CLINICAL MICROBIOLOGY REVIEWS, July 1989, p. 250–269
0893-8512/89/030250-20$02.00/0

Vol. 2, No. 3

Immunopathology of *Schistosoma mansoni* Infection

DOV L. BOROS

Department of Immunology and Microbiology, School of Medicine, Wayne State University, Detroit, Michigan 48201

INTRODUCTION

Schistosomiasis mansoni is a disease of the tropics. According to a survey of the World Health Organization, the disease is endemic in 51 countries, affecting about 100 million people (169). The causative agents are digenetic trematode worms, also called blood flukes, that live in pairs and are attached to the walls of the host mesenteric veins. The male and female worms have a complicated life cycle alternating between aquatic snails (intermediate host), in which asexual reproduction takes place, and humans (definitive host), in whom sexual reproduction occurs. Human infection is initiated during water exposure (planting, fishing, washing, and swimming), when the free-swimming forktailed cercariae penetrate the intact host skin. In the skin, cercariae transform into another larval form, the schistosomulum, that is adapted to live in the higher osmotic environment of the body. Host reaction in the skin is variable and may result in transient dermatitis. Male and female larvae migrate through the skin, blood, and lungs; the worms grow and mature, descend to the liver, mate by pairing, and settle in the mesenteric venous plexus. The small adult worms (male, 10 to 15, and female, 14 to 20, mm long) live in copula, and each female produces about 300 eggs daily. The life span of the worm is 5 to 10 years, and by a variety of mechanisms it is capable of evading the host immune response (95). The worms feed on host erythrocytes and body solutes, and their presence is innocuous to the host. Some of the eggs deposited by the females into the bloodstream pass through the venule walls, cross the intestinal mucosa, reach the lumen, and are evacuated with the fecal material. Eggs that arrive in the outside environment have to reach fresh water for the embryo (miracidium) to hatch and swim to find its intermediate snail host. Penetrating the snails, the miracidia undergo a complicated metamorphosis involving asexual reproduction, and in a few weeks they emerge in the new infectious form, the cercariae. In the definitive mammalian host, eggs that do not reach the intestinal lumen are swept into the portal circulation and are trapped in the intestinal wall, the liver, or the lung and systemic organs and are surrounded by the granulomatous inflammatory response of the host. The continuous egg deposition induces a chronic inflammatory host response that is responsible for the disease syndrome. Most low or mild infections are well tolerated, with minimal symptoms; heavy infections may terminate fatally.

The variety of antigens secreted by the worms or shed during the different developmental stages of the worm life cycle (cercariae, schistosomula, adult male and female, and eggs) provide strong sustained stimuli to the host humoral and T-lymphocyte-mediated immune systems. The aims of this review are to illustrate how the vigorous host response mounted to parasite antigens may lead to the development of pathological events and to describe the regulatory mechanisms that modulate the exuberant immune responses and ameliorate excessive morbidity.

DERMATITIS

Schistosome infection is initiated after cercariae penetrate through the skin and transform into schistosomula, the larval form suited for existence in the host milieu (144). Penetration and migration of cercariae are facilitated by proteolytic enzymes secreted from cephalic glands capable of digesting epidermal keratin (135). Infected individuals exposed to *Schistosoma mansoni* cercariae experience itching within 1 h of water contact. In mild cases, a skin rash appears that consists of rounded, discrete, 1- to 2-mm erythematous papules. Urticariae that persist for several days may also be present. The itchy sensation and papular eruption may take days to disappear, and the healed papules may leave behind a pigmented spot. Severe dermatitis is manifested by an evenly distributed confluent papular reaction. If papules are infected with bacteria, pustules will appear (5, 21). Exposure to cercariae of nonhuman schistosomes causes a severe, intensely pruritic dermatitis in the reinfected host (20). This phenomenon has been extensively investigated in individuals who had been repeatedly exposed to duck schistosomes in lakes of the American Midwest (93). After penetration, cercariae of bird schistosomes die in the skin of the unnatural host and their antigens initiate a sensitization process. On primary host exposure, cercarial dermatitis, called swimmers' itch, causes a mild itch and the appearance of 1- to 2-mm macules at the site of penetration. This reaction is transient and innocuous. After repeated exposures, the individual reacts within 1 h of exposure with intense itch, the formation of papules, and, sometimes, diffuse erythema. About 10 to 15 h later, itchy papules 3 to 5 mm in size develop and become indurated and edematous. In 2 to 3 days, vesicles that may rupture are formed. Histological examination of biopsied skin shows the cercariae confined to

the epidermis. During the first 30 h after exposure, an extensive infiltration of neutrophils and lymphocytes occurs which by day 2 is augmented by the influx of eosinophils. The infiltrating cells kill the penetrated cercariae (50). The symptomatology and histologic picture are consistent with an anamnestic immune reaction (210). The immune basis of cercarial dermatitis in *S. mansoni*-infected individuals is supported by the demonstration of humoral and cell-mediated immune reactivities to cercarial antigenic preparations. Patient sera react with the outer coat of the larvae (Cercarienhüllen Reaktion) (259), which can be also demonstrated by the indirect immunofluorescence (IF) reaction (241, 243). Judging by the immediate and delayed-type hypersensitivity reactions following intradermal injection of cercarial antigens, individuals develop both reagin-type, immunoglobulin E (IgE) skin-binding antibodies (242) and T-cell-mediated reactivity to cercariae (196). The latter is confirmed by specific lymphoproliferation of peripheral blood mononuclear cells (PBMN) stimulated with cercarial antigens (85, 213).

In normal mouse skin, cercarial penetration causes, first, a mild edematous reaction with infiltration of predominantly neutrophilic cells into the epidermis and dermis (91, 274). In previously sensitized animals, the reaction is enhanced; it appears faster and the total granulocyte content of the infiltrate is increased, a major portion of the cells being eosinophils (274). Mast cells degranulate, and the vascular endothelium may show focal degeneration (27). Guinea pigs sensitized with schistosomal antigens react to cercariae with a strong basophil and minor eosinophil infiltration (18). Basophils and free basophil granules are observed in close proximity to the invading larvae (219). Rat peritoneal mast cells exposed to cercariae in vitro undergo degranulation and release histamine (64). In contrast to rodents, normal baboons do not mount an inflammatory skin response to penetrated cercariae. They develop the ability to mount a predominantly eosinophilic infiltration around cercariae only after a prolonged infection (250).

Passive transfer experiments conducted in mice with both immune sera and cells have indicated that both humoral and cell-mediated mechanisms participate in the anticercarial skin response. The early wave of cell infiltration is evoked by the passively transferred antibodies, and the subsequent activity is attributed to T lymphocytes (91). Cercarial extracts also have been reported to activate complement (186) and exert chemotaxis on eosinophils (84). Thus, the initial nonspecific reaction to cercariae is attributed to focal damage and triggering of the complement pathway, which can generate polymorphonuclear infiltration; focal mast cell degranulation and released histamine may account for itching. On secondary or repeated experimental exposures, memory lymphocytes are triggered and elicit both humoral and T-cell-mediated, accelerated, enhanced focal reactions rich in eosinophils. It is presumed that such a reaction is protective and contributes to the attrition and death of the penetrated cercariae (83, 95, 226). It should be noted, however, that a history of dermatitis is only rarely elicited in *S. mansoni*-infected patients who live in areas in which schistosomiasis is endemic.

ACUTE SCHISTOSOMIASIS

Acute schistosomiasis is a clinical syndrome often seen in nonimmune individuals (tourists, immigrants, or the indigenous population) who have been exposed in an endemic area to a primary infection by cercariae (79, 106, 234, 300). The syndrome is sometimes called Katayama fever, described in Japan in persons who acquired a massive infection with *S. japonicum* worms. Acute disease manifestations rarely occur among reinfected individuals living in an endemic area, presumably because of their pre- and postnatal exposures to schistosome antigens via transplacental transfer (61), lactation (249), and repeated infections at an early age. This view is supported by murine experiments in which fetal or neonatal exposure to schistosome antigens induced a state of hyporesponsiveness and diminished the granulomatous responses of adult animals (152, 179).

Symptoms of acute schistosomiasis usually appear 4 to 10 weeks after a heavy exposure to cercariae. This would coincide with the migratory stage of the maturing schistosomula in the lungs and liver, maturation of male and female worms, or early oviposition in the mesenteric veins. The acute (toxemic) syndrome is manifested by fever, malaise, hepatosplenomegaly, eosinophilia, diarrhea, and, in some cases, edema, urticaria, lymphadenopathy, and arthralgia (106, 200, 234, 277). These symptoms are transient and spontaneously disappear with the passage of the infection to the chronic stage. However, neurological, pulmonary, cardiac, hepatic, or intestinal complications may appear with or without granulomatous pathology, sometimes with fatal consequences (36, 106, 168, 277). Moderate elevation in serum globulin, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase levels may occur, indicating liver involvement. In rare cases, acute hepatitis with focal necrosis and eosinophil infiltration are observed (234). The efficacy of antihelminthic therapy at this phase of the infection is equivocal (200). Treatment has been reported to diminish eosinophilia and improve liver function (192) or exacerbate symptoms (154).

The relationship of fecal egg count (indicator of worm burden) to the severity of symptoms is still unclear. Whereas in certain patients a direct relationship was established (159), in others the presence of severe symptoms without a concomitant diminution in fecal egg counts supports the notion that clinical symptoms are induced by schistosomal adult worm and egg antigens. In experimental studies, sequential histologic examination of infected mice showed severe reactive hepatitis around the first eggs deposited in the liver. Microvacuolated hepatocytes were visible adjacent to the eggs, coagulative necrosis was evident, and the area was surrounded by eosinophils (9).

The exact mechanism(s) responsible for the pathogenesis of acute schistosomiasis is still unknown. Both nonimmune and immune mechanisms may participate in the pathogenetic process. Experiments in vitro demonstrated that schistosomula directly activate the alternate pathway of complement (245). Thus, conceivably, the antigens released in large amounts during the migration, maturation, or death of schistosomula may trigger serum complement, with resulting anaphylactoid reactions. At the immune level, immediate-type and immune complex-mediated hypersensitivity reactions can be invoked as possible pathogenic factors. Because IgE antibody levels are elevated at the acute phase of the infection and may correlate positively with the magnitude of the infection (159), heavily infected individuals may develop anaphylactic reactions following parasite antigen-induced degranulation of IgE-coated mast cells (215). Clinical manifestations seen in patients, i.e., skin rash, eosinophilia, pulmonary edema, or diarrhea, are consistent with this contention (36, 106, 234). The temporal relationship between the appearance of symptoms and the release into the circulation of large amounts of worm antigens derived from

schistosomula, adult worms, and eggs has led to the proposal that acute schistosomiasis is a serum sickness-like disease (14, 226, 277). This hypersensitivity reaction occurs at the initial phase of immunization when large amounts of circulating antigens combine with low amounts of early antibodies to form small, soluble, complement-binding complexes. In clinical schistosomiasis, detection of antibodies or circulating immune complexes (CIC) in sera of acutely infected persons indicates the presence of strong immune responses to various worm antigens. One important worm antigen in the circulation is a high-molecular-weight, polysaccharide-like molecule (206) that is secreted by the cecal gut epithelial cells of the worms and is released into the blood by regurgitation. Fractionation of the trichloroacetic acid-soluble material yielded >300- to 66-kilodalton (kDa) polydisperse material named GASP (gut-associated proteoglycan), which upon further fractionation yielded a 90- to 130-kDa substance, PSAP (phenol sulfuric test active peak polysaccharide) (203–205). Human sera showed good precipitation with radioiodinated GASP and PSAP, indicating their value as immunodiagnostic reagents (205). Because acutely infected patients had high levels of anti-GASP and anti-PSAP antibodies (205) during the primary infection, worm gut-derived, excreted-secreted proteoglycans may be the first stimulatory antigens that trigger the humoral immune response (273). Indeed, by the IF technique, sera of infected patients were shown to react with the gut epithelium of adult worms (99, 268). IgM, IgG, IgA, and IgE antibodies were specifically associated with this reaction (172).

Sera of recently infected individuals also showed high IgM antibody levels to GASP (188) or to a circulating polysaccharidelike anodic antigen (CAA) (98–101) now believed to be identical to GASP (201). Thus, the high IgM levels found in patients with Katayama fever (19) have been interpreted as primary immune responses to worm polysaccharide proteoglycan antigens. In fact, it was claimed that acute schistosomiasis can be differentiated from chronic cases on the basis of specific IgM titers and of cercarial/adult antibody ratios (184, 202).

Animal experiments also confirm the presence of circulating worm antigens. Within 3 to 4 weeks of a heavy infection, negatively charged antigens were found in the sera of mice (29) and hamsters (142). By using specific antiserum and a sensitive enzyme-linked immunosorbent inhibition assay, a 41-kDa hydrophobic cercarial polypeptide was detected in the bloodstream of mice within 1 week of the infection (156). Because fecal egg passage does not commence until week 6 to 8 of the infection and initial dermal responses to schistosome antigens are erratic, early detection of circulating schistosomal antigens could facilitate correct early diagnosis. Moreover, because the amount of circulating proteoglycan antigens appears to correlate with the intensity of infection (142), quantitation of circulating antigens could help to assess infection severity.

Whereas ample documentation exists for the appearance of strong humoral responses in acutely infected persons, only a few publications demonstrate the presence of CIC in such individuals. In one study, the severity of illness during the acute phase of the disease was positively correlated with the magnitude of worm burden. Levels of total IgM, IgG, and IgE were elevated in patients, and in heavily infected patients titers of circumoval precipitin reactions and complement fixation tests corresponded with the intensity of infection. Despite the often severe serum sickness-like symptoms, no evidence of complement consumption (C3, C4, and 50% hemolytic complement levels) or renal disease was found (159). Another study that used the ^{125}I-labeled C1q-binding assay to detect circulating complexes measured binding activity in the sera of 14 of 15 acutely infected persons, but only in sera of 2 of 11 chronically infected persons. Serum IgM levels in acutely infected persons were elevated over those measured in chronically infected individuals. Complement fixation tests with adult worm antigens showed significantly higher titers in acute-phase compared with chronic-phase sera. Analysis of the precipitated complexes detected moderate amounts of IgM and IgG antibodies, but no antigens could be found. No correlation was seen between the magnitude of C1q binding and liver and renal function tests (176). Serial determinations of labeled C1q-binding activity in acutely infected patients revealed peak binding ability with maximally elevated IgM levels and eosinophilia by 10 weeks after exposure. These levels correlated positively with the number of eggs excreted in the feces and the index of symptom severity. Following antihelminthic therapy with niridazole, C1q-binding values as well as IgM and IgG levels returned to normal in a small number of patients (158).

Overall, the available evidence indicates that acute schistosomiasis is accompanied by strong host immune responses. The pronounced hypergammaglobulinemia found in humans (16, 26, 106) and mice (251) and the occurrence of autoantibodies in the latter (134) during the acute phase of the disease are indicative of nonspecific polyclonal B-cell stimulation. Whether polyclonal B-cell stimulation occurs in human schistosomiasis and whether it contributes to the immunopathology of the disease remain to be elucidated. Because in a certain number of patients circulating complexes have been found (but the complexed antigens have not been identified), it is possible that the complexes are composed of immunoglobulin-rheumatoid factors (63). Conceivably, both immune and nonimmune mechanisms contribute to the pathogenic process. Whether there exists a preponderant immune factor such as immune complex-induced serum sickness that is responsible for the acute clinical manifestations seen in schistosomiasis is still to be confirmed.

CHRONIC SCHISTOSOMIASIS

Renal Pathology

In Brazil, chronic schistosomiasis is classified into the mild intestinal, hepatointestinal, and severe hepatosplenic (HS) forms of the disease (14). Patients with the mild intestinal form constitute >90% of the infected population. They usually carry a light worm burden and may be asymptomatic or have abdominal pain, transient diarrhea, and bloody stools. Less that 10% of the infected persons develop HS disease, which is manifested by hepatosplenomegaly, Symmers' clay pipestem fibrosis, portal vein obstruction, portal hypertension, ascites fluid formation, and esophageal varices which rupture and cause repeated episodes of hematemesis (97, 141, 233, 277, 280). Among individuals with HS manifestations, 10 to 15% develop the nephrotic syndrome (14). This syndrome may sometimes be attributed solely to a concomitant bacterial infection such as salmonellosis (24), which may increase the incidence of CIC formation and directly or indirectly cause renal disease. However, the helminthic infection alone is sufficient to initiate the nephrotic syndrome.

Renal manifestations develop slowly and appear many years after the onset of HS disease (11). Histologically, renal

tissue shows a spectrum of pathological changes, not necessarily accompanied by clinical syndrome. Early changes include mesangial expansion with amorphous periodic acid-Schiff stain-positive deposits. Mesangial cell hypertrophy and hyperplasia may follow. Basement membrane changes are not marked; subepithelial, subendothelial, and intramembranous deposits may be visible. In more advanced cases, membranoproliferative glomerulonephritis develops and focal glomerulosclerosis is evident (8, 14). Proteinuria may be linked to HS disease manifestations (177, 232). However, glomerulopathy without proteinuria occurs frequently (252) and, when associated with salmonellosis, may be caused by the bacterial rather than the helminthic infection (24).

