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A clinical and pathological study of schistosomal nephritis *

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In a Cairo clinic 17 of 41 patients with chronic pyelonephritis secondary to urinary schistosomiasis presented with classical features of the nephrotic syndrome, two-thirds being hypertensive and the majority having glomerular filtration rates within the normal range. Hypercholesterolaemia was found in one-third of the patients. Urinary sediments from these patients contained a preponderance of pus cells, red cells, granular casts, or pus casts. In addition to patches of pyelonephritis, the glomeruli showed diffuse and focal glomerulosclerosis. Electron microscopy revealed basement-membrane-like deposits in the hypertrophied axial endothelial cells and electron-dense deposits along the glomerular basement membrane. This variety of nephrotic syndrome associated with schistosomal pyelonephritis was the most common cause of nephrotic syndrome seen in the clinic.

During the last few years, we have had the impression that patients with urinary schistosomiasis and secondary bacterial pyelonephritis develop a nephrotic syndrome. The majority of patients admitted to the renal unit are suffering from chronic pyelonephritis secondary to urinary schistosomiasis (Abou-Gabal et al., 1970), and a considerable proportion of them have varying degrees of generalized oedema. In most of those patients the urinary protein loss exceeds 3 g/litre and the serum albumin levels are low. The necessary criteria for the diagnosis of the nephrotic syndrome are therefore fulfilled. In this report the clinical and laboratory findings, together with a study of the pathology and the ultrastructural changes in renal biopsy material from these patients, are described. No other reports of similar observations in *Schistosoma haematobium* infections of the urinary tract are known to the present authors.

MATERIAL AND METHODS

The diagnosis of chronic pyelonephritis in this study was based on case histories, clinical examinations, and laboratory findings, including complete urine analysis. A modified Addis technique (El-Said, 1971) was used to count the exact number of pus cells excreted per hour in urine.

Only confirmed cases of chronic pyelonephritis were included in this study, doubtful cases being excluded. Patients with, in addition to the pyelonephritis, other lesions that could give rise to the nephrotic syndrome (e.g., patients having both chronic pyelonephritis and diabetes) were also excluded. Altogether, 64 cases of chronic pyelonephritis were studied and were classified into two groups: " schistosomal " and " nonschistosomal chronic pyelonephritis ". The schistosomal group included 41 patients (38 males and 3 females) while the nonschistosomal group consisted of 23 patients (11 males and 12 females). The ages of the patients ranged from 7 to 65 years.

Diagnosis of the nephrotic syndrome was based on the occurrence of heavy proteinuria, defined as more than 0.05 g of protein per kg of body weight (i.e., 3 g in the average adult weighing 60 kg) (Cameron, 1970). Hypoalbuminaemia (less than 3 g of albumin per 100 ml) and generalized oedema were present in all but 1 of the patients with the nephrotic syndrome; the latter excreted 5 g of protein per litre of urine without showing signs of hypoalbuminaemia or oedema. Several determinations of urinary and serum proteins were made for every patient in follow-up examinations.

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The diagnosis of chronic pyelonephritis as secondary to urinary schistosomiasis was established by the presence of a past history of urinary schistosomiasis, the finding of schistosome ova in the urine, and/or a positive skin test for schistosomiasis (Abou-Gabal et al., 1970).

Renal tissue was obtained by percutaneous needle biopsy and was immediately fixed in formol for light-microscopy, or in 1% osmium tetroxide buffered with Dalton's buffer solution for electron-microscopy.

RESULTS

Clinical

The frequency of nephrotic syndrome in patients with chronic pyelonephritis, both schistosomal and nonschistosomal in origin, is illustrated in Table 1. It is evident that patients with schistosomal pyelonephritis show a higher proportion of nephrotic syndrome, the differences in the frequency of the nephrotic syndrome in both groups being statistically significant ($0.010 < P < 0.025$).

