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Five hundred years of the nephrotic syndrome: 1484-1984

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SUMMARY

The nephrotic syndrome has emerged over several centuries as the consequence of continued profuse proteinuria, arising in turn from a variety of lesions affecting the glomerulus which impair glomerular ability to retain plasma proteins, in particular, albumin. As a syndrome, it has its own complications and requires its own management irrespective of the underlying lesions. Dissection of these by renal biopsy and by clinical investigation reveals a variety of systemic diseases which affect the kidney, but a majority of primary immune-based diseases appear unique to the glomerulus. Whether the lesion called by Müller and Munk 'nephrosis', and now called minimal change disease and focal segmental glomerulosclerosis is one disease or many, is the subject of intense debate at the moment, as is the relationship between two types of lesion. Only a better understanding of their pathogenesis, and of how the glomerulus normally retains plasma protein, will solve this knotty problem.

Although dropsy (oedema) in adults has been known from classical times (for example, to Hippocrates [1]), the distinction between the various causes of oedema in these early texts — nutritional disturbances, cardiac failure, liver and gastrointestinal disease as well as renal disease — is not possible to define. One sage observation made by Hippocrates about the nephrotic syndrome, however, is familiar to many patients and doctors — that 'when bubbles settle on the surface of the urine, it indicates disease of the kidneys and that the complaint will be protracted'.[1] This effect of albuminuria on the surface tension of urine may even be the presenting complaint of some patients, and the date of onset of profuse proteinuria can usually be determined by direct questioning.

However, in children the causes of severe oedema are a little less complicated, and thus I take as the start of studies of the nephrotic syndrome itself the book *Liber de aegritudinibus infantium*[2] (Fig 1) published about 1484 by Cornelius Roelans (or Roelants) of Mecheln in Belgium (1450-1525). He describes 52 diseases of children, of which the fifty-first is 'swelling of the whole body of the child'. It seems almost certain that he is describing nephrotic oedema here, but the short chapter is mainly devoted to a confused account, based on the Galenical theories of humours, of how the swellings might arise; the kidneys are nowhere mentioned. At the end, however, he states: 'Then the child may be cured by a remedy that I found in a certain pamphlet on diseases of children. Take the tops of the elder plant, and danewort, cook in white wine and wrap the child in hot cloths by applying a poultice in whole or in part, and so cure him'. Perhaps a prospective controlled trial is needed here! Roelans also gives homely advice on

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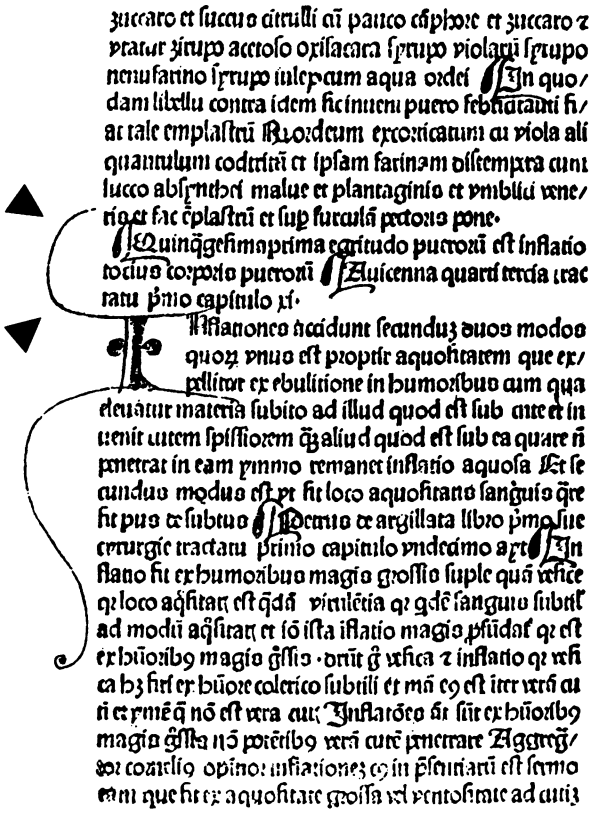

Fig. 1
The page in Cornelius Roelans' *De aegritudinibus infantium* of 1484 which contains perhaps the earliest description of a nephrotic child: 'The fifty-first disease of children is swelling of the whole body of the child'. Reproduced from reference 2.

less abstruse problems of childhood such as teething pains (treat with honey and butter on the gums of the child).

