THE NEPHROTIC SYNDROME IN THE BANTU

A CLINICO-PATHOLOGICAL STUDY

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The nephrotic syndrome is a common clinical problem in South African Bantu adults.[1,2] Some cases are due to well-known causes such as diabetic glomerulosclerosis and systemic lupus erythematosus, but in the great majority the aetiology is obscure. Little is known about the underlying renal pathology in these cryptogenic cases. Our object here is to describe this pathology and to correlate it with the clinical and biochemical features.

SUBJECTS AND METHODS

Forty-four patients with the nephrotic syndrome were studied. In all, clinical and laboratory investigation failed to reveal any of the known causes of the nephrotic syndrome. All except 3 were urbanized Johannesburg Bantu, and all but 2 were unskilled manual labourers. The tribal distribution was similar to that of the Johannesburg Bantu population in general. There were 22 males and 22 females. Three patients were between 14 and 20 years of age, 31 between 20 and 40, and 10 between 40 and 57. Eleven of the females presented with the nephrotic syndrome during pregnancy; 7 of these were the subject of an earlier paper.[3]

All patients satisfied the conventional criteria for the nephrotic syndrome, presenting with oedema, proteinuria, hypoalbuminaemia and hypercholesterolaemia; in about one-third of the patients hypertension or azotaemia were present. In nearly all, the oedema was gross.

Biochemistry

The proteinuria was extremely variable, ranging from 0·5 to 30 G. per litre (Esbach), but in all patients the average urinary-protein excretion was greater than 3 G. per litre. Hypoalbuminaemia was constant, the serum-albumin level varying between 0·2 and 2·0 G. per 100 ml. In 29 patients it was less than 1 G., and in 15 between 1 and 2 G. per 100 ml. According to Kinnear,[4] the normal serum-albumin level in the Bantu is 3·3 $\pm$ 0·3 G. per 100 ml. Hypercholesterolaemia was nearly always present, the

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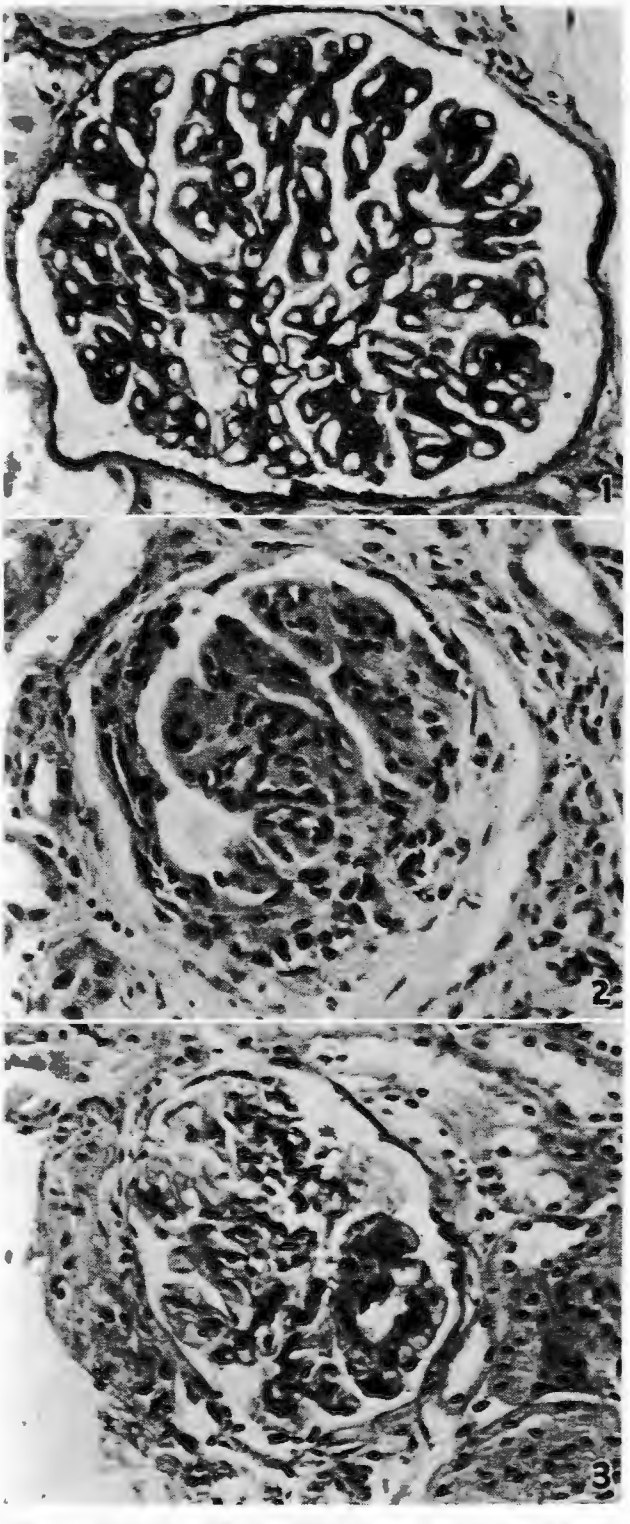


