Immunity anti- Pathogens

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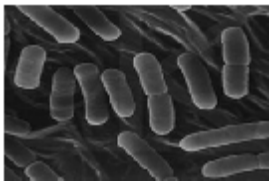
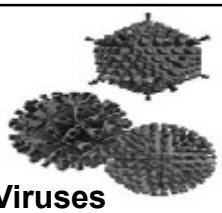
Immune responses to Pathogen

The Invaders . . .

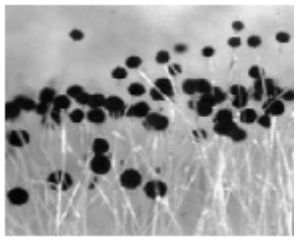
Bacteria



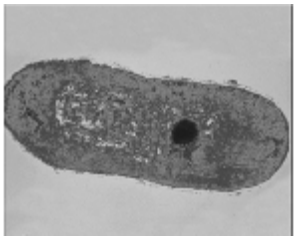


Viruses

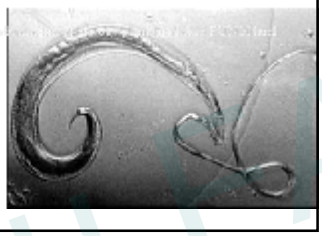
Fungi



Parasites



Worms



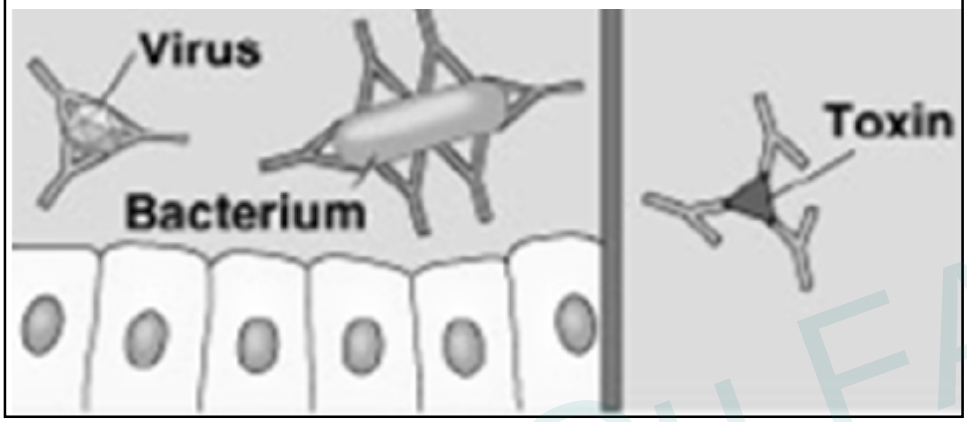
Actions of antibodies

- **Neutralize** bacterial toxins
- **Agglutinate** bacteria, preventing their spread and facilitating phagocytosis
- **Activation the complement** leading to bacterial lysis
- **Attraction** of phagocytes
- attach to the surface of bacteria and act as opsonins, enhance phagocytosis **(Opsonization)**
- **Stimulation** of inflammation
- Prevent adherence of bacteria to their target cells