We now leap forward almost 250 years, to a really remarkable early description of the nephrotic syndrome by Theodore Zwinger III of Basel (1658-1724) in his *Paedoiatreia practica* of 1722.[3] This text is known to some historians of paediatrics,[4] but has been completely ignored by nephrologists. His description of the physical signs of the nephrotic syndrome in chapter 119 is quite remarkable, and is worth quoting in full: 'Oedema, generally called hydrops, is a condition involving swelling of the whole body. From head to foot the skin is a pale dirty yellow, the swelling is oedematous and characterised by inflation of the whole periphery with persistent collections of lymph. The swelling is not hard or tense, but such that the print of a finger remains behind. Commonly, thirst is very great, the bowel action not as free as usual, and the urine is scanty because of obstruction and compression of the tubules of the kidney. The breathing is difficult, often accompanied by anxiety because of the compromised function of chest muscles and diaphragm from the swelling of the skin. Besides, there is a continued fever, and soon a strong desire to sleep appears because the brain is overfull with serum; sleep is poor because of disturbance of the "spiritus animalis". Additionally, there may be a dry cough from irritation of the nerves to the lung by the liquid, salty lymph. At the beginning, the swelling may be small, but later it increases steadily if the remedies used do not have their expected effects, so that

legs, abdomen and even the face are blown up with a bluish colour, and one must fear attacks of suffocation. We have seen children of either sex in whom the eyelids were so swollen they could not open their eyes, and also the genitalia were so swollen and full of serum, that they looked almost transparent. In boys, the virile member was so swollen that they could make water only with difficulty'.

Thus in 1722, more than 100 years before Bright, Zwinger described the nephrotic syndrome and placed the seat of the disease firmly in the kidneys! This is all the more remarkable, because at this time Morgagni had of course not published his great classic *De sedibus et causis morborum,*[5] which established the idea that diseases might arise from specific organs. Incidentally, in this latter work one can find one of the first descriptions of the pale, mottled kidneys of the nephrotic patient.

Zwinger did not, however, perform any tests on the urine that we know of, and it was only after proteinuria had been described for the first time in conjunction with oedema by Domenico Cotugno (1736-1820) in his *De ischiade nervosa commentarius* of 1770, that Richard Bright (1789-1858) and others could put together the triad of proteinuria, diseased kidneys and oedema. Despite the fact that other observers in Britain, notably William Wells of St Thomas' Hospital[7] and John Blackall of Exeter,[8] came close, Bright's claim to having described the nephrotic syndrome in all its detail in his classic *Reports of medical cases* of 1827[9] must be sustained, in conjunction with the chemical observations of his lesser-known colleague, John Bostock (1773-1846), chemist and physician of Liverpool. Bostock[10] quantified the urine and serum proteins by methods depending upon specific gravity, noting that the greater the amount in the urine, the less in the blood. This observation was confirmed in 1829 by Robert (later Sir Robert) Christison of Edinburgh (1797-1882),[11] who stated: 'The specific gravity of the serum has always been lowest where the urine was loaded with albumin. It is hence probable that the albuminous secretion of the urine is nothing more than a transudation of serum from the blood'.

Thus, by 1830 the nephrotic syndrome of profuse albuminuria, hypoalbuminaemia and oedema resulting from diseased kidneys leaking protein into the urine was established.