To establish the immune etiology of schistosomal glomerulopathy, the sera and renal tissues of infected humans have been examined for the presence of CIC. Infected individuals often have elevated total levels of serum IgM and IgG (16, 26). It is probable that only a fraction of those immunoglobulins are antigen specific. In humans, CIC were assayed by immunodiffusion (187), immunoelectrophoresis of acidified dissociated complexes (230), quantitation of the amount of bound serum complement, or precipitation of complexes with polyethylene glycol (248). In one study, results of radiolabeled C1q binding, complement fixation, and polyethylene glycol precipitation tests showed good correlation, but levels of CIC were higher in patients with mild disease than in patients with HS disease. Nevertheless, the precipitated immune complex (IC) contained schistosome antigens that reacted with specific IgM, IgG, and IgE antibodies (49). Subsequent studies showed good correlation among levels of CIC, intensity of infection, and severity of disease as manifested by the amount of circulating antigens and fecal egg excretion (61, 136, 230, 247). Fixation of complement by CIC was confirmed (248), and high levels of C3d breakdown product were found in the sera (136). However, correlation was not always found between the levels of CIC and C3d because the circulating antigens nonspecifically bound complement (246).

Much effort has been invested in identifying the schistosome antigen components that participate in IC formation. Circulating polysaccharide proteoglycan antigens first detected in the sera of heavily infected experimental animals (29, 98, 142) and implicated in serum sickness-like symptoms in acutely infected persons (98–101, 203–206) are the major candidates for IC formation. These consist of GASP/CAA and circulating cathodic antigen (CCA), a positively charged, large sugar moiety-containing molecule; both of these originate from the gut epithelium of the worms (12).

With the introduction of highly specific monoclonal antibody to CCA and of sensitive radioimmunoassay and enzyme-linked immunosorbent assay, circulating CCA and CAA antigens have become detectable in the 1- to 200-ng range. These methods helped to establish a correlation between levels of CCA and intensity of infection. Using the C1q-binding test, a high percentage of patients with HS versus intestinal schistosomiasis could be identified. A decrease in egg excretion with a concomitant drop in CCA levels seen in praziquantel-treated patients further confirmed the significance of circulating antigen levels as possible indicators of heavy infection and HS disease (132). Antigen M was found in the blood, milk, and urine of infected patients and hamsters (58–60, 249) and appears to be related to CCA (201); its occurrence also correlates with the intensity of infection. Demonstration of soluble egg antigens (SEA) in kidney extracts from infected baboons (167) but not mice (121) and of parasite deoxyribonucleic acid in the glomeruli of hamsters (160) provides presumptive evidence that these antigens may enter the circulation in some but not all animal species.

Renal tissues of humans obtained by biopsy or at autopsy were examined for determining the presence of immunoglobulins, complement components, parasite antigens, and IC deposits. By direct or indirect IF, lumpy deposits of IgM, IgG, occasionally IgA and IgE, C1q, and C3 were observed in the mesangial areas and capillary walls in kidneys undergoing proliferative glomerulonephritis (11, 96, 129, 165, 188, 211, 252). The presence of specific antibodies was confirmed by acidic elution of homogenized renal tissue. The eluted IgG bound strongly to adult worm gut and reacted weakly with the outer tegument of the worm (195). Localization of GASP/CAA in the mesangium and capillary basement membrane of patients with membranoproliferative glomerulonephritis and end-stage renal failure indicates a role for this antigen in schistosome-specific nephropathy (211, 256).

Glomerular lesions affecting the mesangial areas could also be produced in heavily infected experimental animals. The renal lesions of infected hamsters consisted of mesangial and endothelial hypercellularity (161). Glomeruli of heavily infected mice showed lesions consistent with nephritis (207), manifested by an increase in mesangial cells, electron-dense deposits, and local thickening of basement membranes (104). However, murine glomerulopathy, unlike human, does not progress to chronic renal failure. Deposits of host immunoglobulin or complement component or both were observed in the glomeruli of infected hamsters (161) and mice. In the latter species, IgM, IgG, IgA, and C3 deposits were seen, IgA immunoglobulin being more prominent at the chronic phase of the infection (104, 107, 127). However, the appearance of immunoglobulin deposits in the kidneys of ostensibly normal uninfected mice cautions against drawing rapid conclusions from this type of study. More convincing proof was obtained by the detection of parasite antigens in CIC and glomerular deposits. Analysis of CIC revealed a maximal antigen content at 9 to 10 weeks of infection. The antigen was complexed with IgM and IgG antibodies (107). An antiserum of high specificity detected CAA deposits in the kidneys of bi- or unisexually infected mice (100, 270). Sequential IF studies showed CAA uptake by Kupffer cells of the liver within 1 week of the infection; by 3 weeks, splenic macrophages contained ingested antigen. Subsequently, antigen was localized within the kidneys, and by 16 to 18 weeks heavy deposits formed within the mesangium (121). By electron microscopy, gold-labeled monoclonal antibodies to CAA and CCA detected both antigens on the glomerular basement membrane and mesangial matrix by 5 weeks postinfection in heavily infected mice. Interestingly, the lower-molecular-size CCA was found in higher amounts than CAA on the glomerular basement membrane, the mesangial matrix, and the luminal membranes of epithelial cells bordering the urinary space. Though IgM and IgG deposits were observed in the mesangium by week 5 of infection, their relation to the antigen deposits remained unexplored (104).

In summary, the existing literature favors the notion that glomerular nephropathy observed in the minority of heavily infected persons with the HS syndrome is an immunologic disease. However, evidence linking nephropathy to the presence of circulating and deposited IC is largely circumstantial. The appearance of the renal syndrome in patients with Symmers' fibrosis, portal vein obstruction, and systemic collateral circulation led to the proposition that renal

damage is caused by CIC that are shunted from the liver to be filtered at the renal level. Because of the partial blockage of the portal circulation and development of collaterals, the normal hepatic clearance of antigens and CIC would become defective; therefore, these substances would arrive in greater amounts in the kidney (14). Partial ligation of the portal vein and induction of portosystemic collateral circulation facilitated deposition of IC within the mesangium of heavily infected mice, lending support to this contention (269). Moreover, glomerular changes are known to occur in patients not infected with schistosomes but suffering from liver cirrhosis in the absence of an infectious condition (28).

The role of the liver in the sequestration of gut-associated GASP and PSAP worm antigens has been demonstrated in both normal and infected mice. Following sequestration, these antigens are degraded and excreted in the urine as low-molecular-weight nonantigenic substances. In lightly infected mice, the clearance of injected antigens is accelerated compared with that in normal controls, probably due to IC formation with specific antibodies (197, 198). The rate of clearance of any CIC is dependent on the physicochemical characteristics of the antigen, isotype and affinity of the bound antibody, and size of the complexes and their ability to bind complement and rheumatoid factor. Thus, the observation that injected labeled GASP is cleared faster in the lightly versus the heavily infected mice is significant, because the former animals are thought to form larger complexes that are cleared rapidly by the liver (199). Anti-GASP IgM and IgG antibody levels diminish in chronically infected patients, and that change may favor the formation of intermediate complexes which are potentially nephritogenic in slight antigen excess (205, 261). The extent of hepatic clearance is also influenced by the cell types and receptor mechanism(s) involved. In the infected host, the bulk of CIC or antigens is sequestered by phagocytic Kupffer cells and perhaps by granuloma macrophages of the liver (199, 244), but sequestration of antigens complexed with IgA antibodies by hepatocytes must also be considered (223). GASP complexed with antibody appears to be sequestered by Fc receptor-mediated phagocytosis, whereas PSAP-containing complexes may be removed by means of galactose receptors that interact with the glycosyl residues on the antigen (198). Supposedly, if the hepatic clearance mechanisms are faulty, then circulating antigens or IC can reach the glomeruli and be deposited on the capillary endothelium. As the infection progresses, the gut-associated antigens initially deposited on the glomerular basement membrane may advance into the mesangium of the glomeruli (104). The size and charge of the antigens are decisive for their localization and possible excretion. Thus, negatively charged CAA may be less prone to sequestration and degradation than the neutral CCA molecule (104). As yet, no information is available on the binding or toxic properties of the parasite polysaccharide proteoglycan antigens. It is conceivable that some parasite-derived substances may be inherently toxic to glomerular endothelium or mesangial cells. In that case, mesangial hypertrophy and proliferation may ensue from deposited ingested antigens alone, without being complexed with antibodies. Indeed, conclusive proof for deposited IC causing glomerular alterations is still missing. Moreover, a clear relationship between the amount of CIC and glomerulopathy has not been established (51). Whether CIC are deposited from the circulation or IC are formed by the binding of antibody onto antigens deposited on capillary endothelium or glomerular basement membrane is still undecided (166). Data on the identity of antigens and isotype of antibodies and on the ability of complexes to bind complement are still sketchy. Nor is it known whether complement is bound solely by antigen-antibody complexes or directly by antigens and what consequences such alternate pathway complement activation may have on kidney pathology. Inconsistent findings, i.e., the presence of antigen but no antibody or that of immunoglobulin but no antigen, weaken the otherwise cogent hypothesis that implicates IC in the induction of renal pathology. Application of highly specific monoclonal antibodies for the identification of antigens within complexes, better IC elution techniques, definition of antibody isotypes, and examination of the interaction among antigens, IC, and mesangial cells should provide more direct proof for the participation of IC in schistosoma-induced renal pathology.

Egg-Induced Granulomatous Pathology

The chronic granulomatous host response around disseminated parasite eggs, aggravated by fibrosis, is the major contributor to the pathology of the disease (83, 200, 226, 228, 255, 279). Granuloma formation is initiated by antigens secreted by the miracidium through microscopic pores within the rigid egg shell (257). Eggs deposited in the circulation of the mesenteric venous plexus disseminate mainly into the intestinal tract and the liver, where each one evokes a granulomatous response. With advanced pathology, collateral circulation develops, eggs disperse systemically, and renal, pulmonary (7), or central nervous system granulomas form. Central nervous system granulomas can also arise from ectopic migration of worm pairs. Hepatic granulomas are initiated after the eggs lodge in the presinusoidal capillary venules. As the granuloma grows, the vessels are first disrupted, with the eventual displacement of hepatic parenchyma. The intestinal tract is the second major site for egg deposition. The mucosa becomes congested, the granulomatous regions increase in connective matrix content, and, rarely, the intestinal wall becomes thickened and constricted (112). In some humans, colonic polyps appear. These are frequent in Egyptian patients, but are absent in infected Brazilian individuals (68).

In clinical schistosomiasis, ethical as well as technical considerations (availability of tissues from biopsy or autopsy material) prevent longitudinal granuloma studies in individuals. Consequently, there is a dearth of knowledge on the composition, size, and modulation of granulomas in humans. Histologic examination of rectal tissue from chronically infected individuals has shown the regular cellular composition of granulomas (lymphocytes, macrophages, eosinophils, etc.), with a wide range of granuloma sizes around freshly laid, embryonated eggs. Examination of both the patients' granuloma sizes and the SEA-specific proliferative responses of their PBMN revealed a positive correlation, confirming the murine experiments (42, 81, 238). The granuloma-forming ability of PBMN from infected persons was also investigated in vitro, using freshly produced eggs from adult worm pairs maintained in culture (114). Recently infected persons have increased capacity for granuloma formation compared with their chronically infected counterparts. The $OKT4^+$ T_H subset was involved in the generation of the granulomas (113).

There is strong evidence that the vigorous host granulomatous response rather than the direct action of a parasite egg antigen(s) is responsible for the pathologic tissue manifestations in schistosomiasis. Microcirculation studies in murine livers showed that the granulomas that form around eggs lodged in the presinusoidal capillaries impede hepatic

blood flow (33). Blockage of the portal blood system then induces portal hypertension. A comparative study of various animal species demonstrated a clear relationship between granuloma size and portal hypertension. Lightly infected mice that show extensive disease symptoms also develop portosystemic collateral circulation (66). Quantitative recovery of worms from autopsied patients has indicated that in some cases heavy worm burden induces collateral circulation through which eggs disseminate into the lungs, where they cause granuloma formation, pulmonary arteritis, and cor pulmonale (67). An additional contributory factor to portal hypertension is Symmers' fibrosis, which develops around branches of the portal veins and appears mostly in adults after many years of infection (68). In heavy infections, continuous granuloma formation and fibrosis together with elevated portal pressure and intense immunologic activity lead to the development of hepatosplenomegaly, initially without derangement in liver function. This is the so-called compensated state of HS disease. In a certain number of patients who progress to decompensated HS disease, ascites fluid forms in the peritoneal cavity and esophageal varices develop. Rupture of varices causes esophageal and gastrointestinal bleeding episodes, with a possible fatal outcome. In such patients, liver malfunction may also lead to hepatic coma. Because jaundice is frequently present in such patients and persistent hepatitis B surface antigenemia is common (25), liver pathology in decompensated cases may be compounded by viral hepatitis (235).

Studies from several geographic locations indicate that severe morbidity appears in only a small percentage of the chronically infected population. Individuals with HS disease usually but not always carry a heavy worm burden, as ascertained by fecal egg counts (67, 92, 178, 253). Whereas this observation is uncontested, the questions remain as to why such individuals permit the development of a very heavy infection and how their immune responsiveness relates to the subsequent morbidity. Besides frequency of exposure (278), the genetic predisposition of individuals has been scrutinized. Development of severe morbidity differed in persons of various racial backgrounds (32). A tentative relationship between the development of HS disease and the occurrence of blood group A has been proposed (55, 182). Similarly, a correlation has been observed between susceptibility to hepatosplenism and the expression of HLA-A1 and HLA-B5 histocompatibility antigens (1). These studies need further extension before conclusive evidence of correlation between genetic background and morbidity is obtained.

Observations in infected mice indicate that granuloma formation may be under local control within the various organs. Murine liver granulomas usually attain the largest size. The cellular constituents of the hepatic granuloma are as follows: lymphocytes, plasma cells, macrophages, epithelioid and giant cells, eosinophils, neutrophils, mast cells, and fibroblasts (254, 257). The sizes and cellular compositions of the granulomas may vary according to host species (3), organ site (283), phase of evolution or involution of the lesion (193), and immunoregulatory influences (sensitization and modulation) (37). The experimentally induced pulmonary granuloma is significantly suppressed by antimacrophage (46) and antieosinophil (189) sera, indicating that these cells are the major mediators of this inflammatory response.

Examination of intestinal granuloma sizes in lightly infected mice has revealed interesting differences. Whereas during the chronic stage of the disease granulomas of the liver and colon spontaneously diminished, the smaller ileal granulomas did not change in size (283). Moreover, passive transfer of spleen cells from chronically infected donors to acutely infected recipients decreased liver and colon granuloma sizes without affecting the ileal lesions. Isolated and dissociated intestinal granulomas analyzed in tissue culture showed that liver, but not colonic or ileal, granulomas produced macrophage migration inhibition factor. Moreover, the T-lymphocyte, mast cell, and eosinophil cell numbers within hepatic granulomas were much higher than colonic lesion numbers (284). These observations indicate that the granulomas of the intestinal tract are under regional (ileal or colonic) control, which may regulate the size, composition, and perhaps timing of resolution of the lesions.

In addition to causing vascular obstruction and subsequent fibrosis, schistosome granulomas may be potentially harmful to adjacent parenchymal cells. The cell populations that comprise the granulomas are in a metabolically activated state, capable of secreting a number of tissue-destructive substances. During phagocytosis, cell activation, or cell death, such substances may diffuse from the granulomas and damage tissue parenchyma cells. Indeed, healed granulomas usually leave behind scar tissue, indicating focal damage and repair (271). Granulomas isolated from murine livers and cultured under in vitro conditions have been shown to secrete lysozyme and β-glucuronidase, as well as collagenase and elastase (224, 264). Macrophages isolated from dispersed hepatic granulomas also secrete neutral proteases (265), prostaglandins, leukotrienes, superoxide anion (76), interleukin-1, and alpha/beta interferon (123). Neutral proteases and superoxide anion can degrade or oxidize cell membrane constituents, with potential tissue damage. The possible tissue-destructive role of these agents in schistosome granulomas is still to be elucidated.

Experiments in infected mice that intended to find a correlation between morbidity and genetic background have yielded equivocal results. Examination of immunopathologic parameters (portal hypertension, hepatic granuloma size, and hepatosplenomegaly) in various inbred strains of mice showed strain dependence which was not linked to the *H-2* region of the major histocompatibility complex. The F1 generation obtained from crossing high and low responders as well as backcrosses showed pathologic manifestations that indicated a polygenic influence (130). Another group has examined mortality, spleen index, dermal response, and lymphoproliferation in congenic mice and concluded that the *H-2* haplotype and especially the I (immune response gene) region influence mortality and the intensity of humoral and T-cell-mediated granulomatous responses. Mouse strains with identical *H-2* genes but genetically different backgrounds showed differences in the immune response (78, 102) (Table 1).

Though the role of granulomas in damaging tissue has been extensively studied, researchers have also explored to some extent the tissue-protective potential of this inflammatory response. Thus, infected immunosuppressed or congenitally athymic nude mice that lack immunocompetent T cells mount only feeble granulomatous responses to eggs, mostly composed of immature macrophages (6, 54, 128, 133, 227). One study showed that infected nude mice kept in aseptic environmental conditions developed less morbidity than their heterozygote littermates (227). This observation supported the notion that a granulomatous response of diminished intensity is favorable for the host. In contrasting studies, the granulomas of T-cell-depleted animals showed liquefactive necrosis in the liver and gut with severe destruction of tissue parenchyma, release of hepatic enzymes, and death (53, 108). Hepatic necrosis adjacent to the smaller

TABLE 1. Genetic influence on granulomatous inflammations

Granuloma inducer	Murine strain used	Intensity of granuloma response	Genetic influence	Reference
Schistosome eggs	C57BL/6J BALB/cJ	Low High	F_1 generation and backcrosses with parents: polygenic influence	130
Schistosome eggs	C57BL/6 Nmri	Low High	F_1 and F_2 generations and backcrosses with parents: *H-2* and other gene influence	70
Schistosome eggs	C3H.B10 C3H./Sn	High Low	Congenic strains with different *H-2* haplotypes: *H-2* influence	102
BCG cell wall	C57BL/6 C3H/He	High Low	F_1 generation and backcrosses with parents: *H-2* and other gene influence	299
Killed BCG in emulsion	C57BL/6 CBA	High Low	F_1 generations and backcrosses with parents: Igh and other gene influence	258

granulomas was also observed in infected nude mice (54) and in animals treated with anti-L3T4 antiserum, which suppressed T-helper cell activity and granuloma formation (191). In the hepatic granulomas of nude mice, diffuse antigenic material was observed by IF. This lent support to the notion that one task of the well-developed granuloma is to sequester the potentially harmful protease-active (17) or other toxic (150) substances secreted by the live miracidium (272). In the absence of mature macrophages, and perhaps eosinophils, the secreted antigens, enzymes, or both diffuse into the liver parenchyma and damage hepatocytes. Another protective role envisioned for granulomas is egg destruction involving egg shell dissolution, invasion, and destruction of the embryo. The protective value for the host is the rapid elimination of the eggs, reduction in antigen contents and inflammatory episodes, and reduced tissue damage. Indeed, it was observed that mice and rhesus monkeys that received a sensitizing injection of eggs showed accelerated destruction of eggs within the liver after a challenge infection (71, 281). The major cell type that destroys the miracidium appears to be the eosinophil (35, 189, 209).

