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EDITORIAL REVIEW

Schistosomal glomerulopathies

Schistosomes are blood flukes that parasitize the venous system of a wide range of animals including birds, cattle and primates. There are seven human pathogenic species of which the most prevalent are *S. hematobium*, found mainly in Africa, *S. mansoni* found in Latin America as well as Africa, and *S. japonicum*, endemic in China and the Far East. According to WHO estimates, some 700 million inhabitants of five continents are at risk, infection being documented in 300 millions [1].

Pathogenicity

The pathogenicity of *Schistosoma hematobium* has been recognized many centuries before discovery of the parasite itself by Theodore Bilharz in 1852 [2]. Thus, several ancient Egyptian papyri referred to a syndrome of hematuria ascribed to a worm acquired through contact with Nile water, and described as being resistant to a variety of herbal treatments [3].

That this was indeed *S. hematobium* is suggested by the discovery of its characteristic ova in the bladders of well-preserved Egyptian mummies by appropriate rehydration techniques [4]. Today, oviposition in the lower urinary tract remains as the main pathogenic feature of *S. hematobium*.

When *S. mansoni* and *S. japonicum* were discovered, their pathogenicity was still ascribed to oviposition, mainly in the intestine, mesentery and hepatic portal tracts. All schistosomal lesions in the lungs, brain, spinal cord, eye and skin are also caused by metastatic oviposition in these sites.

The classical tissue response to deposited ova is granulomatous [5]. As a consequence of the release of "soluble egg antigens" (SEA) [6, 7] through micropores in the egg shell, a cascade of cellular recruitment, activation and release of mediators ends up with the formation of granulomata [8]. These eventually heal by fibrosis, often associated with calcification, which are the major hallmarks of chronic morbidity from schistosomiasis [9].

The kidney and urinary tract in schistosomiasis

The urogenital system is the primary target of *S. hematobium* and occasionally *S. mansoni* infestation. The main initial lesions are found in the urinary bladder, in the form of "pseudotubercles," polyps and ulcers. As these lesions heal, they lead to a wide spectrum of diffuse bladder pathology including "sandy patches," chronic cystitis, bladder calcification, "cystitis cystica" and others [10]. There is evidence that some of these lesions may predispose to malignancy, villous squamous cell carcinoma of the bladder being classically linked with schistosomiasis [11].

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Concomitant lower ureteric involvement with similar chronic inflammatory lesions often leads to obstruction, and less frequently to vesico-ureteric reflux. Although the ureter usually succeeds in overcoming the obstruction by adequate dilatation and hypertrophy of its muscle wall, the kidneys are eventually prone to suffer the effects of back pressure and ascending infection. Secondary stone formation further complicates the picture, which often ends up with chronic renal failure [12].

Morbidity from urinary schistosomiasis is widely variable. While a *British Medical Journal* editorial described it as being a "crippling disease with a tremendous economic loss" [13], a contemporary leading authority in epidemiological research emphasized "the lack of significant interference of the parasitosis with general health" [14]! It is now realized that geographical differences are the reason for this discrepancy. Thus, while clinically overt lower urinary tract lesions are reported to be as few as 2% in Nigeria [15], 10% in Liberia [16] and 14% in Zanzibar [17], they are much more common in Egypt (50%) [18] and Tanzania (52%) [19].

Upper urinary tract pathology, assessed in different populations by ultrasonography [20], intravenous urography or changes in renal function [21] have also shown a wide variation from 9.7% in adult infested subjects in the Niger [22] to 48% in infested school children in the Cameroon [23]. Ecological factors responsible for these variations may include differences in parasitic strains [24], intensity of infestation [25–27], and host susceptibility [28].

Schistosomal glomerulopathy

It was only over the past three decades that attention was drawn to the glomerular lesions associated with schistosomiasis, being unrelated to lower urinary tract involvement. Indeed, the earlier reports came out from Brazil, where only *S. mansoni* exists, in patients with hepatosplenic schistosomiasis [29–31].

The initial clinical observations were adequately supported by a large volume of experimental work, showing glomerular lesions and/or mesangial immune complex deposits in mice [32, 33], hamsters [34–36], rabbits [37], baboons [38], monkeys [39, 40] and chimpanzees [41] exposed to experimental infection. Further clinical reports from Brazil [42–44], Puerto Rico [45], Egypt [46–49], the Sudan [50], Somalia [51], Nigeria [52], Madagascar [53, 54], Arabia [55], Malaysia [56] and others [57], confirmed the identity of schistosomal glomerulopathy as a distinct disease entity. The hallmark of the syndrome is its independence from any oviposition, being mediated by the immune response to circulating schistosomal adult worm antigens. For the first time after many centuries dealing with this parasite, the medical profession then became aware that morbidity from schistosomiasis could be pathogenetically dissociated from granuloma formation.

Epidemiologic impact

Like with other chronic complications of schistosomiasis, the incidence of glomerulopathy seems to be geographically variable. Unfortunately, there are no reliable statistical data, most series being reported from reference centers rather than field surveys, with only a few exceptions [47, 58]. Furthermore, it is becoming increasingly clear that overt renal disease in schistosomiasis is indeed the tip of an iceberg of much more widely prevalent subclinical glomerular involvement, which makes it even more difficult to estimate the true incidence of glomerular pathology.

