Charting New Horizons in Education

Pharmacology of bacterial protein synthesis inhibitors

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Pharmacology

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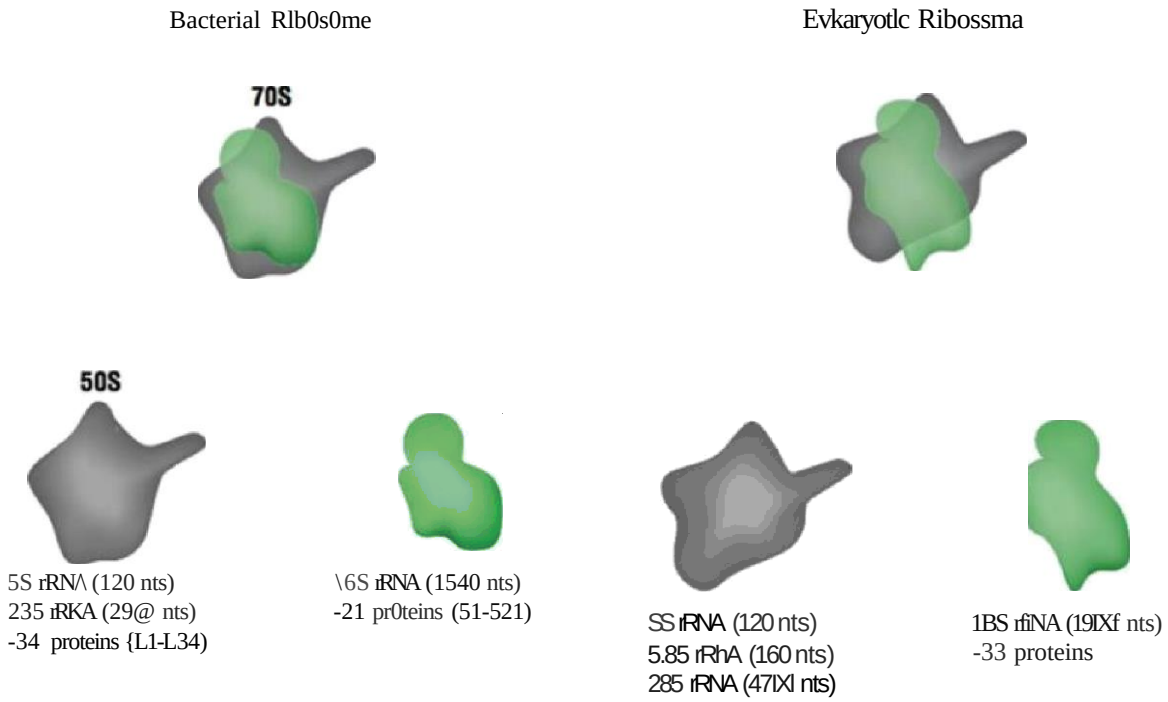
Objectives

- 1- Protein synthesis in bacterial ribosomes
- 2- Mechanism of action of protein synthesis inhibitors antibiotics
- 3- Classification of protein synthesis inhibitors
- 4- Aminoglycosides
- 5- Macrolides
- 6- Tetracyclines
- 7- Chloramphenicol
- 8- Clindamycin

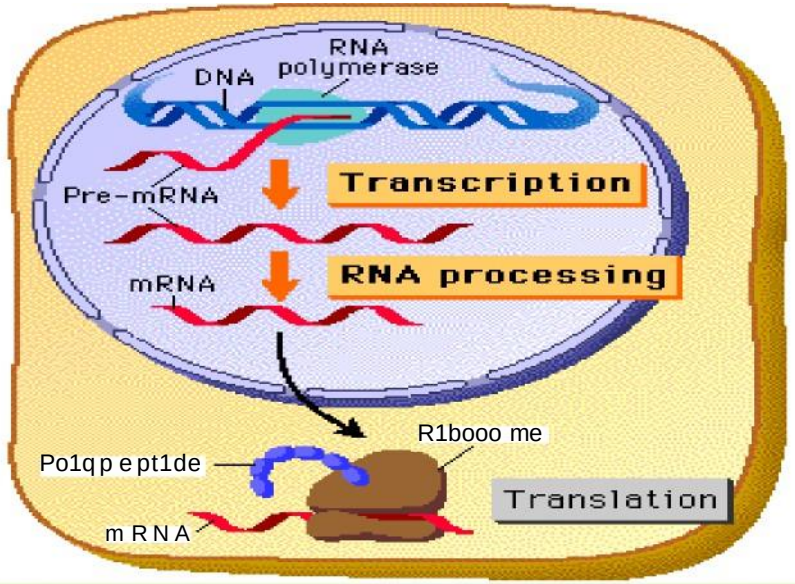
For my students:
It's important to watch the recorded lecture because the mnemonics and stories are not written on the slides.

