IMMUNOPATHOLOGY OF PARASITIC INFECTIONS

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Detection and elimination of "foreign" particles from the body is the major function of the immune system in its primary role of maintaining the biological identity of the individual. A complex system of interacting cells, cell products and modifying factors are involved. The elimination of "foreign" particles or antigen depends upon the efficient interaction of these cells, their products and the modifying factors. If the interactions are deficient or altered, the antigen may persist within the host producing harmful effects like hypersensitivity reactions. These deleterious effects and tissue injury are known as immunologically mediated diseases. The injury may either be temporary or permanent depending upon the efficiency of antigen elimination.'

Basically 4 categories of immunological reactions (Type I–IV) are considered to be the underlying mechanisms for immune injury to the host.[2] These are the immediate hypersensitivity reactions (Type I), complement mediated cytolysis (Type II), the toxic effects of antigen-antibody complexes (Type III) and the cell-mediated delayed hypersensitivity (Type IV) reactions. It must be stressed that in any single pathological process, one, several or all of these groups of reactions may be involved. Immune mechanisms are involved in the pathology of many parasitic infections. The main factors responsible for tissue injury in parasitic infections are: chronicity of the infections, the release of parasitic or host cells in tissues and circulation, alteration and destruction of host tissue, the presence of antigenic components shared by the host and the parasite and the relative inefficiency of the host in eliminating the antigens or cross-reacting antibodies.[3]

IMMUNOPATHOLOGY DUE TO TYPE I (IMMEDIATE HYPERSENSITIVITY) REACTIONS.

Type I reactions are those in which antigens reacting with tissues or cells passively sensitized by antibodies induce the liberation of pharmacologically active mediators.' The mediators released from tissues by antigen-antibody interactions are histamine, serotonin, various forms of kinins and eosinophil chemotactic factor of anaphylaxis. The predominant antibodies which sensitize the tissue for anaphylactic reaction belong to the IgE class reagenic antibodies and are the major determinant of allergy to environmental antigen. IgG may also be homocytotropic in *Ascaris* infections in man.[4] These immunoglobulins which are capable of sensitizing the tissues of the species that produce them are known as homocytotropic antibody[5] and they can bind to target cells such as mast cells or basophils. Release of pharmacologically active mediators produce the clinical symptoms of these diseases: smooth muscle contraction and increased vascular permeability in a variety of tissues.[6] The resultant symptom complex is called anaphylaxis and the predominant mediator responsible for many of the symptoms of anaphylactic shock is histamine. The target organs commonly involved are the respiratory tract, the gastrointestinal tract and the skin. Manifestations of anaphylaxis vary and depend upon the type of sensitizing antibody, the species in which it is produced and the sensitivity of the shock organs. The reactions of anaphylaxis may be local or systemic and the antibodies responsible for Type I reactions may be acquired passively or actively.

Although a number of factors indicate that homocytotropic antibodies may be stimulated in protozoan infections, these have not yet been demonstrated. Wheal and flare (immediate hypersensitivity) reactions were seen in patients with severe amoebiasis, but their serum did not produce hypersensitivity reactions in the skin of monkeys.[7] Goodwin[8] demonstrated antibody that sensitized monkey skin in the serum of patients infected with *Leishmania brasiliensis.*

On the other hand, both long acting (IgE) and short-lived (IgG) homocytotropic anti-

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bodies are demonstrable in the blood of man and animals harbouring helminths.

Eosinophils.

Eosinophilia, homocytotropic IgE antibodies and immediate hypersensitivity are closely associated.[9,10] It is maintained[10] that interaction between homocytotropic antibodies and suitable helminthic antigen, through the mediation of an eosinophilic chemotactic factor, produces eosinophilia in persons infected with helminths.

