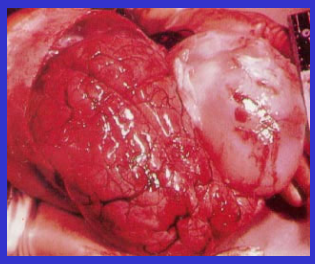
BioMedical Parasitology

Parasitic diseases (parasitoses)



Prof Peter O'Donoghue

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Parasitology

parasite morphology → diagnosis

parasite development → transmission

parasite pathogenicity → pathology

parasite biochemistry → treatment

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Pathology (*pathos* - suffering)

Established fields

- organismal pathology (disease presentation)
- gross pathology (organ/tissue abnormalities)
- histopathology (cellular changes)

Emerging fields

- subcellular (ultrastructural changes)
- molecular (metabolic changes)

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Pathology

Four aspects to every disease process

- aetiology (causative agent)
- pathogenesis (sequence/mechanisms)
- morphological changes (structural changes)
- functional changes (derangements leading to clinical features – symptoms/signs)

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Pathology

Normality preserved through homeostasis

Stressors induce cellular adaptations leading to changes in structure/function; esp.

- hypertrophy (↑ size/function of cells)
- atrophy (↓ size/function of cells)

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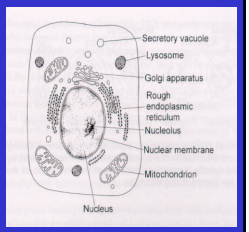
Cell injury

- adaptation
- reversible
- irreversible
- death
  - necrosis (swelling/rupture)
  - apoptosis (condensation)



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Cell injury

Main causes:
- hypoxia (oxygen deprivation)
  [ischaemia, anaemia]
- physical agents
  [trauma, burns, radiation, electric shock]
- infectious agents
  [viral, bacterial, fungal, parasitic]
- chemical agents
  [drugs, poisons, toxins, metabolites]
- immunological reactions
  [hypersensitivity, immunopathology]
- genetic derangements
  [gene defects]
- nutritional imbalances
  [protein deficiencies, lipid excesses]

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Molecular mechanisms of cell injury

- oxygen-derived free radicals
  [cause lipid peroxidation, etc]
- loss of calcium homeostasis
  [gradient imbalances]
- ATP depletion
  [loss of synthetic and degradative functions]
- defective membrane permeability
  [membrane damage, transpoprt loss]

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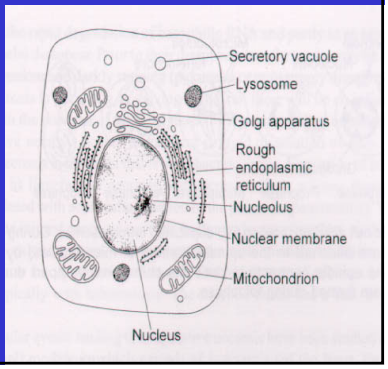
Cell injury

- membrane
- mitochondria
- lysosomes
- endoplasmic reticulum
- nucleus



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Necrosis - critical steps

- loss of membrane function
  (inability to maintain chemical gradients)
- failure of mitochondrial recovery
  (reperfusion injury due to oxygen radicals)
- loss of membrane integrity
  (degradation of phospholipids)

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Necrosis

Morphological changes following cell death
- coagulative (ghosting)
- liquefactive (dissolution)
- fat necrosis (chalky deposits)
- caseous necrosis (cheesy deposits)

Need to differentiate between:
- infection necrosis (caused by pathogen)
- hypersensitivity necrosis (cytotoxic T cells)
- infarction necrosis (loss of blood supply)

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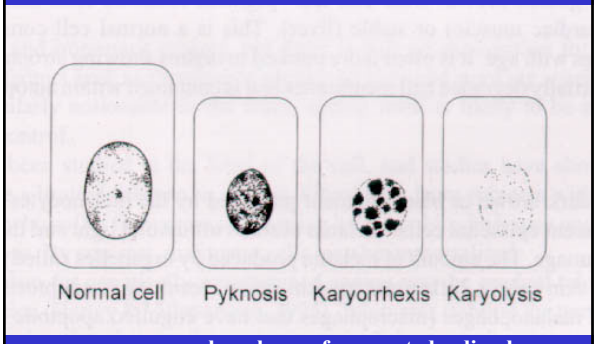
Nuclear degeneration



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Cytoplasmic content

Abnormal cell storage
- lipids
- carbohydrates
- iron (ferritin/haemosiderin)
- copper
- lipofuscin (wear & tear pigment)
- melanin
- carbon

Calcification
- dystrophic (in areas of necrosis/fibrosis)
- metastatic (hypercalcaemia - stores)

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Systemic effects

- inflammation (tissue enlargement)
- oedema (fluid retention)
- haemorrhage (bleeding)

} all contributing to ill-health

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Acute inflammation

- rubor, calor, tumour, dolor (red, hot, swollen, painful)
- congestion (outpouring plasma)
- red hepatisation (red cells)
- grey hepatisation (neutrophils)
- resolution (granular debris)
- complications
  - fibrosis (collagen rich connective tissue)
  - abscess (pus)
  - metastasis (dissemination to distant sites)
  - secondary ischaemia (necrosis)
  - sinuses (blind) or fistulae (connected)

