Current Practice

URINARY TRACT DISEASES

Nephrotic Syndrome

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British Medical Journal, 1970, 4, 350-353

If glomerular damage leads to persistent, heavy proteinuria then a nephrotic syndrome will appear—that is, heavy proteinuria, a low serum albumin, and oedema. Thus the group of patients with the nephrotic syndrome will merge with those showing heavy proteinuria but no oedema. Moreover, the syndrome may have many underlying disease processes, since many conditions can precipitate heavy proteinuria. A simple classification of these glomerular appearances was given in last week's article, while the principal causes of the nephrotic syndrome are listed in Table I.

TABLE I.—*Principal Causes of Nephrotic Syndrome*

	Adults %	Children %
Primary Glomerular Disease:		
Minimal Change Lesion	30	85
Membranous Nephropathy	10	1
Proliferative Glomerulonephritis	40	10
Renal Disease of Systemic Disorders:		
H.S.P. nephritis	0	4
Amyloidosis	10	0
Lupus	7	0
Diabetes	2	0
All others*	1	0
	100	100

*including renal vein thrombosis, myelomatosis, other vascular disorders, drugs, infections, allergies, etc.
H.S.P. = Henoch-Schönlein Purpura

A limited number of conditions accounts for 99% of both adult and childhood nephrotic syndromes; 80% of adult and 96% of childhood cases are caused by primary kidney disease. Most of the usual long lists of "causes" of the nephrotic syndrome are based on few or even single case reports, and are only of significance for the light they sometimes throw on the aetiology of the condition.

Aetiology

The aetiology of proliferative glomerulonephritis was discussed in last week's article. The aetiology of both the two other major groups of primary glomerular diseases is even more obscure. The *minimal change* lesion (Fig. 1) is often found in patients whose attack follows non-specific viral illnesses in the respiratory tract. Occasionally it may be found in nephrotic patients with well-developed specific allergies to pollens, plants, or drugs. This may indicate that some disorder of immunity is present, but support for this suggestion is lacking. Some patients show a lowering of serum complement activity and the appearance of signs of complement activation just after the onset, but whether these are directly related to the condition is unknown.

Membranous nephropathy (Figs. 2 and 3) is even more obscure. The regular palisade of exramembranous deposits seen histologically in the early phases of the condition (Fig. 3) resembles an accumulation of "humps" similar to those seen in acute nephritis from the deposition of soluble complexes. It has been suggested that this condition may result from chronic deposition of soluble complexes in the kidney. Slight support for this idea comes from the rare finding of this appearance in two conditions associated with chronic soluble complex formation: lupus erythematosus and chronic active cirrhosis. It has not been possible, however, to produce the lesion experimentally, and two conditions which may be associated with soluble complex formation—the nephropathies of quartan malaria and secondary syphilis—show minor changes or proliferative glomerulonephritis. Membranous nephropathy in association with renal vein thrombosis is also unexplained unless the renal vein throm-

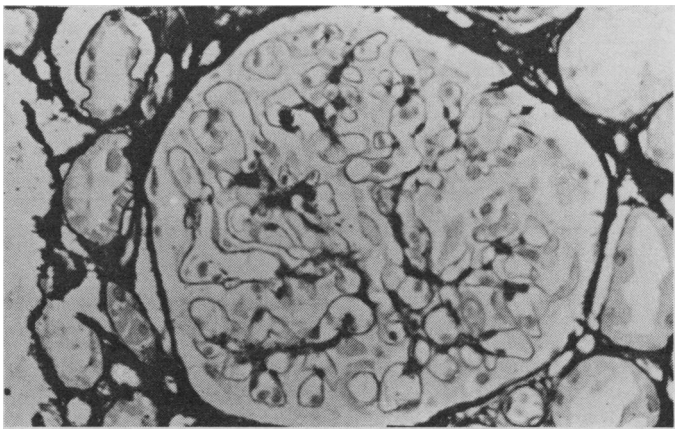

FIG. 1.—The "minimal change" lesion ("lipoid nephrosis"). This glomerulus looks entirely normal, with thin, delicate basement membrane, and only moderate cellularity. Bowman's space and the glomerular capillaries are widely patent. (P.A.S.M. × 166)