  e.g. IgA on mucosal surfaces

Neutralization

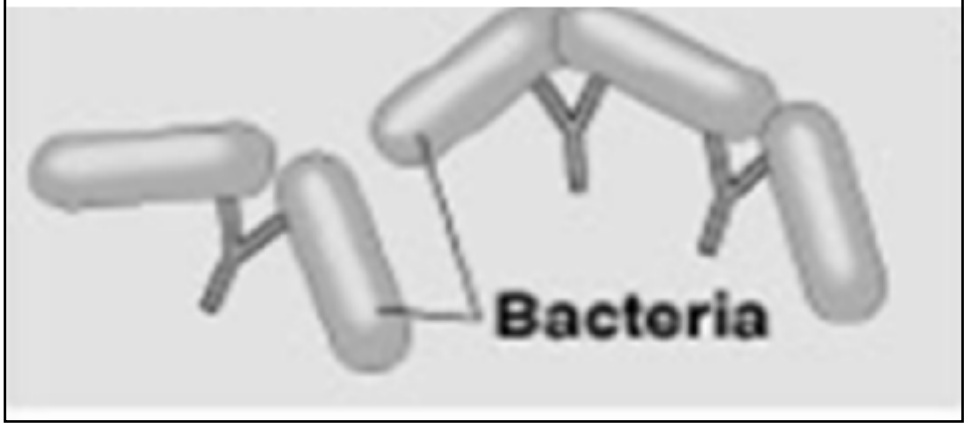
Blocks adhesion of bacteria to mucosa **Blocks active site of toxin**



