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Nephropathy in Patients with Drug Addiction

Evolution of Pathological and Clinical Features

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Summary. The course of the nephropathy in patients with drug addiction has been studied in six subjects. The nephrotic syndrome was the presenting feature in all, with two progressing to terminal renal failure in less than a year.

Serial percutaneous renal biopsies revealed the basic lesion to be a mild non-specific increase in PAS-positive material in the mesangial areas. This was more marked in the two patients with renal failure who, in addition, had segmental PAS-positive material in the glomerular capillary loops, focal tubular dilatation and atrophy, interstitial edema and mononuclear cell infiltration. Immunofluorescent staining revealed lumpy granular staining. IgG, present at the onset of the nephrotic syndrome, subsided as the first two patients developed renal failure, while β_1C and IgM, negative at the onset, became positive. Electron microscopy revealed focal basement membrane thickening and deposition of homogenous, finely granular electron-dense material predominantly in the mesangial areas.

Our findings indicate that renal damage secondary to immune-complex deposits develops in the addict. The presence of interstitial swelling, mononuclear infiltration and tubular dilatation signals rapid deterioration of renal function and a grave prognosis, while their absence indicates a more prolonged indolent course.

The renal complications of drug addiction have recently been the subject of some scrutiny (Citron, 1970; Kilcoyne, 1972; Salomon, 1972; Eknoyan, 1973; Rao, 174; McGinn, 1974). In a review of the medical complications of narcotic addiction, Sapira (1968) stated that renal function in the addict was usually associated with bacterial endocarditis. He, however, also made reference to an unpublished autopsy study among narcotic addicts in Lexington, Kentucky over a 30-year period in which a high incidence of "chronic glomerulonephritis" was noted. Recently the development of the nephrotic syndrome has been reported in these subjects and has been considered to be causally related to drug addiction, inasmuch as no other apparent etiology could be demonstrated. McGinn (1974) and associates, on renal biopsy of five of their seven patients, found "lesion-less disease" which was refractory to steroid and immunosuppressive therapy. By contrast, Kilcoyne (1972) detected focal membrano-proliferative glomerulonephritis with deposition of IgM and β_1C. Salomon (1972) performed percutaneous renal biopsies on 14 unselected heroin addicts with essentially negative urinary findings and normal renal function. Nonspecific increase in mesangial matrix was present in twelve. Of the 5 cases studied by immunofluorescent microscopy, mesangial deposits of IgM were present in 3 and IgG in 2 while the β_1C fraction of complement was negative in 3 and only weakly positive in 2 (Salomon, 1972).

It is apparent that renal involvement due to deposition of immune-complexes occurs in the drug addict and to some extent contributes to the morbidity of these subjects. This communication reports our observations in six drug addicts seen during the past three years and found to have the nephrotic syndrome.

Materials and Methods

Some of the pertinent laboratory results are summarized in Table 1. All patients had ASO titers <125 Todd units and negative LE cell preparations, ANA titers, and hepatitis-associated antigen. Repeated blood and urine cultures were negative in all. Two of the patients had inexorable progression of their renal disease to uremia requiring dialysis within a few months despite steroid and immunosuppressive therapy in one of them. The other four have had a relatively more benign course although proteinuria still persists.

Kidney biopsies were performed under local anesthesia using a modified Vim-Silverman needle. The tissue obtained was processed as previously described from this laboratory (Eknoyan, 1972, 1973).

Results

Structural changes were present in the kidneys of all six patients and are summarized in Table 2.

Ligth Microscopy. A common feature in all the biopsy specimens was a non-specific and mild increase of PAS-positive material in the mesangial areas (Fig. 1). This change was more marked in the first two patients and was also present in their glomerular capillary loops as well in a focal segmental distribution (Fig. 2). These changes became progressively more severe on serial biopsies as renal failure developed in Patients 1 and 2 (Fig. 2 and 3, Table 2).

Another differentiating feature between the first two patients with renal failure and the last four with proteinuria only was the presence of tubular and interstitial changes in the former two. The earliest changes were focal tubular dilatation, interstitial edema and infiltration with mononuclear cells. Subsequently, as renal function deteriorated, tubular atrophy and interstitial infiltration increased and interstitial fibrosis developed (Table 2, Figs. 2, 3).

Immunofluorescent Studies. All the biopsy specimens showed varying degrees of lumpy granular deposits of antibodies or complement (Fig. 4, Table 2). The first biopsy on Patient 1, as well as the biopsies on the last four patients were negative for β_1C. By contrast, β_1C was positive in Patient 2, who presented in renal failure, and became positive in Patient 1 as he developed renal failure (Table 2). Another feature of note was the presence of IgG in the last four patients and on the first biopsy of Patient 1; whereas it was absent in Case 2 who presented in renal failure, and became negative in Case 1 as he developed renal fallure (Table 2: second and third biopsies). Moreover, IgM, present in the biopsy of the first two patients, was at best equivocal in Patients 3 through 6.

