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APPLICATIONS
NEPHROLOGY

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Editor

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SERIES EDITOR'S FOREWORD

Glomerulonephritis has always been regarded as a complex subject. Different forms of the disease can cause death in a matter of weeks, nephrotic syndrome which might or might not prove responsive to steroid therapy, or no symptoms at all. Improved pathological techniques and criteria have permitted a more accurate diagnosis and prognosis to be established for many patients. With increased understanding of the immunological mechanisms involved it has become apparent that many patients presenting with a variety of symptoms and signs may have glomerulonephritis as their primary pathological process.

This book examines the clinical, pathological and aetiological factors involved in the common forms of glomerulonephritis. Each chapter has been written by a recognized expert in the field and provides information of relevance and practical importance to the average clinician. The developments of the last decade have emphasized that glomerulonephritis is no longer a matter only for the nephrologist but a subject on which all clinicians should be well informed.

ABOUT THE EDITOR

Professor Graeme R.D. Catto is Professor in Medicine and Therapeutics at the University of Aberdeen and Honorary Consultant Physician/Nephrologist to the Grampian Health Board. His current interest in transplant immunology was stimulated as a Harkness Fellow at Harvard Medical School and the Peter Bent Brighton Hospital, Boston, USA. He is a member of many medical societies including the Association of Physicians of Great Britain and Ireland, the Renal Association and the Transplantation Society. He has published widely on transplant and reproductive immunology, calcium metabolism and general nephrology.

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MINIMAL CHANGE NEPHROPATHY*

J.M. BOULTON-JONES

This diagnosis has pleasant associations, particularly for adult nephrologists who can be reasonably certain that their treatment will cure the patient made miserable by the nephrotic syndrome. The treatment is effective but entirely empirical. Some tantalizing clues are there for all to see, but no-one has yet identified the cause for the dramatic change in the permeability of the glomerular basement membrane which characterizes this condition or why it should respond so regularly to steroids. There are remarkably few clues in the glomerulus itself: as with the dog which did not bark in the night, the main finding is the absence of histological change. This was first documented in 1905 by Frederick Muller who coined the term 'nephrosis' to describe the kidneys of patients who had been nephrotic but whose kidneys showed no evidence of 'nephritis'; In 1916, Munk described lipoid droplets in the urine of these patients and invented the term 'Lipoid Nephrosis' which is still used today. The introduction of the technique of renal biopsy in 1954 enabled clinicians to examine the tissue of patients much earlier in the natural history of their illness and in the 1960s the present histological classification of the glomerulopathies was constructed and subsequently elaborated by electron and immunofluorescence microscopy. At about the same time as this was happening, clinical trials of prednisolone were undertaken and it was quickly appreciated that some patients, particularly children,

* This chapter was received for publication in January 1988 and therefore all publications made after that have not been considered.

responded dramatically. These observations led to the identification of the diagnostic criteria of MCN.

DEFINITION

Minimal change nephropathy (MCN) is primarily an histological diagnosis. The glomeruli are normal on light microscopy. The only change on electron microscopy is of 'fusion' or more properly 'retraction' of the epithelial foot processes. Glomerular deposits of immunoglobulin or complement are conspicuous by their absence. C3 is often found in small amounts in the afferent arterioles.

Patients present with the nephrotic syndrome and this is included in the definition. Some also require that there should be a prompt response to treatment with steroids. However, many patients with some mesangial cell proliferation will also respond quickly to a course of prednisolone and it is important that they should not be denied this treatment because they do not have true histological minimal change. Therefore all patients with endocapillary proliferation should be included provided that there is no evidence of immune deposits on immunofluorescent examination of the biopsy.

CLINICAL FEATURES

MCN occurs at all ages and in both sexes, but most commonly presents before the age of 10 with a peak incidence during the third and fourth years. Its incidence is between 20 and 70 children per million per year and about 3 adults per million per year. 76% of nephrotic children[1] and 25% of nephrotic adults[2] have MCN. There is an interesting change in the sex ratio with age. Boys outnumber girls by two to one, but among adults the sexes are equally affected. MCN occurs among people of European and Chinese descent but is rarer among those of African origin.