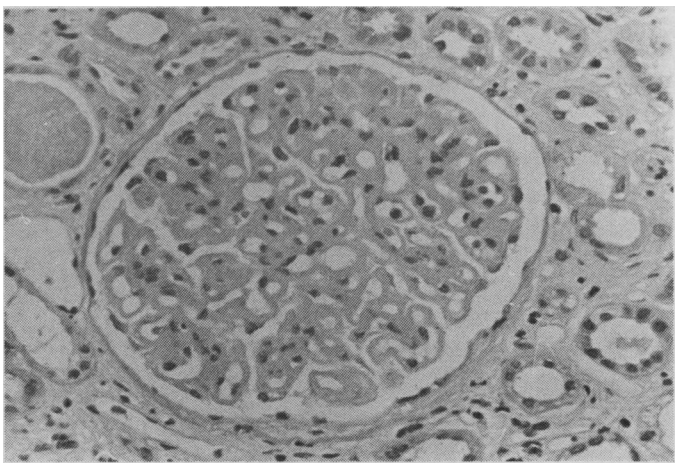

FIG. 2.—Membranous nephropathy. The capillary walls are diffusely thickened in every glomerulus of the biopsy specimen, without any increase in cellularity. The more severely affected glomeruli may show extensive sclerosis. (P.A.S. × 152)

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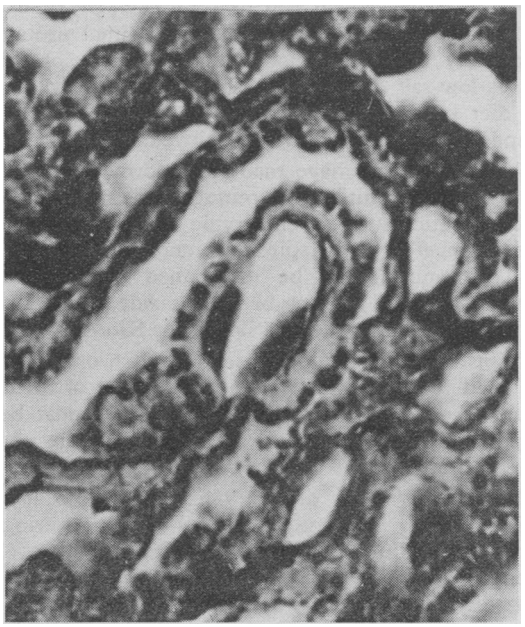

FIG. 3.—Membranous nephropathy: high power examination of the capillary wall. The characteristic lesion in membranous nephropathy lies on the *outside* of the true basement membrane. There is alternation of non-silver staining deposits (which can be shown to contain IgG and C3 component of complement) with argyrophilic "spikes" which may be contiguous with the basement membrane, or separated from it. In more advanced cases there is diffuse sclerosis of the basement membrane with gross thickening and incorporation of deposits within the disorganised structure, and diffuse silver staining. (P.A.S.M. × 1000)

bosis is in fact secondary to the nephropathy rather than vice versa, as has usually been suggested.

Disordered Physiology

The usual explanation for linking heavy proteinuria to the accumulation of oedema may be represented diagramatically (Fig. 4), the result being a patient with expanded extracellular fluid space but a barely normal or low vascular volume. Certainly this is not all; younger patients with good liver function and good protein intake may preserve their plasma albumin concentration in the face of losing even 20 g. of protein daily. More puzzling is the ability of some patients, particularly children, to keep themselves free of oedema even without diuretics with a serum albumin level below 1 g./100 ml. Diuretics, which may diminish the intravascular volume still further, can lead to stable loss of oedema, and albumin infusions to persistent diuresis long after the infused albumin has been lost in the urine. Finally, removal of accumulated oedema by a single acupuncture may not be followed by its reaccumulation, even though nothing else has changed.