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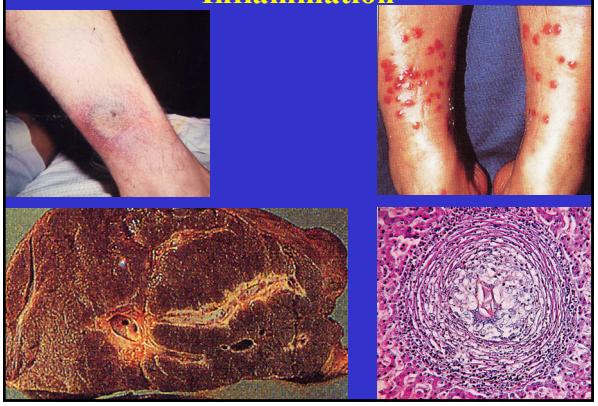
Inflammation



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Oedema

Abnormal collection fluid in extracellular compartment
- protein-rich fluid - exudate
- protein-poor fluid - transudate
- hyperaemia - increased blood volume in organ due to increased arterial flow
- congestion - increased blood volume in organ due to reduced venous outflow

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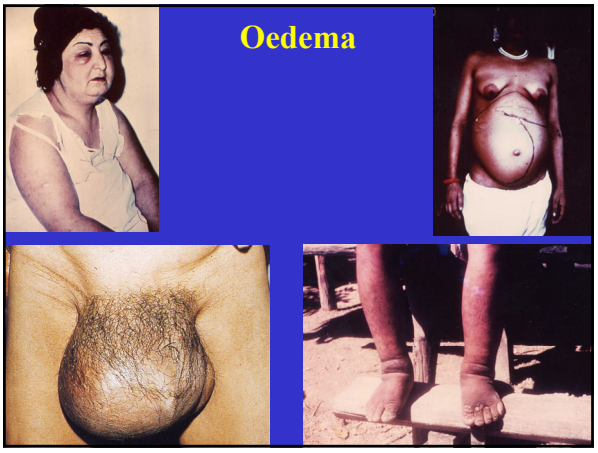
Oedema



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Haemorrhages

Blood vessel rupture
- small - petechiae
- medium - purpura
- large - ecchymoses
- huge - haematoma

Ischaemia
- reduced blood supply
- causes tissue necrosis (infarct)

Thrombosis
- clot (platelets + fibrin)

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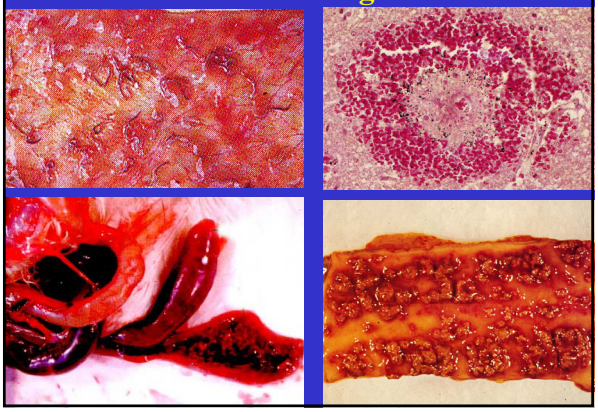
Haemorrhages



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Embolism

Embolism
- passage of mass in blood stream (origin - impaction)
- solid, liquid, gas
- pulmonary (lung)
- systemic (myocardial infarct)
- amniotic (childbirth)
- air (bends)
- fat (fractures)

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Shock

Circulatory collapse
- hypo-perfusion
- hypo-tension

- cardiogenic shock
- hypovolaemic shock
- septic shock
- anaphylactic shock

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Cancer (L. crab)

- Hippocrates observed crab-like tumour
- 10th century - humoral theory
  - four humours = black bile, yellow bile, blood, phlegm (disease due to contamination of blood with black bile, therefore blood-letting therapy)
- 16th century - toxic agents
  - lymphatic accummulation of toxins cause cancer
- 18th century - disease of body tissues
  - recognition of cell unit
- 20th century - cancer = clone of malignant cells
  - due to external agents (microbes/chemicals/radiation)
  - caused by constitutional factors (genetic mutations)

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Cancer

- uncontrolled growth
- invasion and destruction of local tissues
- metastasis (spread)

Diagnosis
- symptoms
- clinical examination
- imaging (CAT, ultrasound, MRI, barium)
- histopathology (cell/tissue examination)

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Cancer

mass - lump - tumour (= swelling)

palpable lump could be:

- abscess
- cyst
- hamartoma (developmental malformation)
- hernia
- neoplasm

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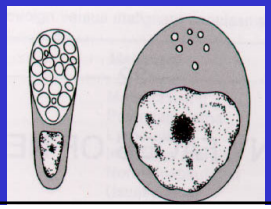
Cancer

Microscopy reveals:

- collagen-rich connective tissue stroma
- ulceration/necrosis (outgrows blood supply)
- increased mitotic activity
- variable size, shape, staining

normal cell



adenocarcinoma cell

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Neoplasms

BENIGN	MALIGNANT
non-metastasizing	metastasizing
small	large
well circumscribed	infiltrative margins
often encapsulated	non-encapsulated
cystic	usually solid
few mitoses	many mitoses
no necrosis	necrosis
rarely lethal	often lethal

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Cancer

Histogenic classification

carcinoma (epithelial tissue)	sarcoma (connective tissue) (mesenchyme)