By definition, MCN presents with the nephrotic syndrome which usually comes on acutely without any warning but may follow a few days after an upper respiratory tract infection, particularly in males. Rarely, the patient may present, and subsequently relapse, during the

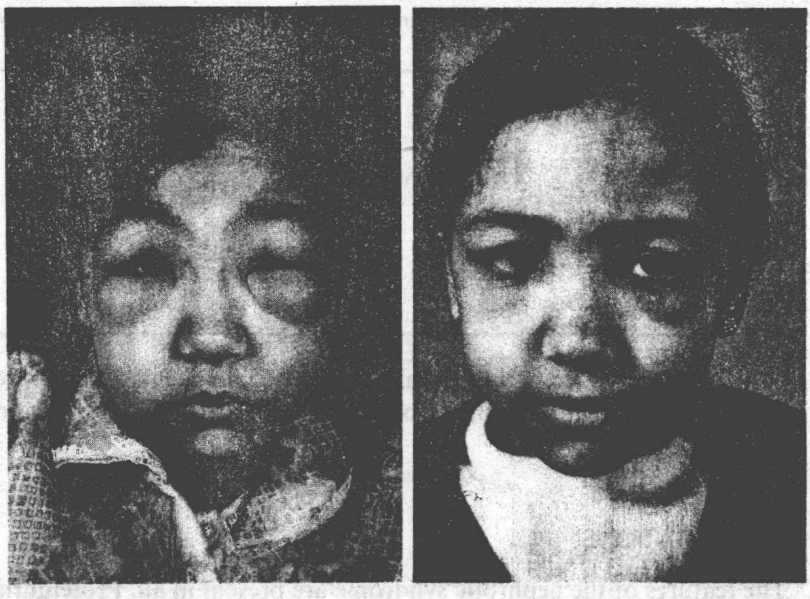

FIGURE 1.1 Photograph of nephrotic girl before and after 'conservative' measures

early summer when the pollen count is high[3,4]. Nearly 40% of children with MCN are atopic[5], but no increase in the incidence of atopy has been found among adults[6].

The oedema of this syndrome is often massive, affecting the face and abdomen of children and the ankles and sacral areas of adults (Figure 1.1). Ascites and pleural effusions may be detected. The skin may become so stretched over the swollen areas that striae develop, particularly on the abdomen and ankles (Figure 1.2). The patient may become breathless because the diaphragm is splinted and because of the increased effort required to remain mobile with water-logged legs. Gastro-intestinal symptoms are common. Patients are anorexic, some have abdominal discomfort and a few vomit frequently. As a result, there is often a loss of muscle mass (Table 1.1).

The physical findings are dominated by the presence of pitting oedema in dependent areas, ascites and pleural effusions. The jugular venous pressure is not raised. Mild hypertension is present in about

TABLE 1.1 Symptoms other than oedema reported in a series of 34 patients with MCN

Malaise	6
Abdominal pain	5
Loin pain	3
Chest pain	1
Nausea	3
Anorexia	2
Vomiting	2
Diarrhoea	2
Breathlessness	3

10% of children and 30% of adults. Macroscopic haematuria is rare but microscopic haematuria is found in about 25% of children and 35% of adults.

INVESTIGATIONS

The features of the nephrotic syndrome are present in all. Proteinuria in excess of 50 mg/kg/day is usual in children. In adults the loss is more than 3.5 g/24 hours. If the serum albumin is very low, the quantity of proteinuria will also drop even though the clearance of albumin remains high. About a quarter of children with MCN present with an albumin of less than 10 g/L and half have a value of between 10 and 20 g/L. The same is true for adults in whom the mean value of serum albumin at presentation is 20 g/L[6].

There is a marked rise in serum cholesterol in all but 5% of patients whether adults[2] or children[1]. This rise affects VLDL and LDL cholesterol. HDL cholesterol is reported variously as normal or low[7]. The serum creatinine is usually within normal limits but is raised in about one third of children, when corrected for age and sex[1], and about 40% of adults[2]. Table 1.2 shows the average values for some of these parameters in relapse and remission for a group of adults.

Selectivity index

This is a measure of the size of molecules crossing the GBM. The index most commonly used is the ratio of the clearance of IgG/the