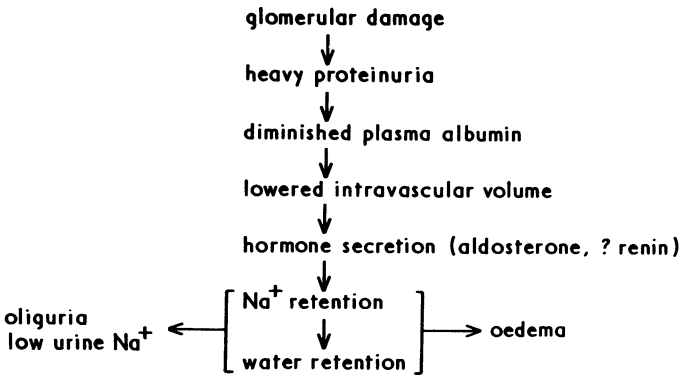

FIG. 4

Clinical Features and Complications

The cardinal complaint is of oedema. In adults this is most prominent around the ankles and leads to ascites and pleural effusions only if massive. In children, however, periorbital oedema is common, often with ascites, even though ankle oedema may be slight. This presumably relates to the better tissue turgor in children. The level of proteinuria and the diminution of serum albumin which will lead to the accumulation of oedema becomes less with increasing age—less than 3 g./100 ml. leading to oedema in old age, while less than 1·0 g. may be tolerated in childhood. The urine contains much protein (over 0·05 g./kg./day), 80 to 95% of which is albumin and other relatively low molecular weight proteins. This loss of low molecular weight protein leads to the accumulation of high molecular weight protein in the plasma, which are shown as beta and alpha 2 globulins by electrophoresis. The relative clearances of large and small molecular weight proteins may be used as an index of severity of glomerular damage (differential protein clearances). The urine may also contain red cells and casts other than hyaline casts, depending on the underlying condition. The blood is frequently milky in appearance from the accumulation of triglyceride chylomicra, as well as cholesterol and phospholipids. The reason for this accumulation is obscure, unless it relates to the relatively high molecular weight of most lipoproteins.

Uraemia and hypertension may be present depending on the underlying renal disease and the severity of the hypovolaemia. A nephrotic syndrome without hypertension, haematuria, or renal functional impairment has been referred to as "pure nephrosis," "lipoid nephrosis," or "uncomplicated nephrotic syndrome." Nowadays such terms would carry the implication that the glomeruli would be normal, or nearly normal, on light microscopy.

It is not generally realized that far from being a purely renal condition the nephrotic syndrome, even in the absence of uraemia, affects every tissue in the body by protein depletion, electrolyte and hormonal imbalance, and alterations in the composition of the blood. Common complications of the nephrotic syndrome may be listed as:

Hypovolaemia	Postural Hypotension Circulatory Collapse Acute Renal Failure
Diminished resistance to infection	Primary Peritonitis Septicaemia Cellulitis Urinary Infections
Protein depletion	Osteoporosis Cutaneous Striae Muscle Wasting Apathy
Altered blood	Arterial Thrombosis Venous Thrombosis (Pulmonary Embolism) Vascular Occlusion
Reduced renal function	Uraemia and all its consequences Hypertension and all its consequences
Miscellaneous	Secondary Renal Tubular Disorders

The particular importance of many of these complications is that they may be accentuated rather than relieved by corticosteroid, diuretic, or cytotoxic agents (Table II), and that if

TABLE II.—*Complications of Treatment*

Diuretics	Antibiotics	Steriods	Cytotoxic Agents
K + depletion Hyponatraemia Hypovolaemia	Rashes Superinfection Bacterial resistance Diarrhoea Specific toxicities	Cushingoid Hypertension Growth failure Delayed puberty Osteoporosis Thrombosis Infection etc.	Stomatitis Cystitis Hair loss Nausea Granulocytosis Infection: bacterial, viral, fungal.

the patient is not going to respond promptly then their use can only do harm. Many of these complications reinforce each other or may be present together.