Agglutination

Enhances phagocytosis

Reduces number of infectious units to be dealt with



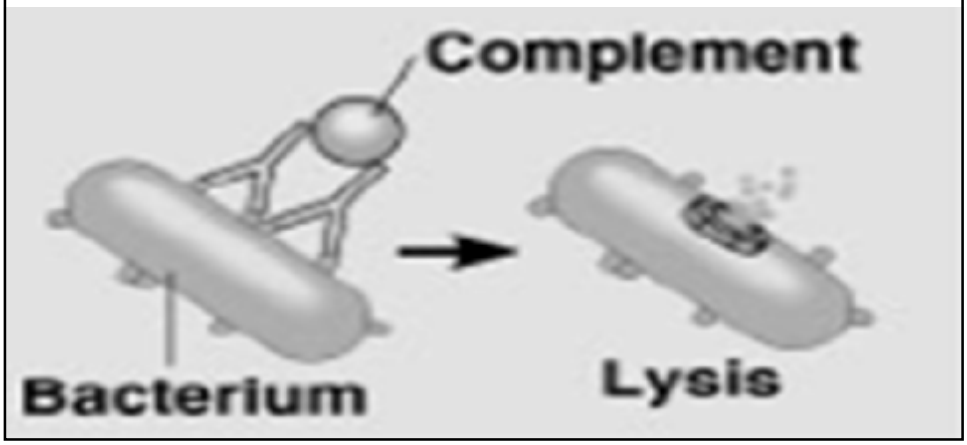
Opsonization

Coating antigen with antibody enhances phagocytosis

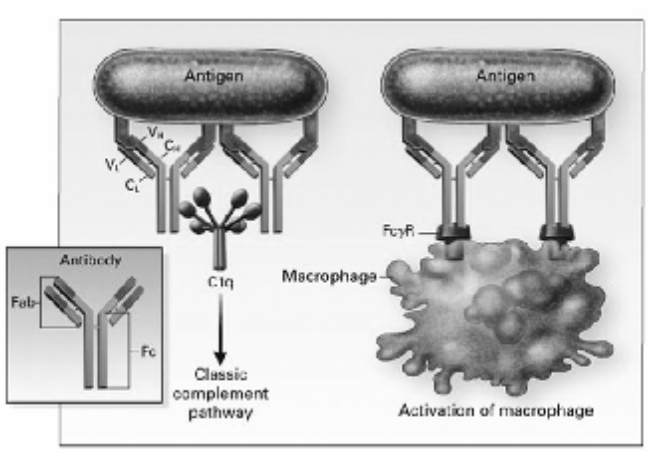
Activation of complement

Cell lysis

Attraction of phagocytes

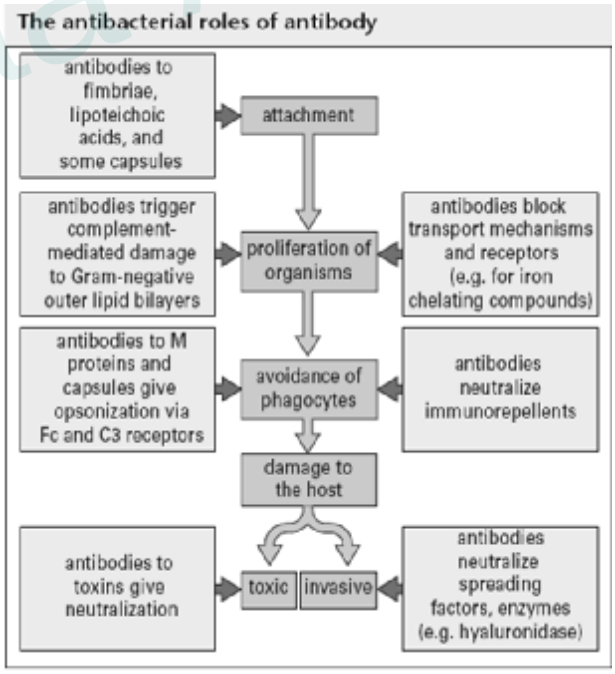


Activation of the classical pathway
Role of Antibodies



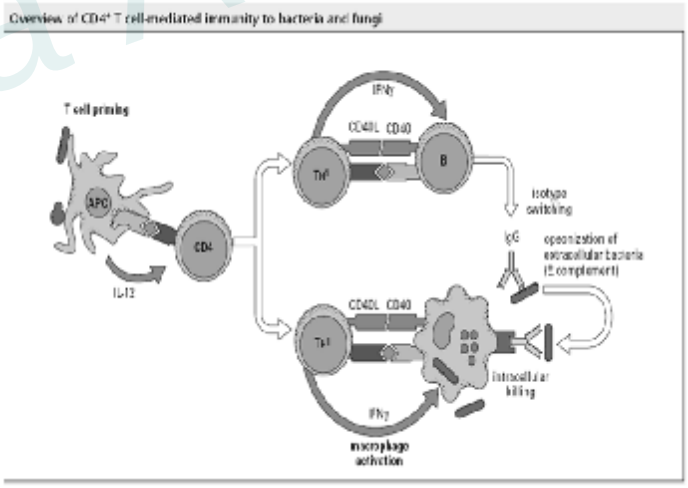
. The activation of the classic complement pathway after binding of C1q to Fc

. The activation of phagocytosis after the cross-linking of Fc receptors and binding of the FcγR on the macrophage.