Evidence indicates that immediate hypersensitivity reactions may play a role in the pathology of some helminthic infections. The best example is Loefflers' syndrome as seen in *Ascaris* infection in man.[1] Symptoms of *Ascaris* pneumonitis, like asthmatic type dyspnoea, cough, wheezing, high but transient eosinophilia and massive infiltration of the pulmonary parenchyma by leucocytes, mainly eosinophillia are caused by the passage of larvae of the worm through the lung. The symptoms of pulmonary infiltration and eosinophilia clear spontaneously after a few days. Passage of larvae of non-human parasites like *Toxocara canis* and *T. cati* through the lung may also produce similar symptoms. Tropical pulmonary eosinophilia (TPE) produced by microfilaria[2] is also considered to be due to severe hypersensitivity reactions to filarial worms.[3]

Increased levels of serum IgE have been observed in patients with filariasis.[4] Filarial infections are usually followed by blood eosinophilia. In addition to TPE, a variety of pathological changes in filarial infections are considered to be due to immediate hypersensitivity. Allergy due to Type I reactions are known to occur in man to migrating stages of *Loa loa* (fugitive swellings) and *Onchocerca volvulus*.[14] The sudden release of the toxic by-products of gravid females of *Dracunculus medinensis* into the human body gives rise to local and systemic hypersensitivity reactions.[5] These include local cutaneous reactions and generalized urticarial rash, intense pruritus, erythema, nausea, vomiting, diarrhoea and dizziness.

A number of animals experimentally infected with *Trichinella spiralis*[13] developed anaphylactic reactions at about the time when IgE and IgG homocytotropic antibodies were produced. In man, skin rash, urticaria, periorbital oedema, wheezing and fever in patients with trichinellosis are consistent with allergic manifestations. These symptoms are maximal between second and third week and are considered to be due to larval migration.[1] Eosinophilia precedes the development of serologic reactions and reagenic antibody was detected in an infection.[6]

Allergic manifestations are produced in man by all three species of human schistosomes. Homocytotropic reagin-like antibodies were demonstrated in the serum of humans[13-17] with schistosomiasis. Penetration of the cercaria in previously sensitized individuals produce urticaria, subcutaneous oedema, leucocytosis and eosinophilia. At the onset of oviposition, the infected person may develop symptoms of anorexia, headache and fever. Skin dermatitis commonly known as "sawah itch" or "swimmers itch" which shows immediate irritation followed by erythema, oedema and pruritus is produced in persons previously sensitized by schistosomes. Wheal and flare reactions have been reported in man in many helminthic infections like ascariasis, creeping eruption, enterobiasis, strongyloidiasis, hookworm infections, trichinosis, filariasis, echinococcosis and schistosomiasis.[10]

IMMUNOPATHOLOGY DUE TO TYPE II (CYTOLYTIC OR CYTOTOXIC) REACTIONS

Type II reactions[18] are those in which antibody directed against antigen on a cell membrane or basement membrane, releases and focuses the lytic activities of the complement on the particular cells, selected by the antibody. The antigen may be an integral part of the cell membrane or may be drug metabolites or microbial products which are absorbed on to the cell membrane from the surroundings. The destruction of the cell may be due to antibodies formed to any of these antigens.

It must be stressed here that at present it is not possible to distinguish true autoantibodies and antibodies against acquired or altered mem-

brane antigens in parasitic infections. Therefore, in this paper the term autoantibody is defined in a very general way. In some reactions mentioned below, true antibodies may not always be involved, the destruction of the cells being secondary to reaction with acquired or altered membrane antigens.

Once the autoantibodies are formed against any cell membrane antigen, like red cell antigen or liver cell antigen, autoallergic Type II tissue damaging reactions become possible, It is also possible that toxins or lipopolysaccharides which are liberated from microorganisms in *vivo* are absorbed on to body cells. Antibody stimulated against these antigens could then react back and destroy those cells.

