these glomeruli \textit{per se} were of no demonstrable functional significance. As his syphilis must have been contracted after birth, the immature-looking glomeruli most probably represented retrogressive changes in previously normal glomeruli, similar to those experimentally produced by Bernstein\textsuperscript{10} in previously normal nephrons, rather than arrested development.

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Complement Consumption and Progression to Post-streptococcal Nephrotic Syndrome
A Report of Two Cases

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SUMMARY
The immunopathogenesis of the nephrotic syndrome which occurs in about 0.3\% of Black children with post-streptococcal glomerulonephritis has not been clearly defined. Findings in 2 out of 582 Black children with post-streptococcal glomerulonephritis who developed nephrotic syndrome suggest that minimal activation in the blood of complement components, particularly C3, early in the nephritic process may determine progression to nephrosis. Differences reported by other workers between normocomplementaemic and hypocomplementaemic patients with post-streptococcal glomerulonephritis support this interpretation.


Although the nephrotic syndrome occurs during and after post-streptococcal glomerulonephritis, the frequency of this complication in developed countries varies from 4.5\% to 30\%. In adults the nephrotic syndrome occurs more often and earlier after streptococcal glomerulonephritis than it does in children and tends to be more severe. In East African children the nephrotic syndrome has been reported to be commonly associated with post-streptococcal glomerulonephritis. Factors which are critical for the development of post-streptococcal nephrotic syndrome have not been identified.

In our experience the nephrotic syndrome is an extremely uncommon complication of a very common disease. Of 582 Black children with post-streptococcal glomerulone-
phritis seen during 1976-1978 who were diagnosed by "strictly defined criteria" and whose immediate outcome was noted, only 2 developed the nephrotic syndrome. The present article describes the clinical features and possible immunopathological mechanism which caused the nephrotic syndrome in these patients.

**CASE REPORTS**

**Case 1**

An 11-year-old Black boy was admitted to hospital with oedema of 1 day's duration. He had not been hospitalized previously and there was no relevant family history of illness. He was well nourished (his weight on discharge was on the 10th Harvard centile for age) but he had infected scabies and generalized oedema. He was not distressed, his blood pressure was 125/90 mmHg, urinary output was satisfactory and the systemic examination was unremarkable. The patient's oedema increased over a fortnight, accounting for a weight gain of 3 kg, but had resolved completely 25 days after admission.

Examination of the urine revealed about 10 leucocytes and 10 red blood cells per high-power field, with 53 g protein in a 24-hour sample. Electrophoresis of the urinary protein showed that it contained 2.9 g albumin, 0.8 g α- and α-globulins, 0.5 g β-globulin and 1.1 g γ-globulin. Serum protein electrophoresis revealed an albumin concentration of 11.7 g/l, and the following globulin levels:

- α-globulin 2.0 g/l, α-globulin 17.3 g/l, β-globulin 12.8 g/l, and γ-globulin 10.3 g/l. The serum cholesterol was 7.90 mmol/l.

The antistreptolysin O titres were 1,280 U/ml on admission, 800 U/ml after the first week and 320 U/ml after the second week. No organisms were cultured from throat and skin swabs. The complement component C3 level was 0.8 g/l on admission and 1.04 g/l 10 days later (normal range (±SD) 0.90 ± 0.19 g/l). The blood urea levels, done at weekly intervals, were 8.3 mmol/l, 10.0 mmol/l and 4.2 mmol/l. Serum sodium, potassium, chloride and plasma bicarbonate levels were normal.

The chest radiograph and intravenous pyelogram were normal. The Wassermann reaction was negative and hepatitis B (surface) antibody (but not the antigen) was detected in the serum. The haemoglobin was 10.3 g/dl and the white cell count was 15 × 10^9/l, with 71% neutrophils, 14% lymphocytes, 6% monocytes and 9% eosinophils.