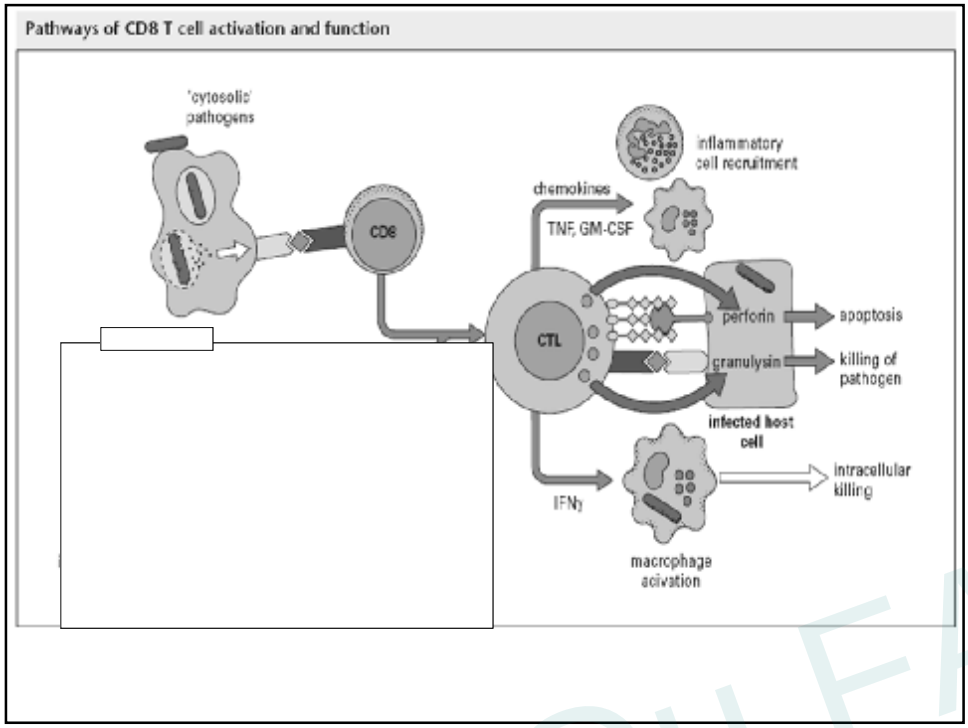


CD4+ T cell mediated immunity to Bacteria

- Naive CD4+ T cells are stimulated by class II MHC antigen-bearing dendritic cells (DCs) via the TCR.
- Co-stimulatory molecules CD80/86 and CD28, induce T cell activation and proliferation.
- Differentiation into either TH1 or TH2 effector cells is strongly influenced by the cytokine environment during this interaction



- Events that favor production of **IL-12 promote TH1**, **Low IL-12 favors TH2** responses.
- Optimal T cell help for either B cells or macrophage responses involves T cell derived cytokines and direct cell contact
- TH1 cells promote opsonizing antibody production and activation of phagocytes by IFNγ.



CD8+ T cell in bacteria infection

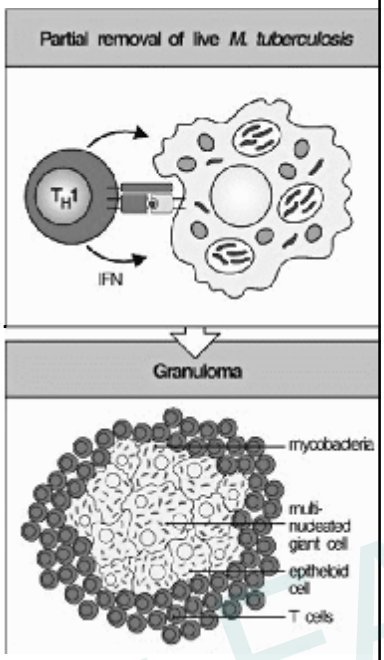
- Naive CD8 T cells are activated by peptides presented via MHC class I molecules, derived from microorganisms that reside in the cytoplasm
- Effector CD8 T cells (CTLs) provide protection by releasing proinflammatory and macrophage activating cytokines
- killing infected host cells via perforin release and Fas.
- In some cases, the release of granulysin from the CTL can also result in killing of the pathogen.

Granuloma formation

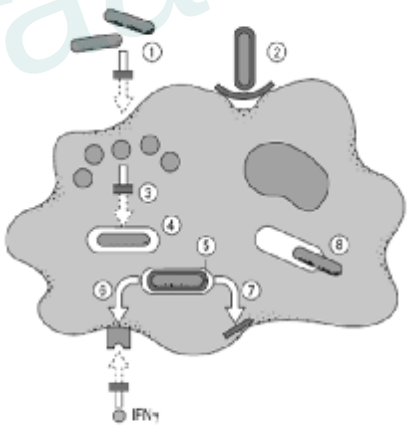
❖ Intracellular pathogens are not quickly eliminated (chronic infections).

❖ The persistent recruitment and activation of macrophages, macrophage-derived multinucleated giant and T cells to an infected tissue can result in the formation of **granulomas**.

❖ associated with:
• chronic bacterial infections, tuberculosis and syphilis,
• schistosomiasis
• response to non-infectious materials
(asbestos).



Evasion mechanisms of bacteria (and some fungi)



(**1**) secrete repellents or toxins inhibit chemotaxis.
(**2**) have capsules or outer coats that inhibit attachment by the phagocyte

(**3**) permit uptake, but release factors that block subsequent triggering of killing mechanisms.