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Carcinomas

epithelial tissue	benign	malignant
squamous	papilloma	sq cell carcinoma
col/cuboidal	papilloma	adenocarcinoma
transitional	adenoma	trans cell carcinoma

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Sarcomas

connective tissue	benign	malignant
connective tissue	fibroma	fibrosarcoma
fat	lipoma	liposarcoma
muscle	myoma	myosarcoma
cartilage	chondroma	chondrosarcoma
bone	osteoma	osteosarcoma
lymphoid	-	lymphoma
skin	nevus	melanoma

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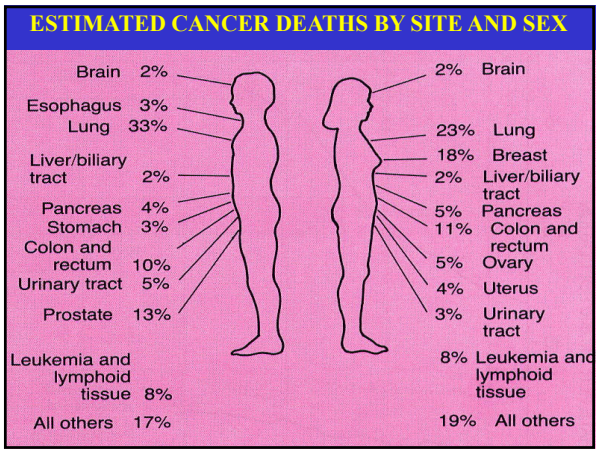

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Host + Parasite ≠ Disease

Outcome of infection dependent on various host-parasite interactions, especially:

- parasite pathogenicity
  - high pathogenicity causes morbidity/mortality
  - low pathogenicity tolerated (commensalism?)
- host responses
  - over-reaction causes pathology (immunopathology)
  - under-reaction fails to clear infection

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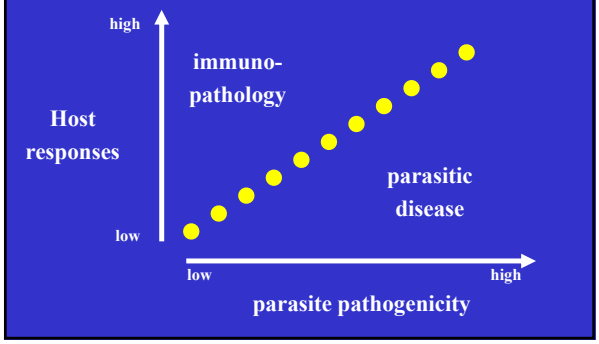
Balance



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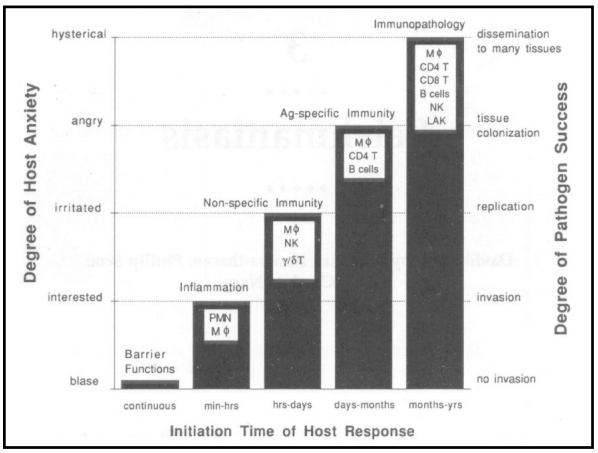

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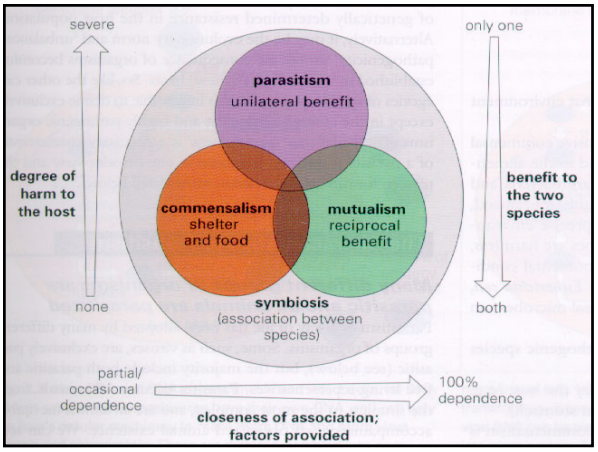

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Co-evolution

Host-parasite interactions

- parasites with a long co-evolutionary history are less pathogenic (some are even border-line commensals or mutualists)
- parasites are poorly adapted to humans (cf. zoonoses) and are more likely to cause serious disease

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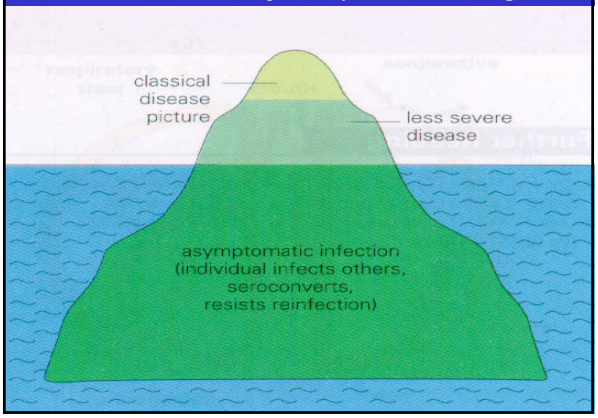
Disease is merely the tip of the iceberg