Clinical Management

Apart from a search for known aetiological agents such as malaria, syphilis, drug allergies, and such systemic conditions as diabetes, systemic lupus, and amyloidosis, the main important division is between those patients with the "minimal change" lesion and those with other conditions. This arises because the prognosis of the "minimal change" group is better, both in the short term (loss of proteinuria and oedema) and in the long term (lack of deterioration in renal function). The best way to make this distinction is to perform a renal biopsy which if carefully examined by an expert using appropriate techniques, will best predict future behaviour. Biopsy is not entirely free of risks, however, even in good hands; and its use in a group where most show "minimal change" pattern (such as children of 1 to 5 years of age) (Fig. 5) may be questioned. A search has therefore been made for tests which will discriminate those

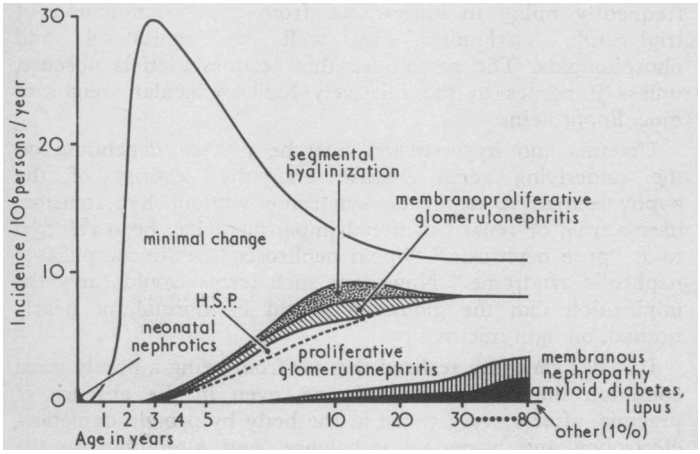

FIG. 5.—Histological appearances found and incidence of the nephrotic syndrome at various ages in Western Europe and the United States (based on a variety of published, and unpublished personal data).

TABLE III.—*Prognostic Features of the Nephrotic Syndrome*

Of Value	Of No Value
Presence or absence of:	Amount of oedema
hypertension	Amount of proteinuria
haematuria	Serum albumin
purpura	Serum protein pattern
Renal function (sometimes)	Length of history
Differential protein clearances	Serum cholesterol
Serum complement concentration	
Age (Fig. 5).	

patients with optically normal glomeruli from the others. Table III contains data which have been shown to be of value in discriminating patients with minimal lesions from the remainder:

The adult or other child with hypertension, haematuria, diminished renal function, a low serum complement, and non-selective differential protein clearances (CIgG/C albumin or transferrin more than 0·20 (20%)) is most unlikely to have a minimal change lesion. On the other hand, a child between 1 and 5 with none of these features can initially be managed without biopsy as "minimal change."

Symptomatic Treatment

This can be applied to all patients irrespective of whether loss of proteinuria can be expected.

(1) *Rest* may be helpful in the oedematous phase but may accelerate venous thrombosis.

(2) *Diet.* A high-protein (1·5 to 2·0 g./kg./day) diet should be given, with at least two-thirds being animal protein; milk and especially cheese are not suitable because of their salt content. A low-salt diet should also be aimed at; with a 100-g. protein diet less than 30 mEq/day of Na^+ is not attainable unless special formula feeding is employed.

(3) *Diuretics.* These have made an enormous difference to nephrotic patients. Initially to remove oedema high doses of powerful diuretics such as ethacrynic acid or frusemide may be needed, together with spironolactone, but nearly all out-patients can and should be maintained on less powerful, cheaper preparations such as bendrofluazide, with or without potassium supplements such as Slow K or Kloref.

(4) *Resins.* Ion exchange resins in the K^+ or NH_4^+ phase may be used to deplete the patient or the diet of further salt. Katonium is an acceptable preparation. Care must be taken in the patient who is also uraemic because of the potassium and acid load imposed.