• inhibit lysosome fusion with the phagosome.
• inhibit the proton pump that acidifies the phagosome, so the pH does not fall.

(**4**) They may secrete catalase which breaks down hydrogen peroxide.

(**5**) Organisms such as *M. leprae* have highly resistant outer coats.

(**6**) Mycobacteria release a lipoarabinomannan, which blocks the ability of macrophages to respond to the activating effects of IFNγ.
(**7**) impaired antigen presenting function.
(**8**) Several organisms can escape from the phagosome to multiply in the cytoplasm.

the response to bacteria can result in immunological tissue damage

Excessive cytokine release can lead to endotoxin shock

If cytokine release is sudden and massive, several acute tissue-damaging syndromes can result and are potentially fatal.

- **Endotoxin (septicemic) shock**,

usually caused by bacterial products released during septicemic episodes.

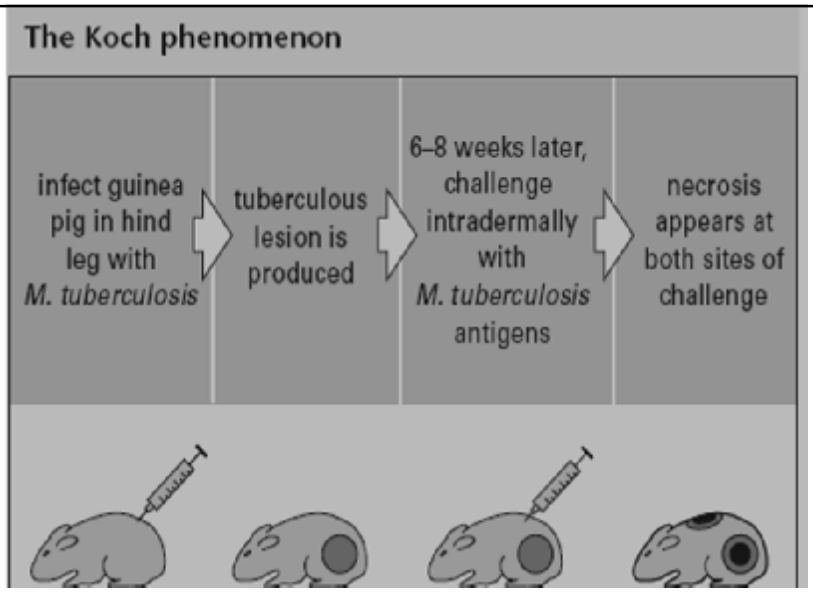
Endotoxin (LPS) from G- bacteria is usually responsible

can be life-threatening fever, circulatory collapse, diffuse intravascular coagulation, and hemorrhagic necrosis,leading eventually to multiple organ failure

the response to bacteria can result in immunological tissue damage

The Koch phenomenon is necrosis in T cell mediated mycobacterial lesions and skin test sites

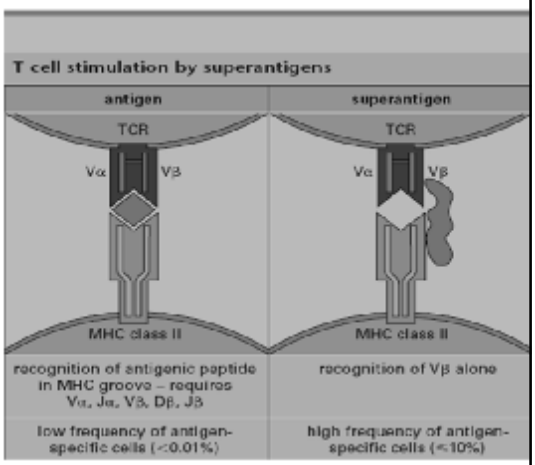
- The **Koch phenomenon** is a necrotic response to antigens of *M. tuberculosis*, originally demonstrated by Robert Koch.
- It may be related to the necrosis that also occurs in the lesions in tuberculosis.
- It is at least partly due to the release of cytokines into a T cell-mediated inflammatory site (**delayed hypersensitivity**).



injection of *M.tuberculosis* or soluble antigens from *M. tuberculosis* into the skin of guinea pigs resulted in a necrotizing reaction both at the challenge site and in the original tuberculous lesion.