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Relationships

- organism - pathogen
- infection - internal/external (infestation)
- disease - pathology (abnormalities)
- illness - symptoms (subjective = felt)
  - signs (objective = seen)

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Infection kinetics

- infection - invasion, establishment
- latent - incubation period, prepatency
- patent - infective (acute)
- chronic or cure - persistence (concomitant)
  - eradication (sterile)

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Epidemiology

Study of disease distribution (temporal/spatial)
- prevalence (cross-sectional) single time point
- incidence (longitudinal) change over time
- intensity (parasite burden per host)

Diseases may be:
- established (endemic/enzootic)
- locally acquired (autochthonous)
- imported/introduced/exotic
- epidemic (outbreak)

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Virulence

Capacity to cause disease (morbidity/mortality)
- often measured as LD_{50} or ID_{50}

Virulence factors
- multiplication
- feeding
- cytotoxicity
- immuno-evasion
- tropism (tissue/cell)
- host specificity (ecological - sympatry)
  (ethological - behaviour)
  (physiological - molecular)

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Pathogenicity/Virulence

Parasites cause disease during:
- Infection
  - ingress, attachment/adhesion, invasion, penetration, perforation
- Movement
  - transport, migration, tissue tropism, lodgement
- Feeding
  - nutrition, ingestion, digestion, metabolism, secretions, excretions, growth, development
- Breeding
  - replication (dynamics/kinetics), reproduction (offspring), egress

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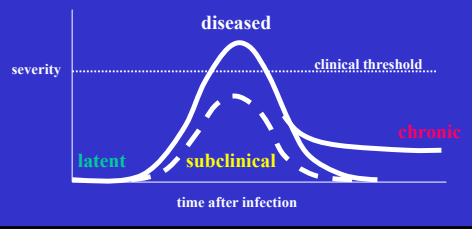
Clinical threshold

Disease related to severity of infection:

- latent infections (incubation period)
- chronic infections (concomitant/premunition)
- subclinical infections (asymptomatic)



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Impact of infectious agents

Viral pathogens
- invade cell, hijack function
- destroy cell, structural deficit
- transform cell (oncogenes/tumor)

Bacterial pathogens
- attach/invade cells
- chemical attack (enzymes/toxins)
- elicit inflammation

Parasitic pathogens
- intracellular → cell destruction
- extracellular → tissue damage
- organ lesions/dysfunction
- immunopathology (hypersensitivity)

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Pathology

Abnormalities arise due to:

- direct effects
- innate immune responses
- acquired immune responses

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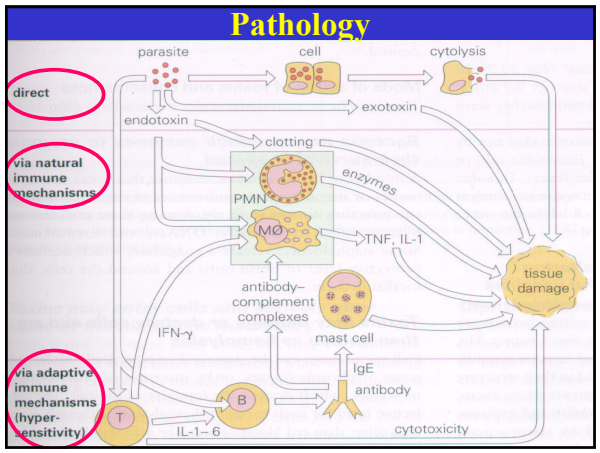
Pathology



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THREE LINES OF DEFENSE

first line BARRIER	second line INNATE	third line ADAPTIVE (ACQUIRED)
nonspecific	nonspecific	specific
parasites encounter external coverings and their secretions	parasites penetrating barriers encounter phagocytes & inflammation	surviving parasites encounter cell-mediated and humoral responses

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Pathology due to direct effects

- cell rupture (e.g. malaria)
- organ blockage (e.g. worms)
- mechanical disruption (e.g. hydatids)

Exacerbated by exotoxin release (secretory/excretory metabolic products)
- entry (into body)
- spread (throughout body)
- defense (against host responses)
- excretion (of waste products)

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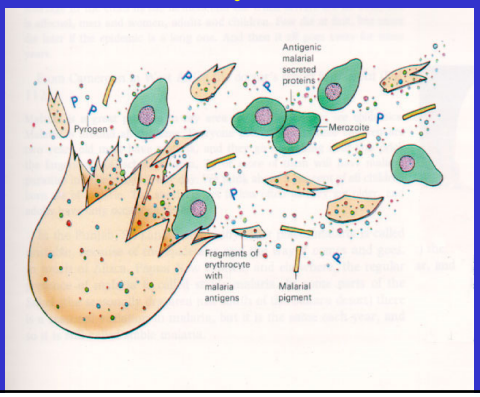
Cell lysis



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Pathology due to innate immunity

- endotoxins
  - released from dying cells (LPS)
  - induce fever, septic shock
- complement
  - immune complex disease (nephritis)
- intravascular coagulation
  - clotting defects
- mast cell degranulation
  - direct activation (anaphylactoid)

