Comparative size of various parasites
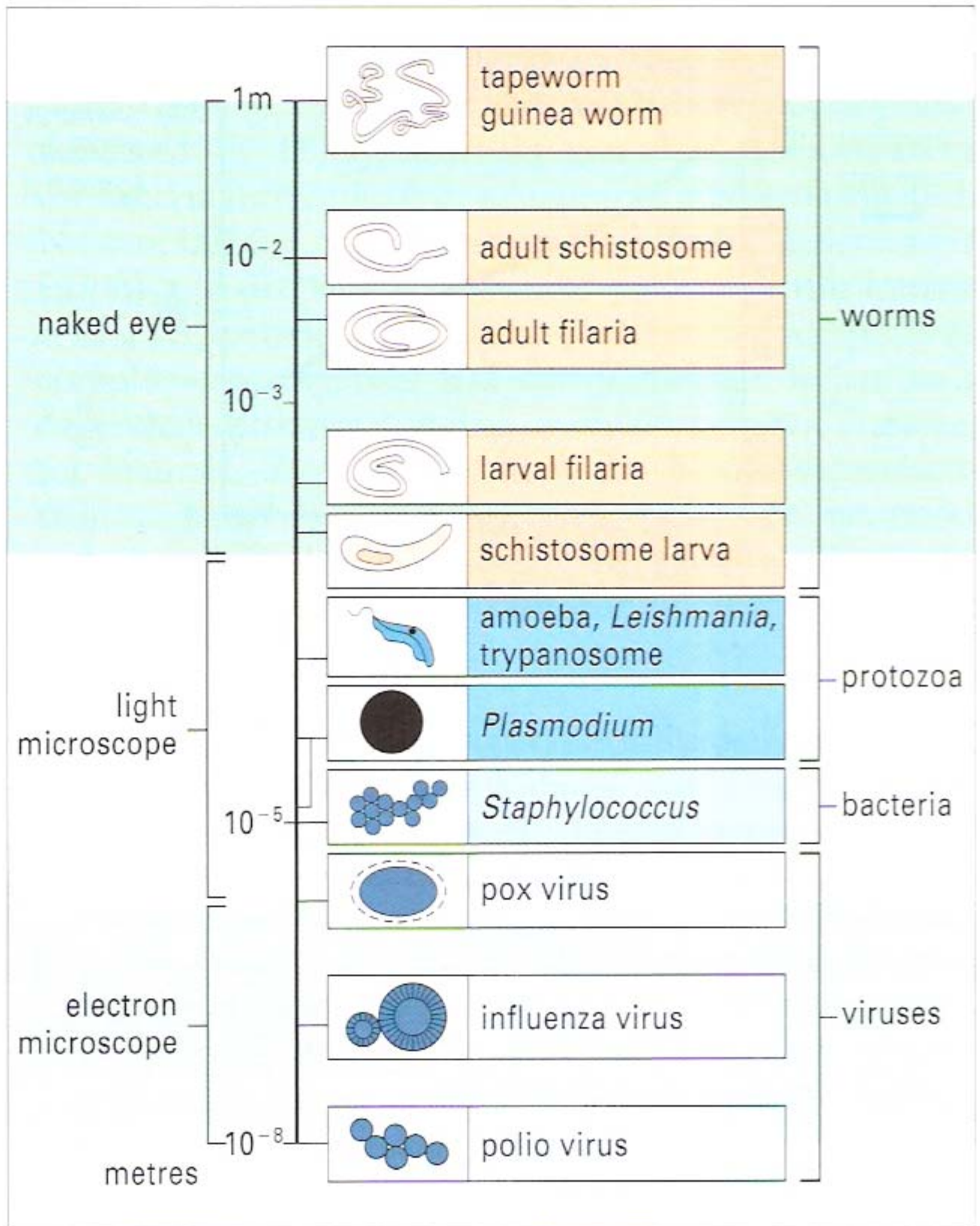

Scale (metres)	Parasite	Group	Visibility
1m	tapeworm, guinea worm	worms	naked eye
10^{-2}	adult schistosome	worms	naked eye
	adult filaria	worms	naked eye
10^{-3}	larval filaria	worms	naked eye
	schistosome larva	worms	naked eye
	amoeba, *Leishmania*, trypanosome	protozoa	light microscope
	Plasmodium	protozoa	light microscope
10^{-5}	*Staphylococcus*	bacteria	light microscope
	pox virus	viruses	electron microscope
	influenza virus	viruses	electron microscope
10^{-8}	polio virus	viruses	electron microscope