Table 1. Frequency of the nephrotic syndrome in schistosomal and nonschistosomal pyelonephritis

Group	Total no. of patients	No. (and percentage) of patients with nephrotic syndrome
patients with schistosomiasis	41	17 (41.4%)
patients without schistosomiasis	23	2 (8.7%)
χ^2 (with Yates' correction)		6.0906

The clinical and laboratory findings in the 17 nephrotic patients in the schistosomal group were as follows. The ages of the patients ranged from 13 to 58 years, and there was a great preponderance of males, only 1 of the 17 patients being female. A history of bilateral loin pain was present in 5 patients, left loin pain in 5 patients, and right loin pain in 1 patient. Fever and rigor were associated with the attacks of loin pain in 4 patients. Associated hepatosplenic schistosomiasis was present in 6 cases.

In patients with liver cirrhosis the ascites was sometimes more marked than the oedema. Hypertension was present in 11 of the 17 schistosomal nephrotic patients (64.7%); 6 patients had severe hypertension with a diastolic pressure of 130 mm Hg or more. Only 4 patients showed some degree of nitrogen retention, having blood urea levels ranging from 55 to 85 mg per 100 ml. The remaining 13 patients had blood urea and creatinine clearance values within the normal range. Anaemia was observed in 7 of the 17 patients and hypercholesterolaemia was found in 6 patients (35.3%).

Urinary sediments showed that pus and blood cells were being excreted at a pathological rate, i.e., more than 200 000 cells per hour, in all the cases. There was a preponderance of pus cells in some cases and of red cells in others. The quantitative count in 2 cases was more than 30 million pus cells and/or red cells per hour. Pus casts were present in 2 cases, and granular casts were found in some other cases. Urine cultures were positive for *Escherichia coli* in 16 cases and for *Salmonella paratyphi* B in 1 case. Living *S. haematobium* ova were detected in the urine of 2 patients and *S. mansoni* in the stools of 2 other patients.

The 2 patients with nonschistosomal pyelonephritis (1 male and 1 female) who presented with nephrotic syndrome were hypertensive and had renal failure; cardiac decompensation was present in both. Urine cultures from both patients were positive for *E. coli*, and the excretion of pus cells in urine was much more pronounced than the excretion of red cells (10.5 million pus cells per hour in one case and 2.7 million in the other). The important laboratory findings in the patients with schistosomal and nonschistosomal nephrotic pyelonephritis are summarized in Table 2.

The mean urinary protein excretion rates in the two groups were compared (Table 3); proteinuria was significantly greater in patients with schistosomal pyelonephritis than in those with nonschistosomal pyelonephritis.

Pathology

Light-microscopy revealed evidence of pyelonephritis in all patients in the " schistosomal " group. Patchy areas of tubular atrophy, thyroid-like areas (dilated tubules with atrophic lining filled with hyaline eosinophilic casts), interstitial cellular infiltration, and interstitial fibrosis were always present, sometimes to a very marked degree (Fig. 1). The glomeruli within pyelonephritic patches showed periglomular fibrosis, intracapsular hyalinizing fibrosis, or invasion by interstitial inflammatory cells; these changes were all considered to be secondary to pyelonephritis.

However, glomeruli not associated with pyelonephritic patches when closely examined were found not

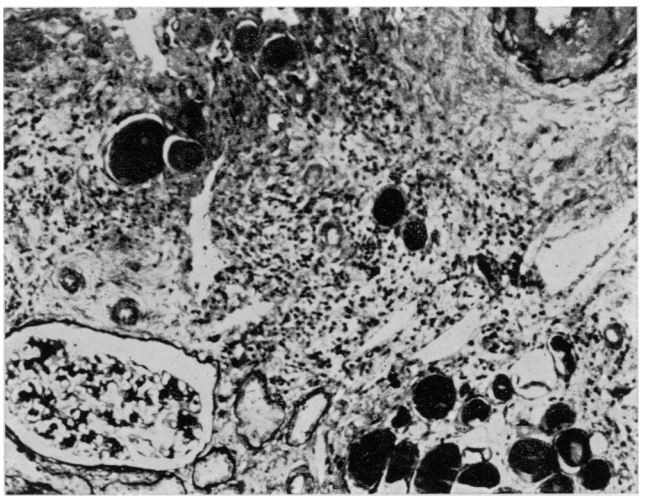

Fig. 1. A patch of pyelonephritis in a patient with schistosomal nephrosis. There is extensive interstitial fibrosis and cellular infiltration, and atrophied areas, dilated tubules, and thyroid-like areas are present. The artery, at the top, is surrounded by dense periarterial fibrosis. (Stained with haematoxylin and eosin; magnification × 112).

