Biomedical Parasitology

ANTI-PROTOZOALS

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Pharmacology

Study of how drugs interact with organisms to produce a change in function

Drug = medicinal substance

- organic or inorganic
- natural or synthetic

- some truth in old wives tales/witches brews
- herbal remedies still being used
- bioscreening for novel compounds
- synthetic analogues created in labs
- problems with supply and demand
- problems with drug resistance
- problems with certification (FDA, TGA)

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Pharmacology

Pharmocodynamics (PD)
study of what drug does to body
- mimic/inhibit normal processes
- inhibit pathological processes
- stimulants, depressants, toxins

Pharmacokinetics (PK)
study of what body does to drug
- Absorption
- Distribution
- Metablism
- Excretion

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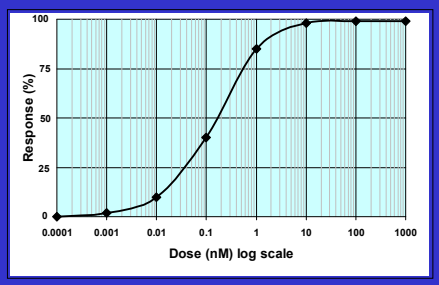
Pharmacodynamics (PD)

DOSE – RESPONSE CURVE



Sigmoidal (S-shaped) curve
reminiscent of logistic growth curve

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Pharmacokinetics (PK)

CONCENTRATION-TIME CURVE

Surge functions
(power + linear/exponential)

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Pharmaceuticals

Action based on selective toxicity (parasite first)

Contra-indicated use - side-effects
- synergism/antagonism

With-holding period - 100-1000x ADI
(acceptable daily intake)

Maximum residue limits

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Products

Names - one international non-proprietary name
- regional nonproprietary names (country)
- several proprietary names (brands)

Oral - tablets, pills, capsules, bolus liquids, emulsions

Parenteral - ampoules, vials, implants (s.c., i.m., i.v., i.p., i.t.)

Topical - liniments, lotions, ointments, dips, shampoos, washes, pour-ons, spot-ons, collars, creams, sprays, powders, aerosols

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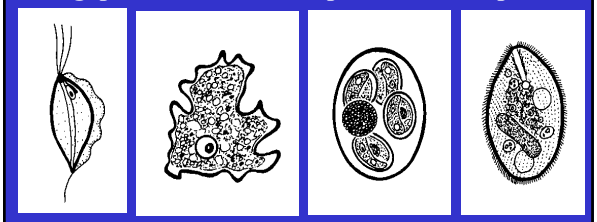
PROTOZOAN DIVERSITY

Mastigophora Sarcodina Sporozoa Ciliophora



flagellates amoebae apicomplexa microspora ciliates

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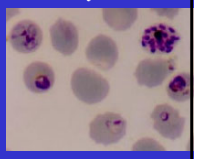
Antiprotozoals (malaria)

1660 - Peruvian Indians use 'fever tree bark' (Cinchona tree)
1820 - quinine isolated from bark
1914-18 - WWI quinine shortage prompted work on synthetics
1928 - pamaquine
1932 - mepacrine
1934 - chloroquine
1939-45 - WWII shortages
1945 - proguanil
1951 - pyrimethamine
1960 - Emergence of chloroquine resistance
1960 - sulphonamides, sulphones
1971 - mefloquine
1974 - series of new compounds from USA
1979 - artemisinin developed in China



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Targeted treatment

	TISSUE STAGE		BLOOD STAGE	
	primary	latent	schizonts	gamonts
Quinine			+++	++
Chloroquine			+++	++
Proguanil	++		++	++
Pyrimethamine	++	+	++	+++
Sulphadoxine/Dapsone	?		+	
Primaquine	++	+++	++	+++
Doxycyline	+	?	++	
Mefloquine			+++	
Halofantrine			+++	
Artemisinin			+++	+
	causal prophylaxis	antirelapse radical cure	suppression clinical cure	prevent spread

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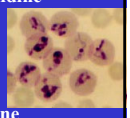
Anti-protozoals (piroplasms)

Babesia

azonaphthalene dyes	- trypan blue
acridine derivatives	- acriflavine
diamidines	- amicarbalide, imidocarb
	- phenamidine, pentamidine
aminoquinolines	- primaquine
macrolide antibiotics	- clindamycin



Theileria

hydroxynaphthoquinone	- menoctone, parvaquone
quinazolinone	- halofuginone

Both

tetracyclines	- oxytetracycline, chlortetracycline

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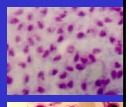
Anti-protozoals (kinetoplastids)

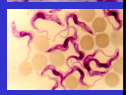
Leishmania

pentavalent antimonials	- stibogluconate, meglumine
polyene antibiotics	- amphotericin B
aminoglycoside antibiotics	- paromomycin