Viable eggs isolated from the liver granulomas of infected mice injected intravenously induce a primary pulmonary granuloma in normal mice (271). Analysis of this pulmonary model established the T-lymphocyte-mediated etiology of the egg granuloma. Granuloma formation is specific and occurs in an accelerated manner in mice presensitized with live eggs (45, 282). It is specific for the egg stage antigens because sensitization cannot be achieved by irradiated cercariae or adult worms of a single sex. Granuloma formation is transferable to normal recipients by lymphocytes, but not by antibodies (282). It is suppressed by neonatal thymectomy (109) and antilymphocyte (110) or anti-T-helper lymphocyte (191) antisera, as well as in thymus-deprived (133) or congenitally athymic nude mice (54, 227). Moreover, granulomas isolated from the livers of acutely infected mice release lymphokines during in vitro culture which act specifically on macrophages and eosinophils (48, 170). The requirement for T lymphocytes in granuloma formation and the correlation of the granulomatous response with other in vivo and in vitro parameters of T-cell-mediated immunity confirm that schistosome egg granulomas are T-lymphocyte-mediated immune responses.

This specific granulomatous response is induced by SEA secreted by the live miracida (45, 153). These antigens extracted with buffered saline from homogenized eggs of the Puerto Rican strain of the worm contain numerous proteins, polysaccharides, and glycoproteins. In the absence of adjuvant, this crude preparation sensitized and induced granulomatous and dermal hypersensitivity in mice (45) and elicited dermal reactions in vivo and lymphoproliferation and lymphokine production in vitro (42, 43, 80, 81, 87, 191). SEA absorbed onto or covalently coupled to insoluble particles such as bentonite or latex also elicit pulmonary granulomatous responses in mice (47, 275). Because the importance of SEA in the immunopathology of the granulomatous disease is recognized, much effort has been invested in the isolation and identification of immunogenic and granuloma-inducing fractions. Over the years, several laboratories have used a variety of preparative methods to fractionate SEA. These include block and polyacrylamide gel electrophoreses, molecular sieving, cation exchange, and affinity and immunoaffinity chromatographies. These methods have yielded several antigenically active molecules that are heterogeneous in size, charge, and biologic activity (Table 2). Some anodic glycoproteins were capable of sensitizing mice for granulomatous hypersensitivity and elicited dermal responses in sensitized guinea pigs (44). At least three antigens were shown to have dermal activity in presensitized animals (52). By sodium dodecyl sulfate-polyacrylamide gel electrophoresis, at least 20 distinct protein bands were obtained from SEA, and of these 20 bands, 6 glycoproteins elicited lymphocyte blastogenic responses (62, 155). By a combination of lectin affinity and anion-exchange chromatography methods, three antigens were isolated from crude SEA. They reacted with antibodies from chronically infected mice and were named major serologic antigens MSA_1, MSA_2, and MSA_3 (221). The highly purified MSA_1, a glycoprotein with an estimated molecular size of 138 kDa, was specific for the egg stage and could be used as an immunodiagnostic reagent with sera of heavily infected humans (143, 222). It appeared to induce granulomatous hypersensitivity in normal mice (220). Another major egg glycoprotein isolated from the Egyptian strain of *S. mansoni* eggs had a molecular size of 70 kDa. It showed a wider antigenic reactivity, cross-reacting with antibodies directed to larval and adult stages of the parasite. Purified major egg glycoprotein elicited delayed dermal responses in acutely infected mice and, without adjuvant, induced granulomatous hypersensitivity in normal animals (151, 185). Immunoaffinity-purified intact or deglycosylated glycoproteins bound to Sepharose beads and injected into naive mice evoked hepatic granulomas, indicating that both peptide and glycosyl determinants are involved in the granulomatous response (287). Other antigenic sub-

TABLE 2. Antigenic preparations obtained from *S. mansoni* eggs

Egg antigen prepn	Biochemical properties	Molecular size (kDa)	Immunologic activity			Reference(s)
			Granuloma	Dermal	Humoral	
SEA	Proteins, glycoproteins, polysaccharides	<10–>200	+	+	+	44, 45, 62, 155
Major serological antigens						220, 221
MSA_1	Glycoprotein	138	+	?	+	
MSA_2	Lipoglycoprotein	450	?	?	+	
MSA_3	Protein	80	?	?	+	
Major egg glycoproteins	Glycoprotein	70	+	+	+	185
Polysaccharide egg antigen	Neutral polysaccharide	>200	?	?	+	34
ω_1 Antigen	Protein	20–50	?	?	+	120
Allergen	Glycoprotein	210	?	+	+	216
Immunoaffinity-purified antigens	Glycoprotein	>40	+	?	+	287

stances obtained from fractionated crude SEA included a neutral >200-kDa polysaccharide egg antigen (34), a 20- to 50-kDa protein named ω_1 that has hepatotoxic effects in T-cell-deprived mice (120), and a 210-kDa allergen that reacted with IgE antibodies of infected humans (216). These antigens possess serologic activity, but their roles, if any, in granuloma induction, are unknown.

The SEA-induced circumoval granulomatous reactions are complex cellular responses that provide protection against the secretions of the disseminated eggs. The physical presence of granulomas and the substances secreted by granuloma cells cause focal tissue damage that terminates by fibrosis. Despite the chronic nature of the granulomatous condition, most infected individuals either are asymptomatic or suffer only mild symptoms of the disease. In a limited number of infected individuals, a complex syndrome develops in the form of HS disease. Many facets of this syndrome are still not understood. The outcome of HS disease depends on a series of immune and nonimmune events that include antigen processing and presentation; T-cell sensitization; lymphokine production; inflammatory cell mobilization, locomotion, and activation; monokine enzyme secretions; and collagen isotype synthesis and degradation. These functions are regulated by a variety of genes that are both outside and within the loci that regulate the immune response. Also, parasite product-host cell (parenchyma, fibroblast, and vascular endothelium) interactions may contribute to the complexity of the phenomena. Thus, it is plausible that, in addition to genes that regulate the intensity of the immune response, other genes should also influence the evolution and outcome of HS disease. Studies that analyze the genetic bases of the *Mycobacterium bovis* BCG cell wall-induced granulomas in mice also determined that the granulomatous inflammation is under polygenic influences (258, 299) (Table 1).

Fibrosis

Fibrosis enhances the disease pathology and contributes to the mortality of schistosomiasis mansoni. It follows the granulomatous inflammatory response (38, 116, 146, 229, 291) and occurs mostly at the site of the resolving granulomatous reactions. However, fibrous bands also appear around portal veins distant from granulomas. Portal fibrosis is partly a sequel to the chronic thrombophlebitis of portal veins. The portal vessels often show subendothelial edema, infiltration of the smooth-muscle layer with eosinophils, and local damage (148). In addition to portal fibrosis, collagen bundles are found in the space of Disse located underneath the liver sinusoids between the endothelium and the hepatocytes (147). Heavily infected patients who develop HS disease present with characteristic Symmers' clay pipestem fibrosis, which appears as wide fibrous bands running along the portal veins (200). Liver function tests in HS patients remain normal because liver parenchyma between the fibrous bands is well preserved. Occlusion of portal venules leads to portal hypertension and to the formation of esophageal varices. Repeated bleeding episodes may cause ischemic necrosis of the liver (13). Analysis of the fibrotic process in humans has yielded some limited but interesting data. Measurement of collagen content and rate of collagen synthesis in fibrotic livers showed a 5- to 40-fold increase over that of normal livers (116, 117). In liver sections, immunocytochemical methods detected type I, type III, and B collagens in portal spaces, fibrous septa, and granulomas (30). Florid granulomas contained mainly type III collagen, and involuting ones contained type I collagen (4).

Fibrosis has been extensively studied in the murine model of schistosomiasis mansoni. In mice, hepatic fibrosis is mostly associated with circumoval granulomas (15, 119). It is still controversial whether classical Symmers' fibrosis develops during mild prolonged infection in this species (15). In infected experimental animals, liver egg load and total liver collagen content (measured by the amount of hydroxyproline in hydrolyzed tissue) stand in direct relationship (69). By contrast, a direct relationship between granuloma size and the degree of fibrosis could not be established. Mice splenectomized at the height of the granulomatous response responded with enlarged granulomas, but increase in granuloma size left total liver collagen content unchanged (164). Conversely, administration of Captopril, an inhibitor of angiotensin convertase, to infected mice suppressed hepatic granuloma sizes but actually increased collagen content (286). In various strains of mice, granuloma size and hepatic fibrosis were found to be unrelated. Both manifestations appear to be under independent control, involving genes both outside and within the *H-2* region of the murine major histocompatibility complex (70).

TABLE 3. Host- and parasite-derived fibroblast stimulatory factors

Source of factor	Biochemical property	Molecular size (kDa)	Biological function	Reference(s)
Culture supernatant of liver granulomas	?	30–40	Stimulates fibroblast proliferation	295, 298
	?	10	Stimulates collagen synthesis	292
	?	22, 50	Stimulates fibronectin synthesis	
	Fibronectinlike	>200	Fibroblast chemoattractant	294
Culture supernatant of liver granuloma macrophages	?	46–57	Stimulates fibroblast proliferation	296
	?	10–16		
T-cell clone from infected murine spleen	?	10–40	Stimulates fibroblast proliferation	175
SEA	Glycoprotein	12	Stimulates fibroblast proliferation	297
Eggs, SEA	?	?	Stimulate fibroblast proliferation, collagen synthesis	40

Biochemical analysis of granulomatous liver slices provided an insight into the fibrotic process. Conversion of proline into hydroxyproline (the constituent of collagen) in granulomatous livers was much faster than that in normal livers (119). The endogenous proline used for collagen synthesis diffuses into the granulomas and is hydroxylated by prolyl hydroxylase. The levels of this enzyme are greatly elevated within the granulomatous livers (118). Examination of the dynamics of hepatic collagen synthesis reveals that at 6 weeks of the infection, during the early phase of egg deposition, synthesis is low. By 8 weeks, granuloma formation is vigorous, and lesions attain maximal size coincident with peak collagen synthesis. In subsequent weeks, a decline in collagen synthesis occurs; just before the onset of immunodulation of the granulomas, synthesis diminishes to less than half of the peak value. The largest net increment in synthesis occurs at 8 weeks (the peak of the granulomatous response), and the smallest occurs by week 11 of infection. At this time, however, total liver collagen content is maximal (260). The high collagen content in the infected liver at a time of decreased synthesis indicates that collagen accumulates because of diminished degradation of synthesized connective-tissue matrix. Indeed, levels of degradative collagenases elastases in granulomatous livers were highest at the peak (8 weeks) of collagen synthesis, but lowest by 11 weeks of the infection (260). Collagenase was localized within granulomas, and its attachment to collagen fibrils within the liver was actually visualized (31). Homogenates of vigorous granulomas yielded significantly more collagenase elastases than their modulated counterparts. The major cellular sources of enzyme production (both active and latent enzymes) were the macrophages and eosinophils of the granuloma (264). Cells obtained from either vigorous or immunomodulated granulomas produced comparable amounts of proteases in culture, yet the latter lesions secreted significantly fewer enzymes. This finding suggested an effect of intragranulomatous protease inhibitors, which was verified by identifying α_2-macroglobulin and α_1-antiprotease inhibitors in culture fluid of granulomas, and of granuloma macrophages. Significantly, fractionation of granuloma extracts revealed that the bulk of the isolated material was in the form of protease-protease inhibitor complexes (265).

Characterization of collagen isotypes showed an accumulation of type III collagen at the peak of the granulomatous response (290), and the lesions also contained type III procollagen and fibronectin (217). Sequential determination of collagen isotypes by indirect IF during the infection showed that the vigorous early liver granulomas contained high amounts of type III but low amounts of type I collagen. As the infection progressed, this relationship changed; the amount of deposited type I collagen rose, and by 20 weeks, in the immunomodulated granulomas, it equalled that of type III collagen. Compared with the hepatic granulomas, much less collagen was deposited in the ileal or colonic granulomas. In the immunomodulated colonic lesions, the amount of the type III collagen was higher than that of type I (149).

At least two different cell types initiate hepatic granuloma fibrosis in humans: fibroblasts and the smooth-muscle cells that dedifferentiate to myofibroblasts (146). It appears that both host immune and parasite factors are involved in triggering fibroblast activation and collagen synthesis (Table 3). In culture, granulomas isolated from homogenized lungs of egg-sensitized mice incorporate significantly more labeled amino acids into protein and collagen than their nonimmune counterparts that form around plastic beads (41). Also, in culture, liver granulomas secrete a soluble nondialyzable factor(s) that induces proliferation of resting dermal guinea pig or allogeneic mouse fibroblasts (295, 298) and stimulates collagen and fibronectin syntheses in resting fibroblasts (291, 292). Adherent macrophages obtained from collagenase-dispersed liver granulomas secrete fibroblast-stimulating factor, indicating a role for this cell population in fibroblast activation. Fractionation of macrophage culture supernatants yielded two fibroblast-active fractions of different molecular weights. These fractions lacked interleukin-1 activity (296). The dialyzed fluid from granuloma macrophage cultures also exerted chemotaxis on guinea pig and human dermal fibroblasts. The chemotactic factor was a 200-kDa molecule likely identical to fibronectin (294). Recent observations indicate that, upon specific stimulation with SEA, T-lymphocyte clones isolated from spleens of infected mice secrete a variety of lymphokines which not only augment the in vitro formation of granulomas around beads, but also stimulate the proliferation of syngeneic fibroblasts. These 10- to 40-kDa size factors apparently provide the first signal (competence factor) to resting fibroblasts that induces cell cycling from phase G_0 to G_1. Maximal proliferation is attained only if insulin and epidermal growth factor, which serve as progression factors to drive the cells to proliferation, are added (175). These observations indicate that antigen-stimulated T lymphocytes can directly stimulate fibroblasts and thus may contribute to the process of fibrosis. In experiments with athymic nude mice devoid of T cells or mice deprived of T-helper lymphocytes, poor circumoval

granuloma formation as well as reduced deposition of collagen fibers were demonstrated. Thus, a role for T lymphocytes in fibroblast recruitment and the induction of collagen production was indirectly confirmed (6, 191, 227). A recent report also suggests the possibility that autoimmune T cells participate in the fibrotic process. Peritoneal T cells of *S. mansoni*-infected mice proliferated in response to denatured collagen and formed large granulomas when the mice were injected with collagen-coated beads. Thus, during rapid collagen synthesis and breakdown in acutely infected mice, collagen-reactive T cells are generated that participate in anticollagen immune responses and thus contribute to chronic inflammation and fibrosis (293). However, initiation of fibroblast activity is not solely dependent on the cellular responses of the granuloma-bearing sensitized host. Some observations also implicate SEA as parasite factors that trigger fibroblast responses. Resting guinea pig or human dermal fibroblasts cocultured with graded doses of SEA underwent dose-dependent cell proliferation. Gel filtration of SEA yielded an active fraction with a 12-kDa molecule that stimulated fibroblast proliferation (297). Moreover, human dermal fibroblasts cultured in the presence of live schistosome eggs or SEA incorporated labeled proline into collagen. However, when larger numbers of eggs were used in the culture, cytopathic effects were seen, i.e., cytoplasmic granulation, cell detachment, and death (40).

In conclusion, though the etiology of human pipestem fibrosis is still not understood, the host immune response appears to be involved in the overall process of fibrosis. Fibrogenesis is triggered mostly, but not solely, by the various cells that participate in the granulomatous inflammatory response. Deposition of nonfunctional fibrous tissue is a major contributory factor to hepatic pathology, HS disease, and host mortality. Fibrous tissue consists of a complex array of connective matrix material and a variety of collagen isotypes. The ratio of deposited collagens (types III/I) influences the stability and reversibility of the fibrotic condition (240). The final outcome of fibrosis is also dependent on the presence and activity of degradative proteases and blocking protease inhibitors. Reversibility of the fibrotic condition in drug-treated mice has been demonstrated (10, 194), but in humans this is a major, still unanswered question. This is especially important in endemic areas where mass antihelminthic therapy is being instituted. To evaluate the extent of fibrosis reliably, clinicians need a better tool than liver wedge biopsy. This invasive method is now being replaced by two new diagnostic tools. One is abdominal ultrasonography, which can visualize the fibrous periportal bands in the livers of patients with Symmers' fibrosis (65, 163), and the other is the measurement in the serum of procollagen III peptides as indicators of newly synthesized type III collagen (126, 237). Recent advances in the understanding of fibroblast activation pathways have provided some insight into the fibrotic process in the schistosome-infected host. Further advances should help investigators to devise means for the prevention or amelioration of fibrogenesis in infected individuals.