One of the many tasks to which these early workers addressed themselves (and which remains uncompleted to this day) was to establish how the oedema came about. The usual explanation is given in Fig 2, which presupposes that, during the active formation of oedema at least, the circulating plasma volume will be low, and that what are usually called Starling forces will operate less avidly than usual because of lowered oncotic pressure in the plasma. This theory was, however, suggested by a certain J-C Sabatier in Paris as early as 1834:[12] 'The serum of the blood being depleted (of albumin) becomes more fluid, thinner and by this it is able more easily to penetrate the walls of the arterial capillaries. If it is possible to suppose that, following this modification of the blood, venous absorption is less active, one can see how in such cases the effusions in the serous cavities and infiltrations of the tissue may arise'.

The problem of how nephrotic oedema accumulates is still not settled,[13] and Dorhout Mees and his colleagues have repeatedly emphasised their own[13-15] and earlier observations[16, 17] that the plasma volume in stable, untreated adult nephrotics is usually *normal,* or even increased. In contrast, many paediatricians (and rather fewer internists) including ourselves have seen *un*treated patients with

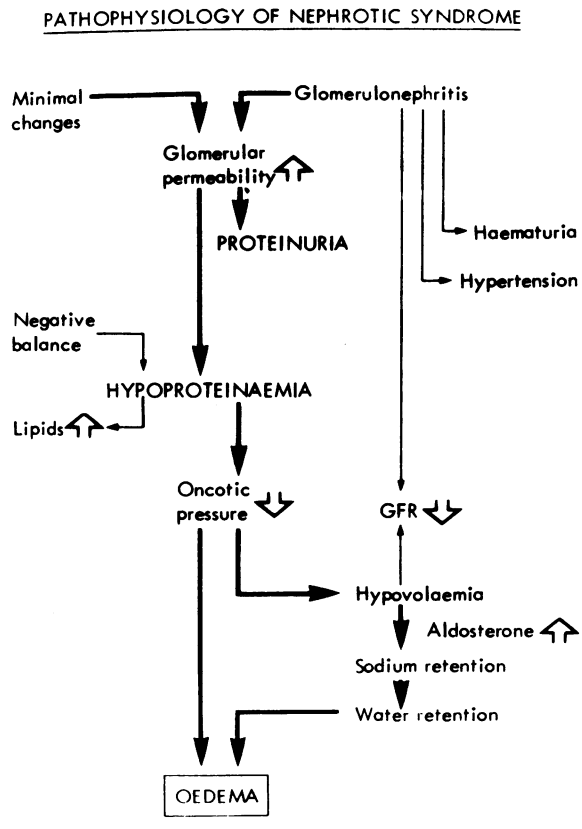

Fig. 2
The usual explanation for the accumulation of nephrotic oedema, which presupposes a reduced plasma volume at least in the phase of active oedema formation (See text).

a nephrotic syndrome, usually with minimal change disease, arrive at hospital already in shock or even in established acute renal failure. Melzer and colleagues[18] pointed out that patients with minimal change disease (who form the great majority of patients with a nephrotic syndrome in childhood) usually have high plasma renins, whilst the levels in most other nephrotic patients are normal.

Thus, it does seem possible to reconcile these disparate observations. Immediately after proteinuria begins, or reaches nephrotic proportions, the plasma albumin falls as a result of both excretion and increased renal catabolism of reabsorbed albumin. The plasma volume contracts, triggering humoral and physical stimuli to the renal tubules which result in more avid retention of sodium, and secondarily of water. Excretion of a water load in nephrotics is reduced in most studies[19] and occasionally true hyponatraemia may be seen as opposed to 'false' or 'dilutional' hyponatraemia dependent on high lipid levels. This retained salt and water is distributed more into the tissues than normally because of the lowered plasma oncotic pressure, but gradually the plasma volume is restored to normal — at the price of an expanded extracellular space, a great increase in total body sodium (which can more than double) and visible oedema. Thus the patient 'purchases' a normal plasma volume in the face of hypoalbuminaemia; but the price is oedema. Equally, if the doctor gives diuretics he will eliminate thia oedema, but the 'price' will be hypovolaemia.

