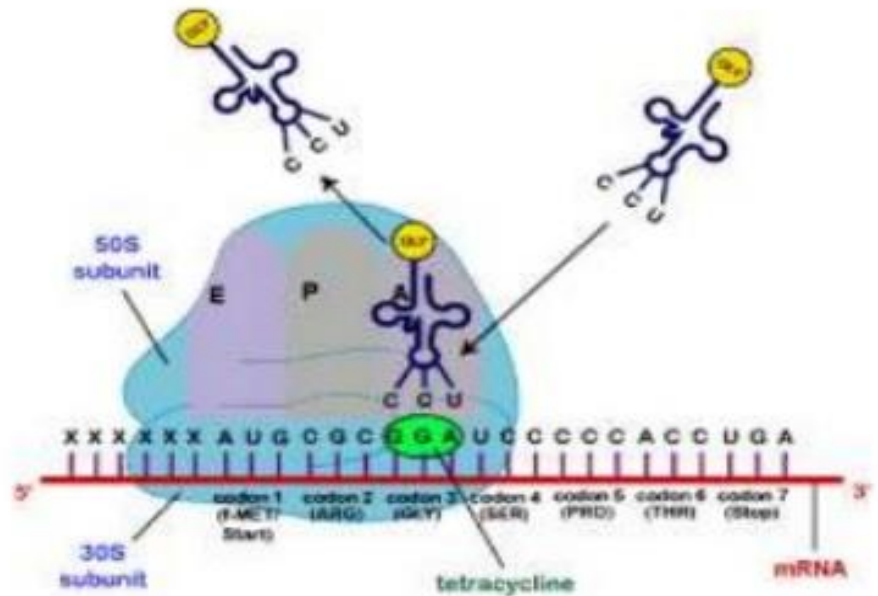
Mechanism of Action

- Following uptake into susceptible organisms by active transport, tetracyclines act by inhibiting protein synthesis.
- Inside the bacterial cell, tetracycline bind reversibly to the 30s subunit of the bacterial ribosome, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA complex.
- This prevents addition of amino acids to the growing peptide & bacterial protein synthesis is blocked.





tetracycline



Therapeutic Uses

1. Rickettsial Infections

- Doxycycline is the drug of choice for treatment of *Rocky Mountain spotted fever* (fever and skin spots caused by ticks).

2. Mycoplasma Infections

- Treatment of *pneumonia* with tetracycline shortens the duration of *fever, cough, malaise* (discomfort, illness, or unease), *fatigue, pulmonary rashes, and radiological abnormalities in the lungs*

3. Chlamydia Infection

- Trachomatis (Eye disorder) and inclusion conjunctivitis
- Nonspecific urethritis, Acute pelvic inflammatory disease.

4. Bacillary Infections

- Tetracyclines are effective for acute and chronic infections including *Tularemia* (acute plague), *Cholera* (*Vibrio cholera*) and gonorrhoea.

5. Other Infections

- Acne: Tetracyclines are useful *acne vulgaris*.
- Gastrointestinal infection
- Sexual infection: Syphilis, Gonorrhoea, etc.

Adverse Effect

- **GI Problem:** Nausea, vomiting, diarrhoea, abdominal discomfort, epigastric burning etc.
- **Phototoxicity:** Sun burn-like skin reaction on exposed part, Onycholysis (detached nail), pigmentation nail etc.
- **Hepatotoxicity:** Fatty liver, jaundice, acidosis, azotemia (increased nitrogenous bodies in blood)
- **Renal Toxicity:** Aggregate uremia, azotemia (due to metabolism of amino acid)
- **Noncalcified Bone:** discoloration and pigmentation of teeth in children may occur due to tetracycline intake by pregnant women
- **Hypersensitivity reaction:** Rashes, urticaria, generalized exfoliative dermatitis, angioedema, anaphylaxis, burning eye, vaginitis etc.
- **Super infection:** through mouth, skin or vagina may be involved; intestinal super infection is most prominent, pseudomembranous enterocolitis is most serious