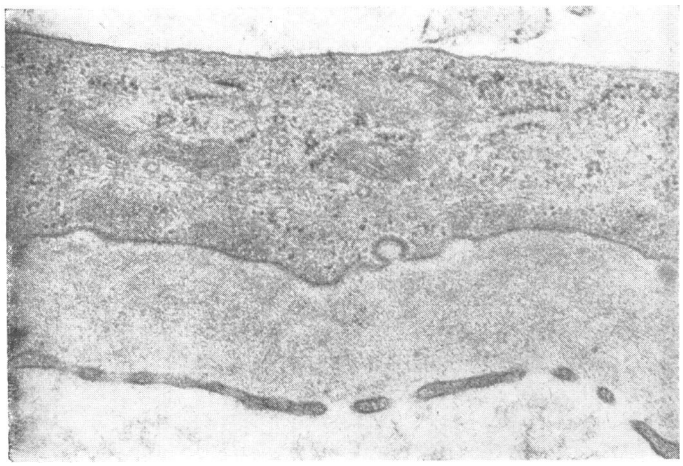

FIG. 1

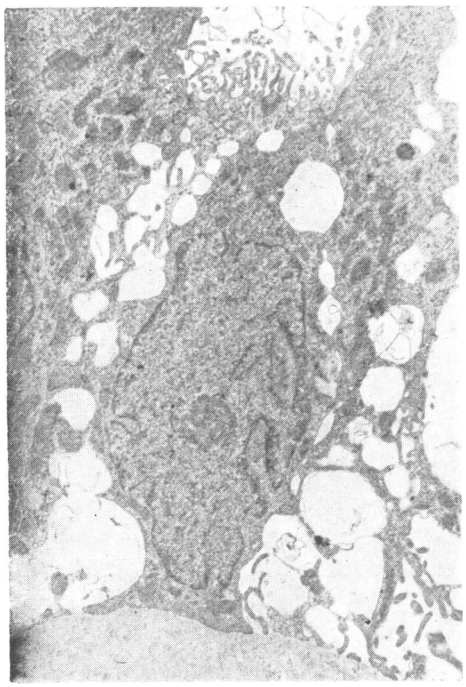

FIG. 2

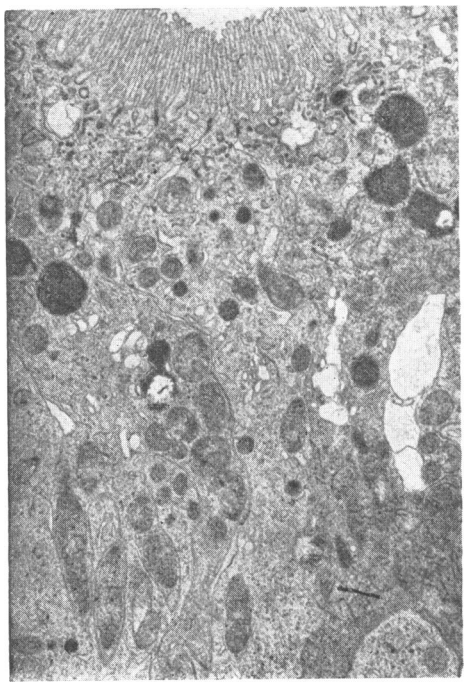

FIG. 5

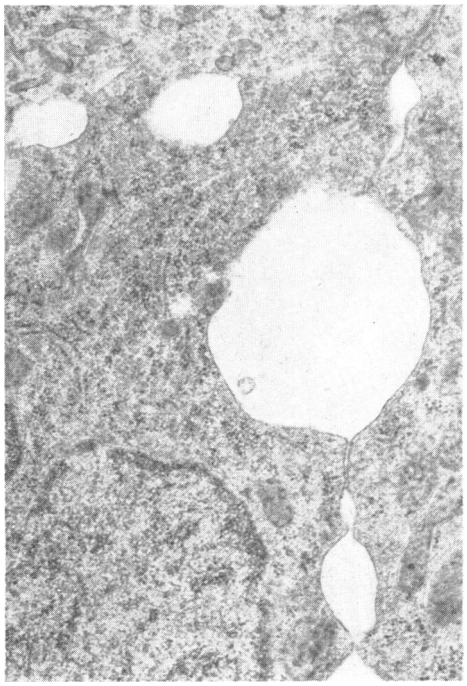

FIG. 3

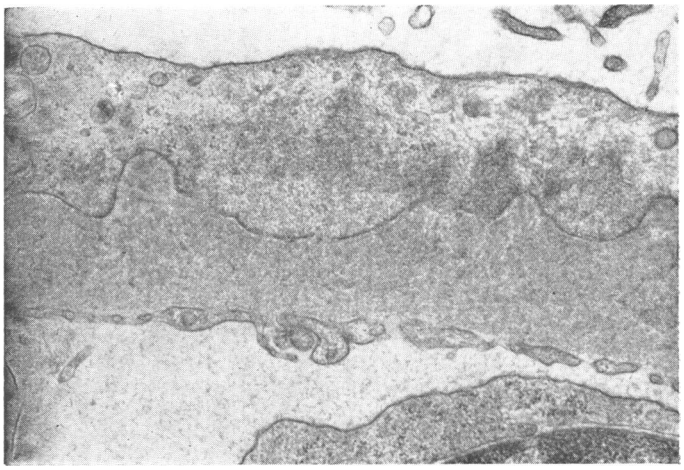

**FIG. 4**

FIG. 1.—Case 1. Glomerular tuft. Epithelial cell (top) has lost its foot processes. The basement membrane is uniformly thickened to 920 mμ. (×34,680.)

FIG. 2.—Case 1. Proximal convoluted tubule. There is gross vacuolation of the epithelium, visible also in the light microscope. The cytoplasm is electron-dense, and the cell appears degenerate. (×5,710.)

FIG. 3.—Case 1. Proximal convoluted tubule. The vacuoles lie between adjacent epithelial cells and communicate one with another. (×32,310.)

FIG. 4.—Case 2. Glomerular tuft. Epithelial cell (top) foot processes are lost. The basement membrane varies in thickness from 560 to 800 mμ. (×18,600.)

FIG. 5.—Case 2. Proximal convoluted tubule. The cell structure is well preserved, in contrast to the tubular cells in Case 1. (×5,490.)

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# Nephrotic Syndrome with Heart Disease: A Reappraisal

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[WITH SPECIAL PLATE FACING PAGE 575]

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**Summary: The evidence that heart failure alone may cause a nephrotic syndrome is inconclusive. Mercurial diuretics, which have also been implicated as a cause of the nephrotic syndrome, had been given in 23 of the 24 well-documented cases.**

**Two cases of heart disease and nephrotic syndrome are described. Glomerular lesions were minimal on light microscopy, but thickening of the glomerular tuft basement membrane and partial fusion of the epithelial cell foot processes were apparent on elecronmicroscopy. The response to prednisone was such as to justify a trial of corticosteroid therapy in such cases despite the presence of cardiac disease.**

## Introduction

Standard textbooks of renal disease usually include heart failure as one cause of the nephrotic syndrome (Strauss and Welt, 1963; Robson, 1967). However, review of the literature shows that patients who have developed this complication have invariably been receiving mercurial diuretics which are themselves alleged to cause the nephrotic syndrome.

The purposes of this paper are threefold: to describe two patients with heart disease who developed the nephrotic syndrome, one of whom had never received mercurial diuretics; to describe the light and electronmicroscopic appearances of the renal biopsies of these patients; and to review the evidence for the statement that heart failure may cause the nephrotic syndrome.