Regulation of the Immune Response

Over the years, correlations have been sought between morbidity and the intensity of immune responsiveness of *S. mansoni*-infected individuals. Comparisons have been made between patients at the acute or chronic stage of the infection, and the mild intestinal versus HS forms of the disease have been examined. Schistosome antigen-induced lymphoproliferation of patient PBMN has been the most widely used immune parameter. In general, acutely infected patients have been shown to respond vigorously to adult worm and egg antigens. In contrast, the antigen-specific response is greatly diminished in chronically infected persons (83, 84, 213). In some cases, the SEA-specific responsiveness has been found to be higher than that directed to soluble adult worm antigens (SWAP). SEA could also elicit production of leukocyte-inhibitory and mitogenic factor lymphokines (140). In chronically infected patients, numerous studies have addressed the question of immune responsiveness versus intensity of infection. In examining PBMN proliferative responses to cercarial antigens, SWAP, or SEA, either no relationship (85, 267) or an inverse one has been seen in heavily infected patients (125, 131). The level of heavy infection appears to be a crucial factor, because PBMN of patients excreting 600 eggs per g of feces reacted well to SWAP after adherent cell removal, whereas those who excreted double that number of eggs failed to respond (208). The diminished reactivity to PBMN is attributed to a variety of modulatory influences detectable in chronically infected persons. Adherent cells present in their PBMN suppress the proliferation of blood lymphocytes. Adherent cell removal usually enhanced lymphocyte reactivity to SWAP, SEA, or cercarial antigens (137, 212, 262, 266). Indomethacin relieves the suppression in cell cultures, indicating that the inhibitory effect is prostaglandin mediated in persons with heavy, but not very heavy, infection (23, 208). A comparative study examining PBMN and splenocyte reactivity to SEA in splenectomized HS patients contradicted previous results and concluded that adherent cells performed an accessory rather than an inhibitory role in antigen-specific lymphoproliferation (236). Adherent cell-mediated suppression was not seen in ambulatory HS patients (266, 267). An effect of suppressor T (T_S) cells was also postulated: the T_S cells acted in both an antigen-specific and a nonspecific manner. Lymphocytes of chronically infected persons incubated with SEA generated cell populations that suppressed mitogen- or SEA-induced lymphoproliferation (89, 239). This in vitro activation of SEA-specific T_S cells was achieved both by SEA and by a protein moiety isolated from crude egg antigens; the induced suppressor activity was greater in patients with high- than in those with low-intensity infection (239). Coculture of splenic cells of splenectomized patients with autologous or allogeneic PBMN demonstrated a predominant antigen-related and a minor mitogen-related T_S cell activity (124). Exogenously added or endogenously liberated histamine exerted strong suppression over the antigen-induced and the mitogen-induced lymphocyte responsiveness of infected individuals (162). Addition of cimetidine (an H_2 histamine receptor antagonist) significantly increased the PBMN responsiveness to SEA and SWAP; histamine was therefore suggested to participate in T-lymphocyte regulation (22). Histamine receptor-bearing T_S lymphocytes were also described to function in suppression of murine liver granulomas (285). Heavily infected individuals, some of whom display the HS syndrome, usually have a low $T4^+/T8^+$ (helper/suppressor T cell) ratio in the circulation due to a decrease in the $T4^+$ cell population. Presumably, the changed ratio favors enhanced systemic immunoregulation by T_S cells (88, 137, 138, 267). Conversely, when such a ratio favors the $T4^+$ helper effector population, a strong inflammatory and inadequate T_S regulatory influence is postulated, a condition conducive to the development of HS disease (267).

The presence of humoral circulating regulatory factors has

been also demonstrated in humans. The suppressed PBMN responsiveness to SWAP or SEA could be alleviated after autologous plasma was replaced by normal human serum (87, 143, 214, 238, 263). Some humoral factors that appeared in chronically infected persons acted in an antigen-specific suppressive mode; others acted nonspecifically, suppressing mitogen-induced lymphoproliferation (94, 171). It is therefore probable that several different circulating substances are responsible for these effects. Thus, all of the following have been implicated in suppression: shed (174) and excreted parasite antigens (57, 103), circulating immune complexes (171, 238), and immunoaffinity-purified anti-SEA idiotype-specific antibodies (180, 218). The latter observation is intriguing in that it indicates the existence in chronically infected patients of functional anti-idiotype-bearing T cells and of idiotype–anti-idiotype interactions.

It is still a challenging task to establish a correlation between the degree of immune responsiveness and the morbidity seen in HS patients. In such persons, IgG and IgE antibody levels to schistosome antigens remain high (51, 136). The same is true for certain circulating antigens and CIC (see preceding section). In a high percentage of HS patients, vigorous delayed skin responses to adult worm or SEA preparations are observed (56, 158). Some individuals also retain a high degree of PBMN responsiveness to SEA or SWAP (125, 157, 238). Yet the patients may have T_S lymphocytes (124), suppressor adherent cells (137), or low $T4^+/T8^+$ cell ratios (137, 267) or can be completely unresponsive to schistosome antigens (125, 137).

An analysis comparing ambulatory and hospitalized HS patients revealed interesting data on immune lymphoproliferative responsiveness (86). Subdivision of patient material into moderate and high PBMN responders to SWAP, SEA, and cercarial antigens revealed that the proportion of high SEA responders was low (23%) among the mostly asymptomatic intestinal patients, moderate in the hepatointestinal group (40%), and very high (67%) in the ambulatory HS group. Responsiveness rapidly declined (20%) in the hospitalized HS group. Based on these data, an attractive hypothesis was advanced that linked immune responsiveness to SEA with the progressive development of clinical disease. During the acute phase of the infection, all patients show strong T-cell-mediated anti-SEA responses. As the infection proceeds to its chronic phase, most patients modulate their responses by a variety of regulatory mechanisms. This down-modulated anti-SEA T-cell response may prevent sustained vigorous granuloma formation and the development of overt pathologic manifestations. In a minority of patients, inadequately controlled anti-SEA responses may allow the continued strong granulomatous reaction and development of organomegaly that progresses to severe hepatosplenic morbidity. In such severe cases, patient lymphocytes may show anergy, a generalized unresponsiveness to immune and mitogenic stimuli (86). This hypothetical sequence of disease development parallels the mechanisms of granuloma immunomodulation described to occur in infected mice. Its confirmation by additional clinical data should greatly advance our understanding of the regulation of the egg-directed granulomatous response in schistosome-infected humans.

A review of the clinicoimmunological studies reveals disparate, sometimes contradictory results. Several factors may be responsible for the observed variability of data. First, the lack of standardization of the antigenic preparations and cultural conditions used provides ample room for divergent contradictory results. Second, the patients are heterogeneous and represent a spectrum of pathologic manifestations. Hepatosplenic disease is often diagnosed according to hepatosplenomegaly, which is only a partially reliable index because, in regions where concurrent bacterial, protozoan, and viral (hepatitis) infections are common, liver enlargement is widespread (25). Third, the parameter PBMN blastogenesis, chiefly used for assessment of immune responsiveness, may not be wholly representative of other T-lymphocyte functions (lymphokine production) within lymphoid organs.

In murine experiments, examination of a different immune parameter, lymphokine production and regulation, has provided an insight into the granulomatous process (37, 81). A similar approach should also be profitable in clinical analysis, because there is a dearth of information on lymphokine production in schistosome-infected humans. Production of migration inhibition factor (157), leukocyte inhibitory factor (181, 289), eosinophil stimulation promoter (173), and mitogenic factor (139) has been described in schistosome-infected patients. A careful analysis of lymphokine production and differential regulation in the intestinal, hepatointestinal, and hepatosplenic groups should provide more incisive information on T-cell responsiveness and its relationship to granuloma formation and morbidity. Finally, the relevance of data on the immune responsiveness of circulating T cells to assess the immune functions of the highly compartmentalized granuloma lymphocytes is questionable. In patients with sarcoidosis (a granulomatous disease of unknown etiology), comparison of blood and lung lymphocyte functions clearly revealed that only data on lung lymphocyte responsiveness were useful in evaluation of the pulmonary granulomatous process.

In the murine model, heavily infected mice develop the HS syndrome (105, 276). In contrast, lightly infected mice tolerate the infection and during the chronic stage of the disease react with significantly diminished hepatic granulomatous responses around freshly deposited eggs (15). Because periodic injections of eggs into normal mice diminished the initially strong pulmonary granulomatous response, an immune "desensitization" process was proposed to have occurred (111). This spontaneous down-modulation of the granulomatous response was extensively analyzed by longitudinal studies at 4 to 20 weeks of the infection. At the peak of the granulomatous response (8 to 10 weeks), delayed dermal reaction and production of the lymphokines, macrophage migration inhibitory factor, and eosinophil stimulation promoter were strong. Lymphokine production declined concurrently with the waning of the granulomatous inflammation (12 weeks and onward). At that time, the specific anti-SEA antibody response was still high (42, 81). Because the diminished granulomatous response could be passively transferred from modulated donors to recipients exhibiting strong granulomatous reactions with lymphocytes but not with antiserum, the cell-mediated immune basis of the modulation has been established (82, 90). Concurrent with the waning granulomatous response, a shift in the ratio of T/B lymphocytes (favoring the latter) was observed in the blood, lymph nodes, spleen, and granulomas of the chronically infected mice (72), and the number of anti-SEA antibody-producing plasma cells in the smaller granulomas increased (39).

By means of extensive passive transfer, selective cell depletion, and cell admixture experiments, a complex network of interacting T-lymphocyte subsets was delineated. A T-helper/effector lymphocyte subset (T_{DH}) having the $Lyt1^+$ $L3T4^+$ markers was found to be involved in the induction and maintenance of the granulomatous response, whereas

another T subset bearing the Lyt2,3 marker was identified as the T_S that regulates the function of the former (37, 73). A third cell population bearing the $Lyt1^+$ marker and capable of transferring granuloma suppression from modulated donors to vigorous recipients was classified as a precursor or inducer of T_S lymphocytes (37, 77). Regulation of the granulomatous response has also been examined and confirmed by the in vitro model of granuloma formation that utilizes eggs or SEA-coated beads and primed splenic lymphocytes. After a few days in culture, cellular aggregates ranging in intensity from a few cells to complete circumoval granulomas surround the antigenic nidi. This model confirmed that $Lyt1^+$ and $Lyt2^+$ cells, respectively, play an inductive or suppressive role in granuloma formation (114, 115). Because admixture of T_{DH} and T_S splenic lymphocytes abrogates migration inhibitory factor lymphokine production in vitro and granuloma formation in vivo, the immune basis of the regulatory mechanism has been confirmed (74, 75).

Apparently, the effector-suppressor T lymphocytes communicate by means of soluble mediators that, in part, are products of the *H-2* region of the murine major histocompatibility complex genes. One suppressor factor obtained from antigen-pulsed spleen cells of chronically infected mice was identified as bearing I-EC subregion determinants of the *H-2* complex. It suppressed the in vitro migration inhibitory factor production by $Lyt1^+$ cells in an antigen-specific and *H-2*-restricted manner (75). Another suppressor factor, added to splenic cultures of vigorous granuloma producers, recruited from a low number of precursor cells a T-suppressor population that suppressed the granuloma-inducing ability of T_{DH} lymphocytes. This suppressor factor bore the $I\text{-}J^+$ marker and recruited $I\text{-}J^+$ T cells (190). This finding corroborated previous observations that showed reversal of the down-modulated granuloma response by injections of anti-I-J antiserum in chronically infected mice (145). The $I\text{-}J^+$ suppressor factor preparations that reportedly suppressed in vivo granuloma formation only in I-J homologous recipients appear to be composed of two chains, one bearing the I-J phenotype and the other having idiotypic (2) or anti-idiotypic activity (225). The latter observation would be consistent with the finding that $L3T4^+$ lymph node T lymphocytes of acutely or chronically infected mice display anti-idiotypic specificity (231). The significance of this finding in the modulation process remains to be elucidated.

In summary, granulomatous inflammation in infected mice is in a state of dynamic equilibrium maintained by inflammatory T_{DH} and regulatory T_S lymphocyte subsets. Following oviposition, egg antigens are presented by macrophages in the context of class II I-A and I-E antigens, and a specific T_{DH} response is induced (122). The strong T_{DH} activity engenders inflammatory lymphokine (migration inhibitory factor and eosinophil stimulation promoter) production. Lymphokines recruit, mobilize, and activate a variety of inflammatory cells that converge around the eggs, create the granuloma, and eventually destroy the ova. Peak granuloma formation (8 to 10 weeks) is followed by the onset of modulation in which T_S cell activity prevails, resulting in diminished but not abrogated granuloma formation (14 weeks and onwards). Concurrently, local and systemic lymphokine production is decreased. The change in the quantity and quality of lymphokines accounts for the lower activation state of granuloma macrophages as reflected by receptor expression on the cell surface (288), tumoricidal activity (183), and O_2^- production (76). The modulated state is actively sustained by newly recruited suppressor T cells that regulate T_{DH} but not T_H cell function as demonstrated by the high levels of circulating antibodies (42, 81). Experimentally, the strong T_{DH} or modulated T_S influence can be reversed by a variety of interventions, proving that the respective cell populations are not eliminated, but rather are under active regulation (37). The diminished, but not abrogated, granulomatous response is advantageous to the host. Whereas the protective sequestrational role of the granuloma is retained, its smaller size and less activated cell populations lessen the possibility of tissue damage.

CONCLUSIONS

Schistosomiasis mansoni is a chronic helminthic disease of the tropics. In the majority of individuals, the infection is well tolerated but some (mostly heavily infected) persons develop HS disease often accompanied by severe morbidity and even death. Most of the host morbidity is the result of the parasite antigen-specific host immune responses that are expressed as inflammatory reactions. These include dermatitis, IC formation, and granulomatous pathology. During the acute phase of the infection, parasite antigens evoke strong humoral and T-cell-mediated immune responses. As the disease advances to chronicity, the level of host responsiveness is diminished. This is conspicuous in experimental murine schistosomiasis in which the T-effector cell-mediated granulomatous response is down-regulated by T-suppressor lymphocytes with salutary effects on morbidity and mortality. In chronically infected humans, peripheral T-lymphocyte responsiveness to parasite antigens is diminished due to the appearance of a variety of immunoregulatory mechanisms. Whether such mechanisms also regulate the intensity of granulomatous responses and whether a down-regulated granulomatous response ensures a mostly symptom-free disease state are still conjectural. The chronic circumoval granulomatous inflammations and the fibrotic sequel are the main causative factors in the pathology of the disease. Whereas the granulomatous responses wax and wane, fibrosis is cumulative and mostly irreversible. In its extreme form (Symmers' fibrosis), it contributes greatly to the systemic manifestations of the disease. Advances made in the understanding of the biologic functions of purified schistosome antigens, the processes of granuloma formation, modulation, fibrous tissue production, degradation, and resorption will help to ameliorate or prevent morbidity in schistosome-infected humans.

ACKNOWLEDGMENT

This work was supported by Public Health Service grant AI-12913 from the National Institutes of Health.

LITERATURE CITED

1. **Abdel-Salam, E., S. Ishaac, and A. A. F. Mahmoud.** 1979. Histocompatibility-linked susceptibility for hepatosplenomegaly in human schistosomiasis mansoni. J. Immunol. **123:** 1829–1831.
2. **Abe, T., and D. G. Colley.** 1984. Modulation of *Schistosoma mansoni* egg-induced granuloma formation. III. Evidence for an anti-idiotypic, I-J positive, I-J restricted, soluble suppressor factor. J. Immunol. **132:**2084–2088.
3. **Akpom, C. A., M. F. Abdel-Wahab, and K. S. Warren.** 1970. Comparison of formation of granulomata around eggs of *Schistosoma mansoni* in the mouse, guinea pig, rat and hamster. Am. J. Trop. Med. Hyg. **19:**996–1000.
4. **Al Adnani, M. S.** 1985. Concomitant immunohistochemical localization of fibronectin and collagen in schistosome granuloma. J. Pathol. **147:**77–85.
5. **Amer, M.** 1982. Cutaneous schistosomiasis. Int. J. Dermatol.

