The Nephropathy of Experimental Hepatosplenic Schistosomiasis

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The glomerular lesions induced in 10 chimpanzees infected with variable numbers of *Schistosoma japonicum* cercariae were studied by means of light and electron microscopy and fluorescent antibody technic. Ten animals served as controls; 5 were uninfected and 5 were only lightly infected. The animals were observed for periods ranging from 3 to 17 months, and by the time of sacrifice, all had developed advanced liver fibrosis. In general, the degree of glomerular injury was related to infection intensity and degree and duration of portal liver fibrosis. Some animals had terminal BUN elevation and slight proteinuria. By light and electron microscopy, in the initial stages, only part of the glomeruli were involved and exhibited mesangial matrix expansion and mesangial cell proliferation with intracellular hyaline droplets. At later stages, a larger number of glomeruli were affected and exhibited diffuse hypercellularity, glomerular basement thickening, mesangial sclerosis and less often, focal necrosis, crescent formation, synechiae and global hyalinization. In addition, there were discrete electron-dense deposits localized in the mesangial area in some glomeruli. Immunofluorescent studies utilizing antisera to chimpanzee γ-globulin and complement (C3) and to human properdin disclosed only faint deposits of C3, apparently in mesangial areas. The association of hepatosplenic schistosomiasis and nephropathy, the possible role of schistosomal antigen and the mechanism(s) of such glomerular injuries are reviewed and compared with the disease in humans and other host species infected with *Schistosoma* (Am J Pathol 76:433–450, 1974).

In 1968, Andrade and Queiroz [1] commented on the frequency of renal lesions in human schistosomiasis mansoni; in 1969, Lima *et al* [2] reported the clinical association of glomerulonephritis and hepatosplenic schistosomiasis. Subsequently, a retrospective study of kidneys from human autopsies of Manson's schistosomiasis has confirmed its relative frequency and correlation with the severe, hepatosplenic form of the disease.[3] It has recently been suggested [4] that a similar association

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may exist in the S *japonicum* endemic focus in the Phillipines. By contrast, this association has not been found in either human [5] or experimental [6] S *haematobium* infection.

In an earlier experimental study [7] chimpanzees exposed to large numbers of S *japonicum* cercariae consistently developed liver pipe stem fibrosis comparable to that seen in the human disease. Many of these animals also showed a peculiar glomerulopathy resembling that reported in man by Andrade *et al.*[3] This had not been noted in chimpanzees infected with S *mansoni* [8] or in control animals.[9] In the present study, these glomerular lesions were reviewed employing conventional light microscopy, ultrastructural and immunofluorescent technics. An analysis of the correlation between liver and kidney lesions was also undertaken; other morbid changes directly related to experimental S. *japonicum* infection had been described in detail previously.[7]

Materials and Methods

As published previously,[7] 15 of 20 young chimpanzees of both sexes were infected with the Japanese strain of S *japonicum* by abdominal skin exposure, with single and repeated doses ranging from a total of 50 to 4,000 cercariae; 5 animals were uninfected controls. Parasitologic, clinical, serologic and pathologic observations were carried out, as previously described,[7] for periods ranging from 3 to 17 months; these included liver biopsies and measurements of portal and intrahepatic blood pressure at laparotomy. At necropsy, liver and kidney tissues were examined; samples were removed freshly prior to exsanguination and perfusion for worm counts. Additional kidney tissue samples were obtained during a complete postmortem examination.

Morphologic and Immunopathologic Studies

Light Microscopy

Pre- and postperfusion kidney tissues of all animals were fixed in buffered formalin and embedded in paraffin; 3- to 4-μ-thick sections were cut and stained with hematoxylin and eosin, periodic acid–Schiff (PAS) and Masson's trichrome stain. The slides were examined independently by two observers (TC and FvL) and were graded as to the degree of renal lesions using a checklist of histologic features adapted from Pirani and Salinas-Madrigal.[10] The degree of each histopathologic change was graded using an arbitrary semiquantitative scale of 0 to 4+. Therefore, normal was graded 0; questionable or marginal, ±; mild, 1+; moderate, 2+; moderately severe, 3+; and severe, 4+. On the average, six to seven sections were examined from each experimental and control animal. Plastic-embedded sections were likewise subjected to analysis, but grading was limited to the glomerular alterations.

Electron Microscopy

Specimens were obtained from 5 animals. In 4, kidney tissue was minced to 1-mm cubes, fixed in 2% glutaraldehyde, postfixed in 2% osmium tetroxide, dehydrated in graded ethanol and embedded in Epon 812.[11] Thick (1 μ) Epon sections were stained with 1% toluidine blue; from selected blocks ultrathin sections were obtained

and stained with uranyl acetate and lead citrate.[12] In one experiment (chimpanzee 59), specimens initially subjected to formalin fixation were similarly processed.

Immunofluorescence Microscopy

The antisera to chimpanzee γ-globulin and C3 were prepared as described for human and monkey proteins.[13] The antibody to human properdin was obtained according to prior description.[14] Renal tissue obtained from 12 animals, including 7 with renal lesions, was rapidly frozen, cryostat sectioned and stained with the above antisera according to Coons' and Kaplan's direct fluorescent antibody technic.[15]

Biochemical Studies

Blood specimens were collected at regular intervals for determinations of fasting serum glucose, blood urea nitrogen (BUN) and total serum protein levels and for serum paper electrophoresis. In 7 animals, samples of urine collected at postmortem examination by puncture of the urinary bladder were tested for the presence of protein. All blood and urinary tests were performed according to standard laboratory technics.