In a series of 162 subjects reported by Lehmen et al [58] from Brazil, those with intestinal schistosomiasis had higher quantities of protein in their urines compared with non-infested subjects. However, only two had overt proteinuria and an abnormal urinary sediment. In a similar group of 240 Egyptian patients, Sobh et al [59] reported a 20% incidence of asymptomatic proteinuria among *S. mansoni*-infected subjects. Renal biopsies obtained from 15 subjects showed light microscopic and immunofluorescence appearances compatible with classical schistosomal glomerulopathy.

The same issue was addressed in a large field study on *S. hematobium*-infested subjects by Ezzat et al [47], who reported Albustix-moderate proteinuria (0.3 to 1 g/liter) in 39.8 and 54.5%, and "heavy" proteinuria (>1 g/liter) in 1.9 and 4.8% of the inhabitants of two Upper Egyptian villages using a perennial irrigation system, with a high prevalence of *S. hematobium* infestation. In a control village using a continuous irrigation system with a low prevalence of *S. hematobium* infestation, only one subject had significant proteinuria. Although the renal biopsy findings in some of these cases reported several years later [60] were compatible with the diagnosis of schistosomal glomerulopathy, lower UT pathology and its upper UT consequences were not excluded as a potential source of proteinuria. Concomitant *S. mansoni* infestation was ruled out only on epidemiological basis, although many patients did have clinically detectable hepatosplenic involvement, which was presumably attributed to *S. hematobium* [61]. In a subsequent post-mortem study of 268 subjects from the same country [62], there was no correlation between glomerular abnormalities and the presence or intensity of *S. hematobium* infestation. However, in another study on 16 asymptomatic *S. hematobium*-infested subjects, attending a University outpatient clinic, Soliman et al [63] found glomerular changes by light microscopy in 18.6% of the renal biopsies. IgG deposits were detected in 68.8%, IgM in 50% and schistosomal antigens in 25% of the cases. It was concluded that *S. hematobium* glomerulopathy may be regarded as a pathological finding without corresponding clinical disease.

Even more negative conclusions were made regarding *S. japonicum*. In a recent study on 244 outpatients infested with this species, Watt et al [64] found no association between schistosomiasis and renal disease. Out of 100 hospitalized patients reported by the same authors, three had significant nephropathy, but this prevalence was not different from that in a similar number of matching, non-infested controls. Schistosomal antigen could not be detected in the only biopsy obtained from the schistosomal group.

The incidence of occult glomerular pathology among patients with *S. mansoni* hepatosplenic disease was variably reported from 12 to 40%. In a post-mortem study Andrade, Andrade and Sadigursky [42] found a wide range of glomerular changes in 12% of subjects with hepatosplenic schistosomiasis who died of different causes. In a subsequent prospective study, Rocha et al [44] found glomerular changes in six out of 15 renal biopsies obtained during surgical splenectomy from a group of patients who had no clinical evidence of renal disease. In a prospective study of 69 patients with liver biopsy-confirmed hepatosplenic schistosomiasis, Barsoum et al [65] found microalbuminuria in 15 asymptomatic patients (21.7%), of whom three had distinct glomerular changes in renal biopsy.

The incidence of overt glomerular disease in schistosomiasis is also difficult to estimate because of four main reasons: (1) the general unawareness of the identity of schistosomal nephropathy as a clinical syndrome; (2) the lack of adequate diagnostic tools in the vast majority of areas where infestation is endemic; (3) in the absence of pathognomonic diagnostic criteria (*vide infra*), the question of coincidence is often raised; and (4) in *S. hematobium* infestation, the clinical, laboratory and even some histopathological features of glomerular disease can mimic those associated with obstructive and/or reflux nephropathy [66]. Accordingly, most of the reported series do not address the all important issue of epidemiology. It appears, though, that there is a remarkable difference in the clinical expression of schistosomal glomerulopathy in different geographical areas. Several studies have specifically denied, on statistical grounds, the importance of schistosomal infestation in altering the prevalence or patterns of glomerular disease. These come from countries like Zimbabwe [67], The Sudan [68, 69] and The Phillipines [64]. Others, on the other hand, have incriminated *S. hematobium* in the pathogenesis of the nephrotic syndrome in up to 42.5% of patients in an endemic area [47]. In their prospective study in Brazil, Rocha et al [44] found positive evidence of overt renal disease in 15% of patients with *S. mansoni* hepatosplenic disease. This matches with an Egyptian series that reported an incidence of 15.9% [65].

Several questions remain open in quite a few developing countries, where schistosomiasis is highly endemic. Has this

Fig. 1. *Principal histopathological patterns in schistosomal glomerulopathy.* **A.** Class I. Axial mesangioproliferative glomerulonephritis in a patient with hepatosplenic schistosomiasis and microalbuminuria. (Hematoxylin and Eosin stain). **B.** Class II. Exudative glomerulonephritis in a patient with hepatosplenic schistosomiasis and chronic salmonellosis. (Hematoxylin and Eosin stain). **C.** Class III-A. Early mesangiocapillary (membranoproliferative) glomerulonephritis in a nephrotic patient with hepatosplenic schistosomiasis. (Hematoxylin and Eosin stain). **D.** Class III-B. Type III mesangiocapillary glomerulonephritis in a nephrotic patient with mixed hepatosplenic schistosomiasis and virus B chronic active hepatitis (Hematoxylin and Eosin stain). **E.** Class III-A. Mesangial IgA deposits, displayed by immunofluorescence, in a renal biopsy showing advanced MCGN from a patient with hepatosplenic schistosomiasis, nephrotic syndrome, moderate hypertension and impaired renal function. **F.** Class III-B. Epi-membranous IgG deposits in the same biopsy shown in Fig. 1d. **G.** Class IV. Segmental glomerulosclerosis in a nephrotic, hypertensive patient with hepatosplenic schistosomiasis. (Masson trichrome stain). **H.** Class V. Early amyloid deposits amid mesangial cell proliferation in a nephrotic patient with mixed *S. mansoni* and *S. hematobium* infestation. (Congo red stain and polarized light examination).