21:44–46.
6. **Amsden, A. F., D. L. Boros, and A. T. Hood.** 1980. Etiology of the liver granulomatous response in *Schistosoma mansoni*-infected athymic nude mice. Infect. Immun. **27**:75–80.
7. **Andrade, Z. A., and S. G. Andrade.** 1970. Pathogenesis of schistosomal pulmonary arteritis. Am. J. Trop. Med. Hyg. **19**:305–310.
8. **Andrade, Z. A., S. G. Andrade, and M. Sadigursky.** 1971. Renal changes in patients with hepatosplenic schistosomiasis. Am. J. Trop. Med. Hyg. **20**:77–83.
9. **Andrade, Z. A., and T. M. Azevedo.** 1987. A contribution to the study of acute schistosomiasis. (An experimental trial.) Mem. Inst. Oswaldo Cruz **82**:311–317.
10. **Andrade, Z. A., and J. A. Grimaud.** 1986. Evolution of the schistosomal hepatic lesions in mice after curative chemotherapy. Am. J. Pathol. **124**:59–65.
11. **Andrade, Z. A., and H. Rocha.** 1979. Schistosomal glomerulopathy. Kidney Int. **16**:23–29.
12. **Andrade, Z. A., and M. Sadigursky.** 1978. Immunofluorescence study of schistosome structures which share determinants with circulating schistosome antigens. Trans. R. Soc. Trop. Med. Hyg. **72**:316–318.
13. **Andrade, Z. A., S. Santana Filho, and E. Rubim.** 1962. Hepatic changes in advanced schistosomiasis. Gastroenterology **42**: 393–400.
14. **Andrade, Z. A., and E. Van Marck.** 1984. Schistosomal glomerular disease. Mem. Inst. Oswaldo Cruz **79**:499–506.
15. **Andrade, Z. A., and K. S. Warren.** 1964. Mild prolonged schistosomiasis in mice: alterations in host response with time and the development of portal fibrosis. Trans. R. Soc. Trop. Med. Hyg. **58**:53–57.
16. **Antunes, L. J., A. P. Reis, J. Pellegrino, C. A. Tavares, and N. Katz.** 1971. Immunoglobulins in human schistosomiasis mansoni. J. Parasitol. **57**:539–542.
17. **Asch, H. L., and M. H. Dresden.** 1979. Acidic thiol proteinase activity of *Schistosoma mansoni* egg extracts. J. Parasitol. **65**:543–549.
18. **Askenase, P. W., B. J. Hayden, and G. I. Higashi.** 1976. Cutaneous basophil hypersensitivity and inhibited macrophage migration in guinea pigs with schistosomiasis. Clin. Exp. Immunol. **23**:318–327.
19. **Asworth, T. G.** 1970. Immunoglobulin levels in Katayama disease. Cent. Afr. J. Med. **16**:127–128.
20. **Baird, J. K., and D. J. Wear.** 1987. Cercarial dermatitis: the swimmer's itch. Clin. Dermatol. **5**:88–91.
21. **Barlow, C. H.** 1936. Is there dermatitis in Egyptian schistosomiasis? Am. J. Hyg. **24**:587–599.
22. **Barsoum, I. S., H. S. S. Dahawi, F. M. Gamil, M. Habib, M. A. El Alamy, and D. G. Colley.** 1984. Immune responses and immunoregulation in relation to human schistosomiasis in Egypt. II. Cimetidine reversal of histamine-mediated suppression of antigen-induced blastogenesis. J. Immunol. **133**:1576–1580.
23. **Barsoum, I. S., C. W. Todd, M. Habib, M. A. El Alamy, and D. G. Colley.** 1983. The effects of indomethacin on *in vitro* peripheral blood mononuclear cell reactivity in human schistosomiasis. Parasite Immunol. **5**:441–447.
24. **Barsoum, R. S., S. Bassily, O. K. Baligh, M. Eissa, N. El-Sheemy, N. Affify, and A. M. Hassaballa.** 1977. Renal disease in hepatosplenic schistosomiasis: a clinicopathological study. Trans. R. Soc. Trop. Med. Hyg. **71**:387–391.
25. **Bassily, S., Z. Farid, G. I. Higashi, I. A. Kamel, N. A. El-Masry, and R. H. Watten.** 1979. Chronic hepatitis B antigenaemia in patients with hepatosplenic schistosomiasis. J. Trop. Med. Hyg. **82**:248–251.
26. **Bassily, S., G. I. Higashi, Z. Farid, and R. E. Williams.** 1972. Serum immunoglobulins in schistosomiasis mansoni. J. Trop. Med. Hyg. **75**:73–75.
27. **Bentley, A. G., A. S. Carlisle, and S. M. Phillips.** 1981. Ultrastructural analysis of the cellular response to *Schistosoma mansoni*. II. Inflammatory response in rodent skin. Am. J. Trop. Med. Hyg. **30**:815–824.
28. **Berger, J., H. Yaneva, and B. Nabarra.** 1978. Glomerular changes in patients with cirrhosis of the liver. Adv. Nephrol. **7**:3–14.
29. **Berggren, W. L., and T. H. Weller.** 1967. Immunoelectrophoretic demonstration of specific circulating antigen in animals infected with *Schistosoma mansoni*. Am. J. Trop. Med. Hyg. **16**:606–612.
30. **Biempica, L., M. A. Dunn, I. A. Kamel, R. Kamel, P. K. Hait, C. Fleischner, S. L. Biempica, C. H. Wu, and M. Rojkind.** 1983. Liver collagen-type characterization in human schistosomiasis. A histological, ultrastructural and immunocytochemical correlation. Am. J. Trop. Med. Hyg. **32**:316–325.
31. **Biempica, L., S. Takahashi, S. Biempica, and M. Kobayashi.** 1983. Immunohistochemical localization of collagenase in hepatic murine schistosomiasis. J. Histochem. Cytochem. **31**: 488–494.
32. **Bina, J. C., J. Tavaraz-Neto, A. Prata, and E. S. Azevedo.** 1978. Greater resistance to development of severe schistosomiasis in Brazilian negroes. Hum. Biol. **50**:41–49.
33. **Bloch, E. H., M. F. Abdel-Wahab, and K. S. Warrren.** 1972. *In vivo* microscopic observations of the pathogenesis and pathophysiology of hepatosplenic schistosomiasis in the mouse liver. Am. J. Trop. Med. Hyg. **21**:546–557.
34. **Boctor, F. N., T. E. Nash, and A. W. Cheever.** 1979. Isolation of polysaccharide antigen from *Schistosoma mansoni* eggs. J. Immunol. **122**:39–43.
35. **Bogitsh, B. J.** 1971. *Schistosoma mansoni*: cytochemistry of eosinophils in egg-caused early hepatic granulomas in mice. Exp. Parasitol. **29**:493–500.
36. **Bogliolo, L.** 1967. The pathogenesis of schistosomiasis mansoni, p. 184–196. *In* F. K. Mostofi (ed.), Bilharziasis. Springer-Verlag, New York.
37. **Boros, D. L.** 1986. Immunoregulation of granuloma formation in murine schistosomiasis mansoni. Ann. N.Y. Acad. Sci. **465**:313–323.
38. **Boros, D. L.** 1987. Granuloma and fibrosis, p. 178–190. *In* J. P. Revillard and N. Wierzbicki (ed.), Tissue fibrosis: immune cells and mediators. Local immunity, vol. 3. Fondation Franco-Allemande, Suresnes, France.
39. **Boros, D. L., A. F. Amsden, and A. T. Hood.** 1982. Modulation of granulomatous hypersensitivity. IV. Immunoglobulin and antibody production by vigorous and immunomodulated liver granulomas of *Schistosoma mansoni* infected mice. J. Immunol. **128**:1050–1053.
40. **Boros, D. L., and M. A. Lande.** 1983. Induction of collagen synthesis in cultured human fibroblasts by live *Schistosoma mansoni* eggs and soluble egg antigens (SEA). Am. J. Trop. Med. Hyg. **32**:78–82.
41. **Boros, D. L., M. A. Lande, and L. Carrick, Jr.** 1981. The artificial granuloma. III. Collagen synthesis during cell-mediated granulomatous response as determined in explanted granulomas. Clin. Immunol. Immunopathol. **18**:276–286.
42. **Boros, D. L., R. P. Pelley, and K. S. Warren.** 1975. Spontaneous modulation of granulomatous hypersensitivity in schistosomiasis mansoni. J. Immunol. **114**:1437–1441.
43. **Boros, D. L., H. J. Schwartz, A. E. Powell, and K. S. Warren.** 1973. Delayed hypersensitivity as manifested by granuloma formation, dermal reactivity, macrophage migration inhibition, and lymphocyte transformation, induced and elicited in guinea pigs with soluble antigens of *Schistosoma mansoni* eggs. J. Immunol. **110**:1118–1125.
44. **Boros, D. L., R. Tomford, and K. S. Warren.** 1977. Induction of granulomatous and elicitation of cutaneous sensitivity by partially purified SEA of *Schistosoma mansoni*. J. Immunol. **118**:373–376.
45. **Boros, D. L., and K. S. Warren.** 1970. Delayed hypersensitivity granuloma formation and dermal reaction induced and elicited by a soluble factor isolated from *Schistosoma mansoni* eggs. J. Exp. Med. **132**:488–507.
46. **Boros, D. L., and K. S. Warren.** 1971. Effect of anti-macrophage serum on hypersensitivity (*Schistosoma mansoni* egg) and foreign body (divinylbenzene copolymer bead) granulomas. J. Immunol. **107**:534–539.
47. **Boros, D. L., and K. S. Warren.** 1973. The bentonite granu-

loma: characterization of a model system for infectious and foreign body granulomatous inflammation using soluble Mycobacterial, Histoplasma, and Schistosoma antigens. Immunology **24**:519–529.
48. **Boros, D. L., K. S. Warren, and R. P. Pelley.** 1973. The secretion of migration inhibition factor by intact schistosome egg granulomas maintained *in vitro*. Nature (London) **246**: 224–226.
49. **Bout, D., F. Santoro, Y. Carlier, J. C. Bina, and A. Capron.** 1977. Circulating immune complexes in schistosomiasis. Immunology **33**:17–22.
50. **Brackett, S.** 1940. Pathology of schistosome dermatitis. Arch. Dermatol. **42**:410–418.
51. **Brito, E., F. Santoro, H. Rocha, M. Dutra, and A. Capron.** 1979. Immune complexes in schistosomiasis. VI. Circulating IC levels in patients with and without nephropathy. Rev. Inst. Med. Trop. Sao Paulo **21**:119–124.
52. **Brown, A. P., H. G. Remold, K. S. Warren, and J. R. David.** 1977. Partial purification of antigens from eggs of *Schistosoma mansoni* that elicit delayed hypersensitivity. J. Immunol. **119**: 1275–1278.
53. **Buchanan, R. D., D. P. Fine, and D. G. Colley.** 1973. *Schistosoma mansoni* infection in mice depleted of thymus dependent lymphocytes. II. Pathology and altered pathogenesis. Am. J. Pathol. **71**:207–214.
54. **Byram, J. E., and F. von Lichtenberg.** 1977. Altered schistosome granuloma formation in nude mice. Am. J. Trop. Med. Hyg. **26**:944–956.
55. **Camus, D., J. C. Bina, Y. Carlier, and F. Santoro.** 1977. A,B,O blood groups and clinical forms of schistosomiasis mansoni. Trans. R. Soc. Trop. Med. Hyg. **71**:182.
56. **Camus, D., Y. Carlier, M. Capron, J. C. Bina, J. F. M. Figueiredo, A. Prata, and A. Capron.** 1977. Immunological studies in human schistosomiasis. III. Immunoglobulin levels, antibodies, and delayed hypersensitivity. Am. J. Trop. Med. Hyg. **26**:482–490.
57. **Camus, D., A. Nosseir, C. Mazingue, and A. Capron.** 1981. Immunoregulation by *Schistosoma mansoni*. Immunopharmacology **31**:193–204.
58. **Carlier, Y., D. Bout, J. C. Bina, D. Camus, J. F. M. Figueiredo, and A. Capron.** 1975. Immunological studies in human schistosomiasis. I. Parasitic antigen in urine. Am. J. Trop. Med. Hyg. **24**:949–954.
59. **Carlier, Y., D. Bout, and A. Capron.** 1980. Detection of Schistosoma "M" antigen in circulating immune complexes and in kidneys of infected hamsters. Trans. R. Soc. Trop. Med. Hyg. **74**:534–538.
60. **Carlier, Y., D. Bout, G. Strecker, H. Debray, and A. Capron.** 1980. Purification, immunochemical and biologic characterization of the schistosoma circulating M antigen. J. Immunol. **124**:2442–2450.
61. **Carlier, Y., H. Nzeyimana, D. Bout, and A. Capron.** 1980. Evaluation of circulating antigens by a sandwich radioimmunoassay, and of antibodies and immune complexes, in *Schistosoma mansoni*-infected African parturients and their newborn children. Am. J. Trop. Med. Hyg. **29**:74–81.
62. **Carter, C. E., and D. G. Colley.** 1979. Partial purification of *Schistosoma mansoni* soluble egg antigen with Con A-Sepharose chromatography. J. Immunol. **122**:2204–2209.
63. **Carvalho, E. M., B. S. Andrews, R. Martinelli, M. Dutra, and H. Rocha.** 1983. Circulating immune complexes and rheumatoid factor in schistosomiasis and visceral leishmaniasis. Am. J. Trop. Med. Hyg. **32**:61–68.
64. **Catto, B. A., F. A. Lewis, and E. A. Ottesen.** 1980. Cercaria-induced histamine release: a factor in the pathogenesis of schistosome dermatitis? Am. J. Trop. Med. Hyg. **29**:886–889.
65. **Cerri, G. G., V. A. F. Alves, and A. Magalhaes.** 1984. Hepatosplenic schistosomiasis mansoni: ultrasound manifestations. Radiology **153**:777–780.
66. **Cheever, A. W.** 1965. A comparative study of *Schistosoma mansoni* infection in mice, gerbils, multimammate rats and hamsters. I. The relation of portal hypertension to size of hepatic granulomas. Am. J. Trop. Med. Hyg. **14**:211–226.
67. **Cheever, A. W.** 1968. A quantitative post-mortem study of schistosomiasis mansoni in man. Am. J. Trop. Med. Hyg. **17**:38–64.
68. **Cheever, A. W., and Z. A. Andrade.** 1967. Pathological lesions associated with *Schistosoma mansoni* infection in man. Trans. R. Soc. Trop. Med. Hyg. **61**:626–639.
69. **Cheever, A. W., M. A. Dunn, D. A. Dean, and R. H. Duvall.** 1983. Differences in hepatic fibrosis in ICR, C3H and C57/BL6 mice infected with *Schistosoma mansoni*. Am. J. Trop. Med. Hyg. **32**:1364–1369.
70. **Cheever, A. W., R. H. Duvall, T. A. Hallack, Jr., R. G. Minker, J. D. Malley, and K. G. Malley.** 1987. Variation of hepatic fibrosis and granuloma size among mouse strains infected with *Schistosoma mansoni*. Am. J. Trop. Med. Hyg. **37**:85–97.
71. **Cheever, A. W., and K. G. Powers.** 1971. Rate of destruction of *Schistosoma mansoni* eggs and adult worms in the tissues of rhesus monkeys. Am. J. Trop. Med. Hyg. **20**:69–76.
72. **Chensue, S. W., and D. L. Boros.** 1979. Population dynamics of T and B lymphocytes in the lymphoid organs, circulation and granulomas of mice infected with *Schistosoma mansoni*. Am. J. Trop. Med. Hyg. **28**:291–299.
73. **Chensue, S. W., and D. L. Boros.** 1979. Modulation of granulomatous hypersensitivity. I. Characterization of T lymphocytes involved in the adoptive suppression of granuloma formation in *Schistosoma mansoni* infected mice. J. Immunol. **123**:1409–1414.
74. **Chensue, S. W., D. L. Boros, and C. S. David.** 1980. Regulation of granulomatous inflammation in murine schistosomiasis: *in vitro* characterization of T lymphocyte subsets involved in the production and suppression of migration inhibition factor (MIF). J. Exp. Med. **151**:1398–1412.
75. **Chensue, S. W., D. L. Boros, and C. S. David.** 1983. Regulation of granulomatous inflammation in murine schistosomiasis. II. T-suppressor cell-derived 1-C subregion-coded soluble suppressor factor mediates regulation of lymphokine production. J. Exp. Med. **157**:219–230.
76. **Chensue, S. W., S. L. Kunkel, G. I. Higashi, P. A. Ward, and D. L. Boros.** 1983. Production of superoxide anion, prostaglandins, and hydroxyeicosatetraenoic acids by macrophages from hypersensitivity-type (*Schistosoma mansoni* egg) and foreign body-type granulomas. Infect. Immun. **42**:1116–1125.
77. **Chensue, S. W., S. R. Wellhausen, and D. L. Boros.** 1981. Modulation of granulomatous hypersensitivity. II. Participation of $Ly1^+$ and $Ly2^+$ T lymphocytes in the suppression of granuloma formation and lymphokine production in *Schistosoma mansoni* infected mice. J. Immunol. **127**:363–367.
78. **Claas, F. H. J., and A. M. Deelder.** 1979. H-2 linked immune response to murine experimental *Schistosoma mansoni* infection. J. Immunogenet. **6**:167–175.
79. **Clarke, V. de V., B. Warburton, and D. M. Blair.** 1970. The Katayama syndrome: report on an outbreak in Rhodesia. Cent. Afr. J. Med. **16**:123–126.
80. **Colley, D. G.** 1971. Schistosomal egg antigen-induced lymphocyte blastogenesis in experimental murine *Schistosoma mansoni* infection. J. Immunol. **107**:1477–1480.
81. **Colley, D. G.** 1975. Immune responses to a soluble schistosomal egg antigen preparation during chronic primary infection with *Schistosoma mansoni*. J. Immunol. **115**:150–156.
82. **Colley, D. G.** 1976. Adoptive suppression of granuloma formation. J. Exp. Med. **143**:696–700.
83. **Colley, D. G.** 1981. Immune responses and immunoregulation in experimental and clinical schistosomiasis, p. 1–83. *In* J. M. Mansfield (ed.), The immunology of parasitic diseases. Marcel Dekker, Inc., New York.
84. **Colley, D. G.** 1987. Dynamics of the human immune response to schistosomes. Balliere's Clin. Trop. Med. Commun. Dis. **2**:315–332.
85. **Colley, D. G., J. A. Cook, G. L. Freeman, Jr., R. K. Bartholomew, and P. Jordan.** 1977. Immune responses during human schistosomiasis mansoni. I. *In vitro* lymphocyte blastogenic response to heterogeneous antigenic preparations from schistosome eggs, worms and cercariae. Int. Arch. Allergy Appl. Immunol. **53**:420–433.