Electron Microscopy. In all glomeruli examined, there was focal mesangial basement membrane changes consisting of finely granular, electron-dense deposits. The basement membrane lining the capillary loops was normal in the last 4 cases with proteinuria only. In the first two patients, however, it was thickened, showed focal fragmentation and dense intramembranous deposits (Fig. 5, 6, Table 2). In addition, endocytoplasmic "virus-like tubular arrays" were present in the biopsy specimens from all cases (Fig. 6, Table 2).

Table 1. Laboratory data in patients with nephropathy of drug addiction

Patient	Date	Serum						Creatinine clearance	Protein excretion	Urinalysis
		Urea Nitrogen	Creatinine	Protein		Lipids				
				Albumin (Gm/100 ml)	Globulin (Gm/100 ml)	Cholesterol (mg/100 ml)	Total (mg/100 ml)			
		(mg/100 ml)	(mg/100 ml)					(ml/min)	(Gm/24 hr)	
1	3/22/72	20	2.3	1.2	3.6	—	—	43	18	5.8 WBC/HPF,
	5/11/72	16	1.2	2.7	3.5	510	1170	98	17	1–2 RBC/HPF
	9/11/72	43	4.5	1.9	3.9	520	1250	25	22.5	Few granular and waxy
	11/8/72	64	5.0	—	—	—	—	—	—	casts, oval fat bodies
	1/23/73	100	13.7	—	—	—	—	8	—	
	2/23/73	190	25	2.3	3.1	—	—	—	—	
	3/27/73	180	29	—	—	—	—	—	1.0	
2	7/11/72	55	5.8	1.4	2.9	530	980	27	16	15–20 WBC/HPF, few
	8/16/72	40	—	1.7	5.1	—	—	—	25	waxy and granular casts
	3/14/73	175	23	1.8	3.5	—	—	6	—	
	5/15/73	105	31	2.3	3.7	—	—	—	29	
3	6/6/72	11	1.0	1.2	2.7	515	771	82	17	5–10 WBC/HPF, granular
	4/18/73	27	1.0	1.8	3.0	—	—	90	9.5	casts, oval fat bodies
4	3/9/71	8	0.9	1.6	3.9	—	—	90	4.2	13–15 WBC/HPF, occasional
	12/28/71	—	—	2.1	4.3	135	424	—	3.8	granular casts
	6/27/72	13	1.2	—	—	—	—	—	—	
5	8/28/72	7	1.1	2.6	3.2	475	217	82	10	10–12 WBC/HPF, 0–3 RBC,
	11/4/72	10	1.1	—	—	—	—	—	31	few granular casts
6	8/13/72	8	1.0	1.4	3.7	355	—	102	11	3–5 WBC/HPF,
										1–5 RBC/HPF.
										Occasional granular casts

Table 2. Renal biopsy findings

Patient	Date	Light microscopy			Immunofluorescent[a] microscopy			Electron microscopy			
		Glomeruli[b]	Tubules	Interstitium	IgG	IgM	β_1C	Focal mesangial deposits	Intramembranous deposits	Foot process fusion	"Virus-like tubular arrays"
1	3/72	Focal: mesangial only	Focal dilatation	Mononuclear infiltration	++	+	0	+	+	±	Few
	9/72	Focal: mesangial and capillary wall	Focal dilatation and atrophy	Increased infiltrate	+	+	++	++	++	+	Few
	3/73	Increased in mesangial and capillary wall. Sclerosis	Increased atrophy	Infiltration and fibrosis	0	0	+++	++	++	++	Few
2	7/72	Focal: mesangial and capillary wall	Focal dilatation	Infiltration fibrosis	±	+	++	++	++	+	Few
	5/73	Extensive in mesangial and capillary wall. Sclerosis	Atrophy and dilatation	Increased fibrosis and infiltration	±	±	+++	++	++	+	Few
3	6/72	No glomeruli	Normal	Normal	++	0	±	++	Normal	±	One
	4/73	Focal: mesangial	Slight tubular dilatation	Normal	0	±	0	+	Normal	—	—
4	1/72	Focal: mesangial	Normal	Normal	+++	±	0	+	Normal	—	One
5	9/72	Focal: mesangial	Normal	Normal	++	±	0	+	Normal	—	Few
6	8/72	Focal: mesangial	Slight tubular dilatation	Normal	++	±	0	+	Normal	±	—

[a] Fluorescence and membranous deposits are graded 0 to 4+ on basis of intensity and extent.
[b] Refers to increased PAS-positive material.