(5) *Albumin infusions* are very expensive and usually of temporary benefit. They may be useful (a) for covering intensive intravenous diuretic therapy, (b) in acute hypovolaemia, or covering situations where it may be feared, and (c) for initiating diuresis in the very resistant patient.

(6) *Antibiotics* should be used therapeutically, not prophylactically, and with bacteriological control, since the flora and infecting agents of the nephrotic patient, particularly in hospital, may be very unusual. Progress in achieving diuresis is best gauged by daily weighing on the same scales; losses of 5 to 30 or even 40 kg. may be achieved, revealing a tiny, wasted patient.

Patients with "Minimal Change" Lesions

This group of patients has a tendency to remit but without treatment (particulary antibiotics) about 70% used to die. If a patient has or is thought to have a minimal change lesion then treatment with cortiscosteroid drugs is justified since 95 to

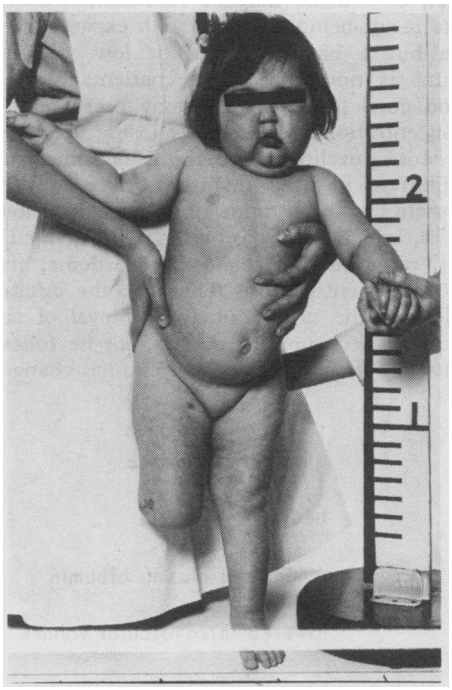

FIG. 6.—Complications of the nephrotic syndrome and particularly its treatment. This two-year-old child had a minimal change lesion, but ran a relapsing steroid-dependent course over nine months. She was stunted, Cushingoid, and obese. Severe hypovolaemia led to temporary oliguria and uraemia. After treatment of this she was severely hypertensive (180/130) and suffered a right femoral artery thrombosis, which led to the loss of the right leg at the knee. She was then treated with cyclophosphamide and has remained well off all treatment for 15 months.

100% respond. If 60 mg./day prednisolone is used then 90% of those who will ultimately lose their proteinuria will have done so by the time four weeks have passed. Many patients then stay well. Corticosteroid therapy may be withdrawn and the patient remains well indefinitely. How and why the drug acts is quite unknown.

Other patterns of behaviour may unfortunately be seen:

Failure to Respond to the Initial Attack.—Of those with the minimal change lesion, only 2 to 3% fail to respond to steroids. These patients usually have the earliest stages of a condition now usually called "segmental hyalinization" or "focal hyalinosis." They are resistant to all treatment, including cyclophosphamide, and their renal function declines slowly into renal failure with obvious focal glomerular sclerosis appearing in a year or two. This group of "non-responders" is augmented by a variable number of patients who (a) were incorrectly assumed to have minimal change on clinical grounds (failure to respond within six or at most eight weeks is therefore an indication for renal biopsy if it has not already been performed) and (b) whose renal biopsies were incorrectly interpreted.

Relapse on Withdrawing Corticosteroids, or shortly afterwards, with repeated relapses. This course is followed by about 40 to 60% of all patients with a minimal change lesion. Management depends on what dose of corticosteroid is needed to keep the patient relapse free, or to treat him in relapse, and what side effects are observed. The principal toxic effects (Fig. 6) are a Cushingoid appearance, hypertension, and, in children (the great majority of this group) growth retardation and delayed puberty. If these are felt to be significant then cyclophosphamide should be used, since the mortality of these patients over five to ten years is considerable. The results with a lower dose (3 mg./kg./day) appear to be as good as those using a higher initial dose with its attendant leucopenia and hair loss. If the patient relapses yet again the higher dose may be employed. Late resistance to steroids is also perhaps an indication to use the higher initial dose with a deliberate controlled leucopenia. At least two-thirds of patients thus treated have lasting remissions off all treatment. How and why the drug acts is again quite unknown.