TABLE I

Complications of the nephrotic syndrome

Common:	Infections	1° peritonitis, cellulitis ± septicaemia
	Thrombosis	venous ± embolism arterial
	Hypovolaemia (± diuretics)	circulatory collapse acute renal failure
	Hyperlipidemia	? accelerated atherogenesis*
	Protein depletion	osteoporosis ± stones striae wasting
Uncommon:	Fanconi syndrome*	
	Fe deficiency anaemia	

* particularly in patients with focal segmental glomerulosclerosis.

One of the complications (Table I) from which nephrotic patients may suffer is **acute renal failure.** The cause of this acute renal failure principally seen in nephrotics with minimal change and focal sclerosing lesions,[20, 25] is not known. Diagnosis may be difficult if the patient presents in this state, since the urine will contain not only large amounts of protein but also red and white cell casts and many red blood cells, presumably the result of associated tubular necrosis. Thus, the appearances exactly mimic those of an acute proliferative glomerulonephritis, with or without crescents, and early renal biopsy is necessary to make the diagnosis (see below). To begin with, this complication of acute renal failure was thought always to be associated with hypovolaemic shock and circulatory collapse,[21] and there is little doubt that this accounts for some cases, often accompanied by septicaemia (see below). Another group of nephrotic patients who go into acute renal failure have been given large doses of contrast media, or non-steroidal anti-inflammatory agents,[22, 23] both of which are known to be nephrotoxic. The latter group is of particular interest since the agents (especially fenoprofen) seem able to *induce* a minimal change nephrotic syndrome, with or without an infiltrate, mainly of T-helper cells, in the interstitium.[24] Finally, and most puzzling, is a group of patients who present in acute renal failure without any antecedent circumstances except growing oedema, without any signs of hypovolaemia, and who have minimal changes in their renal biopsy.[25] These patients tend to be older than 50 and relatively resistant to treatment with corticosteroids; they sometimes do not recover renal function and may succumb because of nutritional and other problems associated with persisting torrential proteinuria — despite their oliguria — together with uraemia. We have seen four such patients, of whom only one survived. Lowenstein and others[26] have suggested that a factor in acute renal failure in these nephrotics may be increased renal interstitial pressure from oedema, but no measurements have been made to support or deny this hypothesis.

Another complication that nephrotic patients may suffer is **thrombosis.** It seems strange that Bright and his colleagues, with their large experience of nephrotic

patients, do not comment on this aspect. This is all the more surprising when we realize that many of their patients (including Mary Sallaway, whose case is described in the *Reports of medical cases,* and whose kidney is still in the Gordon Museum at Guy's Hospital) suffered from amyloidosis;[28] we know now that such patients are particularly prone to develop renal venous thrombosis.[29] However, the first descriptions of renal venous thrombosis came from Osborne in Dublin,[30] who made little of the association, which he found by chance at post mortem in a nephrotic middle-aged man without specific symptoms. The first detailed description of renal venous thrombosis was by Bright's great Parisian contemporary, Pierre Rayer (1793-1862), in his encyclopaedic book and atlas on diseases of the kidney, published in 1840.[31] In this he described two cases of renal venous thrombosis in nephrotics: one being of a young prostitute who had acute loin pain and fever in association with the thrombosis.

There is much controversy about the incidence of renal venous thrombosis in nephrotic patients.[27, 32-36] The only point above contention is that it is much commoner in nephrotic patients with membranous nephropathy, an association which remains unexplained; presumably some as yet unstudied aspect of coagulation is more abnormal in such patients (see below). Several authors[32, 34] have shown that, by careful angiography, up to as many as 40% of nephrotic patients with membranous nephropathy may have small, silent renal venous thrombi, and a lower, but still substantial proportion of patients with other forms of glomerular disease underlying their nephrotic syndrome are similarly affected. However, my associates and I, in common with other workers,[35] have been unable to confirm these findings, only 5-10% showing thrombosis. It may be that there are real geographical variations in the incidence of renal venous thrombosis in membranous nephropathy, and hence in the nephrotic syndrome as a whole.