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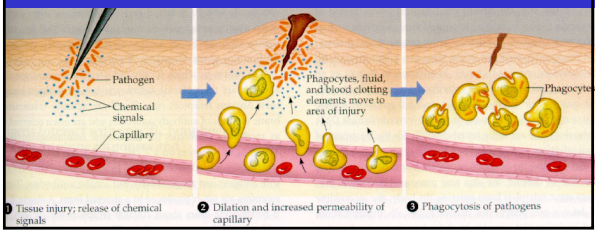
Inflammation

• rubor	redness	vasodilation, incr. flow
• tumor	swelling	outpouring of plasma
• calor	heat	vasodilation
• dolor	pain	stretching of swollen tissues



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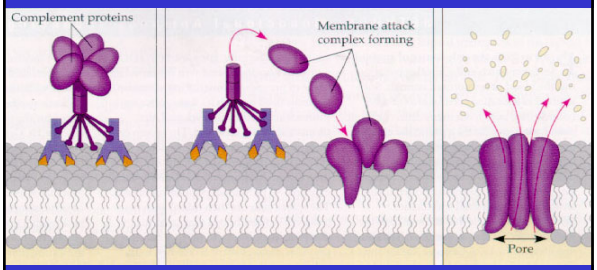
Complement

activation of serum proteins (+/- antibody)
(classic and alternate pathways)



pathogen lysis by membrane disruption

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Pathology due to acquired immunity

hypersensitivity reactions

• type I	anaphylaxis (IgE)	eosinophilia asthma/pruritis
• type II	cytotoxic (Ab)	cell destruction coating
• type III	immune complex (Ag-Ab)	nephritis chronic infection
• type IV	cell-mediated (T cells)	cytotoxic cells macrophages granuloma

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Defenses

- phagocytosis
  - oxidative killing (ROI)
  - non-oxidative killing (cytotoxic granules, RNI)
- cytotoxicity (lymphocytes, NK cells)
- cytotoxic lipids (lipid peroxides)
- cytokines
  - infection control
  - infection pathology

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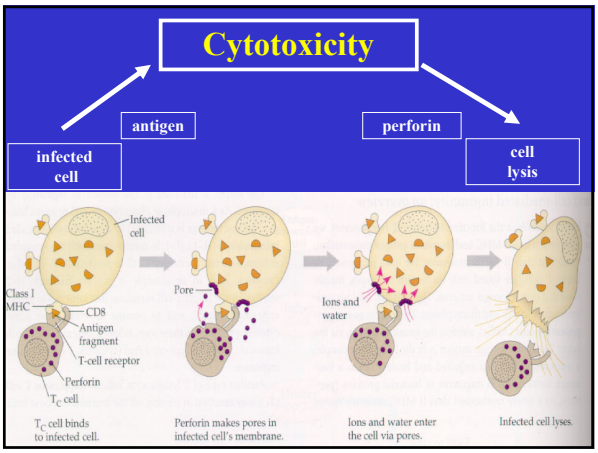
Cytotoxicity



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Reactive intermediates

ROI (reactive oxygen intermediates) oxidative burst

O_2 → O_2^- → H_2O_2 → OH^-

molecular oxygen — superoxide anion — hydrogen peroxide — hydroxyl radicals

RNI (reactive nitrogen intermediates) nitric oxide

L-arginine —(catalysed by cNOS/iNOS; generates NO)→ L-citrulline

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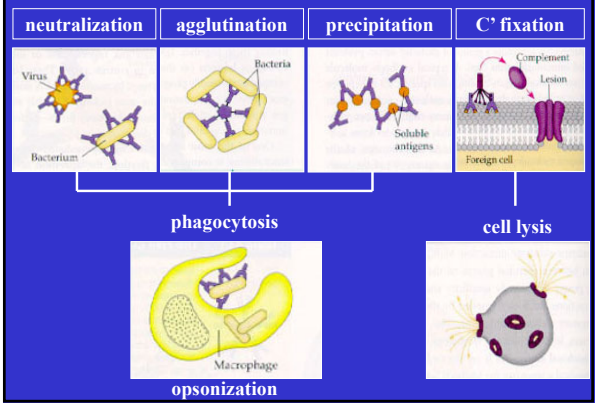
ANTIBODY ACTION



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Pathology site-dependent

Compartmentalization

Intracellular	Extracellular
cytoplasmic nutrients	feed on cells/tissues
protected from Ab	exposed to Ab
cytotoxic agents	opsonization
cell damage	tissue damage
---> protozoa	---> worms

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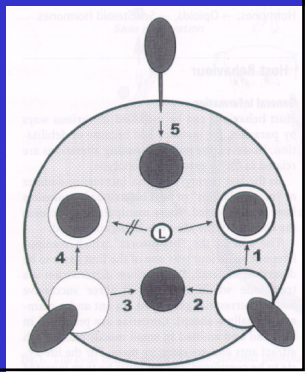
Intracellular parasitism

Parasite entry/location
1 = phagocytosis
2 = cytoplasm
3 = active penetration
4= parasitophorous vacuole
5 = injected thru membrane