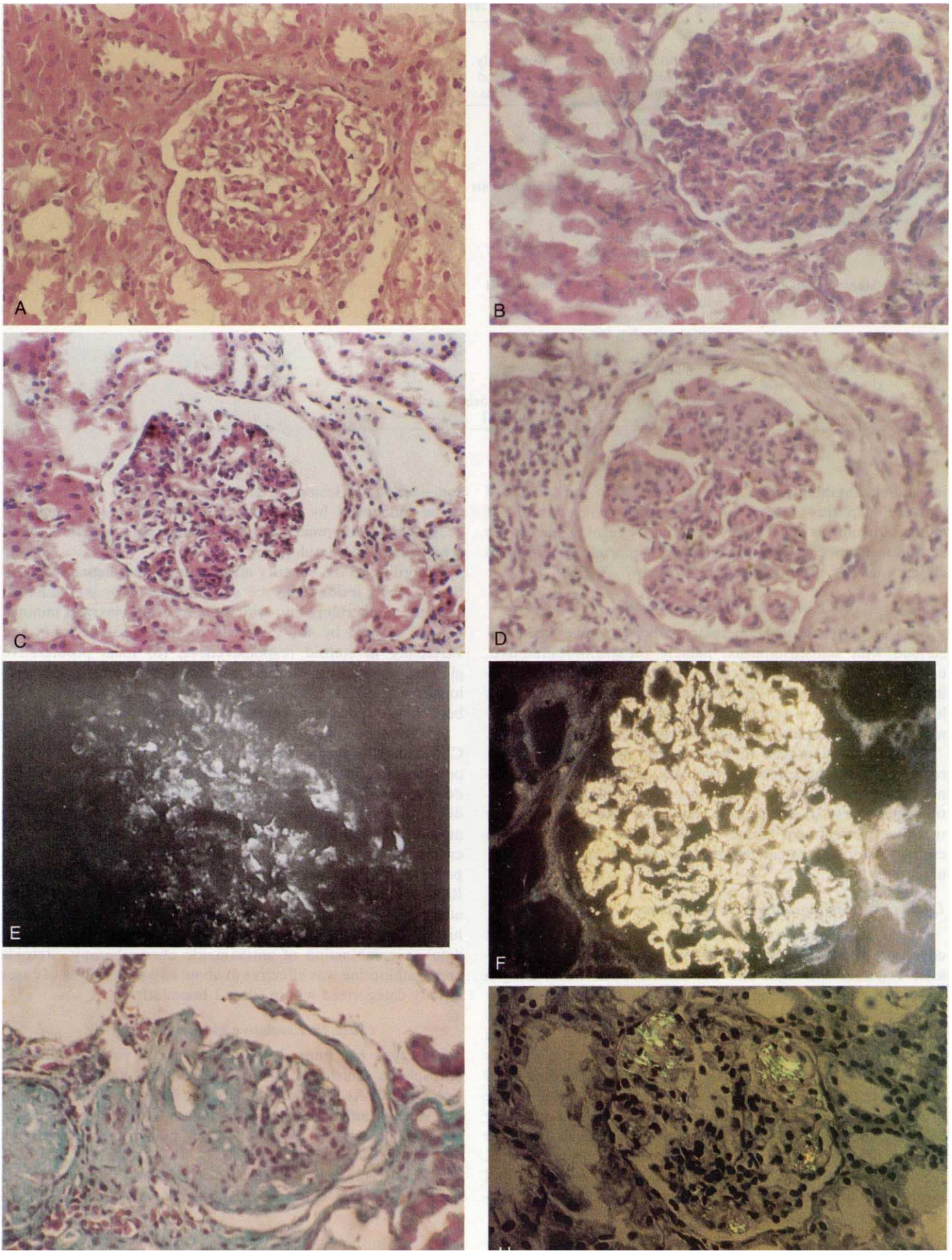
A
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Table 1. Principal clinicopathological features of schistosomal glomerulopathy

Class	Histopathological pattern	Glomerular deposits detected by immunofluorescence	Commonly associated infections	Hepatic fibrosis	Features of renal involvement				Response to treatment
					Asymptomatic proteinuria	Nephrotic syndrome	Hypertension	Progression to ESRD	
I	Mesangioproliferative a) "Minimal lesion" b) Focal c) Diffuse	Mesangial: IgM, C_3, Schistosomal gut antigens	–	±	+++	+	±	?	± (?)
II	Exudative	Endocapillary: C_3, Salmonella antigens	Salmonellosis	+	–	+++	–	?	+++
III	A. Mesangiocapillary (type I)	Mesangial: IgG, C_3, Schistosomal gut antigens (early), IgA (late)	–	+++	+	++	++	++	–
	B. Mesangiocapillary (type III)	Mesangial & subepithelial: IgG, C_3, Schistosomal gut antigens (early), IgA (late)	Hepatitis B	+++	+	+++	+	++	–
IV	Focal & segmental glomerulosclerosis	Mesangial: IgG, IgM, IgA	–	+++	+	+++	+++	+++	–
V	Amyloidosis	Mesangial: IgG	?Salmonellosis ?*E.coli* UTI	±	+	+++	±	+++	–

infestation anything to do with the very high prevalence of glomerulonephritis? Does it modify the supervening patterns of glomerulonephritis accordingly? Is it partly responsible for the steroid resistance of "minimal change" nephrotic syndrome in children, as has been reported in Africa [67, 70–73]?