Patients with Membranous or other Nephropathy

Most adult nephrotics have membranous nephropathy (Fig. 5) and an initial biopsy is directed towards finding the minority with a minimal change lesion. Clearly the overall prognosis of the nephrotic syndrome in adult life is much poorer than in childhood. The prognosis of the membranous lesion is slowly downhill to uraemia and hypertension within 10 to 20 years. The prognosis of the various forms of the proliferative glomerulonephritis is very variable, from a few months in patients with extensive crescent formation to many years in the milder forms.

Neither corticosteroids nor azathioprine in non-toxic doses affect the long-term prognosis of nephrotic patients with these histological lesions in their kidneys. The side-effects of these drugs summarized in Table III and Fig. 6 should be sufficient to deter doctors from using them. Cyclophosphamide has yet to be evaluated by a controlled trial in these patients.

Patients with Other Renal Diseases:

Treatment of causative infections, such as *syphilis,* is of course worth while, but unfortunately *malarial* nephrotic syndromes do not improve if the parasite is eliminated. Immunosuppressive drugs have been used, with variable results, in different centres. *Renal vein thrombosis* is usually diagnosed too late for anticoagulants or surgery to make any difference. No treatment affects *diabetic nephropathy,* including pituitary ablation. The only treatment for *amyloidosis* is to eliminate the cause where one is present, and this is possible. Elimination of the cause will arrest but not reverse the renal damage. *Lupus nephritis* frequently produces a nephrotic syndrome and is one of the few conditions where immunosuppression is logical and effective. Treatment with cyclophosphamide and steroids is probably the best available regimen and, remembering the terrible prognosis of this condition, can be very rewarding (Fig. 7).

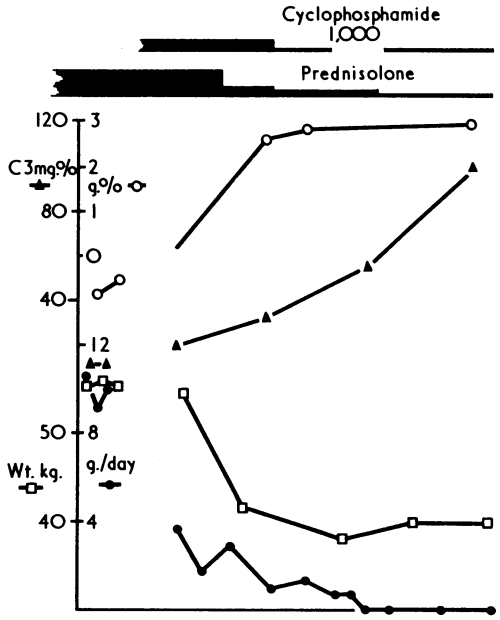

FIG. 7.—One of the few rational uses of immunosuppressant drugs in renal disease: the treatment of lupus nephritis with cyclophosphamide and corticosteroids. The patient, a 21-year-old Chinese girl, had severe lupus glomerulonephritis with a nephrotic syndrome resistant to 60 mg./day of prednisolone. Cyclophosphamide 5 mg./kg./day was started and the steroid dose reduced. The proteinuria (●) decreased, serum albumin (O) rose and a huge diuresis (■) was obtained. The C3 component of complement (▲) rose from 33 mg./100 ml. to 130 mg./100 ml. (normal) indicating a reduction in disease activity. The cyclophosphamide was stopped temporarily when her white blood count fell to 1,000/cu. mm. and was restarted at 1 mg./kg./day.

Further Reading

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