## Case 1

A woman aged 61 was diagnosed in 1957 as having mitral stenosis and incompetence. She remained relatively symptom-free until December 1966, when she complained of increasing dyspnoea and ankle oedema. Cardiac failure was diagnosed, and treated with digoxin, a thiazide diuretic, and weekly injections of mersalyl. There was a good response and the patient remained well until September 1967, when increasing oedema rapidly developed despite intensive diuretic therapy. At this stage she was found to have developed heavy proteinuria and was referred to hospital. On admission she was grossly oedematous but not dyspnoeic. The jugular venous pressure was not raised. Initially only a pansystolic murmur was audible at the cardiac apex, though later an opening snap and mid-diastolic murmur characteristic of mitral stenosis appeared (see below).

Investigations on admission: Hb 15.6 g./100 ml., P.C.V. 50%, E.S.R. 117 mm. in one hour, blood urea 76 mg./100 ml., plasma creatinine 1.3 mg./100 ml., 24-hour creatinine clearance 43 ml./min., plasma cholesterol 860 mg./100 ml., plasma albumin 3.0 g./100 ml., plasma protein electrophoresis showed increased alpha-2 globulin and gammaglobulin, urinary protein excretion 10–27 g./24 hours. High dose intravenous pyelogram was normal; chest *x*-ray picture showed an increase in the transverse diameter of the heart with evidence of increased pulmonary blood flow through the upper zones.

Percutaneous renal biopsy revealed glomeruli which appeared normal in the light microscope. In contrast, there was tubular atrophy with vacuolation of the epithelial cells of the proximal convoluted tubules. Focal collections of chronic inflammatory cells were present in interstitial tissues together with interstitial fibrosis. There was no evidence of disease of the arteries or veins. Electronmicroscopy revealed a widespread uniform basement membrane thickening of the glomerular tuft to 920 m$\mu$, combined with a partial fusion of the epithelial cell foot processes (Special Plate, Fig. 1). Striking changes were seen in the tubules; the proximal convoluted tubules showed marked degenerative changes with extreme electron density of the cytoplasm and gross vacuolation (Special Plate, Fig. 2). The vacuoles were predominantly due to expansion of the intercellular space (Special Plate, Fig. 3), being limited by the cell junctions at the luminal surface. Some of the tubular cells had lost their microvilli, and these cells were being extruded into the lumen of the tubule. A minority of proximal convoluted tubules appeared well preserved, though the vacuolation of the cytoplasm was rather more pronounced than usual. In the distal convoluted tubules and in the collecting tubules individual cells appeared degenerate, and were separated from the surrounding cells.

In view of the "minimal" histological change in the glomeruli on light microscopy, the patient was treated with prednisone in an initial dose of 60 mg. daily. The rapid and complete remission of the nephrotic syndrome which followed can be seen from Fig. I. After three months of steroid treatment the drug was withdrawn, and eight weeks later neither proteinuria nor oedema had recurred, and the serum albumin remained normal.

## Case 2

A man aged 64 presented in June 1967 with a nine-month history of angina of effort and ankle oedema which had been treated without success with a thiazide diuretic. He had never received organic mercurials. On examination the jugular venous pressure was not raised but there was marked ankle oedema. There was palpable left ventricular hypertrophy, and the murmurs of aortic

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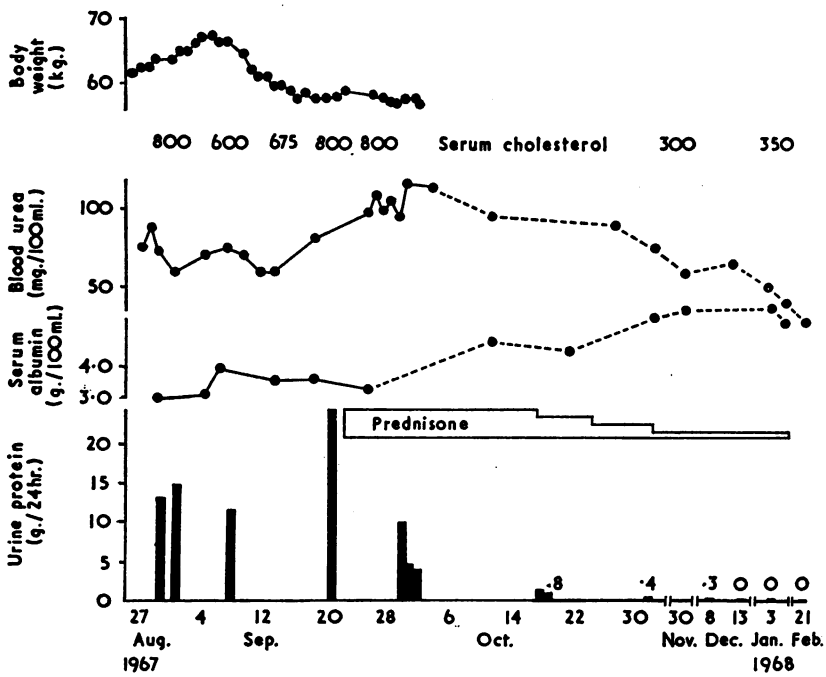