metres

Figure-3 Comparative size of various parasites

Figure-4 Adult schistosome worm pairs in mesenteric blood vessels. Although very exposed to immune effectors, they are highly resistant. Adult schistosomes can persist for an average of 3-4 years.
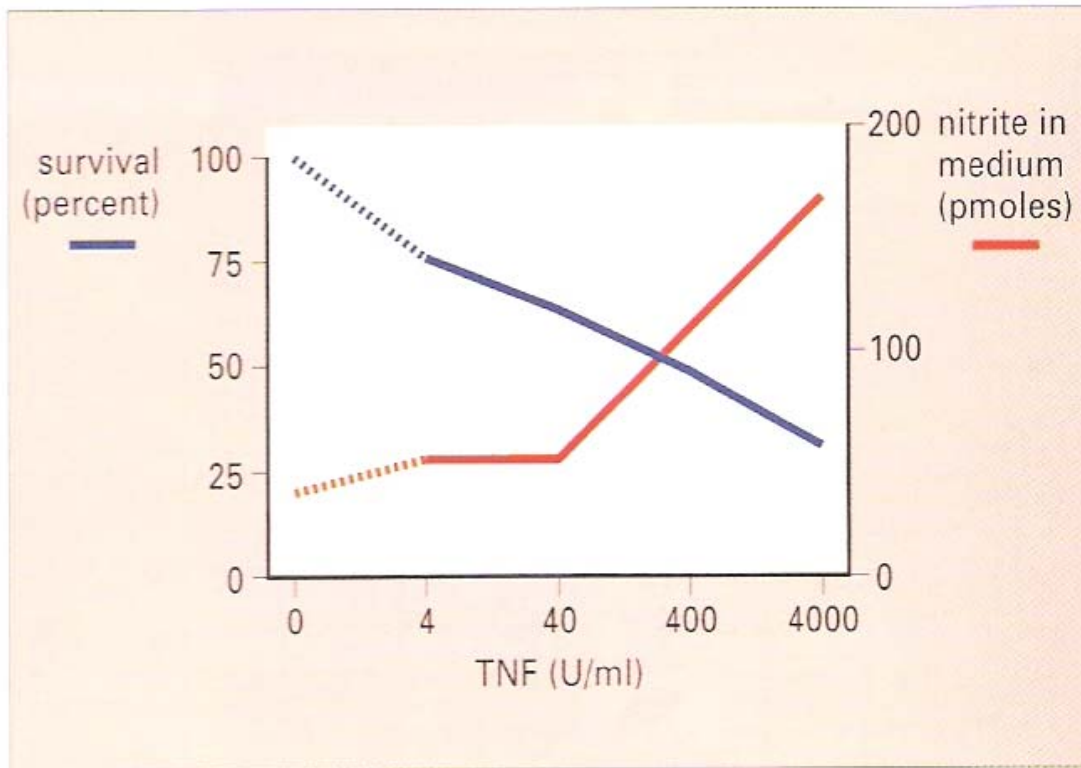
Toxic effect of NO on *Leishmania in vitro*

Figure-5 Evidence that the killing of Leishmania major by activated macrophages is correlated with the release of nitric oxide. Mouse macrophages in culture are activated by recombinant TNFα in a dose-related fashion, the highest doses decreasing parasite survival to about a third of that in control cultures. At the same time the amount of NO released, measured as nitrite present in the culture medium, increases. Interference with NO production allows parasites to survive.
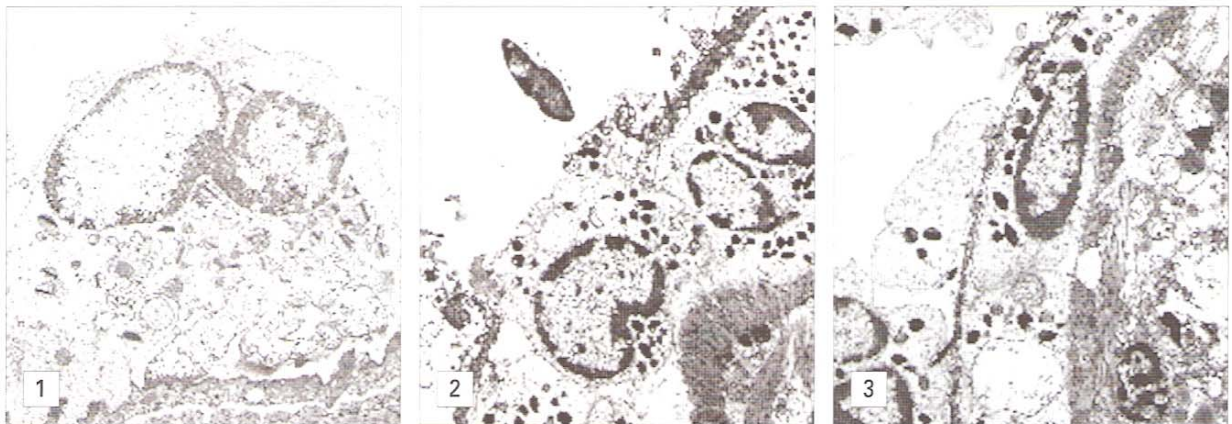
Figure-6 Killing of schistosome larvae by eosinophils. Eosinophils can adhere to schistosomules and kill them. The damage is associated with degranulation of the eosinophils and the release of the contents of the granules onto the surface of the worm. This series of electron micrographs shows adherence of the eosinophils and degranulation onto the surface of the worm larva (1), and stages in the breakup of the worm tegument and migration of eosinophils through the lesions (2 and 3).