The toxicity of superantigens results from massive cytokine release

- Certain bacterial components called **superantigens**
- bind directly to the variable regions of β chains (Vβ) of antigen receptors on subsets of T cells, and cross-link them to the MHC molecules of APCs, usually outside the normal antigen-binding groove.



What effect do superantigens have on T cells?

- All T cells bearing the relevant Vβ gene product are activated without the processing and presentation of the antigen as peptides in the cleft of the MHC molecule

- T cell activation is non specific

- Releasing massive cytokines

fungal infection

Fungal infections are regularly seen in:

- ❖ patients with untreated AIDS;
- ❖ patients with cancer and undergoing chemotherapy
- ❖ patients with transplants on immunosuppressive agents
- ❖ some patients taking long-term corticosteroids.

These clinical findings point to the key roles of neutrophils and macrophage activating TH1 cell responses in antifungal immunity.

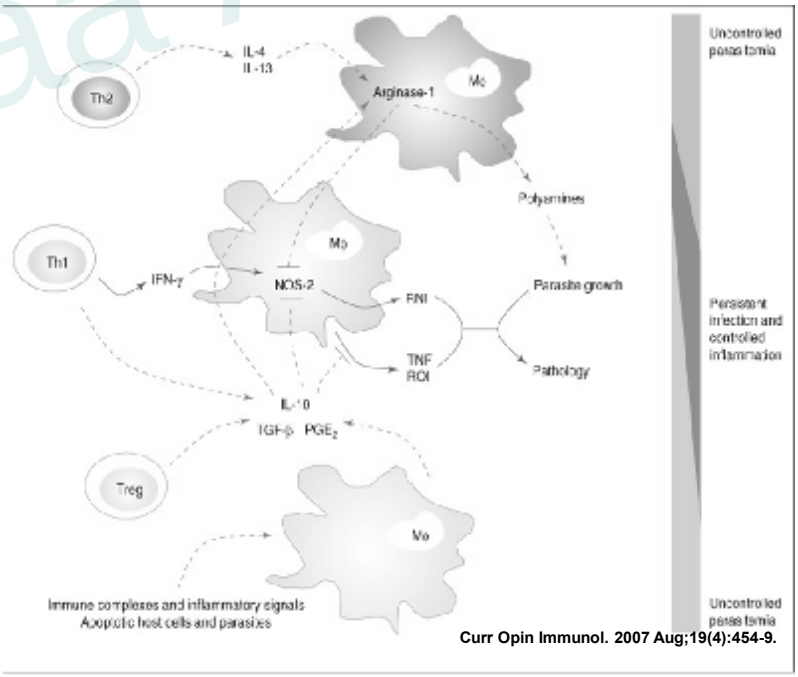
Innate immune responses to fungi

- the skin and normal commensal flora
- Defensins have antifungal as well as antibacterial properties
- Phagocytes (neutrophils & macrophages), are essential for killing fungi

T cell-mediated immunity

Immunity anti-parasites

- in determining the outcome of parasitic infections have
- been extensively investigated.
- As a result of early studies, predominantly in mouse
- infections, certain dogmas have arisen suggesting that:
- • TH1 responses mediate killing of intracellular pathogens; and
- • TH2 responses eliminate extracellular ones.
- However, this is very much an oversimplification of the
- true picture.
- Although the TH1/TH2 paradigm may be a useful tool
- in some situations, it is probably more realistic to consider
- that TH1 and TH2 phenotypes represent the extremes of
- a continuum of cytokine profiles and that perhaps it may
- be more accurate to look at the role of the cytokines
- themselves in the resolution of infectious disease.