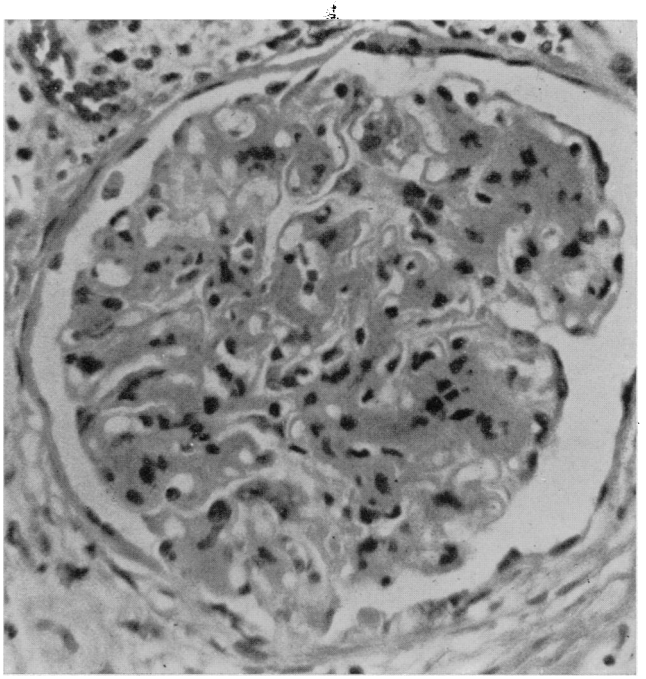

Fig. 2. Diffuse glomerulosclerosis in a patient with schistosomal nephrosis. The capillary walls in the axial region of the glomerulus are thickened and there is focal deposition of eosinophilic material in addition to the diffuse thickening of the capillary walls. (Stained with haematoxylin and eosin, magnification × 338).