Some parasites may act as stimulants of autoantibody against cell membrane antigen. Such autoantibodies initiate tissue or cell damaging (Type II) allergic reactions.'[8] Most of the investigations on autoantibody production in parasitic infections were made on malaria, the red cells being the target cell. Zuckerman[19] has stressed that the erythrocyte destruction in many malarial infections is greatly in excess of what would be due to direct rupture of the infected cells during schizogony. It has been suggested that antibodies produced in malaria react not only with parasitized red cells but also with uninfected cells that may have absorbed malarial antigens. Further it is claimed that red cell autoantibodies may also be implicated.'' It was postulated that an autoimmune haemolysis or opsonization of uninfected red cells is involved, However, no autoantibodies were detected by Coombs tests.[21] It has been suggested[Z2] that a malarial antibody-antigen reaction may occur on the surface of red cells and that due to the involvement of complement, haemolysis of the uninfected cells may occur. Cox[23] considered the red cell destruction to be due to the absorption on to the red cells of a serum-associated parasite antigen that acted as a non-specific opsonin which resulted in the removal of the coated cells in the spleen. The excessive anaemia in malaria therefore, is considered to be due to destruction of uninfected red cells either by antibodies against red cell antigens or those against absorbed antigen.

The black water fever produced in falciparum malaria in sensitized persons is thought to be a case of drug-dependent (quinine) Type II hypersensitivity reaction involving red cells.[20]

Type II reactions have been reported in other parasitic infections like human trypanosomiasis, kala-azar and schistosomiasis.[22-24] The anaemia in these infections is considered to be due to increased destruction of RBC in the spleen probably mediated by antibody and complement. It is difficult to confirm whether these are true autoantibodies directed against red cell antigen or against absorbed antigen.

IMMUNOPATHOLOGY DUE TO TYPE III REACTIONS (ANTIGEN AND ANTIBODY COMPLEXES)

These reactions are due to circulating immunecomplexes lodging in and around small blood vessels causing inflammation and sometimes mechanical blocking of these vessels impeding blood supply to surrounding tissue. There are two types at each end of the spectrum of Type III reactions: a localized acute inflammatory: Arthus reaction and a systemic form: serum sickness. The intensity of the reaction depends upon the concentration of deposition of complexes and on the ability of the antibody to activate complement. The clinical manifestations depend upon where the immune complexes are formed and/or are lodged.

The acute transient nephritis that may be found in P. *falciparum,* P. *vivax* and *P. malariae* and the chronic nephrotic syndrome associated with quartan malaria are now recognised to be of immune complex mediated origin (Type III reactions).[25]

Transient febrile nephritis has long been known in P. *falciparum* infections in man.[26] Usually a mild to a severe proteinuria develops a week or two after P. *falciparum* infections. Renal biopsies taken at this time from patients with acute nephropathy show IgM and complement deposits in the glomeruli. The nephritis responds favourably to antimalarial drugs and after a few weeks the proteinuria resolves and the immunological abnormalities disappear. When present in P. *vivax* infections, the pro-

teinuria is even milder and more transient. Although proteinuria in acute P. *malariae* infections is more severe than those in other malarial infections, it responds to antimalarial drugs.

The chronic nephrotic syndrome associated with P. *malariae* infections is more serious. Almost all West African children with nephrosis had demonstrable P. *malariae* showing association.[2] Immunoglobulin deposits were demonstrated[28] on the glomerular basement membranes in renal biopsies from patients with nephrotic syndrome. IgM was the most predominant class of antibody and some cases showed complement deposition. The demonstration of antigen-antibody complexes supported the hypothesis that the nephrotic syndrome might be due to glomerular damage caused by the deposition of immune complexes.