86. **Colley, D. G., A. A. Garcia, J. R. Lambertucci, J. C. Parra, N. Katz, R. S. Rocha, and G. Gazzinelli.** 1986. Immune responses during human schistosomiasis. XII. Differential responsiveness in patients with hepatosplenic disease. Am. J. Trop. Med. Hyg. **35**:793–802.
87. **Colley, D. G., S. E. Hieny, R. K. Bartholomew, and J. A. Cook.** 1977. Immune responses during human schistosomiasis mansoni. III. Regulatory effect of patient sera on human lymphocyte blastogenic responses to schistosomal antigen preparations. Am. J. Trop. Med. Hyg. **26**:917–925.
88. **Colley, D. G., N. Katz, R. S. Rocha, W. Abrantes, A. L. da Silva, and G. Gazzinelli.** 1983. Immune responses during human schistosomiasis mansoni. IX. T-lymphocyte subset analysis by monoclonal antibodies in hepatosplenic disease. Scand. J. Immunol. **17**:297–302.
89. **Colley, D. G., F. A. Lewis, and R. W. Goodgame.** 1978. Immune responses during human schistosomiasis. IV. Induction of suppressor cell activity by schistosome antigen preparations and concanavalin A. J. Immunol. **120**:1225–1232.
90. **Colley, D. G., F. A. Lewis, and C. W. Todd.** 1979. Adoptive suppression of granuloma formation by T lymphocytes and by lymphoid cells sensitive to cyclophosphamide. Cell. Immunol. **46**:192–207.
91. **Colley, D. G., A. Magalhaes-Filho, and R. Barros-Coelho.** 1972. Immunopathology of dermal reactions induced by *Schistosoma mansoni* cercariae and cercarial extract. Am. J. Trop. Med. Hyg. **21**:558–568.
92. **Cook, J. A., S. T. Baker, K. S. Warren, and P. Jordan.** 1974. A controlled study of morbidity of schistosomiasis mansoni in St. Lucian children, based on quantitative egg excretion. Am. J. Trop. Med. Hyg. **23**:625–633.
93. **Cort, W. W.** 1950. Studies on schistosome dermatitis. XI. Status of knowledge after more than twenty years. Am. J. Hyg. **52**:251–307.
94. **Cottrell, B. J., D. Humber, and R. F. Sturrock.** 1980. An immuno-suppressive factor in the serum of patients with schistosomiasis. Trans. R. Soc. Trop. Med. Hyg. **75**:415–416.
95. **Damian, R. T.** 1984. Immunity in schistosomiasis: a holistic view. Contemp. Top. Immunobiol. **12**:359–420.
96. **de Brito, T., J. Gunji, M. E. Camargo, D. O. Penna, and L. C. da Silva.** 1970. Advanced kidney disease in patients with hepatosplenic Manson's schistosomiasis. Rev. Inst. Med. Trop. Sao Paulo **12**:225–235.
97. **De Cock, K. M.** 1986. Hepatosplenic schistosomiasis: a clinical review. Gut **27**:734–745.
98. **Deelder, A. M., H. T. M. Klappe, G. J. M. J. VanDen Aardweg, and E. H. E. M. Van Meerbeke.** 1976. *Schistosoma mansoni*: demonstration of two circulating antigens in infected hamsters. Exp. Parasitol. **40**:189–197.
99. **Deelder, A. M., and D. Kornelis.** 1981. Immunodiagnosis of recently acquired *Schistosoma mansoni* infection. A comparison of various immunological techniques. Trop. Geogr. Med. **33**:36–41.
100. **Deelder, A. M., D. Kornelis, M. Makbin, H. N. Noordpool, R. M. Codfried, J. P. Rotmans, and B. F. J. Oostburg.** 1980. Applicability of different antigen preparations in the enzyme-linked immunosorbent assay for schistosomiasis mansoni. Am. J. Trop. Med. Hyg. **29**:401–410.
101. **Deelder, A. M., D. Kornelis, E. A. E. van Marck, P. C. Eveleigh, and J. G. van Egmond.** 1980. *Schistosoma mansoni*: characterization of two circulating polysaccharide antigens and the immunological response to these antigens in mouse, hamster and human infections. Exp. Parasitol. **50**:16–32.
102. **Deelder, A. M., E. J. Ruitenberg, E. A. E. Van Marck, and F. H. J. Claas.** 1983. H-2 linked response to *Schistosoma mansoni* in the mouse: immunological and immunopathological aspects. Contrib. Microbiol. Immunol. **7**:3–8.
103. **Dessaint, J. P., D. Camus, E. Fischer, and A. Capron.** 1977. Inhibition of lymphocyte proliferation by factors produced by *Schistosoma mansoni*. Eur. J. Immunol. **7**:624–629.
104. **DeWater, R., E. A. E. Van Marck, J. A. M. Fransen, and A. M. Deelder.** 1988. *Schistosoma mansoni*: ultrastructural localization of the circulating anodic antigen and the circulating cathodic antigen in the mouse kidney glomerulus. Am. J. Trop. Med. Hyg. **38**:118–124.
105. **DeWitt, W. B., and K. S. Warren.** 1959. Hepato-splenic schistosomiasis in mice. Am. J. Trop. Med. Hyg. **8**:440–446.
106. **Diaz-Rivera, R. S., F. Ramos-Morales, E. Koppisch, M. R. Garcia-Palmieri, A. A. Cintron-Rivera, E. J. Marchand, O. Gonzalez, and M. V. Torregrosa.** 1965. Acute Manson's schistosomiasis. Am. J. Med. **21**:918–943.
107. **Digeon, M., D. Droz, L. H. Noel, I. Riza, C. R. Rieumailhol, J. F. Bach, F. Santoro, and A. Capron.** 1979. The role of circulating immune complexes in the glomerular disease of experimental hepatosplenic schistosomiasis. Clin. Exp. Immunol. **35**:329–337.
108. **Doenhoff, M., R. Musallam, J. Bain, and A. McGregor.** 1979. *Schistosoma mansoni* infections in T-cell deprived mice, and the ameliorating effect of administering homologous chronic infection serum. I. Pathogenesis. Am. J. Trop. Med. Hyg. **28**:260–273.
109. **Domingo, E. O., and K. S. Warren.** 1967. The inhibition of granuloma formation around *Schistosoma mansoni* eggs. II. Thymectomy. Am. J. Pathol. **51**:757–767.
110. **Domingo, E. O., and K. S. Warren.** 1968. The inhibition of granuloma formation around *Schistosoma mansoni* eggs. III. Heterologous antilymphocyte serum. Am. J. Pathol. **52**:613–631.
111. **Domingo, E. O., and K. S. Warren.** 1968. Endogenous desensitization: changing host granulomatous response to schistosome eggs at different stages of infection with *Schistosoma mansoni*. Am. J. Pathol. **52**:369–380.
112. **Domingo, E. O., and K. S. Warren.** 1969. Pathology and pathophysiology of the small intestine in murine schistosomiasis mansoni, including a review of the literature. Gastroenterology **56**:231–240.
113. **Doughty, B. L., E. A. Ottesen, T. E. Nash, and S. M. Phillips.** 1984. Delayed hypersensitivity granuloma formation around *Schistosoma mansoni* eggs *in vitro*. III. Granuloma formation and modulation in human schistosomiasis mansoni. J. Immunol. **133**:993–997.
114. **Doughty, B. L., and S. M. Phillips.** 1982. Delayed hypersensitivity granuloma formation around *Schistosoma mansoni* eggs *in vitro*. I. Definition of the model. J. Immunol. **128**:30–36.
115. **Doughty, B. L., and S. M. Phillips.** 1982. Delayed hypersensitivity granuloma formation around *Schistosoma mansoni* eggs *in vitro*. II. Regulatory T cells subsets. J. Immunol. **128**:37–42.
116. **Dunn, M. A., and R. Kamel.** 1981. Hepatic schistosomiasis. Hepatology **1**:653–661.
117. **Dunn, M. A., R. Kamel, I. A. Kamel, L. Biempica, A. El Kholy, P. K. Hait, M. Rojkind, K. S. Warren, and A. A. F. Mahmoud.** 1979. Liver collagen synthesis in schistosomiasis mansoni. Gastroenterology **76**:978–982.
118. **Dunn, M. A., M. E. Maragoudakis, and P. K. Hait.** 1978. Liver collagen hydroxylation in murine schistosomiasis. Biochim. Biophys. Acta **538**:328–333.
119. **Dunn, M. A., M. Rojkind, K. S. Warren, P. K. Hait, L. Rifas, and S. Seifter.** 1977. Liver collagen synthesis in murine schistosomiasis. J. Clin. Invest. **59**:666–674.
120. **Dunne, D. W., S. Lucas, Q. Bickle, S. Pearson, L. Madgwick, J. Bain, and M. J. Doenhoff.** 1981. Identification and partial purification of an antigen ω_1 from *Schistosoma mansoni* eggs which is putatively hepatotoxic in T-cell deprived mice. Trans. R. Soc. Trop. Med. Hyg. **75**:54–71.
121. **El-Dosoky, I., E. A. E. Van Marck, and A. M. Deelder.** 1984. Presence of *Schistosoma mansoni* antigens in liver, spleen and kidney of infected mice: a sequential study. Z. Parasitenkd. **70**:491–497.
122. **Elliott, D. E., and D. L. Boros.** 1984. Schistosome egg antigen(s) presentation and regulatory activity by macrophages isolated from vigorous or immunomodulated liver granulomas of *Schistosoma mansoni*-infected mice. J. Immunol. **132**:1506–1510.
123. **Elliott, D. E., V. F. Righthand, and D. L. Boros.** 1987. Characterization of regulatory (interferon α/β) and accessory (LAF/IL-1) monokine activities from liver granuloma macro-

phages of *Schistosoma mansoni*-infected mice. J. Immunol. **138**:2653–2662.
124. **Ellner, J. J., G. R. Olds, R. Kamel, G. S. Osman, A. El Kholy, and A. A. F. Mahmoud.** 1980. Suppressor splenic T lymphocytes in human hepatosplenic schistosomiasis mansoni. J. Immunol. **125**:308–312.
125. **Ellner, J. J., G. R. Olds, G. S. Osman, A. El Kholy, and A. A. F. Mahmoud.** 1981. Dichotomies in the reactivity to worm antigen in human schistosomiasis mansoni. J. Immunol. **126**:309–312.
126. **El-Mohandes, M., H. Hassanein, N. El-Badrawy, B. Voss, and U. Gerlach.** 1987. Serum concentration of N-terminal procollagen peptide of collagen type III in schistosomal liver fibrosis. Exp. Mol. Pathol. **46**:383–390.
127. **El-Sherif, A. K. and D. Befus.** 1988. Predominance of IgA deposits in glomeruli of *Schistosoma mansoni* infected mice. Clin. Exp. Immunol. **71**:39–44.
128. **Epstein, W. L., K. Fukuyama, K. Danno, and E. Kwan-Wong.** 1979. Granulomatous inflammation in normal and athymic mice infected with *Schistosoma mansoni*: an ultrastructural study. J. Pathol. **127**:207–215.
129. **Falcao, H. A., and D. B. Gould.** 1975. Immune complex nephropathy in schistosomiasis. Ann. Intern. Med. **83**:148–154.
130. **Fanning, M. M., P. A. Peters, R. S. Davis, J. W. Kazura, and A. A. F. Mahmoud.** 1981. Immunopathology of murine infection with *Schistosoma mansoni*: relationship of genetic background to hepatosplenic disease and modulation. J. Infect. Dis. **144**:148–153.
131. **Feldmeier, H., P. Kern, and G. Niel.** 1981. Modulation of *in vitro* lymphocyte proliferation in patients with schistosomiasis haematobium, schistosomiasis mansoni and mixed infections. Tropenmed. Parasitol. **32**:237–242.
132. **Feldmeier, H., J. A. Nogueira-Queiroz, M. A. Peixoto-Queiroz, E. Doehring, J. P. Dessaint, J. E. De Alencar, A. A. Dafalla, and A. Capron.** 1986. Detection and quantification of circulating antigen in schistosomiasis by monoclonal antibody. II. The quantification of circulating antigens in human schistosomiasis mansoni and haematobium: relationship to intensity of infection and disease status. Clin. Exp. Immunol. **65**:232–243.
133. **Fine, D. P., R. D. Buchanan, and D. G. Colley.** 1973. *Schistosoma mansoni* infection in mice depleted of thymus-dependent lymphocytes. Am. J. Pathol. **71**:193–206.
134. **Fischer, E., D. Camus, F. Santoro, and A. Capron.** 1981. *Schistosoma mansoni*: autoantibodies and polyclonal B cell activation in infected mice. Clin. Exp. Immunol. **46**:89–97.
135. **Fukuyama, K., S. Tzeng, J. McKerrow, and W. L. Epstein.** 1983. The epidermal barrier to *Schistosoma mansoni* infection. Curr. Prob. Dermatol. **11**:185–193.
136. **Galvao-Castro, B., J. C. Bina, A. Prata, and P. H. Lambert.** 1981. Correlation of circulating immune complexes and complement breakdown products with the severity of the disease in human schistosomiasis mansoni. Am. J. Trop. Med. Hyg. **30**:1238–1246.
137. **Garcia, A. A., A. L. da Silva, L. R. de Oliveira, N. Katz, G. Gazzinelli, and D. G. Colley.** 1986. Immune responses during human schistosomiasis mansoni. XIII. Immunological status of spleen cells from hospital patients with hepatosplenic disease. Scand. J. Immunol. **24**:413–420.
138. **Gastl, G. A., H. Feldmeier, E. Doehring, C. Kortmann, A. A. Daffalla, and H. H Peter.** 1984. Numerical and functional alterations of lymphocytes in human schistosomiasis. Scand, J. Immunol. **19**:469–479.
139. **Gazzinelli, G., N. Katz, R. S. Rocha, and D. G. Colley.** 1983. Immune responses during human schistosomiasis mansoni. X. Production and standardization of an antigen-induced mitogenic activity by peripheral blood mononuclear cells from treated, but not active cases of schistosomiasis. J. Immunol. **130**:2891–2895.
140. **Gazzinelli, G., J. R. Lambertucci, N. Katz, R. S. Rocha, M. S. Lima, and D. G. Colley.** 1985. Immune responses during human schistosomiasis mansoni. XI. Immunologic status of patients with acute infections and after treatment. J. Immunol. **135**: 2121–2127.
141. **Gigase, P. L. J.** 1982. Hepatosplenic human schistosomiasis: progress and problems. Acta Leiden. **49**:41–53.
142. **Gold, R., F. S. Rosen, and T. H. Weller.** A specific circulating antigen in hamsters infected with *Schistosoma mansoni*. Detection of antigen in serum and urine, and correlation between antigenic concentration and worm burden. Am. J. Trop. Med. Hyg. **18**:545–552.
143. **Goodgame, R. W., D. G. Colley, C. C. Draper, F. A. Lewis, M. L. McLaren, and R. P. Pelley.** 1978. Humoral immune responses in human hepatosplenic schistosomiasis mansoni. Am. J. Trop. Med. Hyg. **27**:1174–1180.
144. **Gordon, R. M., and R. B. Griffiths.** 1951. Observations on the means by which the cercariae of *Schistosoma mansoni* penetrate mammalian skin, together with an account of certain morphological changes observed in the newly penetrated larvae. Am. Trop. Med. Parasitol. **45**:227–243.
145. **Green, W. F., and D. G. Colley.** 1981. Modulation of *Schistosoma mansoni* egg-induced granuloma formation: I-J restriction of T cell-mediated suppression in a chronic parasitic infection. Proc. Natl. Acad. Sci. USA **78**:1152–1156.
146. **Grimaud, J. A.** 1987. Cell-matrix interactions in schistosomal portal fibrosis: a dynamic event, p. 122–137. *In* J. P. Revillard and N. Wierzbicki (ed.), Tissue fibrosis: immune cells and mediators. Local immunity, vol. 3. Fondation Franco-Allemande, Suresnes, France.
147. **Grimaud, J. A., and R. Borojevic.** 1977. Chronic human schistosomiasis mansoni. Pathology of the Disse's space. Lab. Invest. **36**:268–273.
148. **Grimaud, J. A., and R. Borojevic.** 1986. Portal fibrosis: intrahepatic portal vein pathology in chronic human schistosomiasis mansoni. J. Submicrosc. Cytol. **18**:783–793.
149. **Grimaud, J. A., D. L. Boros, C. Takiya, R. C. Mathew, and H. Emonard.** 1987. Collagen isotypes, laminin, and fibronectin in granulomas of the liver and intestines of *Schistosoma mansoni*-infected mice. Am. J. Trop. Med. Hyg. **37**:335–344.
150. **Gutekunst, R. R., H. G. Brown, and D. M. Meyers.** 1965. Influence of *Schistosoma mansoni* eggs on growth of monkey heart cells. Exp. Parasitol. **17**:194–202.
151. **Hamburger, J., S. Lustigman, T. K. A. Siongok, J. H. Ouma, and A. A. F. Mahmoud.** 1982. Characterization of a purified glycoprotein from *Schistosoma mansoni* eggs: specificity, stability, and the involvement of carbohydrate and peptide moieties in its serological activity. J. Immunol. **128**:1864–1869.
152. **Hang, L. M., D. L. Boros, and K. S. Warren.** 1974. Induction of immunological hyporesponsiveness to granulomatous hypersensitivity in *Schistosoma mansoni* infection. J. Infect. Dis. **130**:515–522.
153. **Hang, L. M., K. S. Warren, and D. L. Boros.** 1974. *Schistosoma mansoni*: antigenic secretions and the etiology of egg granulomas in mice. Exp. Parasitol. **35**:288–298.
154. **Harries, A. D., and G. C. Cook.** 1987. Acute schistosomiasis (Katayama fever): clinical deterioration after chemotherapy. J. Infect. **14**:159–161.
155. **Harrison, D. J., C. E. Carter, and D. G. Colley.** 1979. Immunoaffinity purification of *Schistosoma mansoni* soluble egg antigens. J. Immunol. **122**:2210–2217.
156. **Hayunga, E. G., J. F. Duncan, M. Stek, Jr., I. Mollegard, M. P. Sumner, and K. W. Hunter, Jr.** 1986. Development of circulating antigen assay for rapid detection of acute schistosomiasis. Lancet **ii**:716–718.
157. **Helmi-Khalil, S., Jr., M. H. Fahmi, M. H. Ghanem, M. Said, M. El Sawy, M. Nofal, H. N. Awadalla, M. Youssef, D. Mucke, and J. Brock.** 1979. Cell mediated immune (CMI) responsiveness to soluble egg antigen (SEA) and its relation to the occurrence of schistosomal hepatosplenic disease in patients with *Schistosoma mansoni*. Tropenmed. Parasitol. **30**:426–428.
158. **Hiatt, R. A., E. A. Ottesen, Z. R. Sotomayor, and T. J. Lawley.** 1980. Serial observations of circulating immune complexes in patients with acute schistosomiasis. J. Infect. Dis. **142**:665–670.
159. **Hiatt, R. A., Z. R. Sotomayor, G. Sanchez, M. Zambrana, and W. B. Knight.** 1979. Factors in pathogenesis of acute schistosomiasis. J. Infect. Dis. **139**:659–606.