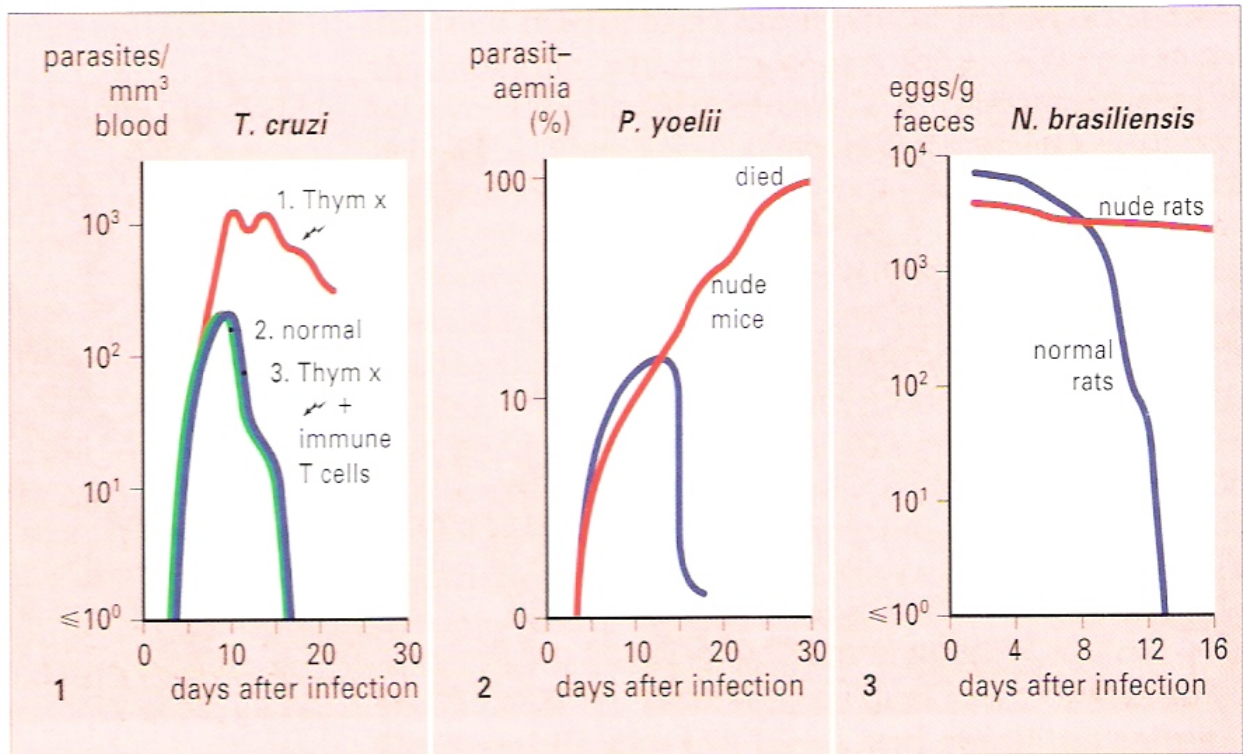## Parasitic infections in T-deprived mice

Figure-7 The first two graphs plot the increase in number of blood-borne protozoa (parasitaemia) following infection. (1) Trypanosoma cruzi multiplies faster (and gives fatal parasitaemia) in mice that have been thymectomized and irradiated to destroy T cells (Thym x). In normal mice, parasites are cleared form the blood by day 16. Reconstruction of T-deprived mice with T cells from immune mice (immune-T) restores their ability to control the parasitaemia. In these experiments both thymectomized groups were given fetal liver cells to restore vital haematopoietic function. (2) Plasmodium yoelii causes a self-limiting infection in normal mice and the parasites are cleared from the blood by day 20. In nude mice the parasites continue to multiply, killing the mice after about 30 days. (3) This graph illustrates the time courses of the elimination of the intestinal nematode *Nippostrongylus grasiliensis* from the gut of rats. In normal rats the worms are all expelled by day 13, as determined by the number of worm eggs present in the rat's faeces. T cells are necessary for this expulsion to occur, as shown by the establishment of a chronic infection in the gut of nude rats.
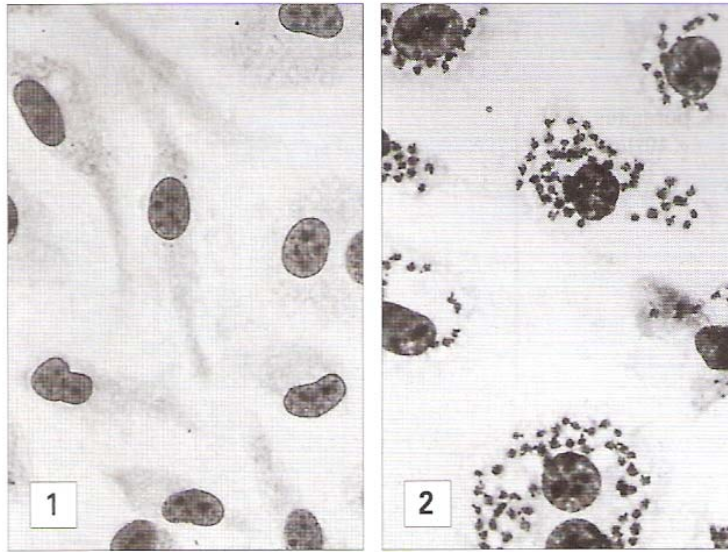
Figure-8 Inhibition of parasite multiplication in macrophages treated with cytokines. Peritoneal macrophages from BALB/c mice, infected 72 hours previously with 10^7 *amastigotes of Leishmania donovani,* were treated with either a supernatant from activated T cells (containing cytokines) or a control supernatant. Cells treated with cytokines do not contain any parasites following cultures (1), whereas untreated macrophages contain many parasites (2). Subsequent studies using recombinant IFNγ and monoclonal antibody against IFNγ showed that the inhibition was mediated by this cyhtoine.