Fig. 1. Glomerulus showing diffuse basement-membrane thickening (periodic-acid Schiff × 480).

Fig. 2. Glomerulus showing marked thickening of the basement membrane and capsular proliferation with crescent formation (haematoxylin and eosin × 480).

Fig. 3. Glomerulus showing thickening of the basement membrane in part of the capillary tuft (periodic-acid Schiff × 480).

plasma-cholesterol level varying between 170 and 820 mg. per 100 ml. In 2 patients the serum-cholesterol level was between 175 and 250 mg. per 100 ml., and in 35 between 250 and 450; in 7 it was greater than 450 mg. per 100 ml. Kinnear[4] found the normal Bantu serum-cholesterol level to be 184 ± 38·9 mg. per 100 ml.

Pathological Material

Pathological investigations on the 44 patients were based on material obtained (*a*) by percutaneous renal biopsy[5] (40), (*b*) at autopsy (3), and (*c*) by biopsy and at autopsy (1). Of the 11 patients who presented with the nephrotic syndrome during pregnancy, renal tissue was obtained after delivery in 9, and both during pregnancy and after delivery in 2. Follow-up pathological examinations were also undertaken in 4 males.

Renal biopsy was uneventful apart from 2 patients in whom it was followed by gross haematuria lasting for 3 days. In one of these, retention of urine caused by blood clot in the bladder developed, and bladder lavage was required; in the other, blood transfusion was necessary.

The specimens of renal tissue were fixed in formol sublimate and sections were cut at 5 μ thickness. Slides were stained with haematoxylin and eosin, the periodic-acid Schiff technique, and elastic-Masson when necessary.

PATHOLOGICAL FINDINGS

Glomeruli

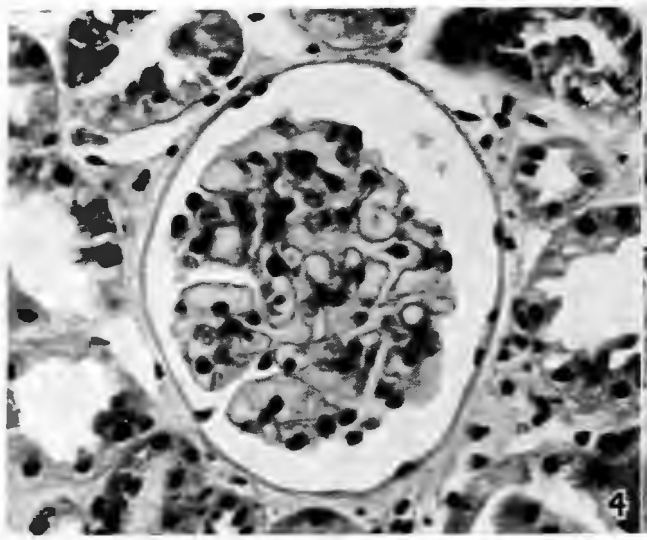
The principal changes were found in the glomeruli and the 44 patients may be classified according to the nature and extent of the glomerular lesions.

(*a*) *Diffuse membranous glomerulonephritis — 25 cases.* In the majority of glomeruli the basement membranes of all the capillaries were thickened, this being best demonstrated with the periodic-acid Schiff stain (Fig. 1). The thickening was variable in extent, with the most severe cases showing progression to partial or complete hyalinization of the glomeruli. In a minority of glomeruli the basement-membrane thickening was focal. Proliferation of endothelial or epithelial cells was seen in only 2 cases. In one this was mild and focal; in the other it was marked and diffuse with a number of glomeruli showing epithelial crescents (Fig. 2).