Correlative Studies

For purposes of relating renal pathology with the degree of liver damage, liver fibrosis was semiquantitatively assessed by a combination of gross and microscopic findings. Accordingly, gross fibrosis was classified as slender, variable or broad, and microscopically graded 1 to 4+ to indicate mild (1+), moderate (2+), moderately severe (3+) and severe (4+) fibrosis (Table 2). In addition, egg counts of liver, lung and colonic tissues and a number of other organs were obtained by the technic of Cheever;[16] these counts were used as an estimate of infection intensity, as shown in Table 2. Finally, the kidney sections of 10 chimpanzees infected with the Puerto Rican strain of *S mansoni* [8] were reviewed for comparison. Some of these animals had developed pipe stem liver fibrosis at the time of sacrifice.

Since the completion of this series, additional tissues and data have become available from a new series of chimpanzees infected with *S japonicum*, some of which were treated with experimental nitro-vinyl-furane drug SQ 18,506, in which a similar protocol has been followed.[17]

Results

Morphologic and Immunopathologic Observations

The description which follows is based on the study of whole kidneys from 10 animals which developed renal lesions. Five animals with *S japonicum* infestation but without evidence of renal disease, and 5 uninfected controls were also studied but are not included on Table 1.

Gross Pathology

In general, kidneys were slightly congested but otherwise unremarkable. Two animals exhibited macroscopic lesions; chimpanzee 59 exhibited contracted granular, pale and firm kidneys with mild reduction of cortical width. Urinary passages and pelvis were normal. A second

Table 1—Histopathologic Findings in the Kidneys of 10 Chimpanzees Infected with **S japonicum**

Chimpanzee No.	Glomerular changes				Tubular changes	Interstitial changes	Vascular changes	Rate
	Hypercellularity	Mesangial matrix expansion	Basement membrane thickening	Adhesions				
11	0	1+	±	0	0	±	0	1+
466	±	2+	2+	0	0	±	0	2+
467	1+	2+	2+	±	0	±	0	2+
744	2+	2+	2+	±	0	±	0	2+
13	3+	3+	3+	±	0	0	0	3+
18	2+	3+	2+	±	0	±	0	3+
192	1+	3+	3+	±	0	0	0	3+
361	3+	3+	3+	1+	0	±	0	3+
782	2+	3+	3+	1+	0	±	0	3+
59	4+	4+	3+	2+	1+	2+	0	4+

chimpanzee (No. 467) showed only one schistosome egg granuloma in one kidney.

Light Microscopy

Except for 1 animal (No. 59) which exhibited diffuse renal disease, in all the remaining animals, lesions were focal in the kidney and sometimes segmental in the glomeruli. Since the tubular and interstitial changes were minimal in 9 animals and no significant vascular lesions were found in the whole group, the rating on Table 1 reflects essentially the glomerular damage. In its mildest form (rate 1+), the alterations, present in only 20% of the glomeruli, were characterized by slight mesangial matrix expansion and focal hypercellularity (Figure 1). A glomerulus from an uninfected control animal is shown for comparison (Figure 2). Animals infected with larger numbers of cercariae (750 to 2,250) exhibited moderate mesangial hypercellularity and sclerosis which involved 30% of the glomeruli (rate 2+), or characteristically, stalk proliferation with large numbers of PAS-positive fibrils (Figure 3) and/or diffuse proliferation with numerous intracellular hyaline droplets (Figure 4) affecting 50 to 70% of the glomeruli (rate 3+). Such hyaline droplets varied in size and distribution; they stained lightly eosinophilic with hematoxylin and eosin and gave a positive reaction with PAS stain. Other glomeruli exhibited segmental proliferation and sclerosis, cellular crescents and/or tuftal adhesions (Figure 5).

In one animal (chimpanzee 59), subjected to the severest infection (4,000 cercariae) and observed for the longest period (17 months), there was diffuse involvement of virtually all glomeruli (rate 4+). A

few glomeruli showed changes as seen in the previous animals, but the majority displayed striking proliferation of cells and mesangial sclerosis (Figures 6–8), often with capsular fibrosis or synechiae (Figure 8). A smaller number of glomeruli showed focal necrosis and neutrophil exudation, and a few were hyalinized. This was also the only chimpanzee in the whole group which presented a contracted and granular kidney with focal tubular atrophy and interstitial inflammation (Figure 6). The inflammatory cells, predominantly lymphocytes, were characteristically accumulated around glomeruli (Figures 6–8).

The histopathologic and laboratory findings of the 10 animals studied are summarized in Tables 1 and 2. Details of other histopathologic abnormalities are given elsewhere.[7] Finally, of the 10 chimpanzees infected with *S mansoni*,[8] 1 developed mesangial hypercellularity and sclerosis.