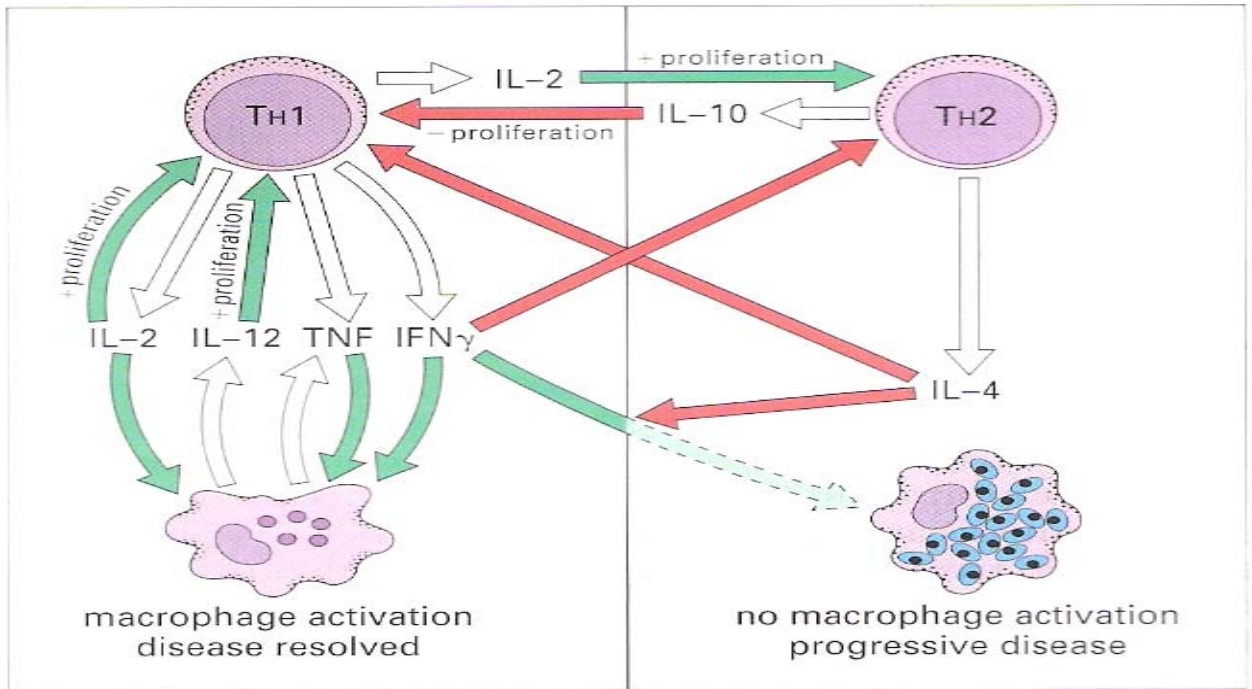## Action of TH1 and TH2 cells in *Leishmania* infection