What is not clear either is *what should be done* about symptomless venous thrombosis if it is found. No prospective study has dealt with the question of what happens in such patients who are *not* anticoagulated (as must happen to their symptomless counterparts who do *not* have angiography), and are thus never diagnosed. It is clear that, in the presence of anticoagulation, symptomless renal venous thrombosis is benign, neither renal functional deterioration nor increase in proteinuria being associated with its presence, either at the time of diagnosis[31, 32] or later. Unfortunately, neither ultrasound nor CAT scanning seems able to equal the performance of invasive angiography in making the diagnosis, a procedure not without risk. Thus, few clinicians perform venography in *all* their nephrotic patients unless symptoms indicate;[36] but many will perform it routinely, or have a lower clinical threshold for performance, in nephrotic patients with membranous nephropathy.

Thrombosis as a whole is a danger which stalks the nephrotic patient, and remains a worrying source of morbidity and mortality. What makes it of particular note is that diuretic treatment, presumably by raising the haematocrit and increasing blood viscosity,[37, 38] may *increase* the chances of thrombosis. It has been a cause of death in our own series of adult[77] and childhood[49] nephrotics, and in a recent series of nephrotic children.[39] However, the pattern of thrombosis is different in adults and children.[27] One large survey of European centres[27, 40] found that almost half the children had arterial thrombosis, whereas in the adults the great majority had venous thromboses, although arterial thromboses are also seen.[27] In children, the arterial thromboses affected almost any artery in the body, intracardiac and pulmonary artery thrombosis being remarkably

common[27, 40] and aortic thrombosis recorded.[27] It is worth noting that the only other group of children who suffer similar major vessel thromboses are those with congenital cyanotic heart disease with high haematocrits. Venous thrombosis is remarkably common in nephrotics. At a clinical level in our own series, 11 of 89 adult-onset minimal change patients had deep venous thromboses, associated with obvious pulmonary emboli in seven, whilst only one had an arterial thrombosis (femoral). Doppler ultrasonography, however, reveals that as many as one quarter of adult nephrotics have thrombi in their deep calf veins.[41] Similarly with pulmonary embolism: less than 5% of adult nephrotics overall will have clinically evident emboli, but ventilation/perfusion isotope scanning reveals that about 15% have evidence of pulmonary emboli.[27, 42] This complication is rare, however, in nephrotic children, as it is in children as a whole. Renal venous thrombosis, whether symptomless or evident. is associated with a high incidence of emboli, averaging about one third of cases in 11 published series.[27]

Why do nephrotic patients show this extraordinary tendency to thrombosis? (Table II). There are many abnormalities of circulating haemostatic proteins,[27] both procoagulant and regulator, in the nephrotic syndrome.[27] In general, those of low molecular weight are lost into the urine in excess of synthesis, and so the plasma concentrations fall (factor IX, X, XI, XII, prothrombin, plasminogen, antiplasmin, antithrombin III, protein C, α_1 antitrypsin); whilst, in those of high molecular weight, synthesis exceeds losses, with a rise in plasma concentrations (Factor VIII/von Willebrand factor, fibrinogen, factor V, factor VII, α_2 macroglobulin). It is difficult to judge what effect all these alterations will make in an individual case. There is already present in the plasma a manifold excess of such factors as VIII, V and VII, and whether further increases produce a prethrombotic state is doubtful. Although antithrombins are lost into the urine (antithrombin III, α_1 antitrypsin) α_2 macroglobulin rises, so that the total antithrombin activity is normal or even raised in most nephrotics. Inhibitors of plasmin are essentially the same serine protease inhibitors, with the addition of α_2 antiplasmin, which protein accounts for much of the *in vivo* activity; this is usually reduced in nephrotic patients. Recently, however, Pollak and his associates[43] have implicated both inhibitors of plasminogen activation and antiplasmin in the genesis of thrombosis in nephrotic patients, particularly renal venous thrombosis in those with menbranous nephropathy.