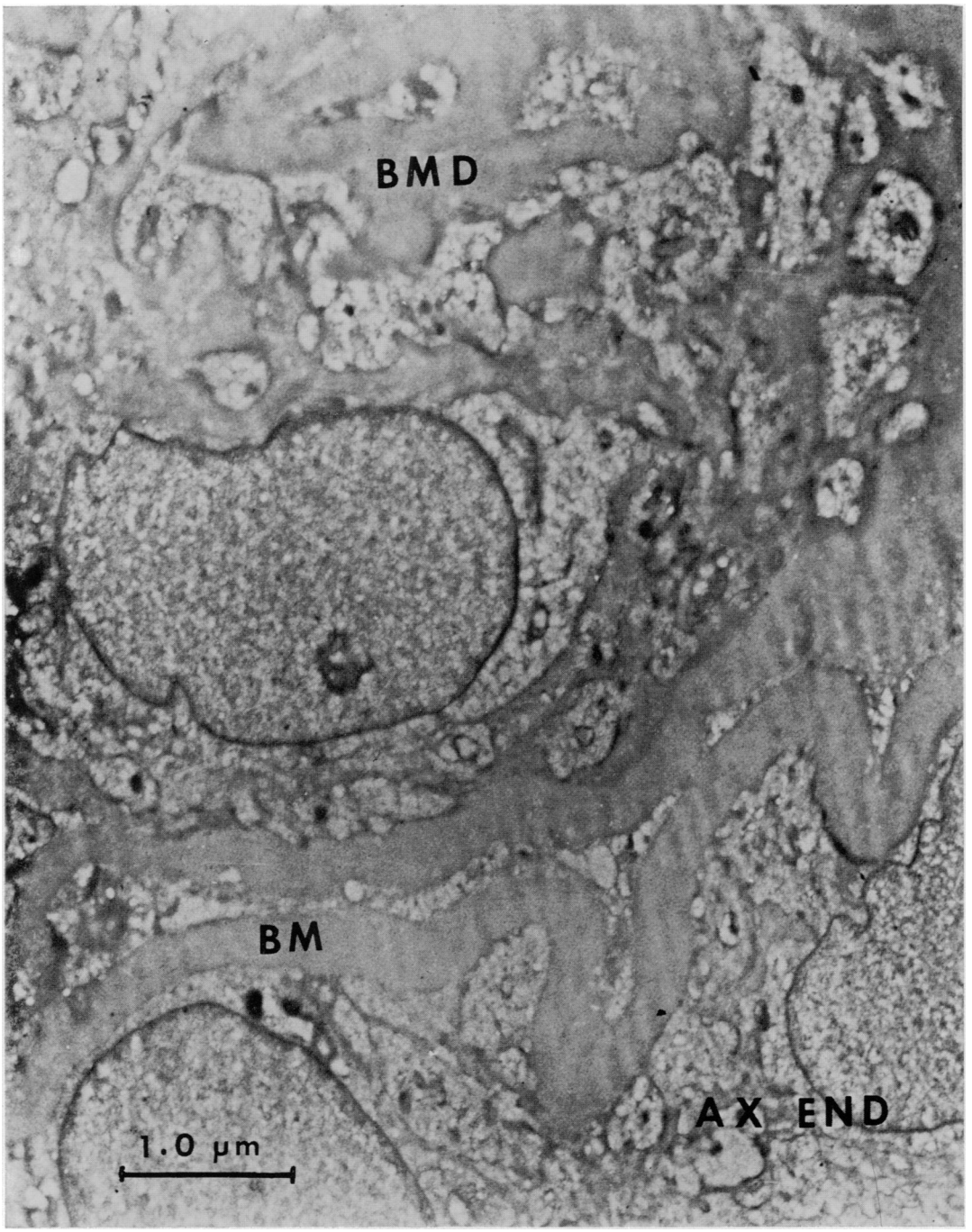

Fig. 3. An axial endothelial cell. There is an excessive deposition of basement-membrane-like material in the cytoplasm. AX END, axial endothelial cell; BM, basement membrane; BMD, basement-membrane-like deposit; D, electron-dense deposit; END, endothelial cell; EPI, epithelial cell.

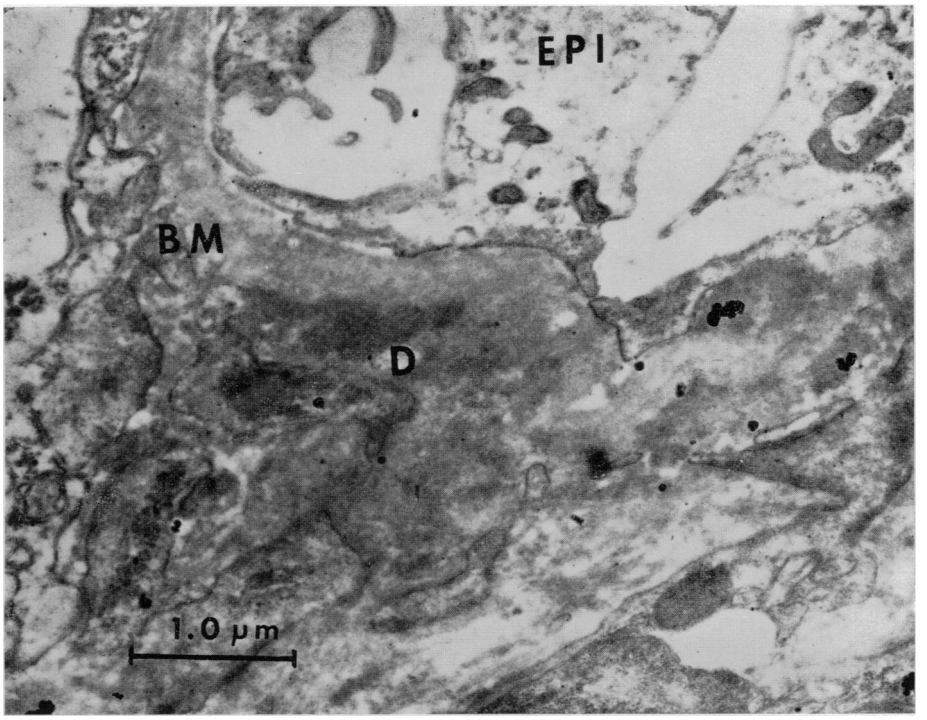

Fig. 4. Electron-dense deposit on the endothelial side of the basement membrane (for key see Fig. 3).