Electron Microscopy

The most prominent and constant change observed was marked mesangial expansion (Figures 9 and 10) occasionally obliterating capillary lumina. This was mainly due to an increase of mesangial matrix (Figure 10A) associated with mild-to-severe mesangial cell proliferation. Collagen fibers were identified in the mesangium (Figure 10C) and occasionally between layers of the glomerular basement membrane (Figure 10A and B). In many samples, the mesangium contained in-

Table 2—Correlation Between Glomerular and Hepatic Lesions with Duration and Intensity of Infection and Serum γ-Globulin Alterations in 10 Chimpanzees Infected with **S japonicum**

Chimpanzee No.	Duration of infection (mons)	No. cercariae*	Mean No. eggs × 10^{2}/g of tissue: Liver	Large bowel	Lung	γG (g%)†	Liver fibrosis (1+ to 4+)‡	Glomerular lesions (1+ to 4+)
11	17	250	2.5	0.5	0.1	5.0	3+ S	1+
466	3	750	19.9	14.8	7.5	2.6	3-4+ S	2+
467	6	2,250	20.9	9.1	10.7	4.0	4+ V	2+
744	5	2,250	9.2	21.9	14.4	3.2	4+ V	2+
13	8	2,000	4.3	3.0	0.3	6.6	4+ B	3+
18	17	2,000	2.6	1.3	0.5	6.2	3-4+ B	3+
192	8	750	7.1	4.4	7.1	5.2	4+ V	3+
361	5	750	2.5	2.7	1.5	4.4	4+ V	3+
782	6	2,250	5.7	8.6	6.8	3.3	3-4+ S	3+
59	17	4,000	5.1	7.3	2.1	7.2	4+ B	4+

* Total number of cercariae after a single or multiple exposures
† Serum γ-globulin at the time of necropsy
‡ S = slender, V = variable, B = broad

tensely electron-dense, spherical-to-ovoid homogeneous bodies corresponding to the PAS-positive granules observed by light microscopy (Figure 4); these ranged in size from that of a mitochondrion to that of a small nucleus (Figure 9). Less frequently, small granular electron-dense aggregates were found in the same location (Figure 10A, thick arrows). On occasion, there was also thickening of glomerular capillary basement membranes due to subendothelial replication of the lamina densa (Figure 10A). In none of the examined cases was there evidence of subepithelial deposits. The epithelial foot processes appeared only focally fused. In addition, in the kidney sections with severe light microscopic changes, polymorphonuclear leukocytes (neutrophils) were often seen in capillaries, usually next to areas of partial denudation of the basement membrane (Figure 9, inset).

Immunofluorescence Microscopy

Some glomeruli displayed only trace amounts of complement (C3) in mesangial areas, but no IgG or properdin deposits could be detected in the same tissues. Also, deposits of C3 were variable and minimal and were seen only in a few animals. No correlation could be established between C3 deposits and glomerular injury.

Biochemical Studies

Detailed biochemical abnormalities have been published elsewhere.[7] Total serum γ-globulin levels at the time of sacrifice are given on Table 2. The relationship between the degree of glomerular injury and BUN elevation is summarized on Table 3. Animals with glomerular disease exhibited BUN levels in the upper normal limit (chimpanzees 11 and 361) or had elevated values. In some animals slight proteinuria (50 to 300 mg/liter) was observed. However, one could not correlate

Table 3—Correlation Between Glomerular Lesion and Terminal BUN in 7 Chimpanzees Infected with **S japonicum**

Chimpanzee No.	Glomerular lesion (1+ to 4+)	BUN* (mg%)
11	1+	9
13	3+	64
18	3+	19
192	3+	28
361	3+	9.0
782	3+	11.8
59	4+	16.0

* BUN in normal controls = 5 to 9 mg%.

such features as the degree of glomerular lesions and urinary protein excretion or raised BUN levels.

Correlative Studies

These studies are summarized in Table 2, from which it can be seen that, in general, animals which developed significant glomerular lesions (rate 2+ to 4+) had been exposed to a large number of cercariae (750 to 4,000) and had pronounced liver fibrosis. However, even in the most severe infections (chimpanzees 467, 744, 13, 17 and 782) renal lesions were not fully developed until 5 or 6 months after exposure and seemed to be preceded by the development of liver pathology. It is of interest to note that the animal with the longest and heaviest infection (Chimpanzee 59) had extremely elevated serum γ-globulin levels (7.2 g%) and pipe stem liver fibrosis and was also the animal in which the severest glomerular disease was observed.

Discussion

Our findings indicate that there is a similar association between schistosomiasis and renal disease in chimpanzees infected with *S japonicum* or, more rarely with *S mansoni*, as has previously been reported in man.[1] To our knowledge, spontaneous glomerulonephritis is very rare in chimpanzees;[18] however, we recently found proliferative glomerulonephritis in a chimpanzee infected with *Plasmodium schwetzi* and *P falciparum*.[19] Malarial nephritis, an immune deposit disease, has also been induced in the rhesus monkey,[13] but these lesions differed significantly from those reported here. Furthermore, glomerular lesions were not detected in our uninfected controls and in early or light *S japonicum* infection. However, glomerular injury became manifest and progressive by the fourth month after heavy exposure, when liver pipe stem fibrosis had become established. Thus, the concept of schistosomal nephropathy has now been experimentally validated.

Characteristically, the early lesions in chimpanzees showed mesangial hypercellularity and matrix expansion resembling human stalk proliferative glomerulonephritis (Figure 3). Advanced lesions showed diffuse hypercellularity, glomerular basement membrane thickening, and occasional tuftal adhesions and crescent formation. In 1 animal with the longest and severest exposure, the picture resembled human chronic proliferative and sclerosing glomerulonephritis (Figures 6–8). PAS-positive hyaline granules were frequently observed in the mesangium (Figures 4 and 9). Otherwise, the findings were remarkably similar to

those of Andrade.[3] In his review of 80 necropsies of the hepatosplenic form of Manson's schistosomiasis, he found that normal glomeruli were present in only 6 cases (7.5%); the remaining showed variable degrees of injury, including chronic diffuse lobular or sclerosing glomerulonephritis in 8 necropsies (10%). In our much smaller series, the latter lesion was seen in only 1 chimpanzee. Lobular glomerulonephritis has also been described in patients with cirrhosis of the liver;[20] the possible relationship of such glomerular lesions to those here described is unclear.