160. **Hillyer, G. V.** 1973. Schistosome deoxyribonucleic acid (DNA), antibodies to DNA in schistosome infections, and their possible role in renal pathology. Bol. Asoc. Med. P. R. **65**(Suppl.):1–22.
161. **Hillyer, G. V., and R. M. Lewert.** 1974. Studies on renal pathology in hamsters infected with *Schistosoma mansoni* and *S. japonicum*. Am. J. Trop. Med. Hyg. **23**:404–411.
162. **Hofstetter, M., M. B. Fasano, and E. A. Ottesen.** 1983. Modulation of host response in human schistosomiasis. IV. Parasite antigen induces release of histamine that inhibits lymphocyte responsiveness *in vitro*. J. Immunol. **130**:1376–1380.
163. **Homeida, M., A. F. Abdel-Gadir, A. W. Cheever, J. L. Bennett, B. M. O. Arbab, S. K. Ibrahium, I. M. Abdel-Salam, A. A. Dafalla, and T. E. Nash.** 1988. Diagnosis of pathologically confirmed Symmers' periportal fibrosis by ultrasonography: a prospective blinded study. Am. J. Trop. Med. Hyg. **38**:86–91.
164. **Hood, A. T., and D. L. Boros.** 1980. The effect of splenectomy on the pathophysiology and egg-specific immune response of *Schistosoma mansoni* infected mice. Am. J. Trop. Med. Hyg. **29**:586–591.
165. **Hoshino-Shimizu, S., T. de Brito, H. Y. Kanamura, A. L. Canto, A. O. Silva, A. R. Campos, D. O. Penna, and L. C. Silva.** 1976. Human schistosomiasis: *Schistosoma mansoni* antigen detection in renal glomeruli. Trans. R. Soc. Trop. Med. Hyg. **70**:492–496.
166. **Houba, V.** 1979. Experimental renal disease due to schistosomiasis. Kidney Int. **16**:30–43.
167. **Houba, V., R. F. Sturrock, and A. E. Butterworth.** 1977. Kidney lesions in baboons infected with *Schistosoma mansoni*. Clin. Exp. Immunol. **30**:439–449.
168. **Houpis, J., J. Oexmann, J. Martin, G. Jacobi, J. Reardon, and G. Waterman.** 1984. Acute schistosomiasis with transverse myelitis in American students returning from Kenya. Morbid. Mortal. Weekly Rep. **33**:445–447.
169. **Iarotski, L. S., and A. Davis.** 1981. The schistosomiasis problem in the world: results of a WHO questionnaire survey. Bull. W.H.O. **59**:115–127.
170. **James, S. L., and D. G. Colley.** 1975. Eosinophils and immune mechanisms: production of the lymphokine eosinophil stimulation promotor (ESP) *in vitro* by isolated intact granulomas. RES J. Reticuloendothel. Soc. **18**:283–293.
171. **Kamal, K. A., and G. I. Higashi.** 1982. Suppression of mitogen-induced lymphocyte transformation by plasma from patients with hepatosplenic schistosomiasis mansoni: role of immune complexes. Parasite Immunol. **4**:283–298.
172. **Kanamura, H. Y., S. Hoshino-Shimizu, M. E. Camargo, and L. C. Da Silva.** 1978. Class specific antibodies and fluorescent staining patterns in acute and chronic forms of schistosomiasis mansoni. Am. J. Trop. Med. Hyg. **28**:242–248.
173. **Kazura, J. W., A. A. F. Mahmoud, K. S. Karb, and K. S. Warren.** 1975. The lymphokine eosinophil stimulation promoter and human schistosomiasis. J. Infect. Dis. **132**:702–706.
174. **Kusel, J. R., P. E. Mackenzie, and D. J. McLaren.** 1975. The release of membrane antigens into culture by S. *mansoni*. Parasitology **71**:247–259.
175. **Lammie, P. J., A. I. Michael, G. P. Linette, and S. M. Phillips.** 1986. Production of a fibroblast-stimulating factor by *Schistosoma mansoni* antigen-reactive T cell clones. J. Immunol. **136**:1100–1106.
176. **Lawley, T. J., E. A. Ottesen, R. A. Hiatt, and L. A. Gazze.** 1979. Circulating immune complexes in acute schistosomiasis. Clin. Exp. Immunol. **37**:221–227.
177. **Lehman, J. S., K. E. Mott, C. A. M. de Souza, O. Leboreiro, and T. M. Muniz.** 1975. The association of schistosomiasis mansoni and proteinuria in an endemic area: a preliminary report. Am. J. Trop. Med. Hyg. **24**:616–618.
178. **Lehman, J. S., K. E. Mott, R. H. Morrow, Jr., T. M. Muniz, and M. H. Boyer.** 1976. The intensity and effects of infection with *Schistosoma mansoni* in a rural community in Northeast Brazil. Am. J. Trop. Med. Hyg. **25**:285–294.
179. **Lewert, R. M., and S. Mandlowitz.** 1969. Schistosomiasis: prenatal induction of tolerance to antigens. Nature (London) **224**:1029–1030.
180. **Lima, M. S., G. Gazzinelli, E. Nascimento, J. Carvalho Parra, M. A. Montesano, and D. G. Colley.** 1986. Immune responses during human schistosomiasis mansoni. Evidence for antiidiotypic T lymphocyte responsiveness. J. Clin. Invest. **78**:983–988.
181. **Lima, M. S., G. Gazzinelli, R. S. Rocha, N. Katz, and D. G. Colley.** 1985. Demonstration of leukocyte inhibitory factor in human schistosomiasis mansoni and its evaluation from patients in an endemic setting. Clin. Immunol. Immunopathol. **37**:351–359.
182. **Lima-Perreira, F. E., E. R. Bortolini, J. L. A. Carneiro, C. R. Mello da Silva, and R. C. Neves.** 1979. A,B,O blood groups and hepatosplenic form of schistosomiasis mansoni (Symmers' fibrosis). Trans. R. Soc. Trop. Med. Hyg. **73**:238–248.
183. **Loveless, S. E., S. R. Wellhausen, D. L. Boros, and G. H. Heppner.** 1982. Tumoricidal macrophages isolated from liver granulomas of *Schistosoma mansoni*-infected mice. J. Immunol. **128**:284–288.
184. **Lunde, M. N., E. A. Ottesen, and A. W. Cheever.** 1979. Serologic differences between acute and chronic schistosomiasis mansoni detected by enzyme-linked immunosorbent assay (ELISA). Am. J. Trop. Med. Hyg. **28**:87–91.
185. **Lustigman, S., A. A. F. Mahmoud, and J. Hamburger.** 1985. Glycopeptides in soluble egg antigen of *Schistosoma mansoni*: isolation, characterization, and elucidation of their immunochemical and immunopathological relation to the major egg glycoprotein (MEG). J. Immunol. **134**:1961–1967.
186. **Machado, A. J., G. Gazzinelli, J. Pellegrino, and W. Dias da Silva.** 1975. *Schistosoma mansoni*: the role of the complement C_3-activating system in the cercaricidal action of normal serum. Exp. Parasitol. **38**:20–29.
187. **Madwar, M. A., and A. Voller.** 1975. Circulating soluble antigens and antibody in schistosomiasis. Br. Med. J. **1**: 435–436.
188. **Magelhaes Filho, A. D. G., A. C. Barbosa, and T. C. Ferreira.** 1981. Glomerulonephritis in schistosomiasis with mesangial IgM deposits. Mem. Inst. Oswaldo Cruz **76**:181–188.
189. **Mahmoud, A. A. F., K. S. Warren, and R. C. Graham.** 1975. Anti-eosinophil serum and the kinetics of eosinophilia in schistosomiasis mansoni. J. Exp. Med. **142**:560–574.
190. **Mathew, R. C., and D. L. Boros.** 1986. Regulation of granulomatous inflammation in murine schistosomiasis. III. Recruitment of antigen-specific I-J$^+$T suppressor cells of the granulomatous response by an I-J$^+$ soluble suppressor factor. J. Immunol. **136**:1093–1099.
191. **Mathew, R. C., and D. L. Boros.** 1986. Anti-L3T4 antibody treatment suppresses hepatic granuloma formation and abrogates antigen-induced interleukin 2 production in *Schistosoma mansoni* infection. Infect. Immun. **54**:820–826.
192. **Mohamed, A. E.** 1985. The Katayama syndrome in Saudia. J. Trop. Med. Hyg. **88**:319–322.
193. **Moore, D. L., D. J. Grove, and K. S. Warren.** 1977. The *Schistosoma mansoni* egg granuloma: quantitation of cell populations. J. Pathol. **121**:41–50.
194. **Morcos, S. H., M. T. Khayyal, M. M. Mansour, S. Saleh, E. A. Ishak, N. I. Girgis, and M. A. Dunn.** 1985. Reversal of hepatic fibrosis after praziquantel therapy of murine schistosomiasis. Am. J. Trop. Med. Hyg. **34**:314–321.
195. **Moriearty, P. L., and E. Brito.** 1977. Elution of renal anti-schistosome antibodies in human schistosomiasis mansoni. Am. J. Trop. Med. Hyg. **26**:717–722.
196. **Moriearty, P. L., and R. M. Lewert.** 1974. Delayed hypersensitivity in Ugandan schistosomiasis. I. Sensitivity, specificity and immunological features of intradermal responses. Am. J. Trop. Med. Hyg. **23**:169–178.
197. **Nash, T. E.** 1982. Factors that modulated clearance and ultimate fate of a specific schistosome antigen (GASP) in schistosome infections. J. Immunol. **128**:1608–1613.
198. **Nash, T. E.** 1983. Fate and mechanism of clearance of PSAP, a schistosome antigen, in schistosomiasis. J. Immunol. **131**: 2520–2523.
199. **Nash, T. E.** 1984. Immune complex size determines the clearance rate of a circulating antigen in schistosome-infected mice.

Am. J. Trop. Med. Hyg. **33**:621–626.
200. **Nash, T. E., A. W. Cheever, E. A. Ottesen, and J. A. Cook.** 1982. Schistosome infections in humans: perspectives and recent findings. Ann. Intern. Med. **97**:740–754.
201. **Nash, T. E., and A. M. Deelder.** 1985. Comparison of four schistosome excretory-secretory antigens: phenol sulfuric test active peak, cathodic circulating antigen, gut-associated proteoglycan, and circulating anodic antigen. Am. J. Trop. Med. Hyg. **34**:236–241.
202. **Nash, T. E., C. Garcia-Coyco, E. Ruiz-Tiben, H. A. Nazario-Lopez, G. Vazquez, and A. Torres-Borges.** 1983. Differentiation of acute and chronic schistosomiasis by antibody responses to specific schistosome antigens. Am. J. Trop. Med. Hyg. **32**: 776–784.
203. **Nash, T. E., M. N. Lunde, and A. W. Cheever.** 1981. Analysis and antigenic activity of a carbohydrate fraction derived from adult *Schistosoma mansoni*. J. Immunol. **126**:805–810.
204. **Nash, T. E., Nasir-Ud-Din, and R. W. Jeanloz.** 1977. Further purification and characterization of a circulating antigen in schistosomiasis. J. Immunol. **119**:1627–1633.
205. **Nash, T. E., E. A. Ottesen, and A. W. Cheever.** 1978. Antibody response to a polysaccharide antigen present in the schistosome gut. II. Modulation of antibody response. Am. J. Trop. Med. Hyg. **27**:944–950.
206. **Nash, T. E., B. Prescott, and F. A. Neva.** 1974. The characteristics of a circulating antigen in schistosomiasis. J. Immunol. **112**:1500–1507.
207. **Natali, P. G., and D. Cioli.** 1976. Immune complex nephritis in *Schistosoma mansoni* infected mice. Eur. J. Immunol. **6**: 359–364.
208. **Olds, G. R., A. El Kholy, and J. J. Ellner.** 1983. Two distinctive patterns of monocyte immunoregulatory and effector functions in heavy human infections with *Schistosoma mansoni*. J. Immunol. **131**:954–958.
209. **Olds, G. R., and A. A. F. Mahmoud.** 1980. Role of host granulomatous response in murine schistosomiasis mansoni. Eosinophil-mediated destruction of eggs. J. Clin. Invest. **66**: 1191–1199.
210. **Olivier, L.** 1949. Schistosome dermatitis: a sensitization phenomenon. Am. J. Hyg. **49**:290–302.
211. **Ott, B. R., P. Libbey, R. J. Ryter, and W. M. Trebbin.** 1983. Treatment of schistosome-induced glomerulonephritis. Arch. Intern. Med. **143**:1477–1479.
212. **Ottesen, E. A.** 1979. Modulation of the host response in human schistosomiasis. I. Adherent suppressor cells that inhibit lymphocyte proliferation responses to parasite antigens. J. Immunol. **123**:1639–1644.
213. **Ottesen, E. A., R. A. Hiatt, A. W. Cheever, Z. R. Sotomayor, and F. A. Neva.** 1978. The acquisition and loss of antigen-specific cellular immune responsiveness in acute and chronic schistosomiasis in man. Clin. Exp. Immunol. **33**:38–47.
214. **Ottesen, E. A., and R. W. Poindexter.** 1980. Modulation of the host response in human schistosomiasis. II. Humoral factors which inhibit lymphocyte proliferative responses to parasite antigens. Am. J. Trop. Med. Hyg. **29**:592–597.
215. **Ottesen, E. A., R. W. Poindexter, and R. Hussain.** 1981. Detection, quantitation and specificity of anti-parasite IgE antibodies in human schistosomiasis mansoni. Am. J. Trop. Med. Hyg. **30**:1228–1237.
216. **Owhashi, M., Y. Horii, J. Imai, A. Ishii, and Y. Nawa.** 1986. Purification and physicochemical characterization of *Schistosoma mansoni* egg allergen recognized by mouse sera obtained at an acute stage of infection. Int. Arch. Allergy Appl. Immunol. **81**:129–135.
217. **Parise, E. R., J. A. Summerfield, E. Hahn, K. H. Wiedmann, and M. J. Doenhoff.** 1985. Basement membrane proteins and type III procollagen in murine schistosomiasis. Trans. R. Soc. Trop. Med. Hyg. **79**:663–670.
218. **Parra, J. C., M. S. Lima, G. Gazzinelli, and D. G. Colley.** 1988. Immune responses during human schistosomiasis mansoni. XV. Anti-idiotypic T cells can recognize and respond to anti-SEA idiotypes directly. J. Immunol. **140**:2401–2405.
219. **Pearce, E. J., and D. J. McLaren.** 1986. *Schistosoma mansoni*: the cutaneous response to cercarial challenge in naive guinea pigs and guinea pigs vaccinated with highly irradiated cercariae. Int. J. Parasitol. **16**:491–510.
220. **Pelley, R. P., and R. J. Pelley.** 1976. *Schistosoma mansoni* soluble egg antigens. IV. Biochemistry and immunochemistry of major serological antigens with particular emphasis on MSA_1, p. 283–290. *In* H. Van den Bossche (ed.), Biochemistry of parasites and host-parasite relationships. Elsevier/North-Holland Publishing Co., Amsterdam.
221. **Pelley, R. P., R. J. Pelley, J. Hamburger, P. A. Peters, and K. S. Warren.** 1976. *Schistosoma mansoni* soluble egg antigens. I. Identification and purification of three major antigens, and the employment of radioimmunoassay for their further characterization. J. Immunol. **117**:1553–1560.
222. **Pelley, R. P., K. S. Warren, and P. Jordan.** 1977. Purified antigen radioimmunoassay in serological diagnosis of schistosomiasis mansoni. Lancet **ii**:781–785.
223. **Peppard, J., E. Orlans, A. Payne, and E. Andrew.** 1981. The elimination of circulating complexes containing polymeric IgA by excretion in bile. Immunology **42**:83–89.
224. **Perotto, J. L., K. R. Falchuk, R. P. Pelley, and K. S. Warren.** 1976. Serum lysozyme and β-glucoronidase in experimentally induced granulomatous inflammation. Ann. N.Y. Acad. Sci. **278**:592–598.
225. **Perrin, P. J., and S. M. Phillips.** 1988. The molecular basis of granuloma formation in schistosomiasis. I. A T cell-derived suppressor effector factor. J. Immunol. **141**:1714–1719.
226. **Phillips, S. M., and D. G. Colley.** 1978. Immunologic aspects of host responses to schistosomiasis: resistance, immunopathology, and eosinophil involvement. Prog. Allergy **24**:49–182.
227. **Phillips, S. M., J. J. DiConza, J. A. Gold, and W. A. Reid.** 1977. Schistosomiasis in the congenitally athymic (nude) mouse. I. Thymic dependency of eosinophilia, granuloma formation, and host morbidity. J. Immunol. **118**:594–599.
228. **Phillips, S. M., and E. G. Fox.** 1984. Immunopathology of parasitic diseases: a clinical approach. Contemp. Top. Immunobiol. **12**:421–461.
229. **Phillips, S. M., and P. Lammie.** 1986. Immunopathology of granuloma formation and fibrosis in schistosomiasis. Parasitol. Today **2**:296–302.
230. **Phillips, T. M., and C. C. Draper.** 1975. Circulating immune complexes in schistosomiasis due to *Schistosoma mansoni*. Br. Med. J. **2**:476–477.
231. **Powell, M. R., and D. G. Colley.** 1987. Anti-idiotypic T lymphocyte responsiveness in murine schistosomiasis mansoni. Cell. Immunol. **104**:377–385.
232. **Queiroz, F. P., E. Brito, R. Martinelli, and H. Rocha.** 1973. Nephrotic syndrome in patients with *Schistosoma mansoni* infections. Am. J. Trop. Med. Hyg. **22**:622–628.
233. **Raia, S., S. Mies, and A. L. Macedo.** 1985. Portal hypertension in schistosomiasis. Clin. Gastroenterol. **14**:57–82.
234. **Raso, P., E. R. P. Pedroso, and J. Neves.** 1986. Patologia da forma aguda, toxemica, da esquitossomose mansoni. Rev. Soc. Bras. Med. Trop. **19**:45–55.
235. **Reboucas, G.** 1975. Clinical aspects of hepatosplenic schistosomiasis: a contrast with cirrhosis. Yale J. Biol. Med. **48**: 369–376.
236. **Reiner, N. E., R. Kamel, G. I. Higashi, A. El Naggar, M. Aguib, J. J. Ellner, and A. A. F. Mahmoud.** 1979. Concurrent responses of peripheral blood and splenic mononuclear cells to antigenic and mitogenic stimulation in human hepatosplenic schistosomiasis. J. Infect. Dis. **140**:162–168.
237. **Rhode, H., L. Vargas, E. Hahn, H. Kalbfleisch, M. Bruguera, and R. Timpl.** 1979. Radioimmunoassay for type III-procollagen-peptide and its application to human liver disease. Eur. J. Clin. Invest. **9**:451–459.
238. **Rocklin, R. E., A. P. Brown, K. S. Warren, R. P. Pelley, V. Houba, T. K. A. Siongok, J. Ouma, R. F. Sturrock, and A. E. Butterworth.** 1980. Factors that modify the cellular-immune response in patients infected by *Schistosoma mansoni*. J. Immunol. **125**:1916–1923.
239. **Rocklin, R. E., J. W. Tracy, and A. El Kholy.** 1981. Activation of antigen-specific suppressor cells in human schistosomiasis