Figure-9 Development of the immune response to Leishmania infection illustrating the cytokines secreted by the different subsets of T cells and their effect on the resolution of the disease, note that IL-12, which is also produced by B cells, promotes the growth of NK cells as well as TH1 cells, and these cells are also a source of IFNγ, the cytokine which is essential for elimination of the parasite.
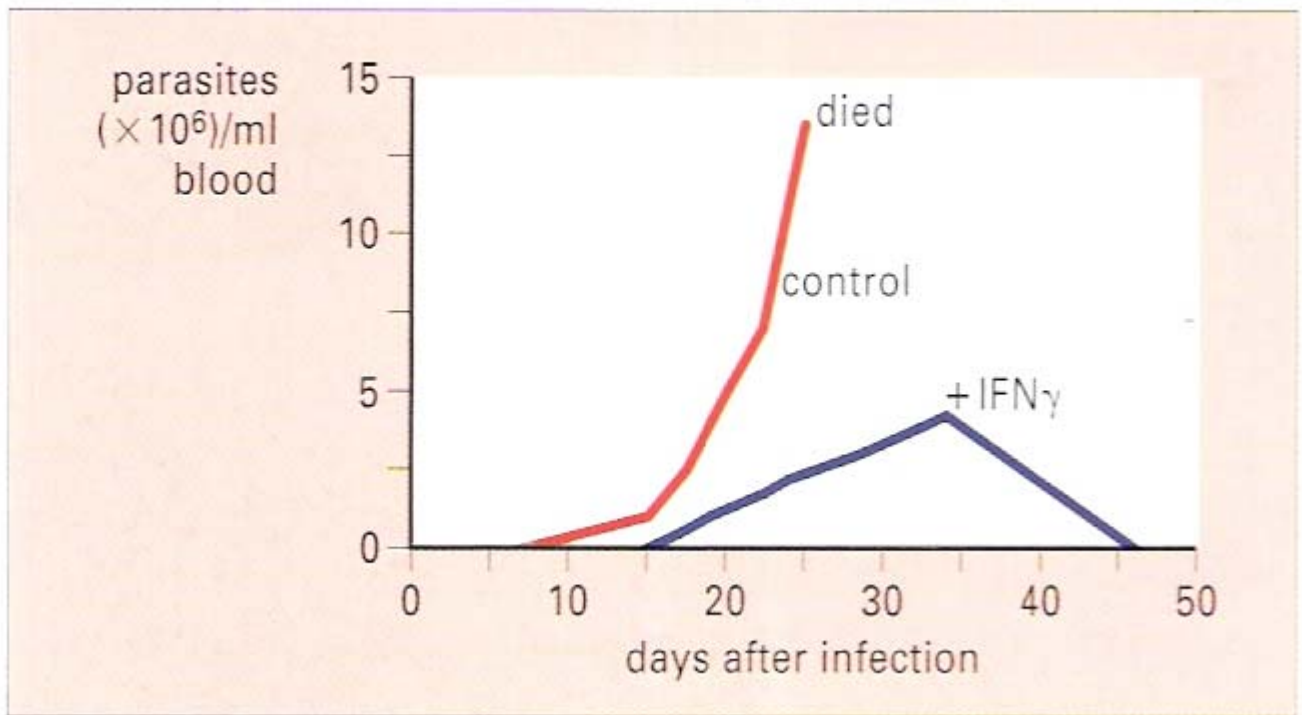
Figure-10 The effect of administration of the T cell cytokine IFNγ on acute infection caused by Trypanosoma cruzi. In this strain of mice, the parasites multiply to kill their host in about 3 weeks. Administration of recombinant mouse IFNγ controls their multiplication which is followed ultimately by their elimination.
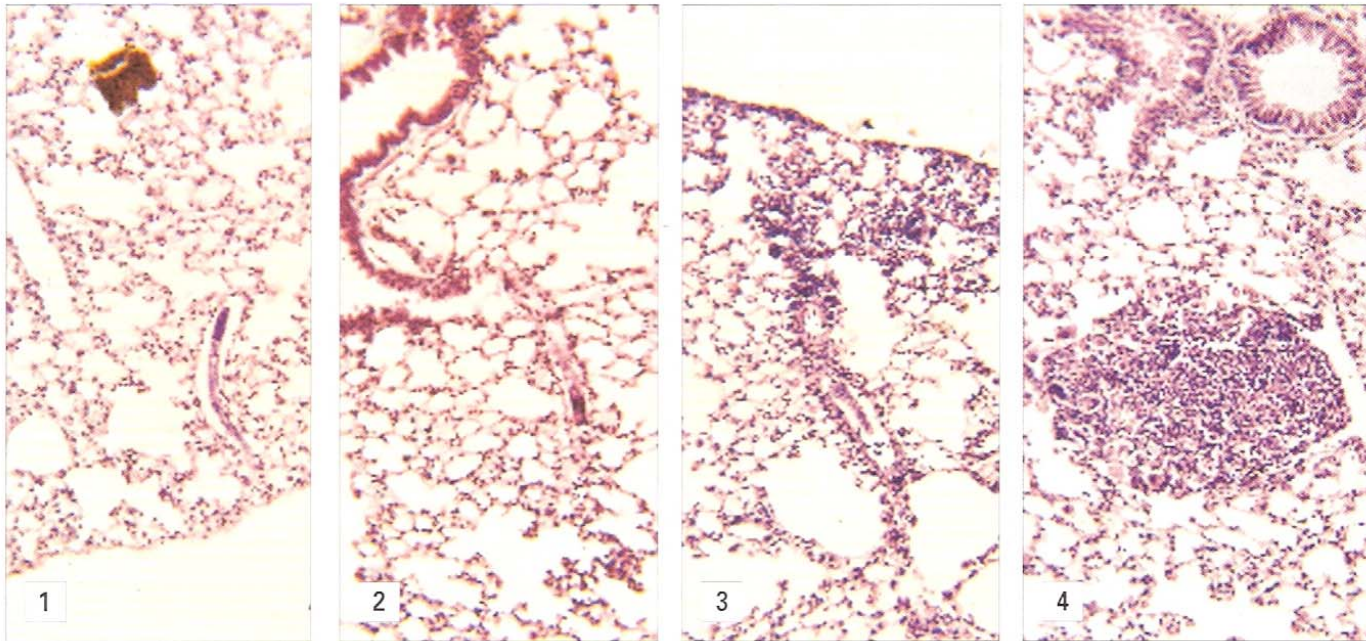
Figure-11 Photomicrographs of mouse lung tissue showing pulmonary foci around migrating schistosomula of Schistosoma mansoni. Lung schistosoma were administered intravenously; panel (1) shows a challenge larva in the naïve mouse at 25 h. In mice protected by vaccination with radiation-attenuated cercariae, infiltrating cells appear as early as 24 h. (2). Panels (3) and (4) show the development of foci 2 and 12 days post-challenge. Bronchoalveolar sampling and mmmunocytochemistry have revealed that CD4 T tymphocytes are a major component of the pulmonary infiltrates. IFNγ is the dominant cytokine produced by these cells in culture and mRNA for IFNγ is induced in whole lung tissue, from which it can be inferred that the protective response is mediated by TH1 cells.