Trypanosoma

trivalent antimony	- antimony tartrate
sulphated naphthylamines	- suramin
aminoquinaldines	- quinapyramine
phenanthride derivatives	- homidium, pyrithidium
aromatic diamidines	- diminazene, isometamidium
melaminophenyl arsenicals	- melarsamine



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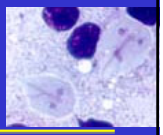
Anti-protozoals (enteric)

	Flagellates blood	Flagellates enteric	Amoebae enteric	Ciliates enteric
1950's diloxanide			+	
chloroquine			+	
1960's iodoquinol			+	
metronidazole	+	+	+	+
furazolidone		+		
1970's emetine	+		+	
erythromycin		+		
tetracyclines		+		
benzimidazoles		+		



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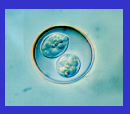
Anti-protozoals (coccidiostatic/coccidiocidal)

ANTIMETABOLITES (antagonists and inhibitors)

Folate antagonists/inhibitors	sulfonamides, ethopabate, diaminopyrimidines
Thiamine antagonists	amprolium
Purine antagonists	glycarbylamide
Mitochondrial inhibitors	4,hydroxyquinolones, pyridone compounds
Membrane ion shunts	polyether, monocarboxylic acid, ionophorous antibiotics

NUCLEOSIDE ANALOGS

Uridine analogs	tiazuril, azauracils
Adenosine analogs	arprinocid, benzyl purine



OTHERS

Organic arsenicals	roxarsone, arsanilic acid, arsenobenzene
Nitrobenzamides	nitromide, zoalene, aklomide
Nitrofurans	nitrofurazone, furazolidone
Bis-(benzylidine amino) guanidines	robenidine
Bis-nitrophenols	nitrophenide
Halofuginone	

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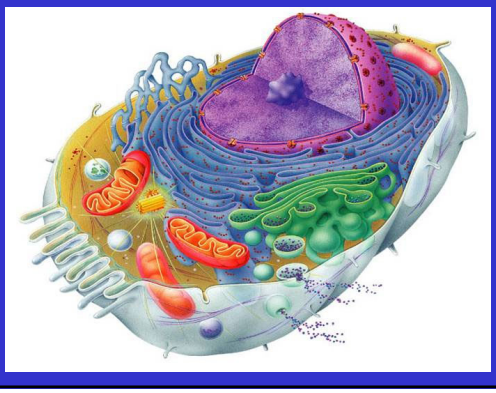
Drug targets: eukaryotes



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MODES OF ACTION

Drugs exhibit selective activity on:

- DNA synthesis
- protein synthesis
- energy metabolism
- membrane function
- microtubule function
- haem(oglobin) interaction
- neurotransmission

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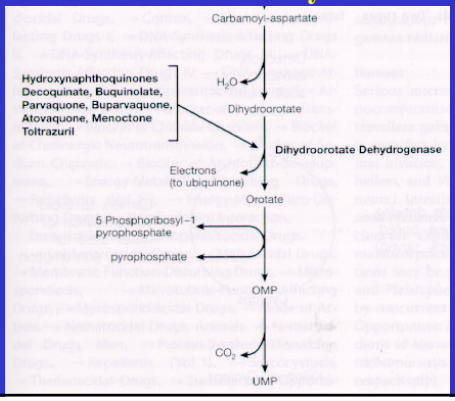
Interfere with DNA synthesis



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DNA synthesis affecting drugs

- interference with dihydroorotate dehydrogenase
  - hydroxyquinolines (decoquinate)
- alkyalation reactions
  - nitroimidazoles (metronidazole)
- interference with purine salvage
  - diloxanide (furamide)
- interference with polyamine metabolism
  - melarsoprol (melarsen)
- interference with cofactor synthesis
  - sulfonamides (sulfadoxine)

⇒ STOP REPLICATION

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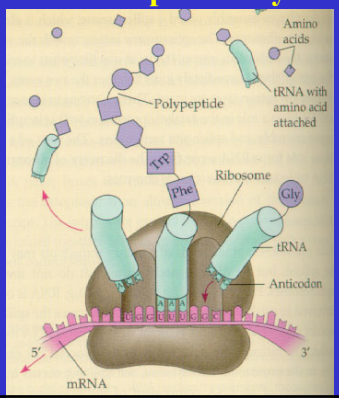
Interfere with protein synthesis



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Protein synthesis-affecting drugs

- emetine (mebadin)
- tetracyclines (oxytetracycline)
- lincosamides (clindamycin)
- macrolide antibiotics (erythromycin)
- aminoglycoside antibiotics (paromomycin)
- glutarimide antibiotics (axenomycin)
- glycopeptide antibiotics (streptothricin)
- diamphenethide (coriban)