(*b*) *Focal membranous glomerulonephritis — 13 cases.* In the majority of glomeruli, only some of the capillaries showed thickening of the basement membrane (Fig. 3). This was usually slight or moderate. In a few glomeruli the basement membranes were diffusely thickened. The occasional glomerulus was histologically normal. In 3 cases a mild, focal, proliferative lesion was present.

(*c*) *Histologically normal glomeruli — 5 cases.* In these cases we failed to find any definite changes in the glomeruli (Fig. 4).

(*d*) *Diabetic nephropathy — 1 case.* One subject, a female aged 50, showed the typical nodular and diffuse lesions of diabetic glomerulosclerosis on renal biopsy (Fig. 6). This finding was unexpected. As was the case in all the other patients in this series, clinical and laboratory investigation before histological examination had not revealed any of the known causes of the nephrotic syndrome. After



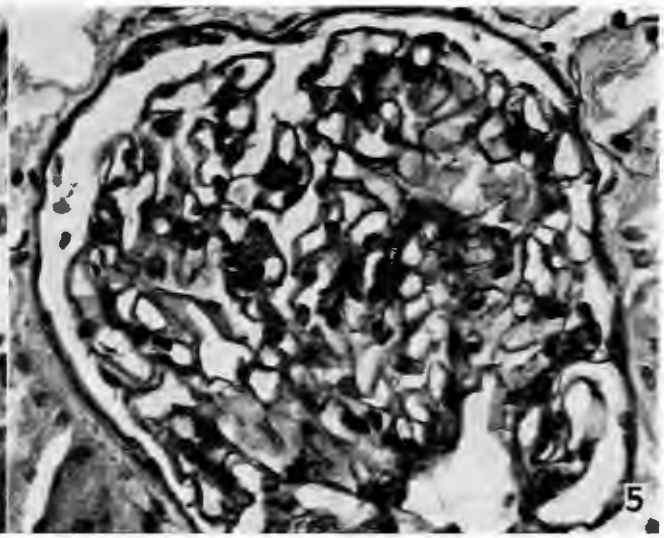
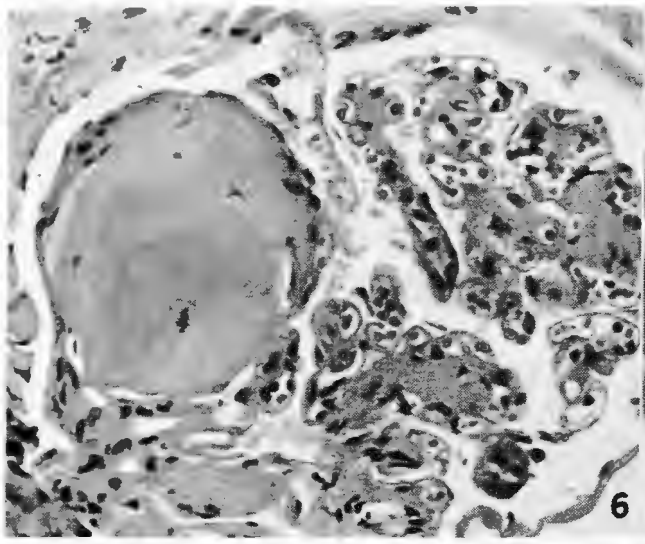


Fig. 4. Histologically normal glomerulus showing thin and delicate basement membrane (periodic-acid Schiff × 480).
Fig. 5. Follow-up biopsy on same patient as in Fig. 4, showing progression to diffuse basement-membrane thickening (periodic-acid Schiff × 480).



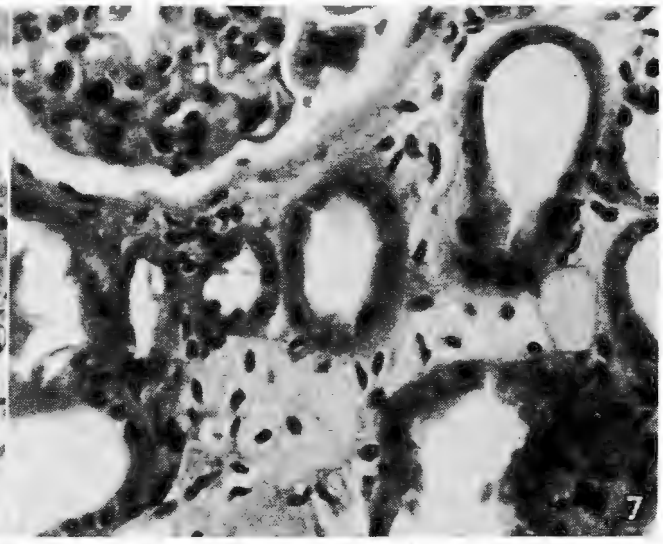


Fig. 6. Typical picture of nodular and diffuse diabetic glomerulosclerosis (haematoxylin and eosin × 480).
Fig. 7. Foamy macrophages in the interstitial tissue (haematoxylin and eosin × 480).