Histopathological classification

Several patterns of glomerular pathology have been described with schistosomiasis, namely mesangioproliferative, exudative, mesangiocapillary (membranoproliferative), sclerosing and amyloid (Fig. 1). Transformation in between these types has been reported in several studies, though controlled confirmatory and quantitative longitudinal studies are not available.

There is good reason to believe that these patterns may reflect certain geographical factors and, indeed, some pathogenetic differences. They certainly modify the clinical presentation and course of the disease, and may also determine the response to treatment (Table 1). This is the rationale for the current histopathological classification of schistosomal glomerulopathies [74].

Class I: Mesangioproliferative schistosomal glomerulopathies

Simple mesangial proliferation (Fig. 1a) is, by far, the most common pattern of glomerular lesions ascribed to schistosomiasis. Together with IgM and C3, schistosomal worm antigen mesangial deposits are most often encountered in this Class.

Class I lesions are the most common and earliest of schistosoma-associated lesions in experimental animals [34, 39]. They have been described in 26.7 to 60% of asymptomatic patients [44, 59, 65] and in 10 to 41.2% of those with established renal disease [44, 48, 50, 75]. They have also been reported as the principal lesions in grafts where schistosomal glomerulopathy recurred shortly after transplantation [76]. There is no agent species predilection to this Class, being reported with *S. hematobium* [60], *S. japonicum* [56], as well as *S. mansoni* [77] infestations. Its proportional contribution among other schistosoma-associated lesions in experimental animals does not seem to be influenced by host species, nor are there prominent geographical differences in its incidence among patients with schistosomal glomerulopathy.

According to the severity and extent of mesangial proliferation, Class I lesions may be subclassified into: (a) "minimal change" glomerulopathy, which differs from classical minimal change disease by the presence of mesangial deposits and variability in steroid responsiveness; (b) focal proliferative glomerulopathy; and (c) diffuse mesangioproliferative glomerulopathy. There is good reason to suggest that the differences between these lesions are only quantitative.

As mentioned earlier, the majority of patients with features of Class I schistosomal glomerulopathy are asymptomatic [44, 59], or have occult urinary abnormalities [65]. Overt proteinuria develops in an as yet undefined proportion of those patients. In different series of patients, about one-third diagnosed with mesangioproliferative lesions also have overt proteinuria, occasionally amounting to the nephrotic syndrome [44, 65]. Hypertension is unusual and renal function is seldom impaired. Response to therapy is difficult to assess, since most series addressing this issue do not break down the cases according to histopathological classes. In our own experience (unpublished data), a combination of antiparasitic chemotherapy, steroids and azathioprine was effective in about two out of three of cases strictly categorized within Class I boundaries.

Class II: Exudative glomerulonephritis

This type has been described mainly in patients with hepatosplenic schistosomiasis complicated by Salmonella infection [78–80]. As the name implies, the basic glomerular pathology is acute inflammatory, with many neutrophils, monocytes, blood platelets and a lot of fibrin amidst the proliferating endocapillary cells (Fig. 1b) [78].

The interaction between schistosomes and different salmonella strains had been described *in vitro* [81], as well as in

experimental animals [82], since the early seventies. Attention to their clinical association was initially drawn in patients with urinary schistosomiasis who used to develop recurrent episodes of acute cystitis, and often pyelonephritis, attributed to concomitant Salmonella infection [83]. Although the acute symptoms were readily controlled by appropriate antibiotic therapy, bacteriological cure was very difficult to achieve in the majority of those patients, who remained as "typhoid urinary carriers" [83] constituting an important public health problem in endemic areas [84].

Later reports highlighted the same phenomenon in patients with hepatointestinal schistosomiasis, who often develop Salmonella-associated episodes of prolonged intermittent pyrexia, abdominal pains frequently associated with bloody diarrhea, tender splenomegaly, vasculitic skin eruption, hair changes and rapidly progressive secondary anemia [78, 79, 85].

It is mostly in these patients with hepatointestinal schistosomiasis [78, 80, 86], and occasionally in those with urinary schistosomiasis [87] that concomitant salmonellosis was reported to induce glomerular injury. The latter ushers in by a rapidly developing nephrotic syndrome, usually without hypertension or significant hyperlipidemia [78]. There is a remarkable hyperglobulinemia [48] which is attributed to the combined effects of polyclonal immunoglobulin response to double chronic infections, inflammatory tissue damage, and hypoalbuminemia. Serum C3 has been consistently reduced in all reported cases. Serum C4, on the other hand, is usually normal or even elevated in conjunction with other acute phase reactants [78, 86]. False positive serology for rheumatoid, syphilis and lupus has been described in a variable proportion of cases, which is attributed to the polyclonal B-cell stimulation.