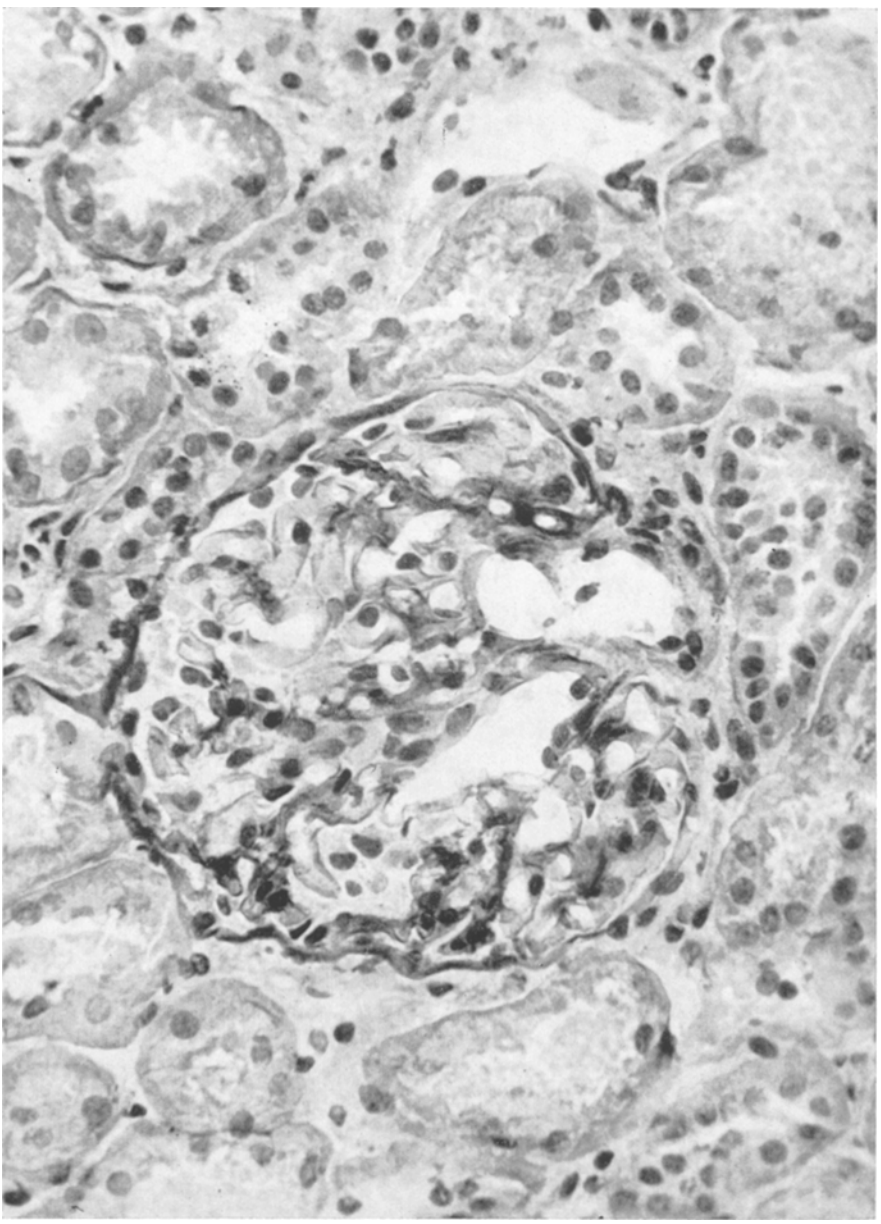

Fig. 1. Light microscopy of renal tissue from Patient 5. There is only a mild increase of PAS-positive material in the mesangial areas. Note the absence of interstitial changes seen in Fig. 2 and the normal appearing tubules (PAS, ×485)