the finding of diabetic glomerulosclerosis was made known to us, thorough re-examination of the patient, including fundoscopy after atropinization, showed the presence of two micro-aneurysms in the left retina, intermittent glycosuria and impaired glucose tolerance.

Pregnancy. Of the 11 patients who presented with the nephrotic syndrome during pregnancy, 9 were found to have diffuse membranous glomerulonephritis, 1 focal membranous glomerulonephritis and 1 histologically normal glomeruli.

Tubules, Interstitium and Vessels

The tubular changes were generally unimpressive. In a few cases the tubules were dilated, atrophied or contained hyaline casts. Lipoid droplets were sometimes observed in the tubular epithelium.

Foamy macrophages were seen in the interstitial tissue in about one-quarter of the cases (Fig. 7). Occasionally, a mild infiltration of lymphocytes or plasma cells was noted. One patient with diffuse membranous glomerulonephritis had well-marked changes of chronic pyelonephritis in a renal biopsy specimen; this was not unexpected since the patient gave a history of recurrent attacks of loin pain, and numerous polymorphonuclear cells were seen on microscopy of the urine. Clinical, radiological or laboratory evidence of urinary-tract infection was present in 10 other patients, including 3 with bilharzia, but in none did histological examination show the changes of pyelonephritis. The blood vessels were normal, except in 2 patients with hypertensive arteriolosclerosis.

RELATIONSHIP BETWEEN THE EXTENT OF THE GLOMERULAR LESION AND THE CLINICAL AND BIOCHEMICAL FINDINGS

For the purposes of this correlation the patients were divided into 2 broad categories according to the extent of the glomerular lesion. In the first were patients with diffuse membranous glomerulonephritis. In the second were those with focal membranous glomerulonephritis together with patients in whom the glomeruli were histologically normal; these 2 varieties were grouped together, since preliminary analysis showed that they were clinically and biochemically similar.

The solitary patient with diabetic glomerulosclerosis was excluded, as were the 11 nephrotic patients who presented during pregnancy. These 11 patients were excluded because in most of them there was diffuse membranous glomerulonephritis, and pregnancy is known to modify considerably the clinical features of the nephrotic syndrome, especially the extent and rate of accumulation of oedema.[6] The inclusion of pregnant patients must also render invalid correlations involving factors such as age and sex. This left 16 patients in each of the 2 groups for correlation with the clinical and biochemical findings. In all of them the correlations were based on the clinical, biochemical and pathological findings during the first admission to hospital.

Age and sex of the patient, severity of oedema, and degree of proteinuria, hypoalbuminaemia or hypercholesterolaemia, could not be correlated with the severity of the lesion.

The duration of the history of oedema correlated roughly with the extent of the lesion. Of the 16 patients with focal membranous changes or histologically normal glomeruli, 10 had a history of less than 1 month, 2 between 1 and 3 months, and 4 longer than 3 months. In the 16 patients with diffuse lesions, the numbers in these 3 time groups were 6, 2 and 8 respectively.

The severity of the lesion was also roughly correlated with the response of the oedema of the nephrotic syndrome to the standard regime of therapy *(vide infra)* in hospital. In the group with focal changes or histologically normal glomeruli, the response was good in 8, partial in 2 and poor in 6. In the group with diffuse lesions the numbers in these divisions were 4, 2 and 10 respectively.

The occurrence of hypertension, haematuria or azotaemia favoured the presence of the more severe grade of glomerular lesion. There were 12 patients with hypertension, 12 with haematuria and 7 with azotaemia. Ten with hypertension, 8 with haematuria and 5 with azotaemia had diffuse membranous glomerulonephritis.