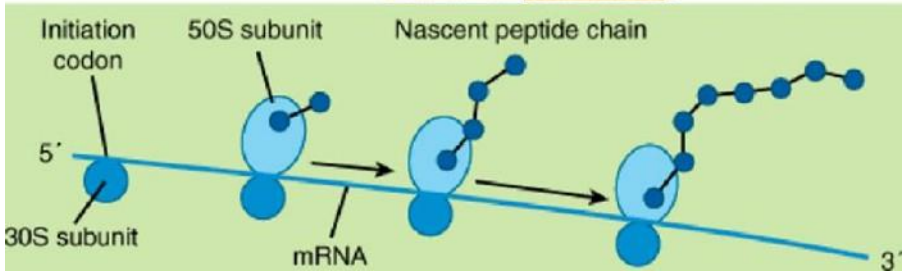
Ribosomes: site of protein synthesis

- Prokaryotic ribosomes are 70S:
- Large subunit: 50 S
    - 33 polypeptides
- Small subunit: 30 S
    - 21 polypeptides
- Eukaryotic are 80S
- Selective toxicity:



- acting at the ribosomal level taking the advantage of major differences prokaryotic and eukaryotic ribosome structure





Aminoglycoside-geated bacterial ceii

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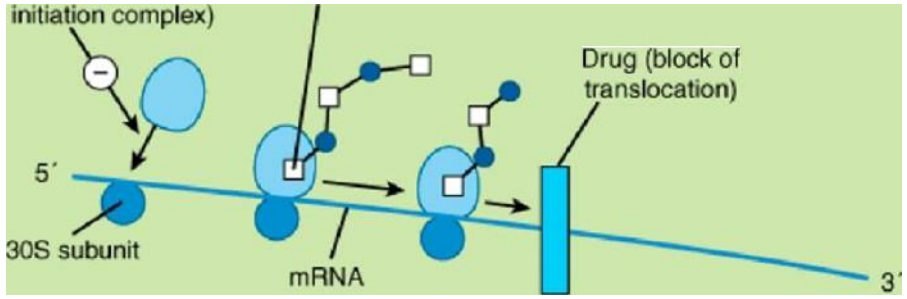
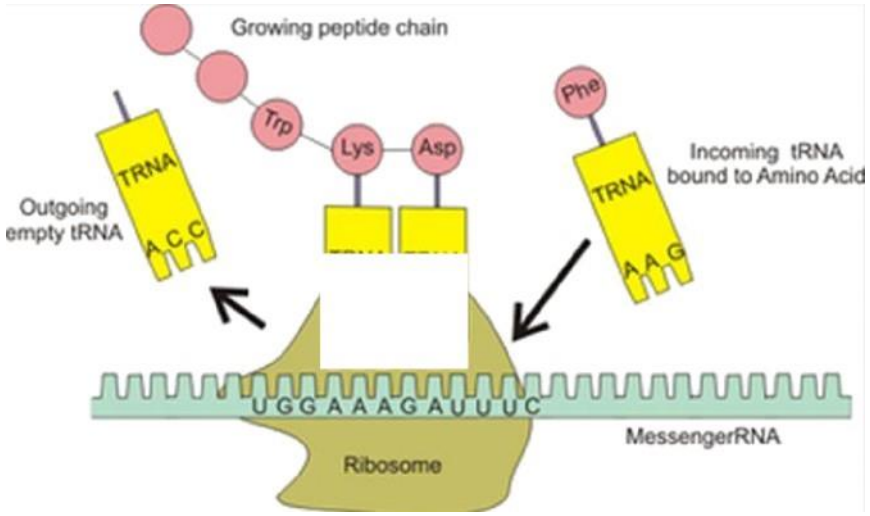


Bacteria protein synthesis



Peptide Synthesis

Protein synthesis in prokaryotic cells occurs in two sites: the nucleus and cytoplasm. A part of the DNA is unwound according to the gene responsible for producing the target protein.