Antinuclear factor, parietal cell and mitochondrial antibodies were not found, but smooth muscle antibodies were present. Renal biopsy showed a picture of diffuse exudative proliferative glomerulonephritis with moderate deposits of C3 and very weak deposits of IgM on the glomerular basement membrane. No deposits of C1q, C4, IgA, IgG or fibrinogen were detected. The patient was treated with penicillin, benzyl benzoate and diuretics. Moderate albuminuria and haematuria were present on discharge 25 days after admission.

When seen 42 days after the onset of his illness, the patient was still in nephrotic relapse, i.e. with mild oedema, hypop-albuminaemia (15 g/l), hypercholesterolaemia (11 mmol/l) and albuminuria. The antistreptolysin O titre was negative and C3 was 1.16 g/l.

**Case 2**

A 9-year-old Black female child was admitted with a 2-week history of oedema and a 1-day history of oliguria. There was no relevant past or family history of illness. She was a well-nourished child (oedema-free weight on the 25th Harvard centile for age) who had oedema of the legs and face. She did not have volume overload and had a blood pressure of 150/100 mmHg. After 6 days the blood pressure decreased to 120/80 mmHg. The rest of the systemic examination was negative. After an initial increase, oedema disappeared in a week, but later increased once again, to decrease finally 6 weeks after admission. The patient, who was oliguric for 5 days, had a diuresis for 2 days followed by a normal urinary output. Examination of the urine revealed 10 leucocytes and less than 5 red blood cells per high-power field, with a protein content of 2.8 g in a 24-hour specimen. Serum protein estimation showed a total protein of 58 g/l, with albumin 21 g/l and α- and β-globulin 18 g/l, γ-globulin 10 g/l and γ-globulin 7 g/l. The serum protein estimation repeated after 35 days showed a total protein of 56 g/l, with albumin 18 g/l and globulins 38 g/l. The serum cholesterol was 7.53 mmol/l.

The antistreptolysin O titre on admission was 1,280 U/ml and less than 166 U/ml after 23 days. The blood urea levels were 6.0 mmol/l on admission and 1.8 mmol/l 23 days later. Serum sodium, potassium, chloride and plasma bicarbonate were normal. The Wassermann reaction was negative.

The chest radiograph showed prominence of the upper lobe vessels with a small pleural effusion on the right side. The heart size was normal. The C-reactive protein was negative. The haemoglobin was 12.0 g/dl and the white cell count was 6.2 × 10^9/l, with 42% neutrophils, 52% lymphocytes and 6% monocytes. The stool examination showed ova of *Trichuris trichiura*.

Antinuclear factor, parietal cell, mitochondrial and smooth muscle antibodies and hepatitis B (surface) antigen were not detected in the serum. The functional assays of complement on admission showed a total haemolytic complement of 105%, alternative pathway 22%, factor B 105%, while immunochromed determinations revealed a factor B level of 0.22 g/l (normal: 0.34 ± 0.14 g/l), C3 0.90 g/l and C4 0.80 g/l (normal: 0.47 ± 0.18 g/l). Twenty-three days later the total haemolytic complement was 73%, the functional assay of the alternative pathway 0%, the functional assay of factor B 20%, immunochromed measured factor B level 0.22 g/l, C3 0.80 g/l and C4 <0.01 g/l. Renal biopsy showed diffuse proliferative exudative glomerulonephritis with heavy deposits of C3 and IgG and slight deposits of IgM, C1q and C4 in a granular pattern on the glomerular basement membrane. No IgA and fibrinogen deposits were detected.

The patient was treated with sulphasalazine, reserpine, furosemide and dihydralazine.