TABLE II

Factors involved in the thrombotic tendency of nephrotic patients

Humoral	Raised factors I, V, VII, VIII
	Raised plasma lipids
Platelets	Hyperaggregability — ? arachidonate↑
Fibrinolysis	Reduced plasminogen
	Antiplasmins
	Loss of antithrombins in urine
Mechanical	Immobility
	Repeated vascular punctures
	Haemoconcentration — viscosity raised
Iatrogenic	Corticosteroids
	Diuretics — worse hypovolaemia

However, it may be that abnormalities of platelet function account for much of the thrombotic tendency in nephrotics.[44] When plasma albumin is reduced, the number of binding sites competing with the platelet cycloxygenase for arachidonic acid is reduced. Thus, more arachidonate is available for thromboxane A_2 synthesis by the platelets, which increases, and *ex vivo* platelets will aggregate supranormally to arachidonate, ADP or collagen, a phenomenon which can be corrected both *in vivo* and *ex vivo* by the addition of albumin.[44] Clinically, the nephrotics at risk of thrombosis are those with a severe reduction in serum albumin to below 20 g/l,[42, 44] and it may be that this hyperaggregability operates through this mechanism. However, our own recent unpublished observations that nephrotic platelets are hyperaggregable to ristocetin, which does not require arachidonate or thromboxane A_2, suggests that this is not the whole story.

The most common complication of the nephrotic syndrome in former times was however infection, which, until the antibiotic era, resulted in early death in the majority of nephrotic children[45, 47] and a considerable number of adults.[48] Even in the present era replete with antibiotics, sepsis is still a problem, accounting for deaths in our own series of children,[49] as well as those of the International Study.[39] The peculiar susceptibility of nephrotic children to infections with encapsulated organisms, in particular *Strep. pneumoniae,* has been noted for many years. This infection seems never to occur in adults, our oldest patient with pneumococcal peritonitis being 21 years of age. It is probable that this peculiar susceptibility is associated with losses of alternative pathway components of the complement system in the urine,[50] although why adults should be protected is not known. Primary peritonitis, usually with septicaemia, is of course the commonest presentation, and a recent analysis of peritonitis shows,[51] as in our own experience, that in children it is still a problem. In Krensky's review of peritonitis over the period 1970-1980,[51] 24 episodes of peritonitis occurred in 19 of 351 nephrotic children: 50% were from *Strep. pneumoniae,* and 25% from *E. coli.*

Another major problem which was a cause of death until the antibiotic era was cellulitis. This can spread with terrifying rapidity in the oedematous tissues of the nephrotic patient, and may arise from splits in the skin occasioned by the swelling. The organism is usually present in the blood stream and can more usually be obtained from the blood than from the local lesion.

The final complication of the nephrotic syndrome that I wish to deal with was heralded by John Blackall in 1811,[8] who noted that the serum of blood drawn from nephrotic patients was milky in appearance; an observation which may well have been made earlier in dropsy, given the popularity of blood-letting in the eighteenth century. Twenty-five years later, Robert Christison established by its solubility in sulphuric ether that this material was indeed fat.[59] We now know[53] that there are complex alterations of lipoproteins in nephrotic patients, with rises in VLDL and LDL cholesterol fractions, although in most patients HDL is normal, being low only in an occasional patient with relentless proteinuria and very low serum albumin; of the subfractions, HDL2 is selectively reduced. In all cases with or without visually evident hypertriglyceridaemia, the total cholesterol is very much elevated in proportion to the reduction in plasma albumin. The reasons for the increased hepatic synthesis of apoprotein, which is responsible, along with urinary losses, for these changes, are poorly understood. Naturally these changes in circulating lipids lead to speculation as to whether nephrotic patients are more susceptible to vascular disease, and in particular myocardial infarction, since