Houba *er al*[29] studied the immunological aspects of this chronic nephrotic syndrome. They showed two patterns of deposits in the renal glomeruli. In one, the immunoglobulin deposits were of coarse granules containing IgG, IgM and complement. In the second, the deposits were of fine granules of a diffuse character containing only IgG without IgM or complement. Immunofluorescent tests with specific antisera to P. *malariae* detected antigens, but P. *falciparum* specific antisera did not detect the antigen.[23]

The ultrastructure of glomeruli biopsies from children with nephrotic syndrome[28,30,31] showed thickening of the basement membrane and fusion of the fine processes of the epithelial cells. These findings support the view that chronic progressive nephrotic syndrome in P. *malariae* is associated with the deposition of circulatory immune complexes in the kidneys. The disease is probably initiated by specific malarial antigen-antibody complexes but is then perpetuated by an autoimmune reaction to damaged host tissue or to the initial antigen-antibody complexes.[2]

Clinical observations show that oedema in nephrotic children may subside, but an asymptomatic proteinuria persists and the renal function deteriorates slowly with hypertension. Some may show rapidly progressive renal failure. The chronic nephrotic syndrome does not respond to antimalarial or immunosuppressive drugs.[20]

It is not known in P. *malariae* infections why a few individuals develop chronic nephrotic syndrome while the others may show only a transient nephritis. It may be that some individuals are genetically predisposed[2] and react in an aberrant manner to P. *malariae* infection. Malaria is known to lower the affinity of antibody against unrelated antigen.[32] Low-affinity antibody is shown to be more likely to produce immune complexes.[33] This may then explain to some extent the formation of the complexes in quartan malaria. Other factors like age at which the infection occurred and the presence of other concomitant infections may also be important.

Lesions of glomerulonephritis-type were reported in Brazilians[34,35] and in Egyptians who had *Schistosoma mansoni* infections. Kidney biopsies showed bound immunoglobulins and complement in glomerular capillary walls. Electronmicroscopy showed deposits of immunoglobulin in association with proliferated mesangial cells. It seems probable that schistosome antigen-antibody complexes may accumulate in the glomeruli and produce mild reactions. Such observations have not been reported in patients with S *haematobium* infections.

IMMUNOPATHOLOGY DUE TO TYPE IV (CELL–MEDIATED) REACTIONS.

Cell-mediated or delayed hypersensitivity[2] is a specifically provoked, slowly evolving, mixed cellular (Type IV) reaction. It is usually presented as a tuberculin or delayed skin test, a red lump in the skin which reaches its peak between 24-48 hours. The reaction is not brought about by circulating antibody, but by sensitized lymphoid cells and can be transferred in experimental animals by means of such cells but not by serum. The reaction appears as an area of enduration and sometimes as erythema of the skin. Another form of delayed hypersensitivity is the granuloma formation.

Histologically an intense inflammatory lesion, packed almost exclusively with mono-

nuclear round cells, lymphocytes and macrophages is seen.[2,36] The delayed hypersensitivity reactions may damage the host by causing vascular blockage and necrosis. It may also produce damage by replacing normal tissue with infiltrating mononuclear cells. Cytotoxic substances produced by the lymphocytes and lysosomal enzymes formed by macrophages may also destroy the tissues.[37]

In spite of intensive research on the delayed hypersensitivity reaction, the mechanisms underlying the phenomenon is not well understood. A possible explanation is that amongst the continuous traffic of lymphocytes passing through the tissues, there are some sensitized cells possibly with "antibody-like receptors" on their surface. These cells interact with antigen they meet in some unknown way to influence other lymphocytes to migrate to the area.[38] In recent years, a group of substances were shown to be released by lymphocytes coming in contact with the antigen to which they were sensitized. This group of non-antibody lymphocyte factors are named lymphokines. The chemotactic factor attracting additional lymphocytes to the site of location of antigen is one of the lymphokines. Another factor which appears to be responsible for inducing proliferation of lymphocytes at the site of localization is known as mitogenic factor. A cytotoxic effect has also been demonstrated in tissue culture experiments affecting lymphocytes and other cells.[38]

Delayed hypersensitivity reactions to protozoan infections like Chagas' diseases, toxoplasmosis, leishmaniasis and trichomoniasis were demonstrated in man.[39,40] Such skin reactions are also present in helminthic infections like ascariasis, toxocariasis[41] and in *Schistosoma mansoni* infections.[42]