- DNA → Topoisomerase/DNA gyrase (relieves supercoiling) →

then RNA polymerase arrange nucleotides

- Transcription occurs in nucleus, resulting in the formation of mRNA.
- The mRNA exits the nucleus and enters the ribosome, where it binds to the ribosome.
- The mRNA enters the ribosome while being associated with rRNA, The tRNA to help translate the mRNA sequence into a protein.
- Three nitrogenous bases (codon) on the mRNA are translated into a specific amino acid.
- The amino acids bind together through peptide bonds to form a protein.

Drugs that inhibit the 30S or 50S ribosomal subunits interfere with protein synthesis. When these drugs inhibit the ribosomal function, the protein will be miscoded, and the bacteria will not grow. This is why these drugs are bacteriostatic

Calssification of bacterial protein synthesis inhibitors

TETRACYCLINES 1

Demeclocycline DECLOMYCIN
Doxycycline VIBRAMYCIN
Minocycline MINOCIN
Tetracycline SUMYCIN

GLYCYLCYCLINES 2

Tigecycline TYGACIL

AMINOGLYCOSIDES 3

Amikacin AMIKIN, OTHERS
Gentamicin GARAMYCIN
Neomycin NEO-FRADIN
Streptomycin STREPTOMYCIN

MACROLIDES/KETOLIDES 4

Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin E-MYCIN
Telithromycin KETEK

OTHERS 5

Chloramphenicol CHLOROMYCETIN
Clindamycin CLEOCIN
Linezolid ZYVOX
Quinupristin/Dalfopristin SYNERCID

Drug	Aminoglycosides	Macrolides Arythromycin ,clarithromycin, Azithromycin ,spiramycin	Chlorameniphecol	Clindamycin	Tetracyclins
Notes	Members: Gentamicin, tobramycin, neomycin, streptomycin Go to new strep	-Concentrated in macrophages and polymorphs(long biological half life -The only intracellular	2CL atoms /2-OH -widely distributed -not used nowadays except in topical eye enfections	Penetrate bone,tissue,fluids	-Containing –OH groups, least in Minocyclin -concentrated in bone teeth
Cidal/static	Bacteriocidal(bc irreversible binding)	Bacteriostatic In high conc.:cidal	Bacteriostatic	Bacteriostatic	Bacteriostatic
spectrum	Narrow spectrum Gram - aerobic	Moderate spectrum	Broad spectrum	Narrow spectrum Gram+ anaerobic	Broad spectrum
30s/50s (At thirty)	30s Irreversible binding	50s Weak reversible	50s Weak reversible	50s Weak reversible	30s Weak reversible
MW	>500	>500	<500	<500	<500 Tigecyclin : >500
Oral absorption	Not absorbed orally (parentral)	Poor absorption	Well abs.	Rapid complete oral abs.	Partial abs. Abs.decreased with foods,antacids,milk,iron

Drug	Aminoglycosides	Macrolides	Chloramenipheco l	Clindamycin	Tetracyclins
BBB	NOT PASS	NOT PASS	PASS:tx meningitis	PASS:tx meningitis	NOT PASS
Placental barrier	Can't PASS And can't pass to breast milk	PASS but not teratogenic- **DRUG OF CHOICE**	PASS And pass to breast milk	PASS but not teratogenic-	PASS And pass to breast milk
Metabolism		Liver	Need glucorunidation in liver(phase II)	Liver	Liver : extensive
Enterohepatic circulation		YES			YES
Excretion	Urine (active in alkaline urine) Excreted unchanged	Bile	Urine (inactive)	Bile	All tetracyclins: 20% bile 80% urine(inactive) Except doxacyclin,minocycline 50% 50%

Synergy - The aminoglycosides synergize with β-lactam antibiotics.
The β-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.