The causative organisms can be isolated from the blood or urine in some 80% of cases. For a conclusive bacteriological confirmation, however, a bone marrow culture is occasionally needed. Serological diagnosis by the well-acknowledged Widal test is unreliable, owing to its low sensitivity and specificity in chronic Salmonella infections [48].

The Salmonella strains involved differ according to geographical location. While *S. paratyphi A* [86, 78] and *S. typhi* [79] are the most common in African reports, *S. typhimurium* [88] and several other strains are incriminated in Brazil [89].

Several mechanisms have been suggested to explain the interaction between schistosomiasis and salmonellosis. In the first place, it is noteworthy that environmental and sociocultural factors play important roles in exposing the same individual to both infections. The chronic immunosuppressive status supervening in patients with chronic schistosomiasis [90], particularly those with hepatic fibrosis [91], may interfere, nonspecifically, with the host's defense against bacterial infection. Whether there is an added specific defect that selects an anti-Salmonella B-cell clone is unknown.

Perhaps the most impressive mechanism is the presence of Salmonella receptors in the tissues of adult schistosomes [92]. Once attached, the bacteria seem to share the parasite's immunological advantage, thereby escaping recognition by the host's antigen-presenting cells. This is achieved by hiding under a cover of the host's MHC antigens and H blood group substance, which impregnate the parasite's tegument [93, 94].

Salmonella endotoxin is one of the classical inducers of innate complement activation via the alternative pathway. The consistent lowering of the serum level of C3, associated with normal C4 suggests that this process indeed takes place *in vivo*. The confluent C3 glomerular deposits supervening in this class of schistosomal glomerulopathy further supports this concept, and provides a convincing pathogenetic explanation for the exudative nature of the glomerular pathology. That Salmonella endotoxins are actually involved in this process has been confirmed by immunofluorescence [80] among the plethora of glomerular deposits characteristic of this syndrome.

Prognosis with adequate treatment is usually good, without any appreciable loss of renal function. Although the constitutional manifestations of salmonellosis as well as the acute glomerular injury can be reversed by antibiotic therapy [79], the disease tends to recur so long as the schistosomes remain alive [95]. It is therefore recommended to aim at a radical cure by combining anti-schistosomal treatment with ampicillin or amoxacillin and cotrimoxazol [78].

Class III: Mesangiocapillary (membranoproliferative) glomerulonephritis (MCGN)

The prevalence of this pattern among asymptomatic patients with *S. mansoni* hepatointestinal disease is low, varying between 6.7 and 20% [44, 65], compared with up to 80% in those with overt renal disease. MCGN was the predominant pattern of glomerular pathology in a number of case reports from different parts of the world [45, 53, 54, 96]. It was also reported as one of the 'types' of glomerular disease associated with *S. hematobium* glomerulopathy [60]. Its proportional contribution in the histopathological profile of uncomplicated schistosomal glomerulopathy seems to yield in favor of focal segmental sclerosis and amyloidosis in certain African populations [50, 75]. This tendency conforms with the general pattern of glomerular diseases in Africa [70–73].

According to light microscopic appearances, the lesions may be subclassified into two patterns: (a) those of type I MCGN (Fig. 1c), characterized by mesangial cell proliferation, matrix expansion (often described as fibrillar [77]), and interposition, reported in 5 to 75% of clinically overt cases; and (b) those conforming with type III MCGN (Fig 1d,f), seen in less than 10% of our cases, with features of membranous nephropathy superimposed on the conventional mesangiocapillary pattern. The extent of mesangial cellular proliferation and matrix expansion is widely variable, which is similar to experimental observations in mice (*vide infra*).

It is uncertain whether the "membranous nephropathy," which has a reported prevalence of 5 to 23.5% in different studies, belongs to this subclass, since a detailed histological description is seldom given. Evidence that schistosomiasis is directly incriminated in the pathogenesis of "pure" membranous nephropathy is indeed very soft, and unlike other histopathological patterns, still lacks convincing experimental support.

In both subclasses of schistosoma-associated MCGN, IgG and C3 are predominently found in the glomerular deposits. IgM and schistosomal antigens are less often seen. IgA is usually associated with late and/or severe lesions (Fig. 1e) [97]. The pattern of glomerular deposition, as seen by immunofluorescence (Fig. 1e,f) and electron microscopy, helps to distinguish the two subclasses, which are essentially mesangial and

subendothelial in subclass-A and also extramembranous in subclass-B.

The usual clinical presentation is the nephrotic syndrome, more gross in subclass-B. Hypertension is encountered in 40 to 50% of all cases [44, 48], but is more frequently found in subclass-A. Clinical and/or ultrasonographic evidence of hepatosplenic schistosomiasis was reported in almost all cases with this pattern of schistosomal glomerulopathy. This observation has been so constant that most students in the area regard hepatic fibrosis as an essential prerequisite for the development of overt schistosomal glomerulopathy.