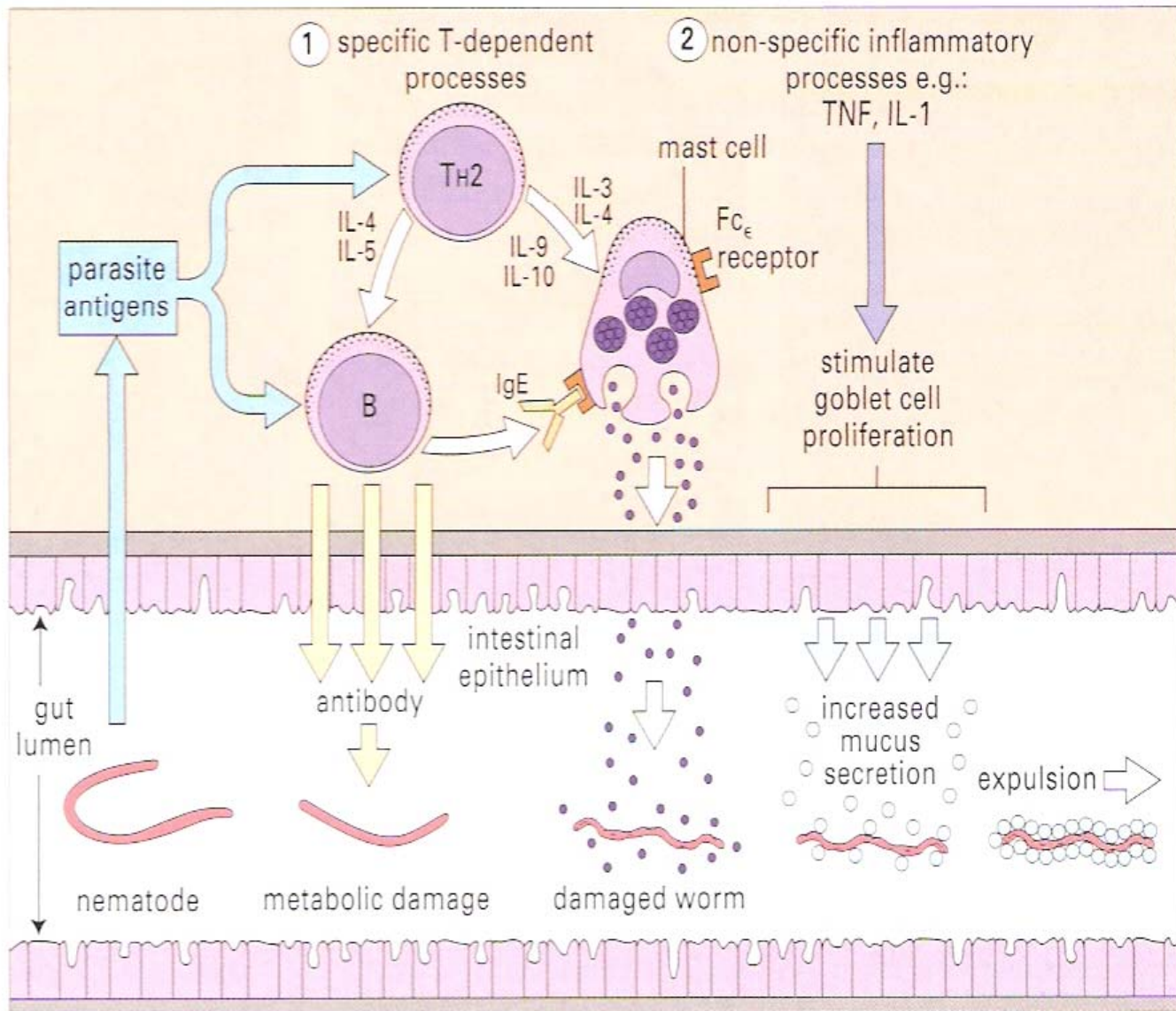# Processes involved in expulsion of nematodes from the gut