FIG. I.—Course of the nephrotic syndrome in Case 1.

stenosis and incompetence were present. Urine examination revealed heavy proteinuria. Investigations on admission: Hb 12.3 g./100 ml., P.C.V. 40%, E.S.R. 94 mm. in one hour, blood urea 34 mg./100 ml., plasma creatinine 0.9 mg./100 ml., 24-hour creatinine clearance 96 ml./min., plasma cholesterol 490 mg./100 ml., plasma albumin 2.3 g./100 ml., urinary protein excretion 5–16 g./24 hours. Intravenous pyelogram was normal; chest *x*-ray picture showed cardiac enlargement.

Percutaneous renal biopsy revealed that a few glomeruli showed varying degrees of ischaemic change from periglomerular fibrosis to hyalinization of the tuft, but the majority of glomeruli were not scarred. However, in these there were focal areas of basement membrane thickening. The tubules showed moderate atrophy proportional to the degree of ischaemic glomerular sclerosis. Interstitial fibrous tissue was increased, with a light lymphocytic and plasma cell infiltration of the stroma. There was intimal proliferation of the interlobular arteries. Electronmicroscopy confirmed the basement membrane thickening of some capillary loops in the glomerular tuft, on average 750 mμ. In these areas there was fusion of the foot processes of the epithelial cells (Special Plate, Fig. 4). The tubules showed focal areas of atrophy corresponding with the scarred glomeruli, but elsewhere the tubular structure was well preserved (Special Plate, Fig. 5).

Treatment was instituted with prednisone in an initial dose of 60 mg. daily. Though the response has been less complete than in Case 1, urinary protein excretion has fallen to subnephrotic levels (Fig. II). The plasma albumin has risen to 5.2 g./100 ml. and oedema has disappeared.

## Discussion

There is no doubt that the inorganic salts of mercury are nephrotoxic (for a review see Emmerson, 1967) and may cause the nephrotic syndrome (Kazantzis *et al.*, 1962). However, the ability of organic mercurials to produce this syndrome has been questioned on the grounds that in every case reported to date the patient had been undergoing treatment for heart failure, which is itself alleged to cause the nephrotic syndrome (Burack *et al.*, 1958). It is pertinent to consider the evidence on which this latter claim rests. Burack *et al.* described the nephrotic syndrome developing in four patients with cardiac failure treated with mercurial diuretics. In the three who survived, treatment with mercurials was continued, and in two the nephrotic syndrome remitted, while the third became oedema-free despite continuing hypoproteinaemia and proteinuria. Our second patient developed the nephrotic syndrome in association with heart disease, never having received mercurials. However, the Table shows that mercurial diuretics had been given to all 22 previously reported cases before the diagnosis of the nephrotic syndrome, suggesting a role for these compounds in the development of this syndrome.