Gammaglobulins were markedly elevated in chimpanzees with hepatic and renal lesions (Table 2); lesser elevations are fairly common in human hepatosplenic schistosomiasis, and there is urinary excretion of large amounts of low and high molecular weight protein.[21] Only slight proteinuria (50 to 300 mg%) was found in this study in animals both with and without light microscopic renal lesions. Proteinuria seems to be the principal manifestation of schistosomal nephropathy in man until an advanced stage is reached. Even in severe human schistosomiasis, death attributable to renal failure is rare.[22] In this study, although the BUN levels were elevated in some chimpanzees (Table 3), impairment of renal function was not evaluated.

The mechanism of glomerular injury remains unknown. It cannot be accounted for by renal egg deposition, since renal granulomata are sporadic and glomerular lesions can become quite widespread. It has been clearly demonstrated that schistosome antigen is found both in sequestered sites[23] and in the circulation,[24–26] particularly in heavy infections; that a variety of antibodies develop in schistosomiasis is also known.[27,28] In a recent workshop on the immunochemistry of schistosome antigens, Bawden and Nash[29] reported that circulating schistosome antigen is an almost pure, branched polysaccharide of 100,000 to 500,000 daltons, derived from the adult worm and not from the egg. This material is only weakly antigenic to rabbits, unless conjugated with methylated bovine serum albumin. It becomes detectable only after high infection thresholds are reached, at which point its serum titers begin to rise in concomitance with the number of worm pairs present. This suggests that a storage mechanism (*eg*, the reticuloendothelial system) has to be saturated before the antigen can spill over into the circulation, reminiscent of the behavior of other high molecular weight polysaccharides such as the dextrans. Contact between circulating antigen and glomeruli or arteries would be facilitated by portocaval collaterals which give antigen direct access from its mesenteric site of origin to the systemic circuit, thus bypassing the hepatic reticuloendothelium. This would better account for the observed correlation between

nephropathy and bilharzial pipe stem fibrosis in man [3] and in chimpanzees. It is therefore conceivable that circulating schistosome antigen could stimulate mesangial cell proliferation and sclerosis.

Hyaline granules were not found in renal glomeruli following treatment of chimpanzees infected with S *japonicum* with SQ 18,506.[17] Conversely, granules have been seen in foci of arteritis associated with severe experimental S *japonicum* infection.[7,17] Such granules, prominent in our material, have been reported in only a single human case thus far.[30] Although it is true that most human cases represent less massive infection than that of our experimental chimpanzees, and granules might be more sporadic and more easily overlooked, it is nevertheless possible that these granules are neither antigen-related nor specific. Immunohistochemical studies of these granules and of the affected glomeruli, with specific reference to circulating schistosome antigen, are greatly needed.

Recently, one of us [31] reported focal proliferative glomerular lesions in S *japonicum*–infected rabbits which had developed portal fibrosis 3 months after exposure. These were far less consistently present and intense than in chimpanzees and, in a subsequent series, they have occurred in only 2 of 14 infected rabbits, and no significant fall in serum complement has been noted. Recently Andrade and Susin [32] reported mesangial deposits of immunoglobulin in mice infected with S *mansoni*, but Brack *et al* [33] did not observe glomerular pathology in S *mansoni*–infected baboons; it is of interest to note that even heavily infected baboons do not develop pipe stem liver fibrosis. It is further noteworthy that nephropathy has remained undetected in S *haematobium* infections [34] which affect the liver architecture to a much lesser extent than do the other two human schistosome species. Thus, renal changes in hosts infected with schistosomes but without pipe stem liver fibrosis have been minor when compared to those which accompany the hepatosplenic stage of the disease.

In regard to the possible role of antibody, or of immune complexes, Silva *et al* [35] studied the early lesions of human kidneys in 8 S *mansoni*–infected patients without clinical or laboratory evidence of renal disease. They observed confluent granular deposits of immunoglobulins and of complement (C3) along the glomerular basement membrane, and claimed the presence of subendothelial electron-dense deposits by electron microscopy. In our observations in chimpanzees, even in advanced lesions, IgG and properdin could not be detected by immunofluorescence, although in some animals an occasional glomerulus exhibited faint deposits of C3. Our electron microscopic studies confirmed

the light microscopic findings in showing marked mesangial expansion. In none of the examined cases was there evidence of subepithelial deposits; however, on occasion, there was thickening of the glomerular capillary basement membrane due to expansion of the subendothelial space (Figure 10A). In addition, small aggregates of electron-dense granular material were seen in the mesangium (Figure 10A); whether they represented immune complexes could not be ascertained. Deposits of immunoglobulin have also been reported in scattered focal glomerular lesions of hamsters [36] and of mice [37] infected with *S mansoni* or *S japonicum*. These occurred as early as 9 weeks and 31 days, respectively, after exposure and were felt to represent immune complexes of DNA–anti-DNA antibody [24,26] as described in human lupus nephritis.