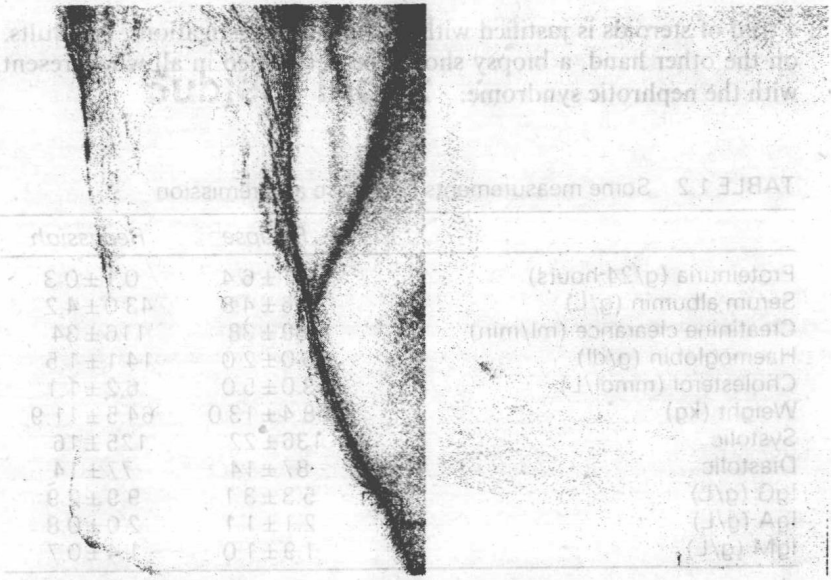

FIGURE 1.2 Photographs of ankle and abdomen of nephrotic patients showing striae caused by oedema

clearance of transferrin. Therefore the smaller the index the greater is the restriction to the passage of large molecules compared with small. MCN is usually associated with a 'selective' proteinuria, which is indicated by a ratio of less than 0.1. This measure is particularly useful in children with MCN, among whom 53% have highly selective proteinuria (ratio <0.1) and only 15% have non-selective proteinuria (ratio >0.15)[1,8]. It is of little use in adults with MCN because half have a ratio of more than 0.15[2].

Renal Biopsy

Renal biopsy is an unnecessary investigation in children under the age of 16 with selective proteinuria and a normal C3 because the probability of the diagnosis being MCN is more than 95% and thus

a trial of steroids is justified without further investigation[1]. In adults, on the other hand, a biopsy should be performed in all who present with the nephrotic syndrome.

TABLE 1.2 Some measurements in relapse and remission

	Relapse	*Remission*
Proteinuria (g/24 hours)	12.1 ± 6.4	0.1 ± 0.3
Serum albumin (g/L)	20.6 ± 4.8	43.0 ± 4.2
Creatinine clearance (ml/min)	89 ± 38	116 ± 34
Haemoglobin (g/dl)	15.0 ± 2.0	14.1 ± 1.5
Cholesterol (mmol/L)	13.0 ± 5.0	6.2 ± 1.1
Weight (kg)	68.4 ± 13.0	64.5 ± 11.9
Systolic	136 ± 22	125 ± 16
Diastolic	87 ± 14	77 ± 14
IgG (g/L)	5.3 ± 3.1	9.9 ± 2.9
IgA (g/L)	2.1 ± 1.1	2.0 ± 0.8
IgM (g/L)	1.9 ± 1.0	1.4 ± 0.7

Every biopsy should be examined by light microscopy, electron microscopy and immunofluorescence techniques. At present, this requires different fixation procedures for the three methods and the biopsy material has to be divided into three parts. It sometimes happens that one of the three portions does not contain glomeruli and the diagnosis has to be made on the evidence available.

Light microscopy

The appearances of the glomeruli, arterioles and tubules should be normal (Figure 1.3). However a substantial minority of patients who subsequently prove to be steroid sensitive have some focal or diffuse mesangial cell proliferation or increase in mesangial matrix (Figure 1.4). Tubular loss is unusual in young patients in whom it may be a sign of focal glomerulosclerosis, but may not be significant in older patients in whom some nephron loss is normal[6].

Electron Microscopy

Electron photomicrographs of the glomeruli are normal except in one respect, which is that the delicate pallisade of foot processes of the epithelial cell on the outside of the GBM is lost together with the slit pores which connect the foot processes (Figure 1.5). This is a non-specific change seen in all glomeruli of patients with proteinuria. Indeed, the number of slit pores per unit length of GBM is inversely proportional to the degree of proteinuria[9]. The finding of electron dense deposits makes response to steroids unlikely[9a].

Immunofluorescence studies

No diffuse deposits of immunoglobulin or complement components are found within the glomeruli. C3 may be present in the walls of some arterioles.

TREATMENT

The purposes of the investigations are to define those patients who will respond to a course of steroids. The reason for including some patients with histological changes as defined above is that their response to prednisolone cannot be distinguished from that of patients with true histological minimal change except perhaps that those with diffuse proliferation may respond more slowly[10]. The results of the immunofluorescence studies are important because it is unlikely that patients whose biopsies contain deposits of immunoglobulin or complement will respond to steroids, except a small group with diffuse mesangial deposits of IgM[11].