Aminoglycosides

Indications

1- UTIs: their use is not common due to a fear of nephrotoxicity.

2- Septicemia , meningococcal meningitis: gentamicin.

3- T.B. streptomycin among 1st line drugs of T.B.

4- Plague (Y. pestis): 1st line.

5-neomycin (toxic): local: oral for gut decontamination, hepatic coma .

6- Gentamicin: combined with other antibiotics:
Infective endocarditis with vancomycin.
Peritonitis with penicillin and Metronidazole.(synergistic effect)

7- Tobramycin: eye drops.

Adverse effects

- Nephrotoxicity(old age, cephalosporins).
- Nerve toxicity: 8th cranial nerve:

  ototoxicity: reversible if early.

- Neuromuscular blocking:

  myasthenia graves , muscle

  weakness treated by Ca gluconate.

Macrolides

Indications	Adverse effects
1- G+ve infections respiratory and ENT infections: 2nd choice after penicillins and cephalosporins . 2- Clarithromycin: eradication of H.pylori in peptic ulcer: 10 days. 3- Syphilis: 2nd choice after penicillin and cephalosporins . 4- Atypical infections: eye and genital infections of chlamydia, atypical pneumonia, Legionnaires' disease . 5- Toxoplasmosis	• GIT upset: common • Cholestatic Hepatitis • Enzyme inhibitor: hepatic cytochrome enzyme: aggravates myopathy induced by statins • Prolongation of QT interval: sudden cardiac death

Chloramenicol

Indications	Adverse effects
2nd , EVEN 3rd CHOICE DUE TO TOXICITY 1-Atypical microorganisms: after macrolides and doxycycline: 3rd choice 2- Meningitis: after penicillins, cephalosporins 3rd choice 3- Cholera: ampicillin, 3rd generation cephalosporins, floroquinolones, 4th choice 4- Eye infections: eye drops	TOXIC • Fatal anemia: rare (immunological): not dose-dependent, irreversible, after stopping the drug. • Bone marrow depression reversible, mild, dose-dependent, during treatment. • Hepatic enzyme inhibitor. • Teratogenic: Gray baby syndrome . Contraindications: blood diseases, pregnancy, lactation, children less than 2 y.

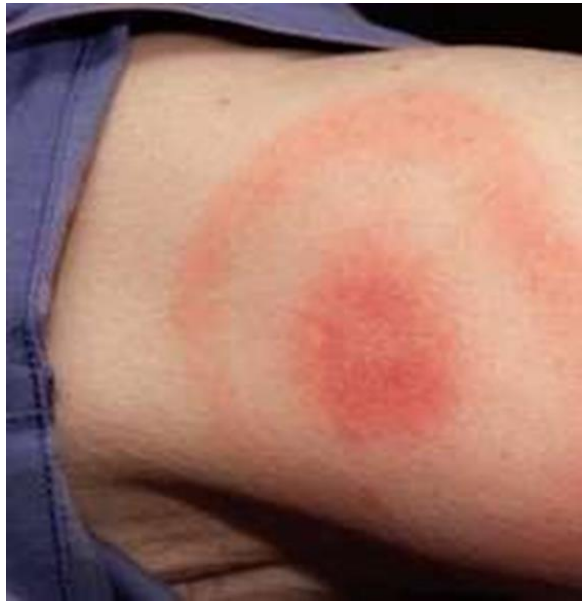
Clindamycin

Indications	Adverse effects
1. Dental infections. 2. Bone, joint infection: osteomyelitis. 3. Toxic shock syndrome :Nafcillin, oxacillin, vancomycin or gentamicin. Note:causes of toxic shock syndrome are staph./strep/clostridium Mnemonic: shock needs only very good care 4. Topical : acne Toxoplasmosis, malaria (off-label).	<u>Pseudomembranous colitis:</u> • 2-20% . • most serious . • May be fatal by Clostridium difficile. • Treatment: oral metronidazole for 7-10 days or oral vancomycin. Pseudomembranous colitis affect intestinal flora, the gram + anaerobic toxin inflame the colon and lead to severe dehydration,diarrhea ,organ failure and death