**DISCUSSION**

Nephrotic syndrome was demonstrated in 2 patients with post-streptococcal glomerulonephritis, one of whom had an unusually mild consumption of complement C3 and the
other no detectable utilization of C3 with activation of the alternative pathway during the early phase of the disease. This is a rare complication of a common disease, with an incidence of at least 0.3% in Black children with post-streptococcal glomerulonephritis. Ninety-two per cent of the 582 children with glomerulonephritis studied had a considerable reduction in C3 levels. In the first patient, C3 on admission was within the normal range although the level rose subsequently by as much as 25%. One interpretation of this result is that there was no significant utilization of complement in the immunopathological process. In this argument the observed difference in results could be due to the possibility (raised by Williams et al.) that serum measurements did not accurately reflect deviations in synthesis and catabolism of complement. However, it is probable that there was activation of C3 during the early phase of the disease, but that this was less severe than is usually associated with post-streptococcal glomerulonephritis. The presence of C3 on the glomerular basement membrane and the significant increase in this component over 10 days would support this.

In case 2, where more detailed studies of complement were performed, most measured components, excepting the functional assay of the alternative pathway, were within the normal range on admission. We have shown in a previous study and have unpublished data that components of both the classic and alternative pathways of complement are activated in a significant number of children with post-streptococcal glomerulonephritis. Therefore, the decreased function of the alternative pathway is not unexpected, and probably not directly related to the development of the nephrotic syndrome. However, 21 days later there was reduction in total haemolytic complement, possibly due to activation of both classic and alternative pathways (C4 and functional assays of factor B and the alternative pathways, respectively). Consumption of complement components other than C3 occurring later in the disease may have been due to an 'auto-allergic' response. Activation of C3, which is a central event in the complement cascade, did not occur to any significant degree in this patient. The level of C3, which was least affected, may be the critical factor in progression from nephritis to nephrotic syndrome. These changes suggest that the initial immunological events which were accompanied by a nephritic episode had undergone modulation and become associated with a nephrotic syndrome. These sequential changes in complement were probably due to fluctuating host immune responses initiated and maintained by the streptococcus, although the combined effects of the latter and some other unidentified agent acting at a later stage of the disease cannot be excluded.

If the degree of complement activation is critical for the development of the nephrotic syndrome, then differences would be expected between patients with low and high levels of complement. These have indeed been recorded although their significance for the immunopathology of the nephrotic syndrome has not been noted. Patients with post-streptococcal glomerulonephritis who have normal or near normal level of complement have a lower serum albumin and higher cholesterol level than patients with hypocomplementaemia. These patients also develop overt nephrosis more frequently. However, as all patients with normal complement levels and post-streptococcal glomerulonephritis do not develop the nephrotic syndrome, factors other than complement must be important.

There is clear experimental evidence in rabbits that both antigen manipulation and variation in host antibody response influence the type of glomerular disease induced. There is also convincing proof that immune responses in general, and those to streptococcal antigens in particular, are under genetic control. Our patients had a vigorous production of antistreptolysin O antibodies. It is possible, however, that antibodies to streptococcal membrane antigens, which are more important in the pathogenesis of glomerulonephritis may have been insufficient or of poor quality. In such a situation complement activation would have been muted.

These findings imply that in most children a vigorous immunopathological process, initiated by the streptococcus, causes excessive complement utilization and results in the clinical picture of post-streptococcal glomerulonephritis. In a small minority of patients, less severe effects, which may be genetically determined, cause minimal activation of complement, particularly C3, early in the disease process, and this may be one factor in the pathogenesis of the nephrotic syndrome.

ADDENDUM

Patient 2, who was seen at follow-up examination 64 days after onset of her symptoms, had minimal oedema and proteinuria, with normal serum albumin and serum cholesterol levels. The functional assays of complement showed a total haemolytic complement of 121%, an alternative pathway of 121%, and a factor B of 121%, while immunochimical estimations revealed a factor B concentration of 0.28 g/l, C3 1.30 g/l, and C4 0.74 g/l.

This study was supported by a grant from the South African Medical Research Council to H. M. C. We are grateful to Dr A. F. Hallett, to Mrs R. Cooper for measurement of complement components, to Dr M. A. Adhikari who assisted in maintaining records of children with post-streptococcal glomerulonephritis, and to the Superintendent of King Edward VIII Hospital, for permission to study the patients.

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