The relation of subclass-B to the hepatitis B virus is intriguing. On one hand, there are those well-defined membranous lesions often associated with mesangial proliferation and immune complex deposition described with virus B infection in Eastern Europe [98], Japan [99] and Southern Africa [100]. On the other hand, there is also a strong association between the hepatitus virus B infection and hepatosplenic schistosomiasis [101, 102], in many patients leading to chronic active hepatitis [103], mainly attributed to increased host exposure and diminished resistance [91]. It is in those patients that class III-B lesions are usually encountered (unpublished data), which suggests that viral hepatitis may "compound" the mesangial lesions of schistosomiasis by adding the membranous element. However, the available data are, as yet, too limited to confirm this speculation.

The clinical course of Class III schistosomal glomerulopathy is often progressive to global sclerosis [49, 104] without adequate response to treatment, particularly in late cases [105–109].

Class IV: Focal and segmental sclerosis (FSGS)

The prevalence of FSGS as the initial renal lesion among patients with schistosomal glomerulopathy varies in different series from 11.2 to 38% [43, 51, 75].

Its identity as one of the patterns of schistosomal glomerulopathy is supported by experimental models in hamsters [34] and baboons [110, 111].

The glomerular lesions cannot be distinguished from those with idiopathic FSGS (Fig. 1g). Focal mesangial cell proliferation is fairly common, and schistosomal antigens have been occasionally detected by immunofluorescence. There is a fairly high prevalence of IgA deposits in schistosomal cases [97], an observation that conforms with experimental findings [112]. Although these deposits may be innocent bystanders related to the associated hepatic fibrosis [113, 114], their pathogenetic potential [115] should not be overlooked (*vide infra*).

There are no specific clinical features that distinguish this class of schistosomal glomerulopathy from others apart from the worse prognosis. This may be partly attributed to the higher incidence of hypertension and more profound proteinuria (unpublished data).

Class V: Amyloidosis

The prevalence of amyloidosis (Fig. 1h) among other glomerular lesions varies from 16.7 to 39% in different series [50, 51, 116] with an apparently higher frequency in African patients. Its relationship with schistosomiasis is confirmed by several experimental models including mice [117] and Syrian hamsters infected with *S. hematobium* [36], or *S. mansoni* [35] and *S. japonicum*-infected rabbits [118].

Table 2. Principal pathogenetic factors in schistosomal glomerulopathy

1. Schistosomal antigens
2. Autoimmunity
3. The "liver effect"
Porto-caval shunts
Impaired macrophage function
IgA deposition
4. Host susceptibility

Schistosoma-associated amyloidosis is not species-dependent. It has been noticed with almost equal frequency among patients with *S. mansoni* and *S. hematobium* infestations. Hepatic fibrosis does not seem to influence the development of amyloidosis. In our own series, 20% of patients had evidence of recurrent salmonellosis and 30% had persistent *E. coli* urinary tract infection. The significance of these infections in the pathogenesis of amyloidosis is uncertain (*vide infra*).

Patients with schistosoma-associated amyloidosis can not be clinically distinguished from those with other forms of schistosomal glomerulopathy. Nephrotic syndrome is the usual presentation. Neither hypertension nor hypotension have been observed with any higher frequency. Extra-renal amyloid deposits in the liver and spleen have also been occasionally described. Whenever reported, the principal fibrillar material was AA protein [116].

Prognosis is poor. Earlier impressions of favorable response to anti-schistosomal treatment [119] could not be confirmed by repeat biopsy in longitudinal studies [116].

Pathogenesis

There is convincing evidence that the initial glomerular injury in schistosomal glomerulopathy is mediated by specific parasitic antigens (Table 2). Although soluble egg [38] and tegument [120] antigens have been detected in certain studies, worm antigens have been incriminated in the vast majority. These have been detected as circulating antigens in infested patients [121–124] as well as in experimentally infected animals [125–127]. Specific antibodies of all major immunoglobulin classes have also been detected in the sera of infested patients [128].

Although schistosomal worm antigens have occasionally been detected before any immunoglobulins in the glomeruli of experimental animals, they are usually found amid several other glomerular deposits, comprising all the major immunoglobulin classes and several complement components. These observations were made by *in situ* immunofluorescence [53, 75, 129–131], as well as by indirect immunofluorescence and countercurrent electrophoresis of kidney eluates obtained from autopsy and renal biopsy material from patients with schistosomal glomerulopathy [60, 120].

Antigenic differences between different schistosomal species may play a role in defining their eventual glomerular affinity. This is particularly prominent in experimental animals, where glomerulonephritis can be readily induced by *S. mansoni* and *S. japonicum*, but not by *S. hematobium* [132], amyloidosis being an exception [36]. In this context, it is noteworthy that despite an almost equal prevalence of *S. hematobium* and *S. mansoni* in