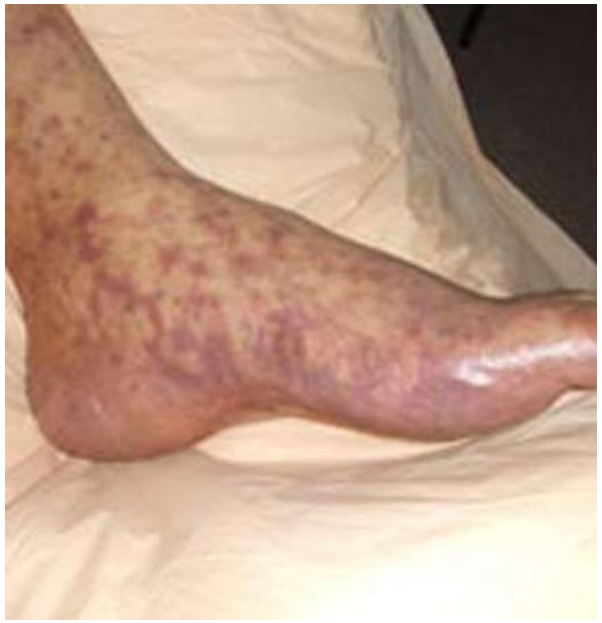
Tetracyclines

Indications	Adverse effects
1 -calm my leg: 2nd choice after Macrolides (Chlamydia,mycoplasma,legionella) 2-BRC: 1st choice, 2nd choice: macrolides: borrelia: tick-born spirochetes: Lyme disease: **doxycycline** 100mg twice daily for 14 days Rickettsia: rocky mountain fever: 100mg **doxycycline** twice daily for 7-10 days Coxiella: Q fever : 100mg **doxycycline** twice daily for 14 days 3- Cholera: 300 mg doxycycline single oral dose 4- Acne: doxycycline oral with topical clindamycin 5- SIADH(syndrome of inappropriate ADH secretion) : **DEMECLOCYCLINE** (antagonize ADH)	1- Teeth, bone: Discoloration and deformity in growing teeth and bones (contraindicated in pregnancy, lactation and in children < 8 years) 2- Renal impairment (should be also avoided in renal disease) 3- GIT upset: peptic ulcer 4- liver: liver cell failure, cholestatic jaundice 5- kidney: nephrogenic DI, Fanconi syndrome (outdated tetracyclines) 6- Photosensitivity