FOLLOW-UP PATHOLOGICAL EXAMINATION AND DEATHS

In hospital, all patients were treated on a standard regime of bed-rest; a high-protein, low-salt diet; and diuretics of the chlorothiazide type. Outpatient therapy was largely confined to chlorothiazide diuretics. Because of the shifting and relatively illiterate character of the African population, only one-quarter of our patients were followed up, the period of observation varying between 2 and 22 months.

Follow-up Pathological Examinations

In 5 patients renal biopsy was performed twice. In the first 2 of these, the nephrotic syndrome was associated with pregnancy, and biopsy was done at the 16th week of pregnancy, and again shortly after the delivery of full-term normal infants. In both patients both biopsies showed the changes of diffuse membranous glomerulonephritis, and no progression in the renal lesion was demonstrable.

In the third patient, a male aged 21, the first biopsy showed normal glomeruli (Fig. 4), but in the second, done 15 months later, diffuse membranous glomerulonephritis was found (Fig. 5). This change was accompanied by the disappearance of oedema, a rise in the serum-albumin level from 0·5 to 1·9 G. per 100 ml., and a fall in the serum-cholesterol level from 470 to 205 mg. per 100 ml. The proteinuria persisted at an average of 3·5 G. per litre, and the blood-urea level remained within normal limits.

In the fourth patient, a male aged 26, diffuse membranous glomerulonephritis was seen in the first biopsy. The second biopsy, 10 months later, showed considerable progression of the lesion with hyalinized and fibrosed

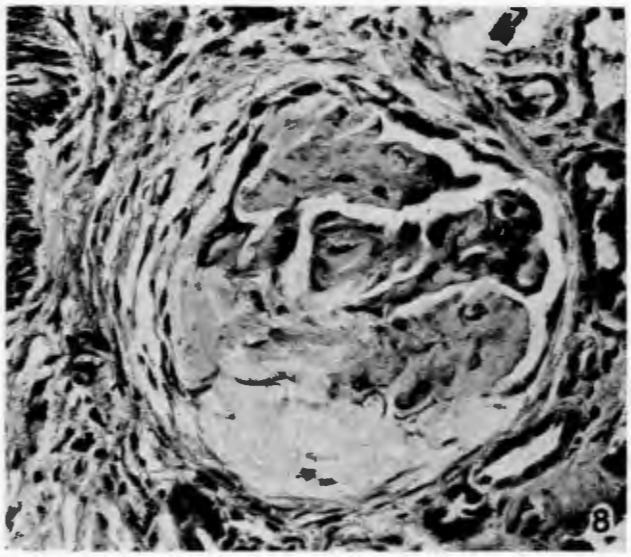


Fig. 8. Follow-up biopsy showing progression of membranous changes to glomerular hyalinization (haematoxylin and eosin × 480).

glomeruli (Fig. 8). This change was accompanied by the disappearance of oedema, an elevation in blood pressure to 160/120 mm.Hg, and a rise in the serum-albumin and blood-urea levels from 0·3 G. and 31 mg. to 1·9 G. and 60 mg. per 100 ml., respectively. Proteinuria fell from an average of 6 G. to 2 G. per litre. The serum-cholesterol level remained at about 280 mg. per 100 ml. A year later this patient was readmitted with epistaxis and the blood-urea level was found to be 400 mg. per 100 ml., the serum-albumin level 3·0 G. per 100 ml., and the serum-cholesterol level 150 mg. per 100 ml. The haemoglobin level was 7·9 G. per 100 ml., and 2 weeks after admission he died. Necropsy was not performed.

The fifth patient is of interest since the findings in his case provide evidence suggesting that the nephrotic syndrome may be caused by infection of the urinary tract. The patient, a male aged 56, presented with swelling of the feet, dysuria, lower abdominal pain, vomiting, diarrhoea and headache of one week's duration. On

examination he was extremely ill with a temperature of 102°F. and gross generalized oedema. Numerous red blood cells and polymorphonuclear leukocytes were present in the urine, and *B. coli* and *B. proteus* were cultured from it. The proteinuria varied from 6 to 12 G. per litre, and the serum-albumin, serum-cholesterol, and blood-urea levels were 1·5 G., 251 mg., and 274 mg. per 100 ml., respectively. A diagnosis of the nephrotic syndrome associated with acute pyelonephritis was made and therapy with chloramphenicol was instituted. Within 3 weeks the urinary infection cleared, the oedema diminished considerably, and the blood-urea level fell to 49 mg. per 100 ml. Renal biopsy at this stage showed mild, focal, membranous and proliferative changes, but no evidence of pyelonephritis. The absence of signs of pyelonephritis may have been due to the fact that the biopsy was performed when resolution of the renal infection was well advanced. Alternatively, the pyelonephritic changes might have been missed by the biopsy needle, it being well known that such changes tend to be focally distributed. On cystoscopy and retrograde pyelography, the only abnormal finding was a mild stricture of the urethra. Two months after admission the patient was clinically and biochemically normal. Sixteen months later he was still well and a renal biopsy at this time was completely normal.