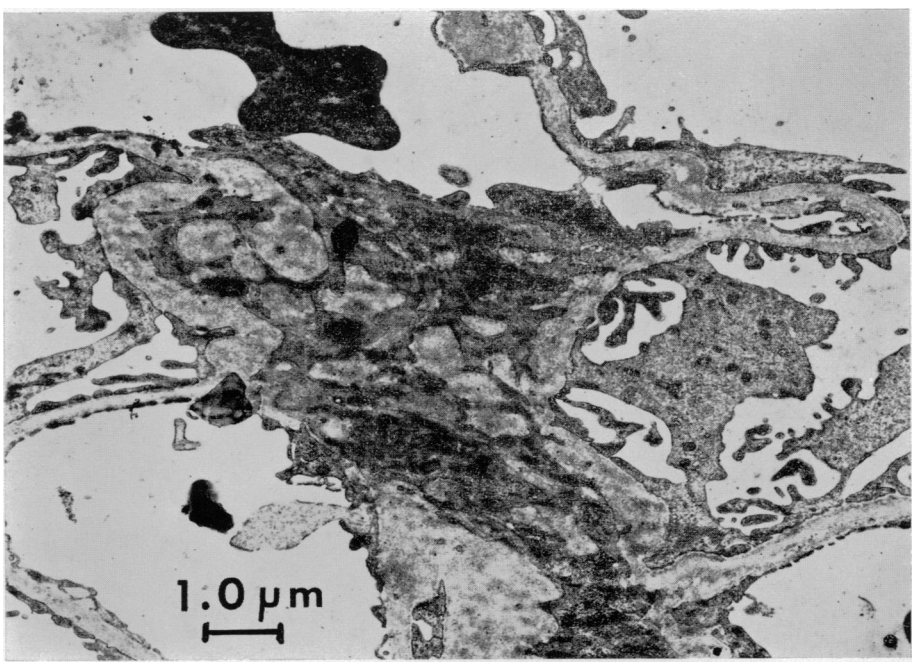

Fig. 5. Axial-cell cytoplasm, showing electron-dense deposits intermingled with basement-membrane-like deposits (for key see Fig. 3).

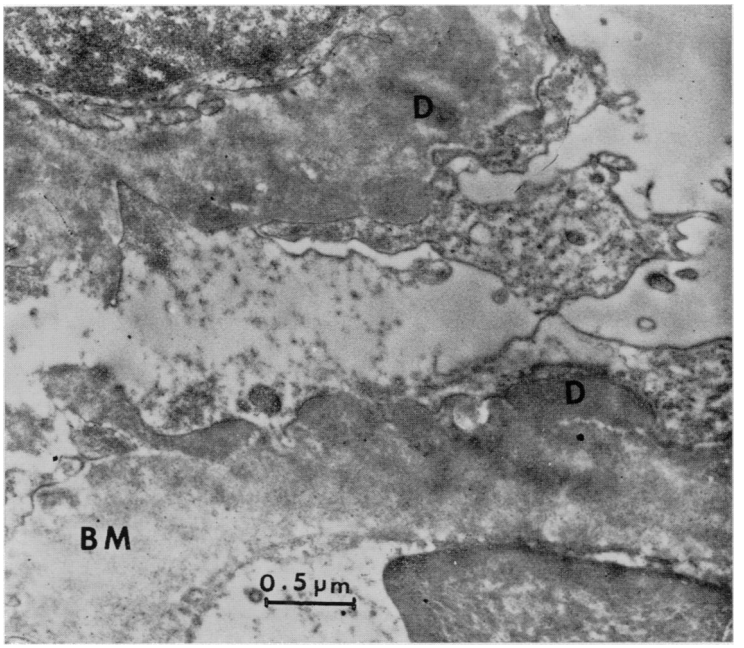

Fig. 6. Electron-dense deposits permeating the glomerular capillary basement membrane and adding to its thickness (for key see Fig. 3).