L = lysosome



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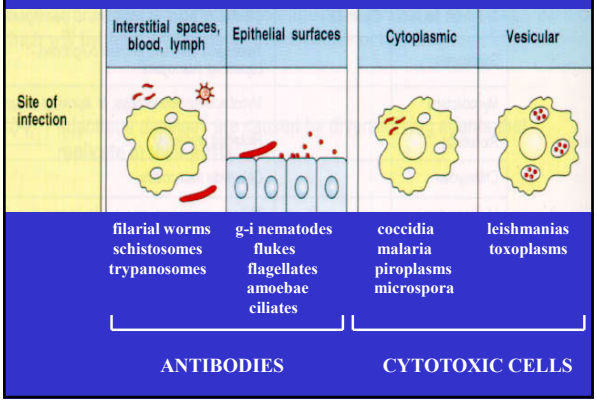
COMPARTMENTS



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Twelve categories of disease

- inflammatory (swelling)
- cardiovascular (ischaemia)
- neoplastic (tumor/cancer)
- genetic (hereditary)
- development (growth)
- endocrine (hormonal)
- nutritional (metabolic)
- autoimmune ('self')
- mechanical (trauma)
- end stage (senescence)
- iatrogenic (due to treatment)
- idiopathic (unknown)

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Parasite Pathology

Damage to host occurs in five categories

- **mechanical** (physical damage, obstruction)
  (e.g. feeding *Haemonchus, Dictyocaulus* in lungs)
- **digestive** (host cells digested by enzymes)
  (e.g. *Paramphistomum* feeding)
- **depletive** (parasites use host nutrients)
  (e.g. tapeworms)
- **allergenic** (hypersensitivity)
  (e.g. reaction to *Strongyloides* larvae)
- **anaemic** (blood loss - feeding/bleeding/lysis)
  (e.g. hookworms, *Sarcocystis, Babesia*)

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Parasitic disease (parasitoses)

Parasites cause disease by:

- stealing nutrients
  (ingestion, absorption..)
- destroying cells
  (ingestion, lysis…)
- migrating through tissues
  (tunneling, tracking..)
- lodging in tissues
  (obstruction, space-occupying lesions..)
- provoking host reactions
  (inflammation, hypersensitivity..)

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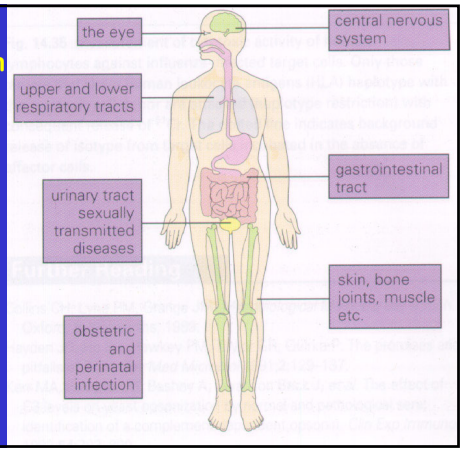
Systems approach



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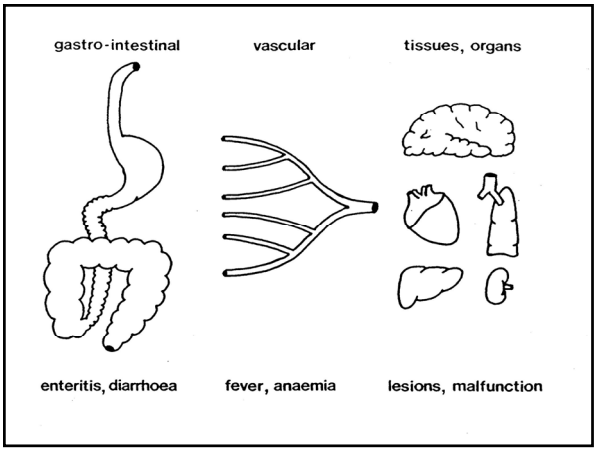

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Systems approach

- alimentary tract
- respiratory system
- urogenital system
- nervous system
- cardiovascular system
- skin

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Alimentary tract

- anorexia (loss of appetite)
- diarrhoea (frequency & consistency)
- vomiting (regurgitate)
- abdominal pain (local, referred)

- oedema (swollen tissues)
- dehydration (water loss)
- anaemia (reduced haematocrit)
- hypoalbuminaemia (reduced albumin)
- eosinophilia (increased eosiniphils)
- plasma pepsinogen (stomach damage)
- liver enzymes (liver damage)

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Diarrhoea

Excessive evacuation of too fluid faeces

Five main types of diarrhoea

- secretory
- osmotic
- exudative
- malabsorptive
- deranged motility

scours

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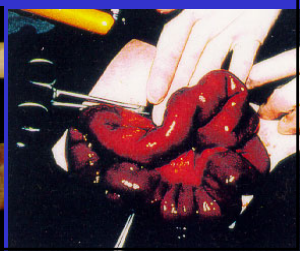
Complications

enteritis
coccidia

eosinophilic enteritis
hookworm



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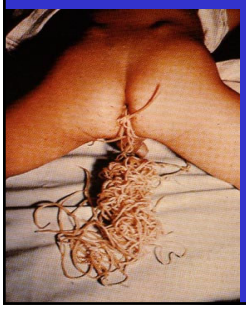
Complications

ascarid obstruction

whipworm prolapse



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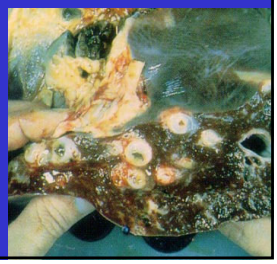
histopathology

necrotic abscess
amoebic dysentery

pipestem fibrosis
liver fluke



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Respiratory system

- anorexia (loss of appetite)
- sneezing (URT clearance)
- coughing (LRT clearance, wet/dry)
- nasal discharge (mucus)
- tachypnea (rapid respiration)
- dyspnea (difficult breathing)
- eosinophilia (increased eosinophils)