Symptomatic measures

The patient's main symptom is oedema, and this can be considerably eased by the use of diuretics. Care must be taken because oedema is not only the patient's symptom but is also the body's defence in

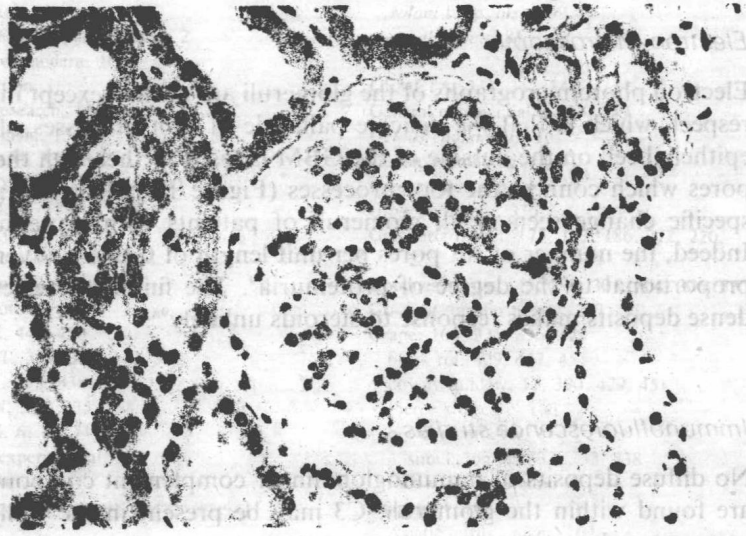

FIGURE 1.3 Normal glomerulus

maintaining the circulating volume. Overtreatment may result in a reduction in circulating volume and renal blood flow and may therefore precipitate or aggravate renal failure. The dose of a diuretic such as frusemide should therefore be titrated against the amount of oedema, standing blood pressure and renal function. The patient's weight can also be a useful guide. Sometimes very large doses of frusemide, such as 500 mg bd are required. This frequently causes severe thirst and the patient should be warned to restrict fluid intake to 1.5 L day. Using these measures, it is usually possible to restrict the oedema to bearable proportions until prednisolone has secured a remission. The average weight lost between relapse managed by diuretics and remission in adults was 3.9 kg in the Glasgow series[6].

Sometimes more radical measures are required when the patient presents with a nephrotic crisis. These patients look ill and feel dreadful. As well as being oedematous, they are anorexic and vomit continuously, so that their nitrogen balance is negative and they quickly

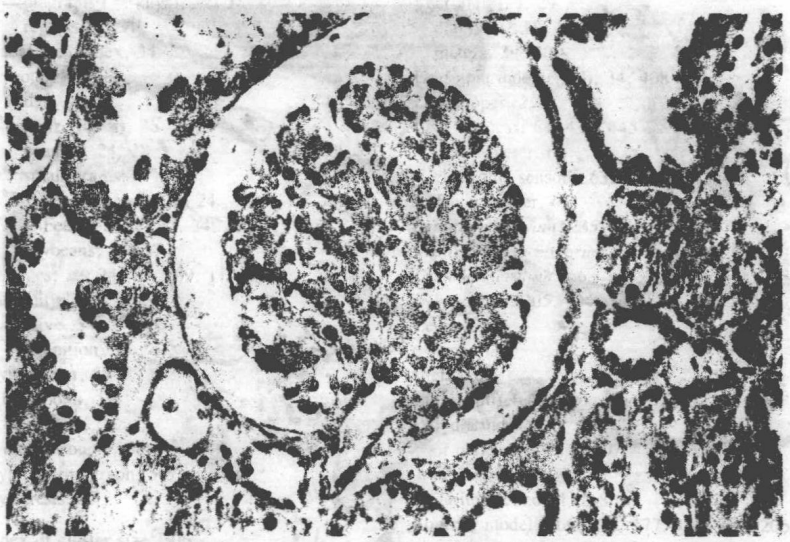

FIGURE 1.4 Mesangial proliferation in glomerulus of patient with steroid responsive nephrotic syndrome

lose muscle mass. Renal failure may develop. Intravenous salt-poor albumin combined with intravenous frusemide should be given in an attempt to reduce the oedema, which also affects the bowel wall, without causing contraction of their circulating volume. Once they can eat again, the crisis is over and routine measures can be introduced. Although this treatment is logical and appears to work well, its logic is at variance with recent observations which show that albumin infusion into a patient with a normal circulating volume increases glomerular permeability and leads to huge increases in proteinuria[11a]. Thus most of the infused protein is excreted within 24–48 hours. It is likely, therefore that patients in nephrotic crisis are hypovolaemic as a result of excessive use of diuretics.

Diet

The traditional response to heavy proteinuria is to increase the protein content of the diet in the hope of increasing hepatic synthesis of