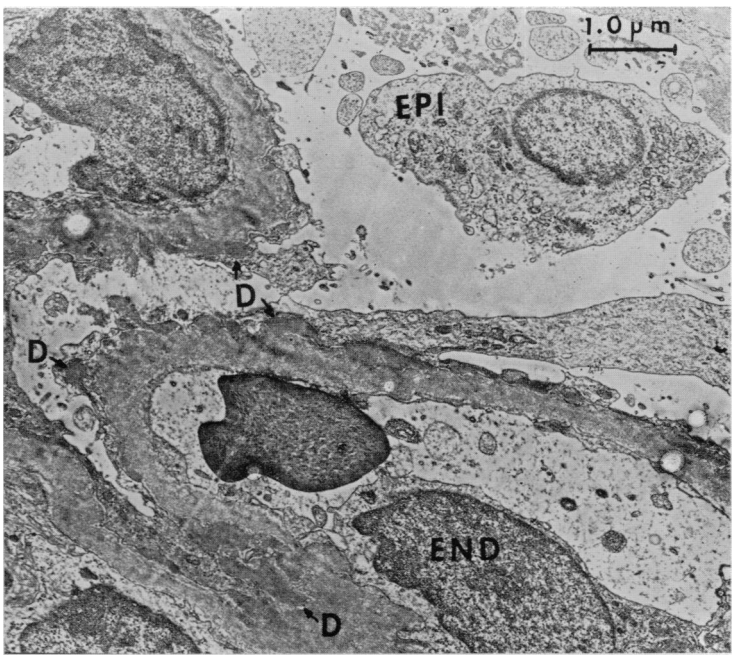

Fig. 7. The epithelial foot-processes are confluent, spreading over the external surface of the basement membrane. Subepithelial electron-dense deposits are arranged in a more or less linear distribution (for key see Fig. 3).

Table 2. Laboratory data for patients with schistosomal and nonschistosomal nephritis

Estimation	Schistosomal nephritis (mean ± standard deviation)[a]	Nonschistosomal nephritis (mean)[b]
protein in urine	7.2 ± 1.7	5
serum albumin	18 ± 5	19
serum globulin	31.3 ± 7	27
serum cholesterol	3.07 ± 1.521	3.00
blood urea	0.384 ± 0.141	1.05
haemoglobin	102 ± 25.5	74
liver cirrhosis (%)	35.2	0.0
hypertension (%)	64.7	100
total number of patients	17	2

[a] Levels of urine and blood constituents are given in g/litre.
[b] Since there were only 2 nonschistosomal cases the standard deviation could not be calculated.

to be normal; they presented a picture of glomerulosclerosis very similar to the diffuse glomerulosclerosis of the diabetic (Fig. 2). There was a membranous homogeneous thickening of the capillary walls that was more conspicuous in the axial region of the glomerulus, decreasing gradually towards the periphery of the tuft. The thickened capillary walls were positive to periodic-acid–Schiff's reagent (PAS) and in some areas were fibrillar. The glomerular capillaries usually remained patent. The glomerulosclerotic changes appeared uniform and diffuse in all glomeruli outside the patches of pyelonephritis. In three biopsies, focal sclerotic hyalinization in addition to the diffuse glomerulosclerosis was observed in the axial regions. Usually, no changes were noted in the cellular population of the glomerulus. Hyalinization of the glomerular arterioles was observed in some biopsies and there was a tendency for this change to correlate with the occurrence and the degree of hypertension in the patients.