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Irritated mucous membranes

sneezing — coughing

nasal cavity | pharynx/larynx | trachea | brochi(oles)

Oestrus	*Mammonogamus*	*Capillaria*	larval
Lingatula	*Rhinoestrus*	*Filaroides*	migration
			Dictyocaulus
			Muellerius

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Difficulty breathing

dyspnea at rest

obstruction of passages | filled alveoli (pneumonia/oedema) | compressed alveoli (emphysema)

inspiratory	mixed	expiratory
Filaroides	*Angiostrongylus*	*Dictyocaulus*
Oestrus	*Toxoplasma*	*Metastrongylus*
Schistosoma	*Pneumocystis*	*Muellerius*

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Lungworm

Angiostrongylus *Dictyocaulus*

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Uro-genital system

- haematuria (blood in urine)
- proteinuria (protein in urine)
- oesinophilia (increased eosinophils)

- sterility (infertility)
- abortion (foetal death)
- congenital abnormalities (dev. defects)

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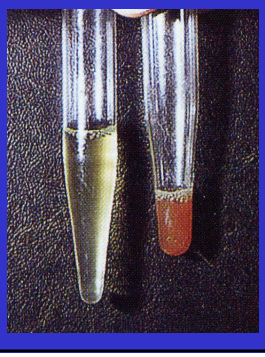
Urinary infections

nematodes
- *Capillaria*
- *Dioctophyma*
- *Stephanurus*

trematodes
- *Schistosoma*

protozoa
- *Klossiella*



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Reproductive tract

• *Trichomonas*	vaginitis, infertility, abortion
• *Trypanosoma*	abortion
• *Sarcocystis*	abortion, haemorrhage
• *Neospora*	abortion, paralysis
• *Toxoplasma*	abortion, congenital defects

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Nervous system

- anorexia (loss of appetite)
- depression (reduced vitality)
- stupor coma (unconscious)
- seizures (convulsions)
- ataxia (loss of movement)
- paresis (partial paralysis)
- paralysis (motor/sensory)
- dysmetria (unable to direct motions)
- muscle weakness/tremor (innervation)
- erratic behaviour (motor, cognitive)

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CNS

Forebrain (cerebrum, diencephalon)	Brainstem (midbrain, medulla oblongata, pons, vestibular nuclei)	Cerebellum	Spinal cord
depression, stupor, coma, convulsive seizures, mild hemiparesis	depression, stupor, coma, reduced consciousness, hemiparesis, tetraparesis, head tilt, twisting, turning or circling ataxia	ataxia, wide-based stance, dysmetria, intention tremor, muscle weakness	sensory dysfunction (hypersthesia, hyposthesia), paresis, paralysis, spinal reflex abnormalities, muscle atrophy
P: *Toxoplasma* P: *Plasmodium* P: *Encephalitozoon* N: *Toxocara* N: *Dirofilaria* C: *Cysticercus* C: *Coenurus* T: *Schistosoma* A: *Chrysomya*	P: *Toxoplasma* P: *Plasmodium* P: *Encephalitozoon* N: *Dirofilaria* C: *Cysticercus* C: *Coenurus* T: *Schistosoma*	P: *Toxoplasma* P: *Plasmodium* P: *Encephalitozoon* N: *Toxocara* C: *Cysticercus* T: *Schistosoma* A: *Chrysomya*	P: *Toxoplasma* N: *Angiostrongylus* N: *Toxocara* N: *Ancylostoma* C: *Coenurus* T: *Schistosoma*

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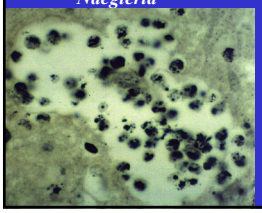
CNS infections

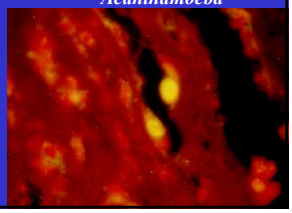
meningoencephalitis

- EME eosinophilic meningoencephalitis - *Angiostrongylus*
- PAM primary amoebic meningoencephalitis - *Naegleria*
- SAM secondary amoebic meningoencephalitis - *Entamoeba*
- GAM granulomatous meningoencephalitis - *Acanthamoeba*

Naegleria



Acanthamoeba



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CNS infections

lesions

- hydatid disease - *Echinococcus*
- neurocysticercosis - *Taenia solium*
- toxoplasmosis - *Toxoplasma*
- schistosomiasis - *Schistosoma japonicum*
- trichinellosis - *Trichinella spiralis*

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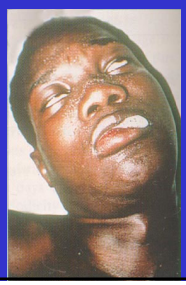
CNS infections

ischaemia

- sleeping sickness - *Trypanosoma brucei*
- cerebral malaria - *Plasmodium falciparum*