In none of the reports cited has the antigen moiety of the putative complexes been identified, nor has it been shown that the presence of these proteins in glomeruli was evidence of immunologic injury rather than of nonselective trapping. Our inability to demonstrate immunoglobulin or significant amounts of complement in altered glomeruli is of interest, since no difficulty was experienced by one of us in demonstrating such materials in malarial nephritis [13] or, more recently, in the hypocomplementemic nephritis of monkeys infected with *Trypanosoma brucei*.[38] However, the transient nature of immune complexes in certain experimental models is well known,[39] and despite our negative findings by immunofluorescence, in schistosomal nephropathy their role, on balance, must remain uncertain.

The role of cell-mediated immunity has been well documented in schistosome granulomas,[40–43] but there is as yet no indication of its intervention in schistosomal nephropathy, unless accumulations of lymphocytes around altered glomeruli (Figures 6–8) are considered as suggestive evidence.

In conclusion: What is thus far known about schistosomal nephropathy is very incomplete and highly speculative. The analogy of the nephropathy in the chimpanzee with Andrade's findings in human patients [3] is remarkably close and suggests that this experimental model may be used for clarifying some aspects of the pathogenesis of schistosomal nephropathy.

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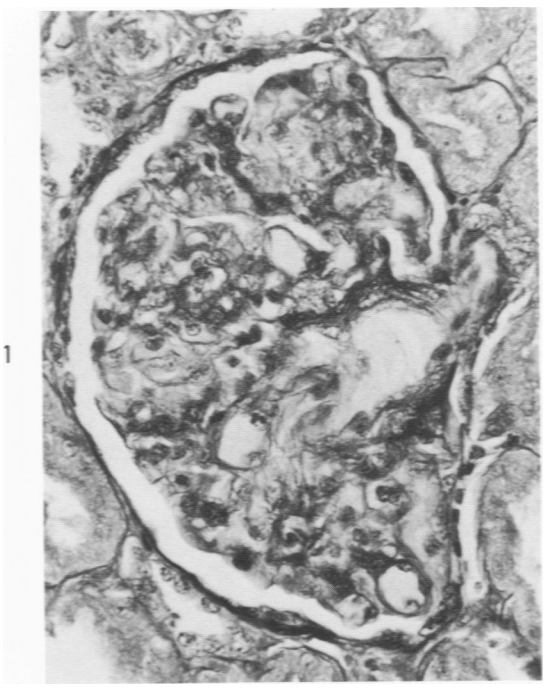
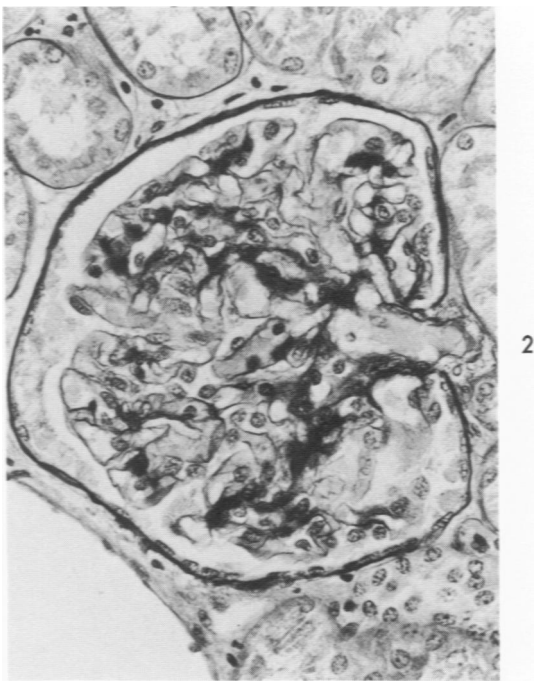
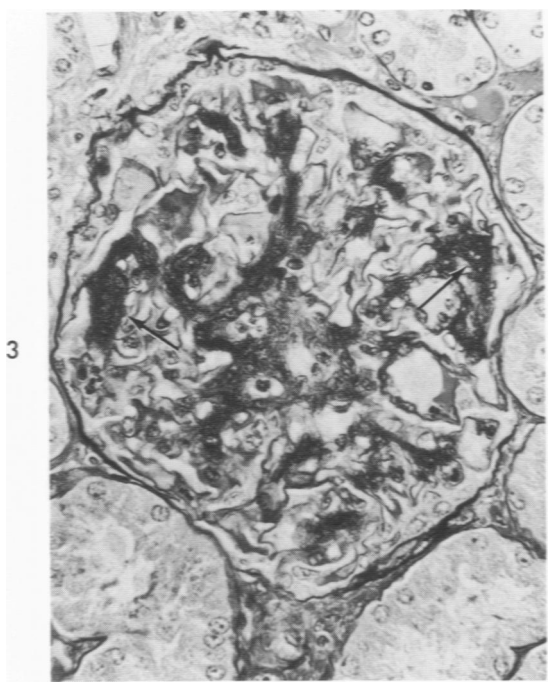
Note Added in Proof

Since this paper was sent to press an additional publication reporting on the induction of glomerulonephritis in Swiss mice infected with *S mansoni* has appeared in an abstract form (Natali PG, Cioli D: Immune complex nephritis in mice infected with *Schistosoma mansoni*. Fed Proc 33:757, 1974). The authors reported mesangial accumulation of PAS-positive material and granular deposits of immunoglobulin and complement in the glomeruli. They further claimed the detection of parasitic antigen in glomerular eluate in some animals and suggested that this form of glomerulonephritis is mediated by immune complexes.