Table 3. Proteinuria in schistosomal and nonschistosomal pyelonephritis

Group	No. of cases	Mean quantity of protein in urine (g)	Standard deviation
patients with schistosomiasis	41	3.1	± 3.6
patients without schistosomiasis	23	1.3	± 1.2
calculated t (Welch–Aspin test)	2.925		

Electron-microscopy showed the more important changes to be localized in the axial endothelial cells and the axial cytoplasmic matrix. The axial cells were hypertrophied and contained an excess of deposits similar to basement membrane in their cytoplasm (Fig. 3). Electron-dense deposits were found on the endothelial side of the basement membrane, in particular near to, or underneath, the axial endothelial cells (Fig. 4), and similar deposits were seen in the cytoplasm of the axial cells (Fig. 5). Electron-dense deposits were also seen to permeate the basement membrane of the glomerular capillaries, adding to its thickness (Fig. 6). No " humps " like those described in poststreptococcal glomerulonephritis were observed. Epithelial cells sometimes retained their foot processes but more commonly they had become confluent and were spread over the external surface of the basement membrane (Fig. 7). In these areas, linear electron-dense deposits were seen along the cytoplasmic border of the epithelial cells.

DISCUSSION

Evidence has been presented by Gelfand (1962, 1964, 1968) to suggest that chronic pyelonephritis might arise in severe urinary schistosomiasis and that it might, in turn, be another factor in the causation of hypertension or chronic renal failure in people living in an area where urinary schistosomiasis is endemic. Gelfand did not refer to the development of a nephrotic syndrome in schistosomal nephritis, but we have found schistosomiasis to be the most common of all diseases presenting with a nephrotic syndrome in this renal unit; it was responsible for 50.5% of all cases of nephrosis. The difference in the frequency of the nephrotic syndrome between patients with schistosomal and those with nonschistosomal pyelonephritis was statistically significant. In all patients with schistosomiasis the history of urinary schistosomiasis and complicating pyelonephritis definitely preceded the manifestation of the nephrotic syndrome, indicating that the nephrotic syndrome in those patients was a complication of schistosomal nephritis, and not the converse.

It is commonly observed that many patients with

schistosomal nephritis without the nephrotic syndrome die from renal failure. It is probable that patients with schistosomal pyelonephritis whose glomerular function is relatively unimpaired may show a nephrotic syndrome, while those with an impaired glomerular filtration rate show nitrogen retention but no nephrotic syndrome. Oedema in the former group of patients will disappear with the fall in the proteinuria that follows the progressive impairment of glomerular function. However, patients with schistosomal nephritis and the nephrotic syndrome sometimes die from renal failure while they still have marked proteinuria and oedema.

Histologically, the glomeruli of these patients with nephrotic schistosomal pyelonephritis in areas away from pyelonephritic patches, showed a characteristic lesion—namely, a diffuse thickening of the glomerular capillary walls particularly in the axial region of the glomerulus, sometimes associated with focal thickening of the capillary wall. This lesion is very similar to those first described by Andrade & Queiroz (1968) in the renal glomeruli of patients dying from the hepatosplenic form of schistosomiasis, and confirmed in a later report (Andrade et al., 1971). Similarly, the electron-dense deposits observed in this study by electron-microscopy are morphologically identical with those found in the kidneys of patients with hepatosplenic schistosomiasis (Da Silva et al., 1970). Similar, but less pronounced, lesions, seen by light- and electron-microscopy, have also been described in patients with hepatic cirrhosis. Such lesions were called hepatic glomerulosclerosis by Sakaguchi et al. (1965), and cirrhotic or hepatic glomerulonephritis by Fisher & Perez-Stable (1968).

The possible mechanisms by which the heavy proteinuria in schistosomal nephritis gives rise to the nephrotic syndrome are as follows.

(1) The proteinuria might result from damage to the glomerular filtration barrier, leading to the leakage of excess protein in the glomerular filtrate; an immunological basis for this damage is most likely. The schistosome worms and their ova produce a range of somatic and metabolic antigens (Andrade et al., 1961; Smithers & Williamson, 1961; Kent, 1963), and under carefully defined conditions in experimental animals circulating antigen–antibody complexes can produce glomerular lesions in which deposits containing antigen, antibody, and complement become localized on the epithelial side of the glomerular basement membrane. Similar lesions have been reported in patients with renal lesions of systemic lupus erythematosus (Sabbour, 1966). In the nephrotic syndrome associated with *Plasmodium malariae* infections, renal lesions containing immunoglobulin, complement, and malarial antigens have been described.