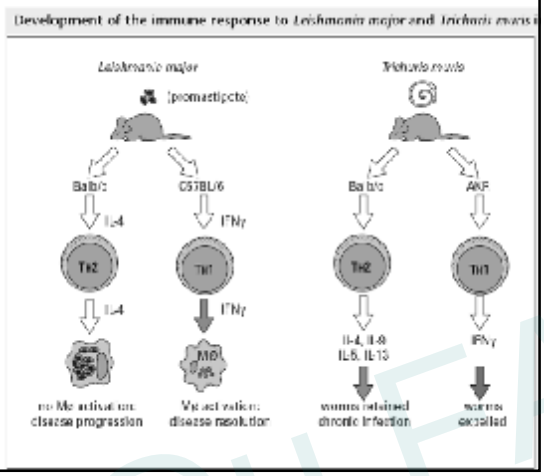


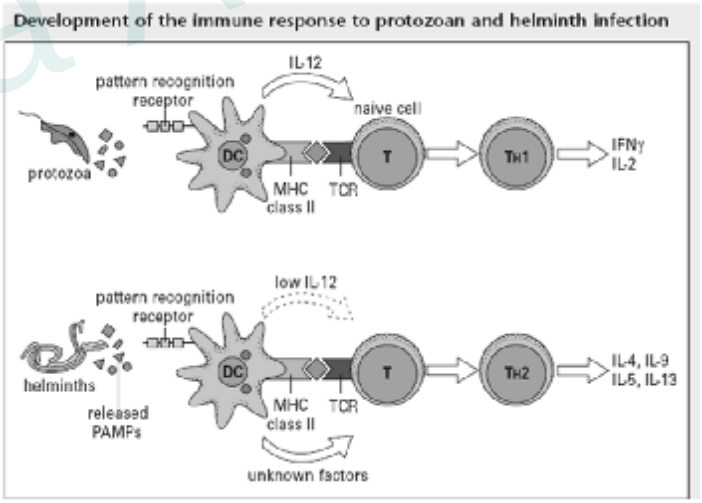
Curr Opin Immunol. 2007 Aug;19(4):454-9.

T cell responses to protozoa depend on the species

in mouse models, the induction of TH1 cells with concomitant upregulation of IFNγ and nitric oxide (NO•) is crucial for protection of mice from leishmania.

Strains of mice driving TH2 responses on infection, manifested by high levels of IL-4, IL-13, IL-10 and antibody, develop progressive and ultimately lethal disease





Early recognition of parasites by antigen-presenting cells (APCs), for example dendritic cells, determines the phenotype of the adaptive response

The cytokines produced by CD4+ T cells can be important in determining the outcome of infection. Helper T cells have been phenotypically divided into TH1 and TH2 and more recently regulatory T cell subsets based on the cytokines produced.
As TH1 and TH2 cells have contrasting and crossregulating cytokine profiles, the roles

Parasites have many different escape mechanisms

- **Parasites can resist destruction by Complement**
- **Intracellular parasites can avoid being killed by oxygen metabolites and lysosomal enzymes**
- ***Other parasites acquire a surface layer of host antigens***

schistosomes, acquire a surface layer of host antigens so that the host does not distinguish them from 'self'.

- Schistosomules cultured in medium containing human serum and red blood cells can acquire surface molecules containing A, B, and H blood group determinants.

Parasites have many different escape mechanisms

- **Some extracellular parasites hide from immune attack**

Some species of protozoa (e.g. *Entameba histolytica*) and helminths (e.g. *T. spiralis*) form protective cysts, while

- adult worms of *Onchocerca volvulus* in the skin induce the host to surround them with collagenous nodules. Intestinal nematodes and tapeworms are preserved from many host responses simply because they live in the gut.