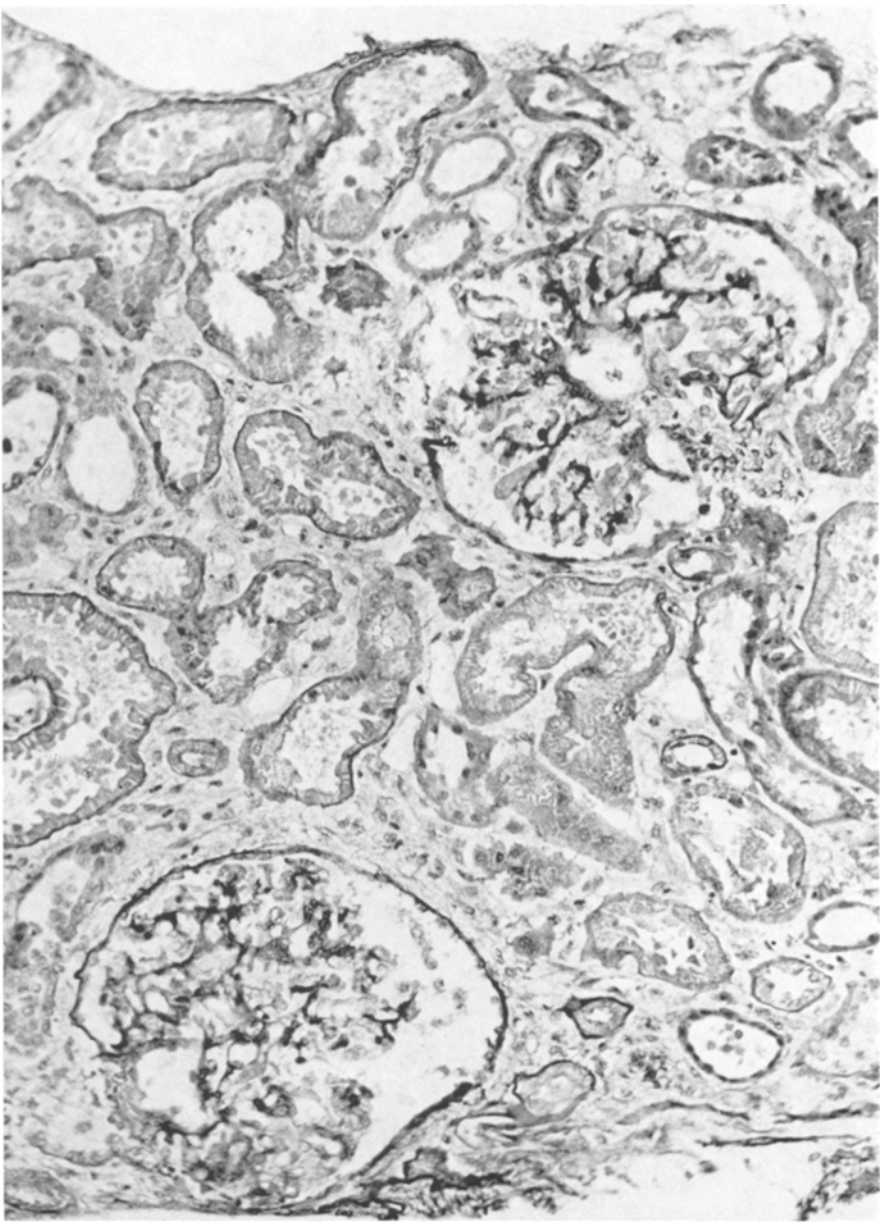

Fig. 2. Section of first kidney biopsy of Patient 1 showing two glomeruli demonstrating the mild increase in PAS-positive material primarily in the mesangial areas. Note the tubular dilatation, the interstitial edema and slight mononuclear cell infiltration(PAS, ×215)