Da Silva et al. (1970) reported that in schistosomiasis the glomerular lesions contain IgG, IgM, and complement (detected by immunofluorescence methods). Further studies should be made to determine whether the immunoglobulin represents anti-schistosomal antibodies and whether schistosomal antigens can be identified. The immune reaction might also be produced by the combined effect of bacterial and schistosomal antigen.

Damaged renal tissue in pyelonephritis can liberate antigenic material that stimulates an autoimmune reaction. The prolonged and repeated action of these antigenic stimuli could lead to glomerular changes akin to those produced experimentally in animals subjected to repeated antigenic stimulation, which showed a sequence of glomerular changes from cellular proliferation to glomerulosclerosis and amyloidosis (Laufer et al., 1959). The diffuse and focal basement-membrane-like deposits in the glomerular capillaries and the axial cytoplasmic matrix demonstrated in this study might be the result of such antigenic stimulation.

(2) The proteinuria might be the result of a toxic effect or idiosyncrasy to the antimony compounds used in the treatment of schistosomiasis. However, the nephrotic syndrome did not develop soon after treatment was started. Moreover, some of the patients with schistosomal nephrosis did not receive treatment for schistosomiasis at any time in their lives.

(3) Diminished tubular reabsorption of protein filtered through the glomeruli was also considered to be a possible mechanism for the production of proteinuria in the nephrotic syndrome in general. The importance of this factor may be more pronounced in diseases such as pyelonephritis, which is characterized by extensive tubular damage, and, in particular, urinary schistosomiasis, which gives rise to an obstructive uropathy (stricture ureters and bladder-neck obstruction).

(4) If there is also a leakage of proteins through the schistosomal lesions in the urinary tract (e.g., the polypi, cystitis cystica, cystitis glandularis, bladder ulcers), the loss will contribute to the hypoalbuminaemia, which is essentially glomerular in origin.

RÉSUMÉ

ÉTUDE CLINIQUE ET ANATOMO-PATHOLOGIQUE DE LA NÉPHRITE SCHISTOSOMIENNE

Sur 41 malades admis dans un hôpital du Caire (Egypte) pour schistosomiase urinaire et pyélonéphrite chronique secondaire, 17 étaient atteints d'un syndrome néphrotique avec forte protéinurie (plus de 3 g de protéines par jour), hypoalbuminémie (moins de 3 g/100 ml) et œdème généralisé. Dans ce groupe de 17 patients, 11 (64,7%) présentaient de l'hypertension, 4 (23,3%) un certain degré de rétention azotée et 6 (35,3%) de l'hypercholestérolémie. Le sédiment urinaire montrait la présence de pus, d'érythrocytes, de cylindres granuleux et leucocytaires.

Des biopsies ont été pratiquées chez les malades néphrotiques en vue d'étudier les altérations du tissu rénal par microscopie optique et électronique. Dans tous les cas, les lésions de pyélonéphrite étaient manifestes. En dehors des zones atteintes, on observait de la sclérose glomérulaire avec épaississement homogène des parois vasculaires, plus accentué dans la région axiale du glomérule. Au microscope électronique, les cellules endothéliales axiales apparaissaient hypertrophiées. Des dépôts opaques aux électrons étaient décelés dans la membrane basale et dans le cytoplasme des cellules axiales.

Selon les auteurs, un mécanisme immunologique est probablement à l'origine des lésions de l'appareil glomérulaire et de l'atteinte de la fonction de filtration. D'une part, les schistosomes et leurs œufs renferment une variété d'antigènes somatiques et métaboliques. Les complexes antigène-anticorps circulants produiraient des lésions du glomérule par fixation à son niveau d'antigènes, d'anticorps et de complément. D'autre part, les lésions de pyélonéphrite pourraient amener la libération de matériel antigénique provoquant une réaction d'auto-immunité responsable des altérations glomérulaires.

On estime que la schistosomiase urinaire est le principal facteur étiologique des syndromes néphrotiques observés dans la région.

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