⇒ DENY BUILDING BLOCKS

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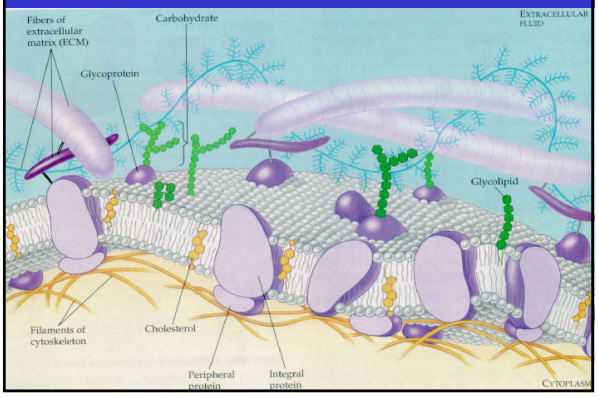
Interfere with membrane function



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Membrane function disturbing drugs

- amphotericin B (amphozone)
- polyether antibiotics (monensin)
- mepacrine (atabrine)
- bunamidine (buban)
- praziquantel (droncit)
- diethylcarbamacine (carbam)

⇒ DISRUPT MEMBRANE INTEGRITY/FUNCTION

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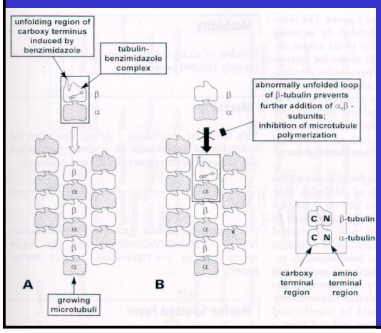
Microtubule function affecting drugs

- benzimadazoles (albendazole)



⇒PARALYSE PARASITES

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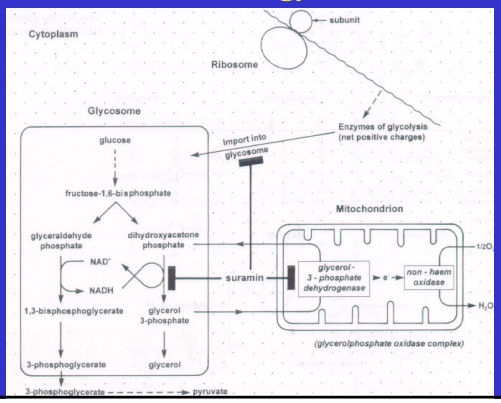
Interfere with energy metabolism



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Energy metabolism disturbing drugs

- rotenoids
- iodoquinol (ioquin)
- suramin (germanin)
- antimonials (sodium stibogluconate)
- clopidol (clopindol)
- robenidine (robenz)
- amprolium (amprol)
- arsenicals (carbasone)
- clorsulan (curatrem)
- isothiocyanates (bitoscanate)
- halogenated monophenols (disophenol)
- halogenated bisphenols (bithionol)
- salicylanilides (niclosamide)
- cyamine dyes (pyrvinium)

⇒ STARVE or SUFFOCATE PARASITES

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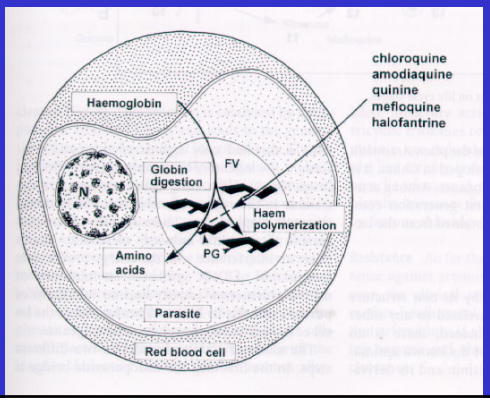
Interfere with haem utilization



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Haem(oglobin) interaction

- artemisinin (artemether)
- amodiaquine (amodiaquine)
- halofantrine (halofantrine)
- chloroquin (chlorochin)
- quinine (various)
- mefloquine (laricur)

⇒ STARVE PARASITES

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DRUG USE

Huge range of chemicals used for parasite:

chemotherapy (curative)
- static drugs (arrest development, reversible)
- cidial drugs (irreversible damage - lethal)

chemoprophylaxis (preventive)
- stop infection
- limit infection

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PROBLEMS

Emergence of drug resistance due to:
- under-dosing (sublethal doses)
- poor compliance (treatment not completed)

Resistance found against:
- antimalarials (chloroquine)
- anticoccidials (ionophores, sulfonamides)
- anthelmintics (white/clear drenches)
- insecticides (DDT, organophosphates)

Need to understand mode of action of drug

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Possible mechanisms of resistance

DRUG LEVEL

- Exclusion
  - decreased drug import
  - increased drug export
- Sequestration
  - drug-binding molecule
  - drug compartmentalization
- Metabolism
  - pro-drug not activated
  - increased drug inactivation

TARGET LEVEL

- Modified
  - decreased affinity
- Amplified
  - increased sequestration
  - increased threshold
- Missing
  - target bypass
- Repaired
  - increased damage repair
- Protected
  - protected by substrate

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Have come a long way! But…..

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