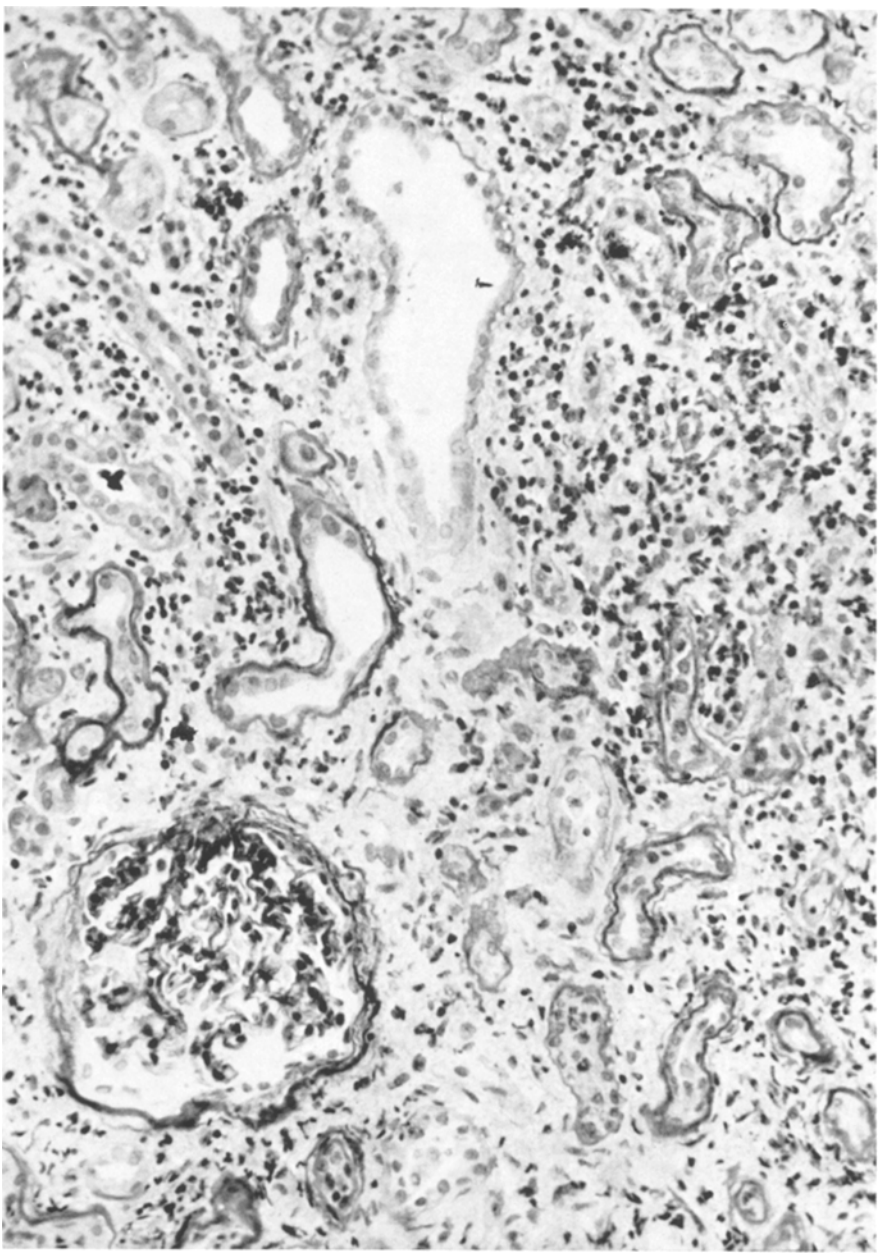

Fig. 3. Third biopsy from Patient 1, one year following the first biopsy shown in Fig. 2. The glomerular PAS-positive material is increased with early sclerotic changes and increased matrix in the vascular pole. The tubular changes of atrophy, degeneration and dilatation and the interstitial edema and mononuclear cell infiltrate are now more marked (PAS, ×215)

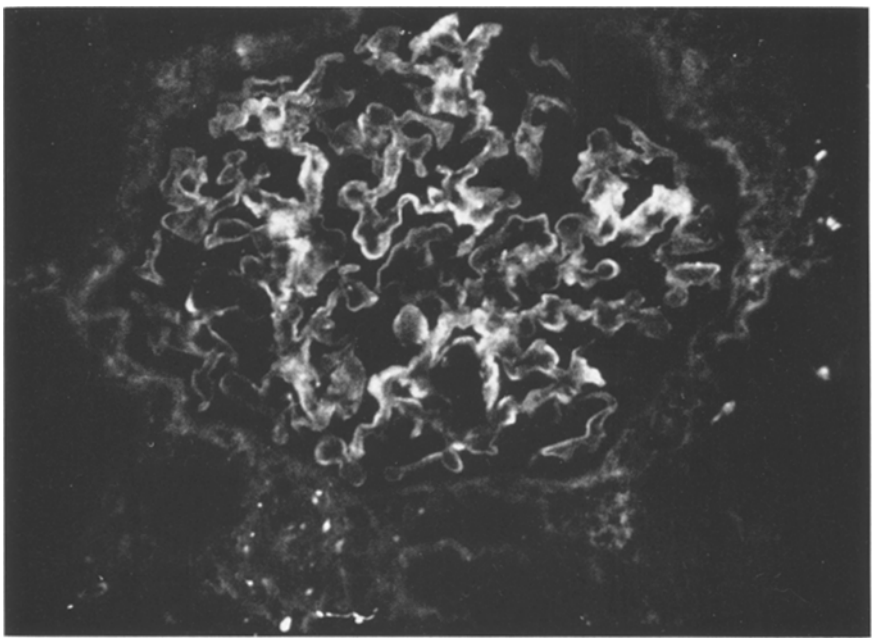

Fig. 4. Section of kidney from Patient 5 stained with fluorescein-labelled anti-IgG. Granular immunofluorescence is present in the glomerular capillary loop which is more accentuated and confluent in the mesangial areas. A linear appearance in parts of the glomerular capillary loop is present but is not as prominent as the granular staining in the mesangial areas (×500)