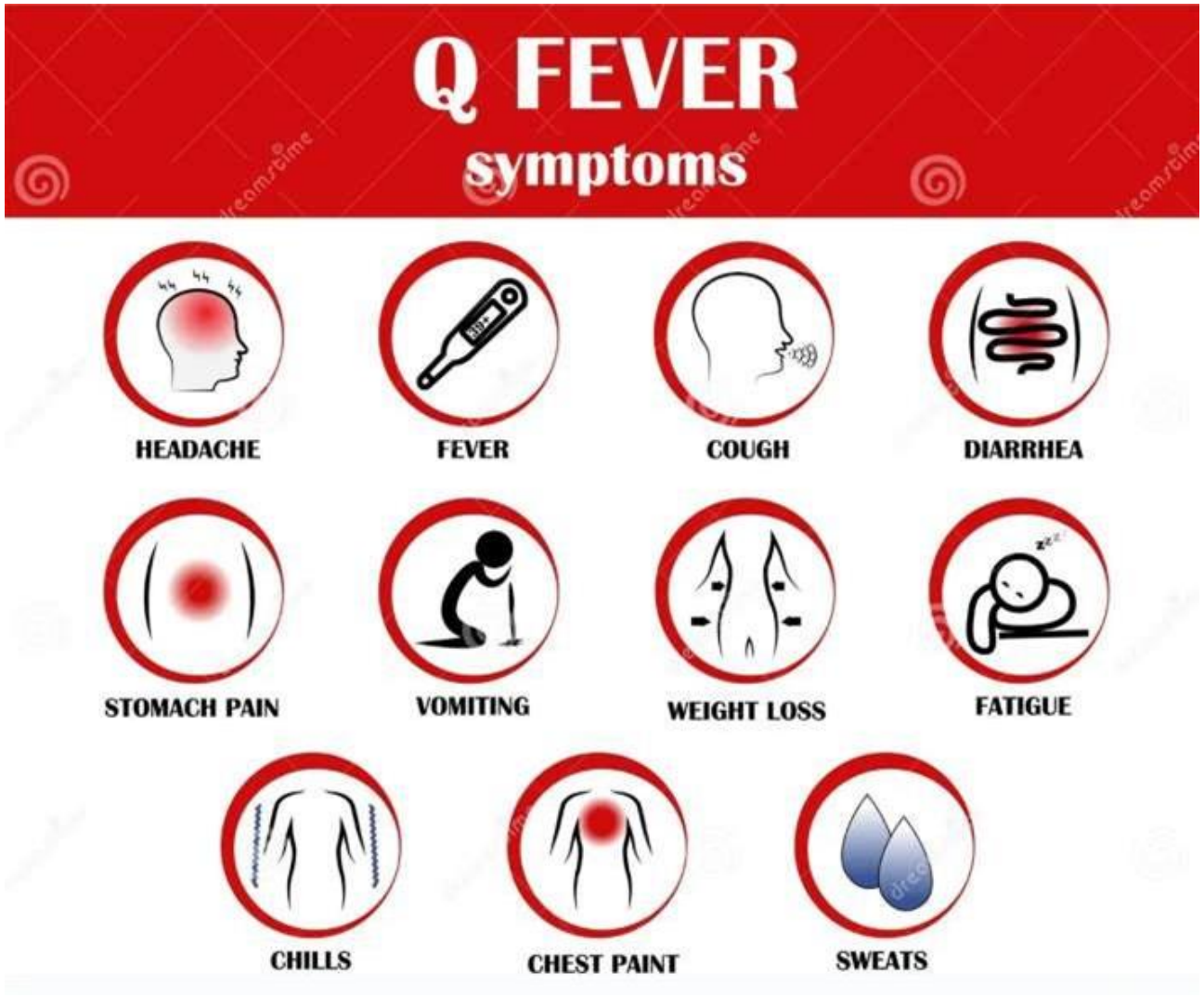
Lyme disease



Fever
Osteomyelitis
Bull eye rash

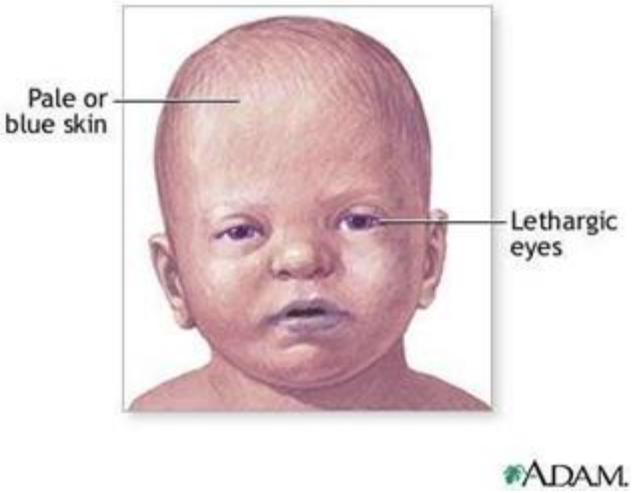


Rocky mountain spotted fever



Teratogenicity of Chloramphenicol

There are no literature reports linking the use of this drug in pregnancy to birth defects
Its administration late in pregnancy has been associated with adverse effects in the neonate
(**grey baby syndrome**).
Low capacity to glucoronyl transferase enzyme and underdeveloped renal function →a decreased ability to excrete the drug → drug accumulates to levels that interfere with the function of mitochondrial ribosomes »»» poor feeding, depressed breathing, cardiovascular collapse, cyanosis ("grey baby") and death.



«Wherever the art of medicine is loved,
there is also a love of humanity.»

- Hippocrates-

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