In 1 patient, a male aged 33, biopsy and necropsy specimens of renal tissue were examined. Biopsy during his first admission with the nephrotic syndrome showed the changes of diffuse membranous glomerulonephritis. Six months later he was readmitted with acute bacterial endocarditis complicating rheumatic mitral incompetence, and died. At necropsy the renal findings were unchanged.

Deaths

Despite the limited follow-up, it is known that at least 8 of the 44 patients in this series have died. Two have already been mentioned. The third was a female aged 30, who presented with the nephrotic syndrome during pregnancy. Shortly after delivery of a normal full-term infant, she developed venous thrombosis and recurrent pulmonary embolism, and died in congestive cardiac failure. This was confirmed at postmortem examination, which also showed that the kidneys were histologically normal.

In a fourth patient, a female aged 40, the nephrotic syndrome failed to respond to therapy. On renal biopsy focal membranous glomerulonephritis was found. Two months after admission she developed cancrum oris, which progressed rapidly and resulted in death in 2 weeks. Necropsy was not performed. A fifth patient, a male aged 25, was also resistant to therapy. Renal biopsy showed diffuse membranous glomerulonephritis. After 1 month in hospital he requested to be discharged and, according to his relatives, died at home 6 months later.

In the remaining 3 patients who died, the nephrotic syndrome was complicated by azotaemia when first diagnosed. In the first of these, a male aged 22, the blood-urea level was 200 mg. per 100 ml. on admission. He died 4 weeks later in pulmonary oedema with a blood-urea level of 340 mg. per 100 ml. At necropsy the kidneys showed diffuse membranous glomerulonephritis progressing to hyalinization.

In the second azotaemic patient, a male aged 20, the initial blood-urea level was 60 mg. per 100 ml., and renal biopsy at this time showed diffuse membranous glomerulonephritis. Over a period of 1 year the blood-urea level rose to 265 mg. per 100 ml., when death occurred after an episode of convulsions, vomiting and rectal bleeding. Necropsy was not performed.

The third azotaemic patient, a male aged 32, remained grossly oedematous, with a blood-urea level varying between 70 and 100 mg. per 100 ml. throughout most of his 2 months' illness. Three days before death he became markedly acidotic, the carbon-dioxide-combining power falling to 9 mEq./l., and the blood-urea and serum-potassium levels rising to 195 mg. per 100 ml. and 6·2 mEq./l., respectively. At postmortem examination the kidneys were histologically normal.

DISCUSSION

In this study, membranous glomerulonephritis was shown to be the principal lesion underlying adult Bantu cases of the nephrotic syndrome of unknown cause. In focal or diffuse form, the lesion was present in nearly 90% of all such cases. In most instances it was the sole glomerular lesion; in a few it was associated with proliferative changes, usually mild. In the remaining 10% the glomeruli were histologically normal. Changes in the tubules and blood vessels were generally unimpressive. In the interstitial tissue foamy macrophages were often found.

It would be generally agreed that focal and diffuse membranous glomerulonephritis are variants of the same condition, differing only in degree, since they may be found together in a single specimen and the focal form may progress to the diffuse.[7] Evidence is now accumulating that cases of the nephrotic syndrome with normal glomeruli on light microscopy constitute a further variant, representing the earliest stage in the development of membranous glomerulonephritis. In one of our nephrotic patients successive renal biopsies demonstrated the progression from histologically normal glomeruli to diffuse membranous glomerulonephritis. Joekes *et al.*[7] have observed the change from normal glomeruli to focal membranous glomerulonephritis.