[*Illustrations follow*]







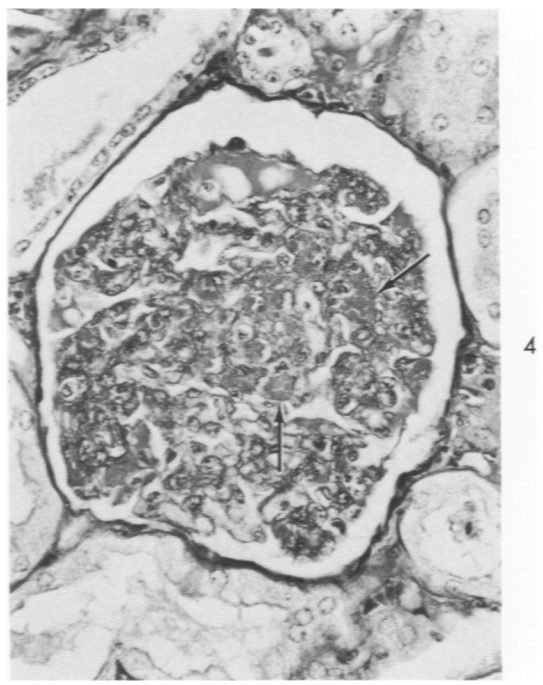
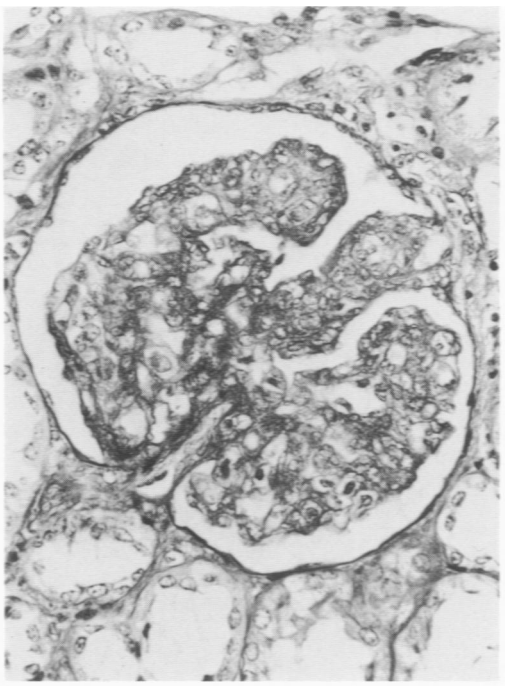


Fig 1—Chimpanzee 11 (rate 1+); glomerulus exhibiting mesangial matrix expansion and narrowing of capillary loops (PAS, approximately × 300). **Fig 2**—Normal uninfected chimpanzee control; glomerulus with delicate mesangial matrix, widely patent capillary loops and thin glomerular basement membranes (PAS, approximately × 250). **Fig 3**—Chimpanzee 18 (rate 3+); glomerulus exhibiting increase in mesangial matrix and mesangial cell hypercellularity (*arrows*). The mesangial matrix is comprised of large numbers of PAS-positive fibrils. There is narrowing of some capillary loops and wrinkling of glomerular basement membranes (PAS, approximately × 250). **Fig 4**—Chimpanzee 13 (rate 3+); glomerulus exhibiting marked proliferation of cells. Numerous PAS-positive droplets (*arrows*) are evident. The capillary lumen is reduced in most peripheral loops (PAS, approximately × 250).



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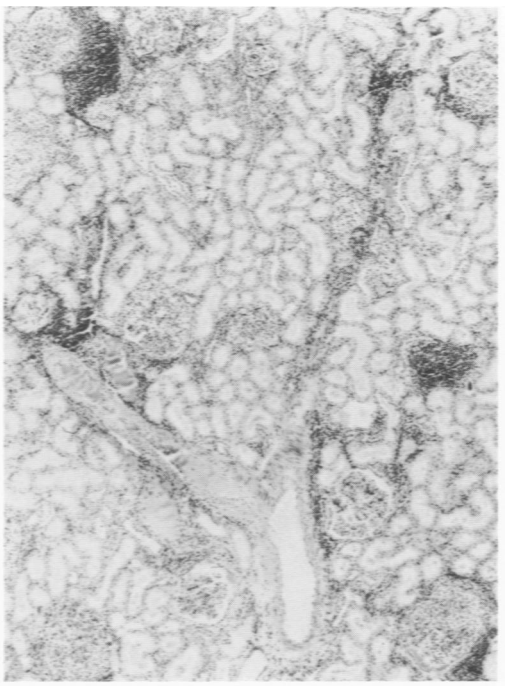

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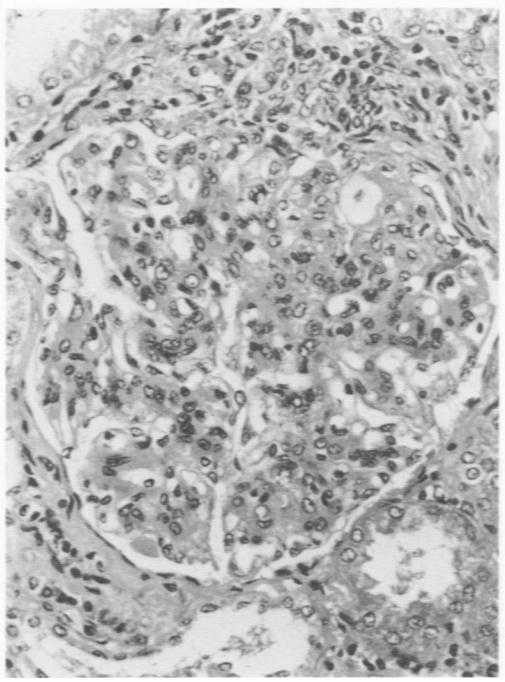