Discussion

A variety of renal diseases may result from the repeated injection of drugs with the apparently contaminated paraphernalia which drug addicts utilize. First is the focal or diffuse glomerulonephritis which develops in patients with bacterial endocarditis (Gutman, 1972; Tu, 1969). Next is the lesion associated with acute viral hepatitis, characterized by proteinuria of less than 2 gm/day and focal increase in PAS-positive material in the mesangium (Eknoyan, 1972, 1973). Renal involvement with necrotizing angiitis has also been reported (Citron, 1970). Another group of these patients may present with acute renal failure secondary to myoglobinuria due to muscle injury at the site of self-injection of water which is apparently used during withdrawal (unpublished observation). Finally, nephrotic syndrome of no apparent etiology is gradually becoming recognized as occurring in greater frequency in the drug addict (Kilcoyne, 1970; Eknoyan, 1973; Rao, 1974; McGinn, 1974).

The nephrotic syndrome of the patients described in this report falls in this latter group and could be categorized under the idiopathic variety. The negative blood cultures as well as the absence of fever, significant cardiac murmurs and hematuria mitigate against the possibility of bacterial endocarditis. All six patients were repeatedly hepatitis-associated antigen negative by radioimmunoassay and had no laboratory or clinical evidence of hepatic functional impairment. Cases 1

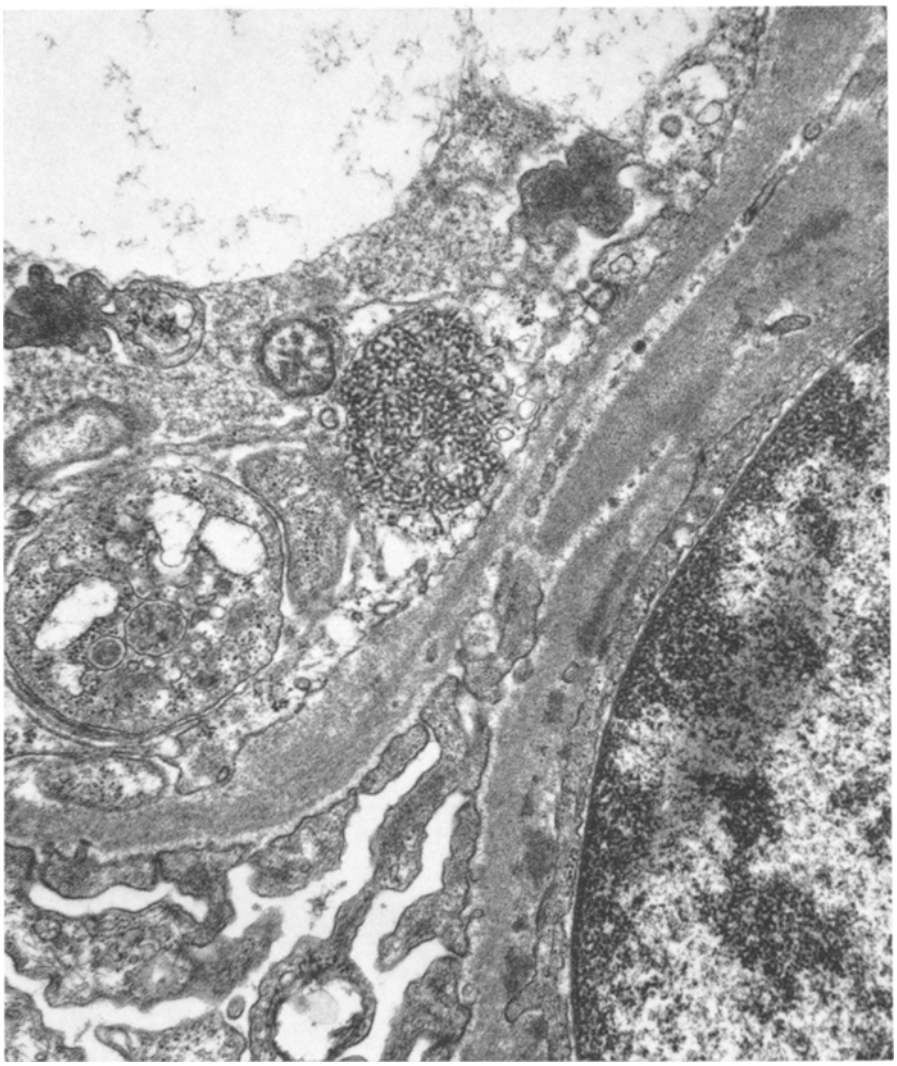

Fig. 5. Electron micrograph of renal tissue from first biopsy on Patient 1. Note the deposits of electron-dense material in the basement membrane in the lower right part of the illustration, and in its center the "virus-like tubular arrays" in the endothelial cell (×30700)