Authors subscribing to the view that heart failure alone may cause the nephrotic syndrome tend to assume that renal venous hypertension is the mechanism responsible. Thus it is known that acute experimental constriction of the renal vein causes proteinuria (Wégria *et al.*, 1955), and renal venous thrombosis may cause the nephrotic syndrome. Some proteinuria is commonly found with heart failure, but it is uncertain whether the rare occurrence of a nephrotic syndrome in such patients represents an extension of the process responsible for the lesser degrees of proteinuria or whether it is due to some other factor. The development of a nephrotic syndrome in a few patients with constrictive pericarditis is also usually taken to indicate that a high central venous pressure is the mechanism responsible. However, all such patients appear to have received mercurials (Blainey *et al.*, 1954; Broustet *et al.*, 1957; Daugherty *et al.*, 1962). A high jugular venous pressure was not a feature of the cardiac patients who developed the nephrotic syndrome (see Table). Details are available for 15 patients, and in 12 of these the jugular venous pressure was raised to less than 2 cm. above the sternal angle.

One should realize, however, that the onset of the nephrotic syndrome may lower a previously raised venous pressure by reducing the plasma volume. In this context the gradual development of the mitral diastolic murmur in Case 1 during response to treatment is of interest. The intensity of such

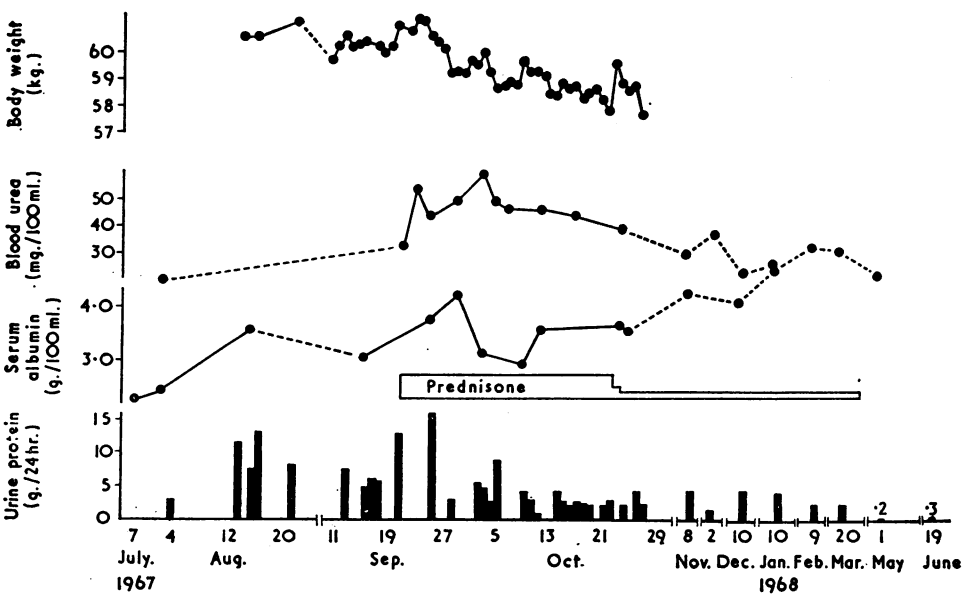


FIG. II.—Course of the nephrotic syndrome in Case 2.