Leishmaniasis and schistosomiasis are the two best examples of cell-mediated immunological reactions in the pathogenesis of parasitic diseases.[36] Leishmaniasis is a spectral disease[43] similar to leprosy and the harmful hypersensitivity reaction is closely associated with immunity (protective). At one extreme, relatively little host-reactivity is seen resulting in massive multiplication of the parasite and resultant disease manifestations whereas at the other extreme the massive host reactivity causes

immunopathological manifestations. It is now considered[36] that the common lesion in the cutaneous leishmaniasis, oriental sore, is at the mid-point in the spectrum. In this condition, a few weeks after the bite of an infected sandfly, a nodule develops in the skin that ulcerates for a few months, remains in that state for up to a year and then heals slowly. At one end of the spectrum is lupoid leishmaniasis in which healing is poor and the scars are surrounded by ulcerating nodules. There is marked cellular response with granuloma formation, many plasma cells and few or no parasites. There is marked delayed dermal hypersensitivity on testing with leishmania antigen. At the other end, is the relatively rare diffuse cutaneous leishmaniasis where there is a primary non-ulcerating nodule with similar metastatic dermal lesions. There is a mass of macrophages full of leishmania and little inflammatory infiltration and the delayed dermal reactivity is absent.[1]

On the other hand, schistosomes do not multiply within the definitive host but several developmental stages are present in the host. The schistosomulae are found in the skin and lungs, the adult worms in the mesenteric veins, while the eggs are trapped in the tissues, mainly in the intestine, liver, lungs, and urinary tract. Protective immunity to schistosomiasis is directed against the schistosomulae while immunopathological reactions are to the egg antigens.[36] The eggs contain antigens which cross-react with cercariae and possibly with schistosomulae; however, the inflammatory reaction in the host is stage — specific to eggs.[44]

The disease syndrome associated with chronic schistosomiasis is due to granuloma formation around the eggs.[45] The soluble egg antigens secreted through ultramicroscopic pores[46] are thought to induce cell mediated hypersensitivity and egg granuloma in S. mansoni infections.[4] These soluble egg antigens kontain enzymes which facilitate the passage of the egg through the tissues. The antigenic secretions sensitize the host, resulting in the development of thymic, lymphocytic memory cells. These on further antigenic stimulation release lymphokines, which influence the migration of macrophages and eosinophils. The lymphocytes, macrophages and eosinophils

gather about the eggs in the tissue forming granulomas. Continual secretion of antigens results in chronic inflammation characterized by epithelioid cells, giant cells and fibroblasts. Probably due to the release of lymphotoxins, lysosomal enzymes and toxic substances in the egg antigens, large areas of tissues are destroyed. Healing is accompanied by the formation of a fibrous scar and the inflammation and the scar tissue cause the enlargement of the liver.[36]

IMMUNOSUPPRESSION IN PROTOZOAN DISEASES.

Both humoral and cell-mediated immunosuppression may occur in protozoan infections. It is known that acute malaria produces temporary immunosuppression to some unrelated antigens e.g. tetanus toxoid.[48] Its effect is maximum at the height of parasitaemia. This effect was shown to be on humoral and not on cell-mediated responses.[49] Immunological response to malaria was also considered to aggravate an otherwise latent or benign viral infections to produce the lymphoproliferative Burkitts' lymphoma.[50] Simultaneous infection of malaria and toxoplasmosis give rise to particularly severe disease in mice. The depression in haemagglutinin and haemolysin response in toxoplasmosis was considered to be a reduced response in antibody of the IgM class possibly due to antigenic competition.[51] Trypanosome infections may interfere with the cooperation of T and B lymphocytes to lead to excessive production of partially nonspecific IgM and immunodepression of responses that require the T and B-cell cooperation.[52] Trypanosomes appears to be immunosuppressive in animals for humoral and cell-mediated responses. Patients with kala-azar respond poorly to TBA vaccine.[53]

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