and 6 did have a past history of acute viral hepatitis. An immune-complex disease of the kidney with a similar pathology has been shown to occur in viral hepatitis irrespective of the demonstrated presence or absence of hepatitis-associated antigen (Eknoyan, 1972). However, the available short-term follow-up studies by Conrad (1964) and our own experience have not shown an active progression of this renal lesion. Furthermore, the only reported instances, so far, of nephrotic syndrome in association with viral hepatitis have been in patients with chronic hepatitis associated antigen positive hepatitis (Combes, 1971;

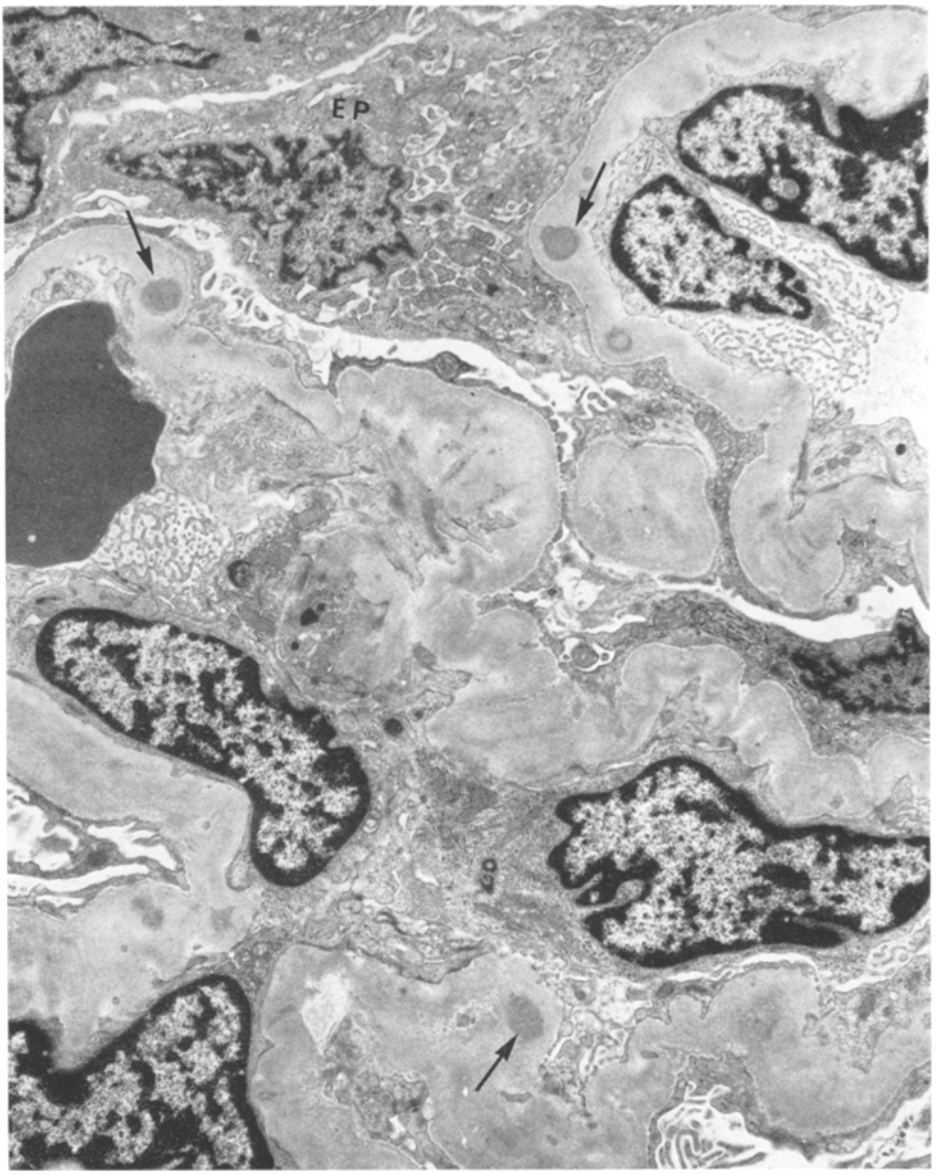

Fig. 6. Electron micrograph of renal tissue from first biopsy on Patient 2. Deposition of electron-dense material in basement membrane is indicated by arrows. There is increased infolding of the basement membrane in the mesangial area, and limited fusion of epithelial cell (*EP*) foot processes (×8200)

Randall, 1971) which was not the case in these patients. It is then to this group of patients with nephrotic syndrome of no apparent etiology occurring in the drug addict that we refer to as having the nephropathy of drug addiction.