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Cardiovascular-haemato-system

- anaemia (reduced haematocrit)
- leucopenia (reduced leucocytes)
- oesinophilia (increased eosinophils)

- cardiac dysfunction (arrhythmia)
- vasculitis (vessel inflammation)
- oedema (swollen tissues)

- fever (elevated temperature)
- lethargy (drowsiness/apathy)
- anorexia (loss of appetite)
- weakness (feeble)

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Myocarditis/vasculitis

parasite	location	consequence	condition
T cruzi	striated muscle	dysfunction	granuloma
Schistosoma	hep/port veins	haemorrhage	granuloma
Angiostrongylus	pulmon artery	dyspnea	granuloma
Dirofilaria	pulmon artery	exercise intol	vasculitis
Elaeophora	cephalic artery	occlusion	sclerosis
Onchocerca	thoracic aorta	epilepsy	calcifications
Spirocerca	aorta	asymptomatic	thickening
Strongylus	mes arteries	pyrexia	arteritis

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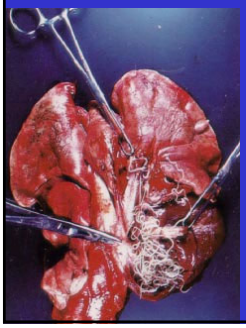
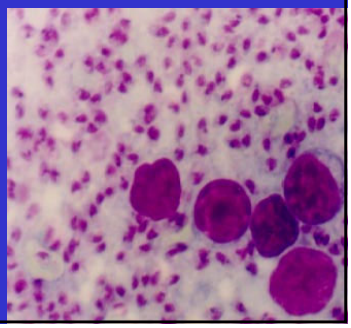
Cardiovascular lesions

heartworm | Chagas disease

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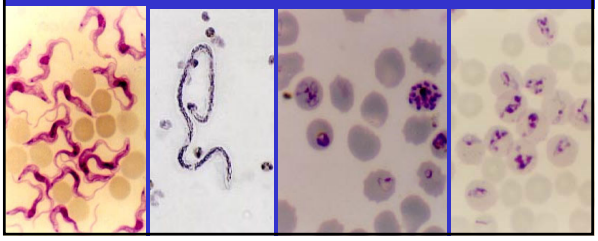
Blood infections

extracellular
trypanosomes
microfilaria

intracellular
haemosporidia
piroplasms



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Skin

- pruritis (itching)
- erythema (patchy inflammation)

- scales (flakes)
- crusts (scabs)
- excoriations (peeling)
- alopecia (hair loss)
- nodules (lumps)
- papules (pimples)
- vesicles (fluid-filled)

- pigmentation abnormalities (patches)
- lichenification (reddish eruption)
- anaemia (reduced haematocrit)

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Dermal lesions

subcutaneous larval migrans | tick bite serosanguineous blister


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Alopecia

sarcoptic mange (scabies in humans) | psoroptic mange mites


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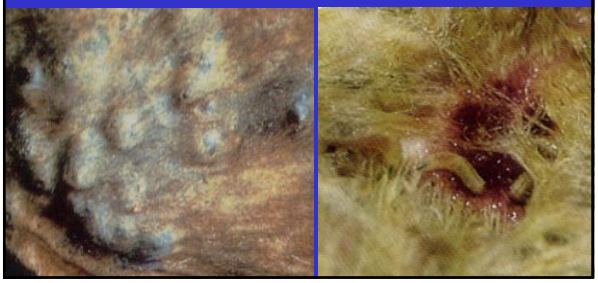
Flesh eaters

cattle grubs (fly larvae)

sheep flystrike (fly larvae)



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Gross disfigurement

kala azar (flagellates)

elephantitis (filarial nematodes)

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Progressive pathology

tissue infection → localized inflammation → histiocytic reaction → lymphoid infiltration → granuloma formation → fibroblastic reaction

intracellular infection → no inflammation → infection necrosis → granulocytic inflammation → mononuclear infiltration → granuloma formation

vasculitis → thrombosis → infarction ····→ haemorrhage

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Summary

pathology structural/functional changes

need to know your pathogen

and how the host will react

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Clinical Review

Site	Symptoms	Transmission	PROTOZOA	HELMINTHS	ARTHROPODS
Gut	diarrhoea, blockage, anaemia	faecal-oral	amoebae diplomonads coccidia Ciliates	round-, pin-, whip-,thread-, hook-worms tapeworms enteric flukes	-
Blood	anaemia, fever, ischaemia	vector-borne	trypanosomes haemosporidia Piroplasms	filiarial worms blood flukes	-
Tissues	lesions dysfunction inflammation	predator-prey	cyst-forming coccidia microspora	hydatids cysticerci liver flukes Trichinella	-
- skin	lesions	direct	-	-	flies fleas lice mites ticks

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EVOLUTION OF VIRULENCE

OLD SCHOOL OF THOUGHT (not always supported by data)

- parasitism evolves towards avirulence
  - not in best interest to kill host
  - many long-term host-parasite associations are avirulent
  - Many recent host-parasite associations are highly virulent

NEW SCHOOL OF THOUGHT (increasing support)

- trade-off hypothesis (virulence & transmission negatively correlated)
- increase in virulence leads to decrease in transmission
  - (dead hosts do not actively transmit infections)

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