Figure-12 The expulsion of some intestinal nematodes occurs spontaneously a few week after primary infection. There seem to be two stages in the expulsion, which is achieved by a combination of T-dependent and T-independent mechanisms. (1) T cells (predominantly TH2 cells) respond to parasite antigens and induce (a) the production of antibody by B cells that have proliferated in response to IL-4 and IL-5, (b) the proliferation of mucosal mast cells, in response to IL-3, IL-4, IL-9 and IL-10, and (c) hyperplasia of mucus-secreting goblet cells in the intestinal epithelium. The worms are damaged by antibody together with products of IgE-sensitized mast cells which degranulate following contact with antigen, and so release histamine which increases the permeability of the intestinal epithelium. These processes are not sufficient to eliminate

the worms. (2) Non-specific inflammatory molecules secreted by macrophages, including TNF and IL-1, contribute to goblet cell proliferation and cause increased secretion of mucus. The mucus coats the worms and leads to their expulsion. The numbers of goblet cells in the jejunal epithelium and the secretion of mucus increase in proportion to the worm burden. The antigen-specific effector T cells are generated early in infection and the rate-limiting step is the onset of antibody damage. The relative importance of these various processes varies with the infecting nematode.

Relative importance of antibody-dependent and -independent responses in protozoal infections

parasite and habitat		antibody-dependent			antibody-independent	
		importance	mechanism	means of evasion	importance	mechanism
T. brucei free in blood		++++	lysis with complement which also opsonizes for phagocytosis	antigenic variation	–	
Plasmodium inside red cell		+++	blocks invasion, opsonizes for phagocytosis	intracellular; antigenic variation	liver stage +++ blood stage +++	cytokines macrophage activation
T. cruzi inside macrophage		++	limits spread in acute infection, sensitizes for ADCC	intracellular	+++ (chronic phase)	macrophage activation by IFNγ and TNFα, and killing by NO and metabolites of O_2
Leishmania inside macrophage		+	limits spread	intracellular	++++	

Figure-13 This table summarizes the relative importance of the two immune responses, the mechanisms involved and, for antibody, the means by which the protozoan can evade damage by antibody. Antibody is the most important part of the immune response against those parasites that live in the bloodstream, such as African-trypanosomes and malarial parasites, whereas cell-mediated immunity is active against those like *Leishmania* that live in the tissues. Antibody can damage parasites directly, enhance their clearance by phagocytosis, activate complement or block their entry into their host cell and so limit the spread of infection. Once inside, the parasite is safe from its effectors. *Trypanosoma cruzi*

and *Leishmania* are both susceptible to the action of oxygen metabolites release by the respiratory burst of macrophages, and to nitric acid oxide. Treating macrophages with cytokines enhances release of these products and diminishes entry and survival of the parasites. Malarial parasites within the red cell may be destroyed by some secreted products of activated macrophages, including hydrogen peroxide and other cytotoxic factors.

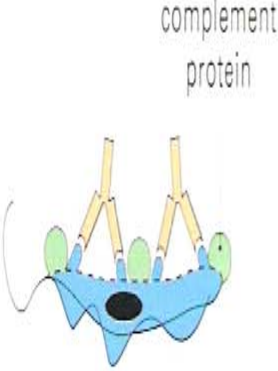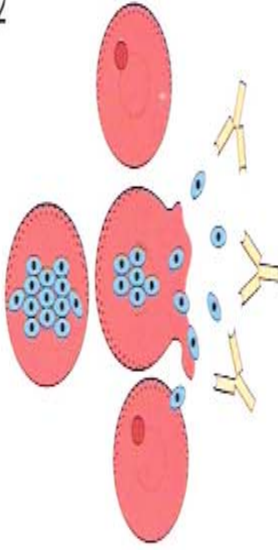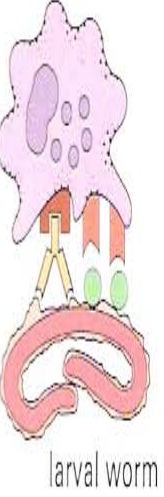Mechanisms by which specific antibody controls some parasitic infections

parasite	*Plasmodium* sporozoite, intestinal worms, trypanosome	*Plasmodium* sporozoite and merozoite, *Trypanosoma cruzi*, *Toxoplasma gondii*	*Plasmodium*, trypanosome	schistosomes, *Trichinella spiralis*, filarial worm larvae
mechanism	1 complement protein	2	3	4 larval worm
effect	direct damage or complement-mediated lysis	prevents spread by neutralizing attachment site, prevents escape from lysosomal vacuole, prevents inhibition of lysosomal fusion	enhancement of phagocytosis	antibody-dependent cell-mediated cytotoxicity (ADCC)

Figure-14 (1) Direct damage, antibody activities the classical complement pathway, causing damage to the parasite membrane and increasing susceptibility to other mediator. (2) Neutralization. Parasites such as Plasmodium spp. spread to new cells by specific receptor attachment; blocking the merozoite binding the site with antibody prevents

attachment to the receptors on the erythrocyte surface and hence prevents further multiplication.

(3) Enhancement of phagocytosis. Complement C3b deposited on parasite membrane opsonizes it for phagocytosis by cells with C3b receptors (for example macrophages). Macrophages also have Fc receptors.