Admittedly, the specificity of the association of the nephrotic syndrome with drug abuse may be circumstantial. However, the increasing number of such patients being recognized and the course and pathology described herein would strongly suggest that this may well be a new form of nephropathy. If so, this may best be referred to as due to drug addiction rather than one of the addictive drugs—specifically heroin—since most patients have used more than one drug and one of our patients (Case 3) had used heroin on two occasions only. In addition, one of the patients reported by McGinn (1974) had used cocaine only.

Few long-term follow-up observations of drug addicts who develop renal lesions have been published (Kilcoyne, 1970; McGinn, 1974; Rao, 1974). This report of such patients followed up by serial biopsies to the incipience of uremia clearly demonstrates that, in some, this can lead to end-stage renal disease in a rather rapidly progressive fashion. In addition, the present experience, albeit limited, has demonstrated the seeming futility of steroid and immunosuppressive therapy in these patients. McGinn (1974) reported a similar experience.

On the basis of our studies and the few reports in the literature it is possible to characterize the evolution of the pathological and clinical features of this disease. The basic lesion observed on renal biopsy is a mild non-specific increase in PAS-positive material in the mesangium. The presence of immune-complexes in our patients is evidenced by the positive stainings of IgG and β_1C and electron-dense deposits in the mesangial basement membrane. Thus, these patients seem to fall into a mild form of what has been described as focal by Heptinstall (1966) or mesangiopathic glomerulonephritis by Germuth (1973). Conceivably, the relatively more severe involvement of the glomeruli in the first two patients (Fig. 3) could be secondary to the progressive interstitial changes.

The course of the disease in these patients may fall into one of two forms. The first, illustrated by our Cases 3–6, is characterized by massive proteinuria, normal BUN, and while their creatinine clearance may be slightly reduced (80–100 ml/min) there is no progressive deterioration of renal function, at least over the two years they have been followed. Renal biopsy in this group reveals glomerular changes consisting only of a slight increase in PAS-positive material in the mesangium, negative immunofluorescent staining for β_1C but positive staining for IgG. The patients reported by Salomon (1972) had essentially similar biopsy findings but with normal urinary findings. Presumably that would constitute the stage that precedes the onset of clinical nephrotic syndrome seen in our patients. The second form is illustrated by our first two cases who, in addition to massive proteinuria, demonstrated rapid deterioration of renal function eventuating in uremia in less than a year. The renal biopsy findings in this group initially showed essentially the same glomerular changes as the first group. In addition, however, there was tubular dilatation and atrophy as well as interstitial edema and infiltration with mononuclear cells. As the disease progressed in this group there was involvement of the capillary loops in addition to the mesangium, the tubular changes of atrophy became more prominent, interstitial fibrosis developed and immunofluorescent staining for β_1C and IgM became positive while the staining for IgG diminished.

Excluding the progressive changes of Cases 1 and 2, and as we have previously described (Eknoyan, 1973), the renal alterations in drug addicts independent of

their clinical presentation, share the same immunofluorescent staining characteristics in the majority of instances. In addition, they are characterized by the presence of endothelial microtubular inclusions, the so-called "virus-like tubular arrays" (Table 2, Fig. 5). This was interpreted (Eknoyan, 1973) to suggest that the renal lesions that develop in drug addicts are possibly a specific entity ascribable to drug addiction, and that there may well be only one pathogenetic mechanism shared by the renal lesions of the nephropathy of drug addiction with those of bacterial endocarditis and viral hepatitis which develop in these subjects. Whether the antigenic stimulus is a viral or bacterial agent introduced into the circulation of the addict, the drug itself, its vehicle, or other impurities is purely speculative at the moment. Independent of the etiology of the antigen introduced, it appears that it is its repeated intravenous injection which seems to initiate an immunologic process that results in renal damage secondary to immune-complex deposits.

The possible salutary effects of successful drug withdrawal on the course of the renal lesion deserves consideration. Patient 1 continued the use of heroin up to the development of uremic symptoms. It is tempting to speculate that, analogous to the renal functional and pathological improvement that follows recovery from acute viral hepatitis and to the successful antibiotic treatment of bacterial endocarditis, the nephropathy of patients with drug addiction might undergo remission if the periodic introduction of the offending agent is discontinued. There is, obviously, a need for more critical investigation and diligent long-range follow-up of these patients before some of the questions raised can be answered.

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