*Details of Documented Cases*

| Author | No. of Cases | Cardiac State when seen with Nephrotic Syndrome | Mercurials | Renal Histology (Light) Microscopy | Steroids | Response |
|---|---|---|---|---|---|---|
| Derow and Wolff (1947) | 1 | ? | + | None obtained | − | — |
| Preedy and Russell (1953) | 1 | Not in failure | + | Degenerative changes in tubules and capsular epithelium | − | — |
| Munck and Nissen (1956) | 1 | All developed the nephrotic syndrome without worsening of their cardiac state | + | None obtained | − | — |
| | 2 | | + | " " | − | — |
| | 3 | | + | " " | − | — |
| | 4 | | + | Substantially normal | − | — |
| Riddle *et al.* (1958) | 1 | Not in failure | + | All three showed normal glomeruli with focal degeneration and regeneration of tubules | − | — |
| | 2 | " " " | + | | − | — |
| | 3 | " " " | + | | − | — |
| | 4 | Mild cardiac failure | + | None obtained | − | — |
| | 5 | " " " | + | " " | − | — |
| Clennar (1958) | 1 | Not in failure | + | Traces of tubular damage with regeneration. Glomeruli intact | − | — |
| Burston *et al.* (1958) | 1 | J.V.P. + 1 cm. | + | Normal glomeruli. Tubular degeneration | − | — |
| Joekes *et al.* (1958) | 1 | Not in failure | + | Normal glomeruli. Tubular atrophy | + | Complete |
| | 2 | J.V.P. + 2 cm. | + | Some ischaemic glomeruli, occasional basement membrane thickening. Tubular atrophy | − | — |
| Burack *et al.* (1958) | 1 | J.V.P. + 5 cm. | + | Patchy thickening of basement membrane | + | None |
| | 2 | J.V.P. + 10 cm. | + | Normal | − | — |
| | 3 | ? | + | None obtained | + | None |
| | 4 | ? | + | Normal | − | — |
| Thayer *et al.* (1961) | 1 | J.V.P. normal | + | Normal glomeruli, some tubular atrophy | − | — |
| Becker *et al.* (1962) | 1 | J.V.P. + 12 cm. | + | Slight focal thickening of basement membrane with focal proliferation. Hydropic degeneration of proximal tubules | + | Complete |
| Cameron and Trounce (1965) | 1 | J.V.P. raised | + | Membranous glomerulonephritis. Tubular atrophy | − | — |
| Present cases | 1 | J.V.P. normal | + | Normal glomeruli. Tubular atrophy | + | Complete |
| | 2 | J.V.P. " | − | Focal basement membrane thickening. Some tubular atrophy | + | Partial |

a murmur is related among other things to the cardiac output. It seems reasonable to postulate that in this patient the cardiac output was low initially owing to hypovolaemia and that when this was corrected the murmur became audible. The precise definition of cardiac failure is debatable, but the height of the central venous pressure seems particularly unsuitable as a criterion when the nephrotic syndrome is also present. It appears that the evidence available is inadequate to establish whether or not heart failure can itself cause the nephrotic syndrome without simultaneous exposure to mercurial diuretics. It may be that the circulatory disturbances due to heart disease summate with the effects of mercurials to produce the nephrotic syndrome (Cameron and Trounce, 1965). Impaired availability of nutrients to cells exposed to a potentially toxic chemical might conceivably underlie such an association.

In view of these uncertainties it is relevant to consider whether histological appearances help to clarify the role of mercury. Apart from an occasional clearly ischaemic glomerulus in Case 2 the appearances of the glomeruli in our patients were indistinguishable on electron microscopy (Special Plate, Figs. 1 and 4), though only Case 1 had received mercurials. There were, however, differences in the renal tubules, those in Case 1 corresponding with previous descriptions of light microscopic abnormalities seen in patients with mercurial intoxication (Preedy and Russell, 1953 ; Riddle *et al.*, 1958 ; Burston *et al.*, 1958), whereas in Case 2 tubular abnormalities were proportional to the ischaemic glomerular damage. The tubular abnormalities ascribed to mercury are not, however, specific, and gross tubular atrophy may occur in other conditions such as renal venous thrombosis. The latter condition cannot completely be ruled out in Case 1, though the prompt response to steroids makes this diagnosis unlikely. Histological examination therefore does not allow a precise evaluation of the aetiological role of mercury in the nephrotic syndrome associated with heart disease.

The histological appearances do, however, raise a matter of therapeutic importance, since in both our patients, and in 12 of the 15 previously reported cases in which these were studied, glomerular changes were "minimal" to light microscopy. This finding on biopsy in the nephrotic syndrome usually indicates a favourable outcome and a good response to steroid therapy (Rose and Black, 1967), which may occur even when acute renal failure has developed (Conolly *et al.*, 1968). The complete remission produced by steroids in our first patient and the worth-while improvement produced in the second indicate that a trial of steroid therapy should be given to patients with the nephrotic syndrome who have minimal glomerular abnormalities even in the presence of serious heart disease.

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