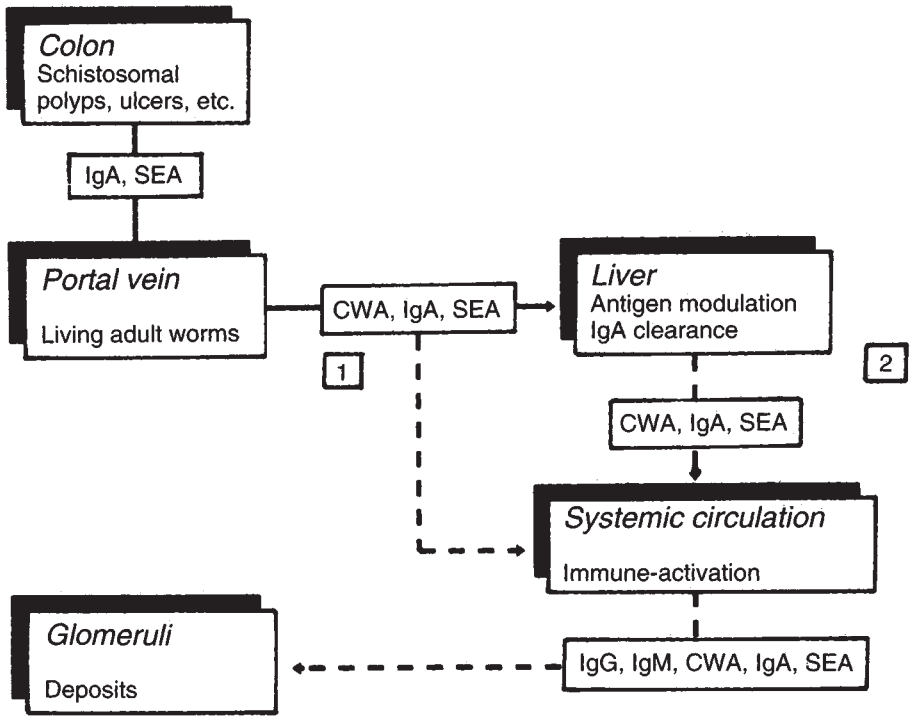

Fig. 2. *The "liver effect" in the pathogenesis of schistosomal glomerulopathy.* Soluble egg antigens (SEA), specific IgA of colonic origin and circulating worm antigens (CWA) are carried along the portal vein (solid lines) to the liver, where they are cleared or modulated. In the presence of porto-systemic shunts [1] or impaired hepatic macrophage functions [2], schistosomal antigens as well as mucosal IgA may find their way to the systemic circulation [dashed lines], provoke an IgM and/or IgG response, leading to glomerular immune deposits.

Africa, it is the latter that has been mostly associated with glomerulopathy, with only a few exceptions [47, 54, 133] which have been subsequently challenged [62, 66].

Even within the same species differences in strains [134] may also reflect on glomerular pathogenicity. In addition to its epidemiological importance [135], this issue may be of immunological interest if antigenic differences in between those strains are identified.

Out of over a hundred schistosomal antigens isolated *in vitro*, only a few have been also identified as circulating antigens *in vivo* [121, 122, 136, 137]. These mostly originate from the gut of adult worms, as the latter regurgitate their digestive juices into the host's blood stream. Relatively more recent studies have shown that it is those gut antigens that are mostly detected in the glomerular deposits [75, 129, 130, 138].

Mesangial localization of immune complexes containing gut antigens is the rule. Yet the extramembranous IgG deposits encountered in some experimental models [139] and cases [60] of schistosomal glomerulopathy suggest that *in situ* immune complex formation may take place as well. Relevant to this suggestion is the demonstration of glomerular deposits of "free" schistosomal antigens in experimental animals [38] and of the closely associated anti-HBV antibodies in humans [140].

The chances of detecting schistosomal antigens are reduced with progression of the lesions. Although some studies have found a positive correlation between the *development* of glomerulopathy and the infecting cercarial load in animals [35, 36, 141] or the intensity of infestation in patients [30], the *severity* of the lesions does not seem to depend on such parameters [35, 142]. These data may suggest that despite the importance of schistosomal antigens in the initiation of glomerular pathology, other factors may have something to do with the further evolution of the lesions.

Autoimmunity is one eligible mechanism of progression. Reference has been made earlier to the polyclonal B-cell response in schistosomiasis [143], particularly when associated with hepatic fibrosis [144, 145]. The remarkable hyperglobulinemia described in most clinical reports includes elevation of the major three immunoglobulin classes [48, 128, 146] and may explain the "false positive" serology for rheumatoid factor, ANF, VDRL and others. Anti-nuclear antibodies have been found in the sera and glomerular deposits in experimental animals [147] as well as in humans [148] with schistosoma-induced glomerulopathy. The public anti-DNA idiotype 16/6 ID and anticardiolipin antibodies have been recently found in the sera of patients with chronic *S. mansoni* infestation; the pattern of their serum levels was distinctive in those with glomerular involvement [149]. Antiglomerular basement membrane antibodies have been described in almost one-third of the patients in a recently reported series [150].

Although these observations suggest a potential role of autoimmunity in the progression of schistosomal glomerulopathy, as yet there is no direct evidence that they perpetuate or enhance glomerular pathology.

Another factor commonly associated with evolution of the glomerular lesions is hepatic fibrosis. This is probably one reason why *S. mansoni* has been most frequently associated with glomerulopathy. In most animal models, liver fibrosis usually precedes [33, 151] and often correlates [41, 110] with the glomerular lesions. As mentioned earlier, conforming clinical and post-mortem observations have been made in humans. Even with *S. hematobium*-associated glomerulopathy, hepatic fibrosis has been reported as a prerequisite for the development of glomerular lesions in mice [152] and is described in a large proportion of reported clinical material [60].