mansoni by fractions of soluble egg antigens nonadherent to Con A sepharose. J. Immunol. **127**:2314–2318.
240. **Rojkind, M., M. A. Giambrone, and L. Biempica.** 1979. Collagen types in normal and cirrhotic liver. Gastroenterology **76**:710–719.
241. **Sadun, E. H., R. I. Anderson, and J. S. Williams.** 1962. The nature of fluorescent antibody reactions in infections and artificial immunizations with *Schistosoma mansoni*. Bull. W.H.O. **27**:151–159.
242. **Sadun, E. H., and R. W. Gore.** 1970. *Schistosoma mansoni* and *S. haematobium*. Homocytotropic reagin-like antibodies in infections of man and experimental animals. Exp. Parasitol. **28**:435–449.
243. **Sadun, E. H., M. J. Schoenbechler, and M. Bentz.** 1965. Multiple antibody response in *Schistosoma mansoni* infection: antigenic constituents in eggs, cercariae and adults (excretions and secretions) determined by flocculation reactions, cross absorption and double diffusion studies. Am. J. Trop. Med. Hyg. **14**:977–995.
244. **Salama, M. M. A., W. S. Aronstein, J. B. Weiss, and M. Strand.** 1984. Monoclonal antibody identification of protein antigens in the liver of mice infected with *Schistosoma mansoni*. Am. J. Trop. Med. Hyg. **33**:608–620.
245. **Santoro, F., P. J. Lachmann, A. Capron, and M. Capron.** 1979. Activation of complement by *Schistosoma mansoni* schistosomula: killing of parasites by the alternate pathway and requirement of IgG for classical pathway activation. J. Immunol. **123**:1551–1557.
246. **Santoro, F., A. Prata, C. N. Castro, and A. Capron.** 1980. Circulating antigens, immune complexes and C3d levels in human schistosomiasis: relationship with *Schistosoma mansoni* egg output. Clin. Exp. Immunol. **42**:219–225.
247. **Santoro, F., A. Prata, A. E. Silva, and A. Capron.** 1981. Correlation between circulating antigens detected by the radioimmunoprecipitation-polyethylene glycol assay (RIPEGA) and $C1_q$-binding immune complexes in human schistosomiasis. Am. J. Trop. Med. Hyg. **30**:1020–1025.
248. **Santoro, F. Y., D. Bout, D. Camus, and A. Capron.** 1977. Immune complexes in schistosomiasis: IV. C3, C4 and $C1_q$ characterization and correlation between C3 in serum and circulating IC levels. Rev. Inst. Trop. Sao Paulo **19**:39–42.
249. **Santoro, F. Y., Y. Carlier, R. Borojevic, D. Bout, P. Tachon, and A. Capron.** 1977. Parasite M antigen in milk from mothers infected with *Schistosoma mansoni* (preliminary report). Ann. Trop. Med. Parasitol. **71**:121–123.
250. **Seitz, H. M., B. J. Cottrell, and R. F. Sturrock.** 1987. A histological study of skin reactions of baboons to *Schistosoma mansoni* schistosomula. Trans. R. Soc. Trop. Med. Hyg. **81**:385–390.
251. **Sher, A., S. McIntyre, and F. von Lichtenberg.** 1977. *Schistosoma mansoni*: kinetics and class specificity of hypergammaglobulinemia induced during murine infection. Exp. Parasitol. **41**:415–422.
252. **Silva, L. C., T. Brito, M. E. Camargo, D. R. Boni, J. D. Lopes, and J. Gunji.** 1970. Kidney biopsy in hepatosplenic form of infection with *Schistosoma mansoni* in man. Bull. W.H.O. **42**:907–910.
253. **Siongok, T. K. A., A. A. F. Mahmoud, J. H. Ouma, K. S. Warren, A. S. Muller, A. K. Handa, and H. B. Houser.** 1976. Morbidity in schistosomiasis mansoni in relation to intensity of infection: study of a community in Machakos, Kenya. Am. J. Trop. Med. Hyg. **25**:273–284.
254. **Smith, M. D.** 1977. The ultrastructural development of the schistosome egg granuloma in mice. Parasitology **15**:119–123.
255. **Smithers, S. R., and M. J. Doenhoff.** 1982. Schistosomiasis, p. 527–607. *In* S. Cohen and K. S. Warren (ed.), Immunology of parasitic infections. Blackwell Scientific Publications, Ltd., Oxford.
256. **Sobh, M. A., F. E. Moustafa, F. El-Housseini, M. T. Basta, A. M. Deelder, and M. A. Ghoniem.** 1987. Schistosomal specific nephropathy leading to end-stage renal failure. Kidney Int. **31**:1006–1011.
257. **Stenger, R. J., K. S. Warren, and F. A. Johnson.** 1967. An ultrastructural study of hepatic granulomas and schistosome egg shells in murine hepatosplenic schistosomiasis mansoni. Exp. Mol. Pathol. **8**:116–132.
258. **Sternick, J. L., D. J. Schrier, and V. L. Moore.** 1983. Genetic control of BCG-induced granulomatous inflammation in mice. Exp. Lung Res. **5**:217–228.
259. **Stirewalt, M. A., and A. S. Evans.** 1955. Serologic reactions in *Schistosoma mansoni* infections. I. Cercaricidal, precipitation, agglutination and CHR phenomena. Exp. Parasitol. **4**:123–142.
260. **Takahashi, S., M. A. Dunn, and S. Seifter.** 1980. Liver collagenase in murine schistosomiasis. Gastroenterology **78**:1425–1431.
261. **Theofilopoulos, A. N., and F. J. Dixon.** 1980. Immune complexes in human diseases. A review. Am. J. Pathol. **100**: 531–594.
262. **Todd, C. W., R. W. Goodgame, and D. G. Colley.** 1979. Immune responses during human schistosomiasis mansoni. V. Suppression of schistosome antigen-specific lymphocyte blastogenesis by adherent/phagocytic cells. J. Immunol. **122**:1440–1446.
263. **Todd, C. W., R. W. Goodgame, and D. G. Colley.** 1980. Immune responses during human schistosomiasis mansoni. VII. Further analysis of the interactions between patient sera and lymphocytes during *in vitro* blastogenesis to schistosome antigen preparations. Am. J. Trop. Med. Hyg. **29**:875–881.
264. **Truden, J. L., and D. L. Boros.** 1985. Collagenase, elastase and nonspecific protease production by vigorous or immunomodulated liver granulomas and granuloma macrophages/eosinophils of *S. mansoni* infected mice. Am. J. Pathol. **121**:158–167.
265. **Truden, J. L., and D. L. Boros.** 1988. Detection of α_2-macroglobulin, α_1-protease inhibitor, and neutral protease-antiprotease complexes within liver granulomas of *Schistosoma mansoni*-infected mice. Am. J. Pathol. **130**:281–288.
266. **Tweardy, D. J., G. S. Osman, A. El Kholy, and J. J. Ellner.** 1983. Abnormalities of immunosuppression in patients with hepatosplenic schistosomiasis mansoni. Trans. Assoc. Am. Physicians **96**:393–400.
267. **Tweardy, D. J., G. S. Osman, A. El Kholy, and J. J. Ellner.** 1987. Failure of immunosuppressive mechanism in human *Schistosoma mansoni* infection with hepatosplenomegaly. J. Clin. Microbiol. **25**:768–773.
268. **Van Helden, H. P. T., W. J. Terpstra, B. M. Okot-Kotber, and V. M. Eyakuze.** 1975. Are there stage-specific characteristic immunofluorescence patterns in schistosomiasis? Trans. R. Soc. Trop. Med. Hyg. **69**:309–311.
269. **Van Marck, E. A. E., A. M. Deelder, and P. L. J. Gigase.** 1977. Effect of portal vein ligation on immune glomerular deposits in *Schistosoma mansoni* infected mice. Br. J. Exp. Pathol. **58**: 412–417.
270. **Van Marck, E. A. E., A. M. Deelder, and P. L. J. Gigase.** 1981. *Schistosoma mansoni*: anodic polysaccharide antigen in glomerular immune deposits of mice with unisexual infection. Exp. Parasitol. **52**:62–68.
271. **von Lichtenberg, F.** 1962. Host response to eggs of *Schistosoma mansoni*. I. granuloma formation in the unsensitized laboratory mouse. Am. J. Pathol. **41**:711–731.
272. **von Lichtenberg, F.** 1964. Studies of granuloma formation. III. Antigen sequestration and destruction in the schistosome pseudotubercle. Am. J. Pathol. **45**:75–93.
273. **von Lichtenberg, F., M. P. Bawden, and S. M. Shealy.** 1974. Origin of circulating antigen from the schistosome gut. An immunofluorescence study. Am. J. Trop. Med. Hyg. **23**:1089–1091.
274. **von Lichtenberg, F., A. Sher, N. Gibbons, and B. L. Doughty.** 1976. Eosinophil enriched inflammatory response to schistosomula in the skin of mice immune to *Schistosoma mansoni*. Am. J. Pathol. **84**:479–500.
275. **von Lichtenberg, F., T. M. Smith, H. L. Lucia, and B. L. Doughty.** 1971. New model for schistosome granuloma formation using a soluble egg antigen and bentonite particles. Nature (London) **229**:199–200.
276. **Warren, K. S.** 1963. The contribution of worm burden and host response to the development of hepato-splenic schistosomiasis

mansoni in mice. Am. J. Trop. Med. Hyg. **12**:34–39.
277. **Warren, K. S.** 1973. The pathology of schistosome infections. Helminth. Abstr. **42**:592–633.
278. **Warren, K. S.** 1973. Regulation of the prevalence and intensity of schistosomiasis in man: immunology or ecology? J. Infect. Dis. **127**:595–609.
279. **Warren, K. S.** 1982. The effect of immunopathogenesis of schistosomiasis: *in vivo* models. Immunol. Rev. **61**:189–213.
280. **Warren, K. S.** 1984. The kinetics of hepatosplenic schistosomiasis. Semin. Liver Dis. **4**:293–300.
281. **Warren, K. S., and E. O. Domingo.** 1970. Granuloma formation around *Schistosoma mansoni*, *S. haematobium* and *S. japonicum* eggs. Size and rate of development, cellular composition, cross sensitivity and rate of egg destruction. Am. J. Trop. Med. Hyg. **19**:292–304.
282. **Warren, K. S., E. O. Domingo, and R. B. T. Cowan.** 1967. Granuloma formation around schistosome eggs as a manifestation of delayed hypersensitivity. Am. J. Pathol. **51**:735–756.
283. **Weinstock, J. V., and D. L. Boros.** 1981. Heterogeneity of the granulomatous response in the liver, colon, ileum and ileal Peyer's patches to schistosome eggs in murine schistosomiasis mansoni. J. Immunol. **127**:1906–1909.
284. **Weinstock, J. V., and D. L. Boros.** 1983. Organ-dependent differences in composition and function observed in hepatic and intestinal granulomas isolated from mice with schistosomiasis mansoni. J. Immunol. **130**:418–422.
285. **Weinstock, J. V., S. W. Chensue, and D. L. Boros.** 1983. Modulation of granulomatous hypersensitivity. V. Participation of histamine receptor positive and negative lymphocytes in the granulomatous response of *Schistosoma mansoni*-infected mice. J. Immunol. **130**:423–427.
286. **Weinstock, J. V., M. N. Ehrinpreis, D. L. Boros, and J. B. Gee.** 1981. Effect of SQ 14225, an inhibitor of angiotensin I-converting enzyme, on the granulomatous responses to *Schistosoma mansoni* eggs in mice. J. Clin. Invest. **67**:931–936.
287. **Weiss, J. B., W. S. Aronstein, and M. Strand.** 1987. *Schistosoma mansoni*: stimulation of artificial granuloma formation *in vivo* by carbohydrate determinants. Exp. Parasitol. **64**:228–236.
288. **Wellhausen, S. R., and D. L. Boros.** 1981. Comparison of Fc, C3 receptors and Ia antigens on the inflammatory macrophage isolated from vigorous or immunomodulated liver granulomas of schistosome-infected mice. RES J. Reticuloendothel. Soc. **30**:191–203.
289. **Wolfson, R. L., S. E. Maddison, and I. G. Kagan.** 1972. Migration inhibition of peripheral leukocytes in human schistosomiasis. J. Immunol. **109**:123–128.
290. **Wu, C. H., M. A. Giambrone, D. J. Howard, M. Rojkind, and G. Y. Wu.** 1982. The nature of the collagen in hepatic fibrosis in advanced murine schistosomiasis. Hepatology **2**:366–371.
291. **Wyler, D. J.** 1983. Cytopathology of parasitic disease. Ciba Found. Symp. **99**:190–206.
292. **Wyler, D. J., H. P. Ehrlich, A. E. Postlethwaite, R. Raghow, and M. Murphy.** 1987. Fibroblast stimulation in schistosomiasis. VII. Egg granulomas secrete factors that stimulate collagen and fibronectin synthesis. J. Immunol. **138**:1581–1586.
293. **Wyler, D. J., P. J. Lammie, A. I. Michael, L. J. Rosenwasser, and S. M. Phillips.** 1987. *In vitro* and *in vivo* evidence that autoimmune reactivity to collagen develops spontaneously in *Schistosoma mansoni*-infected mice. Clin. Immunol. Immunopathol. **44**:140–148.
294. **Wyler, D. J., and A. E. Postlethwaite.** 1983. Fibroblast stimulation in schistosomiasis. IV. Isolated egg granulomas elaborate a fibroblast chemoattractant *in vivo*. J. Immunol. **130**: 1371–1375.
295. **Wyler, D. J., and L. J. Rosenwasser.** 1982. Fibroblast stimulation in schistosomiasis. II. Functional and biochemical characteristics of egg granuloma-derived fibroblast-stimulating factor. J. Immunol. **129**:1706–1710.
296. **Wyler, D. J., M. J. Stadecker, C. A. Dinarello, and J. F. O'Dea.** 1984. Fibroblast stimulation in schistosomiasis. V. Egg granuloma macrophages spontaneously secret a fibroblast stimulating factor. J. Immunol. **132**:1142–1148.
297. **Wyler, D. J., and J. W. Tracy.** 1982. Direct and indirect effects of soluble extracts of *Schistosoma mansoni* eggs on fibroblast proliferation in vitro. Infect. Immun. **38**:103–108.
298. **Wyler, D. J., S. M. Wahl, A. W. Cheever, and L. M. Wahl.** 1981. Fibroblast stimulation in schistosomiasis. I. Stimulation *in vitro* of fibroblasts by soluble products of egg granulomas. J. Infect. Dis. **144**:254–262.
299. **Yamamoto, K., and M. Kakinuma.** 1978. Genetic control of granuloma response to oil-associated BCG cell wall vaccine in mice. Microbiol. Immunol. **22**:335–348.
300. **Zuidema, P. J.** 1981. The Katayama syndrome: an outbreak in Dutch tourists to the Omo National Park, Ethiopia. Trop. Geogr. Med. **33**:30–35.