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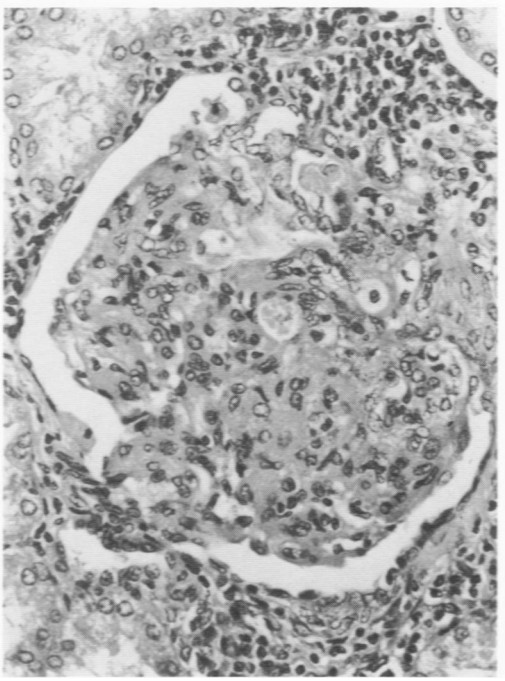

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Fig 5—Chimpanzee 782 (rate 3+); glomerulus showing marked proliferation of cells and accentuation of the lobular pattern. A tuftal adhesion is evident. There is narrowing of many capillary loops; the glomerular basement membrane shows several irregularities (PAS, approximately × 250). **Figs 6–8**—Chimpanzee 59 (rate 4+); all photomicrographs are from the same experiment. **6**—Low power photomicrograph portraying prominent interstitial inflammatory infiltrate predominantly accumulated about glomeruli (H&E, approximately × 35). **7**—Glomerulus showing mesangial hypercellularity, sclerosis and thickening of capillary loops. Periglomerular inflammation and capsular fibrosis are evident (H&E, approximately × 220). **8**—More advanced glomerular lesion with residual hypercellularity, increase in mesangial sclerosis and tuftal adhesions. Most capillary loops are obliterated or reduced to a slit-like space (H&E, approximately × 220).