Electron microscopic studies provide further evidence. According to Hall,[8] electron microscopy has shown that the normal basement membrane of the light microscopist is probably a composite structure consisting of attenuated endothelial cytoplasm, basement membrane proper and epithelial foot processes. In nephrotic patients with normal glomeruli on light microscopy, Farquhar *et al.*[9] have found that electron microscopy always shows a replacement of the foot processes by broad masses of epithelial cytoplasm and, in many cases, there is also swelling of the endothelial cells and of the basement membrane proper. In the nephrotic patients with membranous changes visible on light microscopy, the electron microscopic findings were similar but more marked. If the unitarian concept of membranous glomerulonephritis is accepted, it means that some degree of this lesion is constantly present in Bantu patients with the nephrotic syndrome of unknown cause.

This pattern of histological appearances in Bantu nephrotic patients differs considerably from that found in British and American adults with the idiopathic form of the nephrotic syndrome,[7,10-13] in 30 - 60% of whom membranous glomerulonephritis or normal glomeruli are found.

The remainder show proliferative glomerulonephritis or, less commonly, chronic glomerulonephritis, in which it is difficult to determine whether the original lesion was membranous or proliferative in nature. In the Bantu series a frank proliferative lesion was found in only one patient, and even this was associated with diffuse membranous involvement. In a series from Australia,[14] however, the pattern was similar to that of the Bantu, except that patients with normal glomeruli were commoner than those with membranous glomerulonephritis. The reason for these varying patterns is unknown.

Clinical, laboratory, radiological or histological evidence of urinary-tract infection was present in about one-quarter of the Bantu nephrotic patients. The association of pyelonephritis with the nephrotic syndrome has also been noted by others.[11-14] In most cases it has not been clear whether the infection caused, complicated or was incidental to the syndrome. It is more likely that the infection is a complication or incidental, particularly in view of the well-known susceptibility of nephrotic patients to infection in general. For this reason our own case, in which a severe urinary-tract infection and the nephrotic syndrome presented together, and, following therapy, disappeared together, is of considerable interest. It strongly suggests that the infection was in some way responsible for the nephrotic syndrome.

Our ability to predict the degree of membranous glomerulonephritis from the clinical and laboratory findings was limited. Age, sex, severity of oedema and the degree of proteinuria, hypoalbuminaemia and hypercholesterolaemia bore no relationship to the severity of the glomerular lesion. On the other hand, a long history of oedema, the presence of haematuria, azotaemia or hypertension, and a poor response to therapy in hospital, tended to be associated with the more severe degrees of membranous glomerulonephritis. The correlations, however, were at best very rough, there being a considerable degree of overlap. These findings accord with the experience of most other workers except that of Galán and Masó,[15] who could not relate the extent of the lesion to the duration of the history, and Blainey *et al.*,[10] who found that patients with minimal glomerular changes had less proteinuria and higher blood-cholesterol levels than those with diffuse membranous glomerulonephritis.

The course and prognosis of membranous glomerulonephritis in the Bantu appear to be similar to those in White subjects. Deaths from infection, thrombo-embolism, electrolyte disturbance, or progression to chronic glomerulonephritis with uraemia or hypertension, were observed in the present series. It is important to note that all but the last of these complications may cause death at a time when the kidneys are histologically normal or show relatively minor changes. In 2 patients in whom biopsy was performed in the 16th week of pregnancy and again shortly after delivery, no progression of the membranous glomerulonephritis was seen. This accords with our previous clinical studies,[6,16] which showed that the foetal and immediate maternal prognosis in pregnant Bantu nephrotic patients was usually favourable.

Finally, this study shows that if care is taken by the clinician to exclude the known causes of the nephrotic syndrome, such as systemic lupus erythematosus and diabetic glomerulosclerosis, the chances of the pathologist uncovering such a cause are very small. This happened once in the present series of 44 cases, with the finding by the pathologist of the lesion of diabetic glomerulosclerosis. Even in this case reassessment showed that, had the eye-grounds been examined more thoroughly, the diagnosis of diabetic glomerulosclerosis could have been made without recourse to biopsy.

SUMMARY

The renal histology in adult Bantu patients with the nephrotic syndrome of unknown cause was studied.

Focal or diffuse membranous glomerulonephritis was found in 90%; in the remaining 10% the glomeruli were histologically normal, but evidence is presented that these cases may represent an early stage of membranous glomerulonephritis.

There was a limited correlation between the degree of membranous glomerulonephritis and the clinical and biochemical findings.

The course and prognosis of membranous glomerulonephritis in the Bantu appear to be similar to those in White subjects.

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