The "liver effect" is not attributed to hepatocellular injury

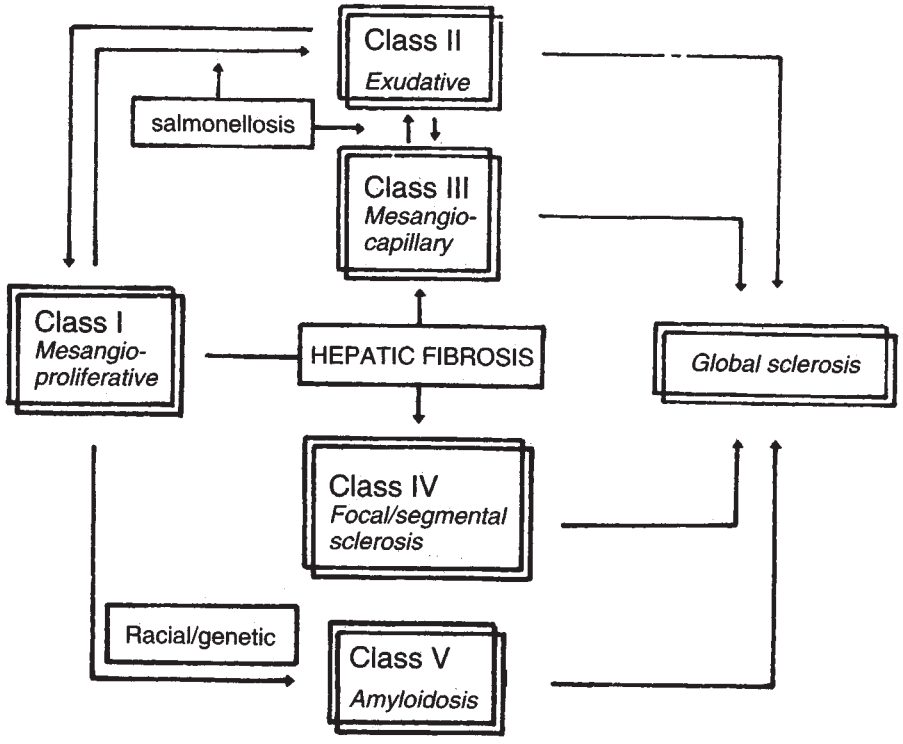

Fig. 3. *Suggested three phase evolution (from left to right) of schistosomal glomerulopathy.*

[153], nor to disorders of lymphocyte subpopulations [144, 145, 154], or serum immunoglobulin or complement profiles [153]. Margination of the liver, as in the experiments where the portal vein is ligated in mice [151] or in those where a portocaval shunt was created in chimpanzees [155], seems to be the crucial factor. It appears that deprivation of the immune-modulating functions of the liver [156] permits circulating schistosomal antigens to build up to the critical levels needed for glomerular deposition.

It is generally accepted that shunting of portal blood, carrying the primary load of worm antigens, into the systemic circulation is the main mechanism by which the liver is "marginated" in patients with schistosomal glomerulopathy. Yet, in a recent study using technitium-labeled sulphur colloid clearance curves [157], it was shown that the severity of glomerular lesions, as well as proteinuria, correlated with impairment of hepatic macrophage function [97]. These data suggest that hepatic bypass may also be a functional consequence of hepatic fibrosis, in addition to the physical shunting of portal blood.

In the same study [97], it was shown that impairment of hepatic macrophage function also correlated with glomerular IgA deposits which, like in a mouse model [112], were mainly seen in advanced lesions. This suggests that the spectrum of "hepatic margination" in schistosomal glomerulopathy includes impaired clearance of IgA [158, 159], which may add to the glomerular injury by its own right [114, 115] (Fig. 2).

Racial and genetic factors may be involved in defining the development and severity of schistosomal glomerulopathy. In the first place, it is known that racial factors are important in the susceptibility to infestation [160, 161], and its acute [162] and chronic complications [28]. Genetic factors modify the immune response to schistosomal antigens [163]. They are also involved in defining the susceptibility to certain complications. This is suggested by the association between HLA-B5 and *S. mansoni* intestinal polyposis [164], A1, B5 with hepatic fibrosis [165], and A28 with glomerular disease [166].

Schistosoma-associated amyloidosis may be a variant of the host's immune response to persistent antigenic stimulation [167]. Despite contradictory data in hamsters [35, 36], no clinical correlation has been reported between the development of amyloidosis and the duration and intensity of infestation. In most studies, the mean age of patients with this class of schistosomal glomerulopathy was even younger than that for other classes. It was mostly sex-linked, males being more commonly affected. Together with the distinct geographical variation in the prevalence of this class [30, 116], these data suggest the involvement of genetic influence in its pathogenesis. Such factors may influence the kinetics of the host's immune response, thereby generating the right immune complexes [168], or the macrophage/monocyte/mesangial response, thereby favoring amyloidogenesis. Studies in this particular aspect of the pathogenesis of schistosomal glomerulopathy are under way.

In summary, the available data on the pathogenesis of schistosomal glomerulopathy suggest that the disease may be triphasic (Fig. 3). Mesangial deposition of circulating gut, and possibly soluble egg antigens of different schistosomal species almost certainly induces the initial glomerular injury which usually manifests by mesangial hypercellularity (Class I lesions) with only a few clinical sequelae. Further progression into the second phase of overt renal disease seems to be more complex, involving a multiplicity of agent and host factors that ultimately

determine the predominent line of pathological evolution into one or another of the four classes characterized respectively by exudative, mesangiocapillary (membranoproliferative), focal and segmental sclerosing or amyloid glomerulopathies. The final progression into end-stage renal disease may be even less specific, obeying the general rules of late glomerular pathology that supervene in other diseases regardless of etiology.

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