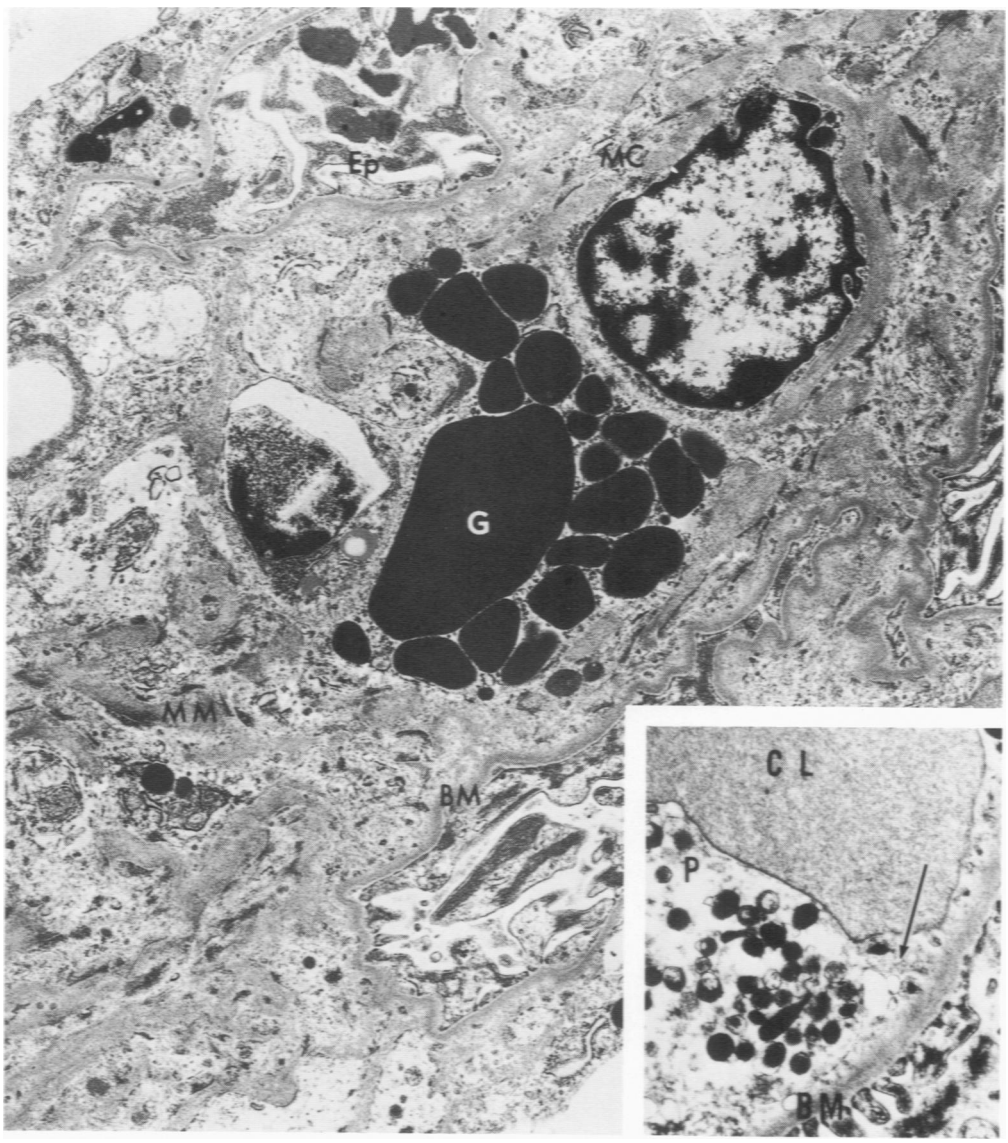

Fig 9—Electronmicrograph of a portion of a glomerulus showing marked increase of the mesangial matrix (*MM*) with presence of numerous osmiophilic granules (*G*). *MC*=mesangial cell, (*BM*=basement membrane, *Ep*=epithelial cell (approximately × 16,600). **Inset**—Electronmicrograph showing portion of a polymorphonuclear leukocyte (*P*) adjacent to the basement membrane (*BM*). There is disruption of the endothelial lining (*arrow*), and there appears to be direct contact between the polymorphonuclear leukocyte and the basement membrane. *CL*=capillary lumen (approximately × 19,000).

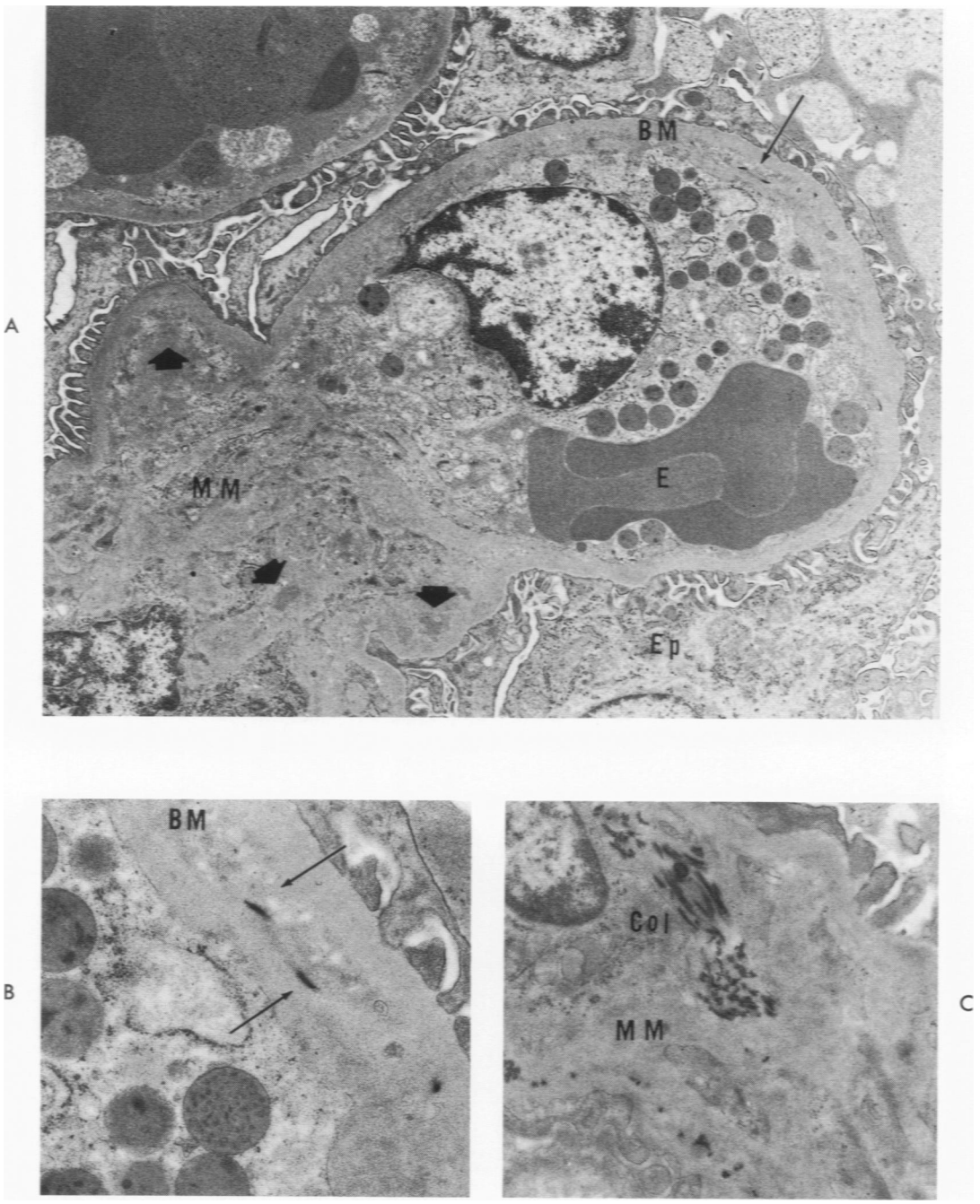

Fig 10—All micrographs are from the same glomerulus. **A**—Electronmicrograph of a portion of a glomerulus showing marked mesangial expansion and irregular masses of granular electron-dense material (*short arrows*) in the mesangial matrix (*MM*). Collagen fibers (*long arrow*) are present in a thickened basement membrane (*BM*). *E*=erythrocyte, *Ep*=epithelial cell (approximately × 15,500). **B**—Detail of **A** showing collagen fibers (*arrows*) between layers of basement membrane (*BM*) (approximately × 23,000). **C**—Mature collagen (*Col*) present in the mesangial matrix (*MM*) (approximately 24,000).