(4) Eosinophils, neutrophils, platelets and macrophages may be cytotoxic for some parasites when they recognize the parasite via specific antibody (ADCC). The reaction is enhanced by complement.
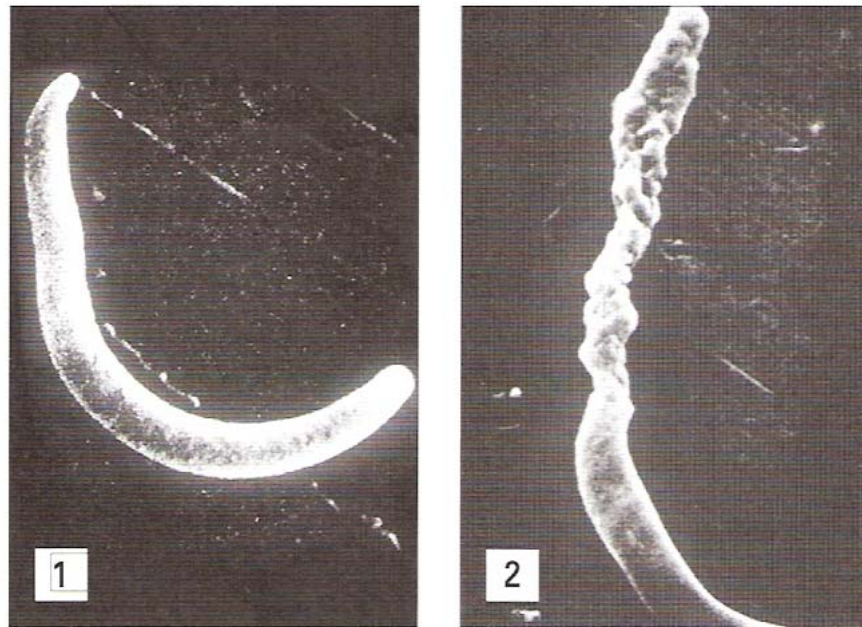

Figure-15 Direct effect of specific antibody on sporozoites of malaria parasites, these scanning electron micrographs show a sporozoite of *Plasmodium berghei*, which causes malaria in redents, before (1) and after (2) incubation in immune serum. The surface of the sporozoite is damaged by the antibody which pertubs the outer membrane, causing leakage of fluid. Specific antibody protects against infection with Plasmodium spp. at several of the extracellular stages of the life cycle. The antibody is stage specific in each case.
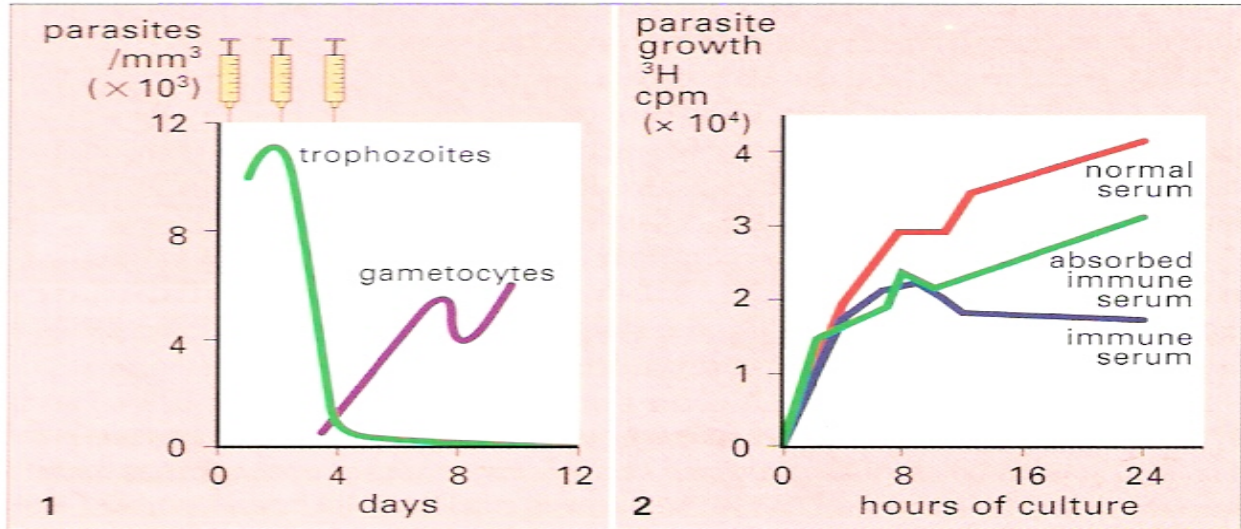
Effect of antibody on malarial parasites

Figure-16 (1) Transfer of γ-globulin from immune adults to a child infected with *Plasmodium falciparum* caused a sharp drop in parasitaemia. Specific antibody acts at the merozoite stage in the life of the parasite and prevents the initiation of further cycles of multiplication in the blood. The development of gametocytes from existing intracellular forms is unaffected.

(2) In culture, the presence of immune serum blocks the continued increase in number of P. knowlesi (a malarial parasiteof monkeys), as measured by incorporation of ^{3}H-leucine. It stops multiplication at the stage after schizont rupture by preventing the released merozoites from invading fresh red blood cells. The inhibitory activity of the immune serum can be reduced by prior absorption of the specific antibody with free schizonts.