similar changes in the blood fats of control populations are known to be associated with increased mortality from vascular causes. It has proved surprisingly difficult to give an answer to this apparently simple question.[54, 55] From the beginning, it seemed that children and young adults with a nephrotic syndrome and precocious atheroma suffered from relentless nephrotic syndromes, and a number had what we would now recognise as focal segmental glomerulosclerosis (FSGS) lesions.[46, 56, 57] In fact, it emerges from follow-up studies[58] that rather few other patients remain nephrotic for long periods of time — only one-third had a nephrotic syndrome for more than four years in our study. The remainder either lose filtering surface and go into renal failure, with diminishing proteinuria, or remit spontaneously or in response to treatment. It is noticeable that in progressive FSGS with renal failure, profuse proteinuria may persist right into terminal renal failure and even require nephrectomy. Thus, only a tiny proportion of nephrotics are subjected to continuous hyperlipidaemia over many years. Finally, many of these patients have underlying glomerular disorders complicated by hypertension, itself a powerful risk factor in the genesis of vascular damage.

Thus the question is not a simple one. Anecdotally, there is no doubt that some nephrotics suffer thrombosis of their coronary arteries,[59-61] and it is tempting to attribute this as a complication of their nephrotic state as one would any other thrombosis, or as a result of the lipid alterations. Because of small numbers, it has not proved possible to study individual subgroups particularly at risk (for example patients with focal segmental glomerulosclerosis) but overall our large nephrotic population in the South-East of England did *not* show a mortality significantly in excess of a carefully-matched local control population.[58] Other papers on the subject have not made similar comparisons with appropriate controls.[59-61]

Until 1950, our knowledge of the underlying histopathology of the kidney in nephrotic patients was based on those unfortunates coming to post mortem either through renal failure, or through some complication of the condition.[45-48, 62] It was known well before 1900 that a nephrotic syndrome could complicate diabetes, syphilis,[8] treatment with mercury,[8, 30] amyloidosis,[63] and last of all Schönlein-Henoch purpura[64] and systemic lupus.[65] It had been known even earlier that a nephrotic state might complicate post-scarlatinal nephritis,[66] and thus some idea of 'secondary' and 'primary' nephrotic syndromes was established quite early. However, the histology of these 'primary' nephrotic syndromes continued to puzzle workers in the field from 1900 onwards. In general, they could see few changes using the optical microscopy of the period in many of these nephrotics dying of complications, including those suffering from syphilis. Friedrich von Müller of Marburg (1858-1941) made his major (and dubious) contribution to nephrology in 1905[67] by introducing the term 'nephrosis' as an antithesis to 'nephritis', implying a 'degenerative' lesion of the kidney rather than an 'inflammatory' one; this term was popularized by Fritz Munk (1879-1945)[68] who mainly studied syphilitic nephrotic syndromes. The techniques of the period could not distinguish the early changes of membranous nephropathy, almost certainly present in these patients, from normality; and it was not until 1932 that ET Bell,[69] using newer stains, described severe membranous nephropathy. Workers of the period were unable to accept the possibility of a functional defect in the glomerulus without changes visible on optical microscopy, and thus the idea of 'pure nephrosis' (minimal change disease, as it would now be called) as a tubular lesion became current. About the same time, Henry Christian[48] and Louis Leiter[45] in the United States pointed out the similarities of primary and secondary

forms of severe proteinuric disease with oedema, and introduced the terms 'syndrome of nephrosis', or 'nephrotic syndrome', to emphasise the relationship, which gradually achieved popularity.[70]

We recognise now, following the introduction of percutaneous needle renal biopsy to the study of glomerular disease in the early 1950s by Poul Iverson and Claus Brun in Denmark,[71] and Robert Kark and Bob Muehrcke (then a medical student) in the United States,[72] that as well as the many different clinical circumstances associated with the nephrotic syndrome, a variety of different types of histopathology may underly it,[73, 74] thus making the dissection by the technique of needle biopsy a major feature of the management, at least in adults. The pattern of underlying histopathology for an unselected British population of nephrotics is shown in Fig 3. This is based on a personal series of more than 500 patients with onset over the age of 15, and for 200 children biopsied up to 1970, when we ceased to biopsy every nephrotic child.

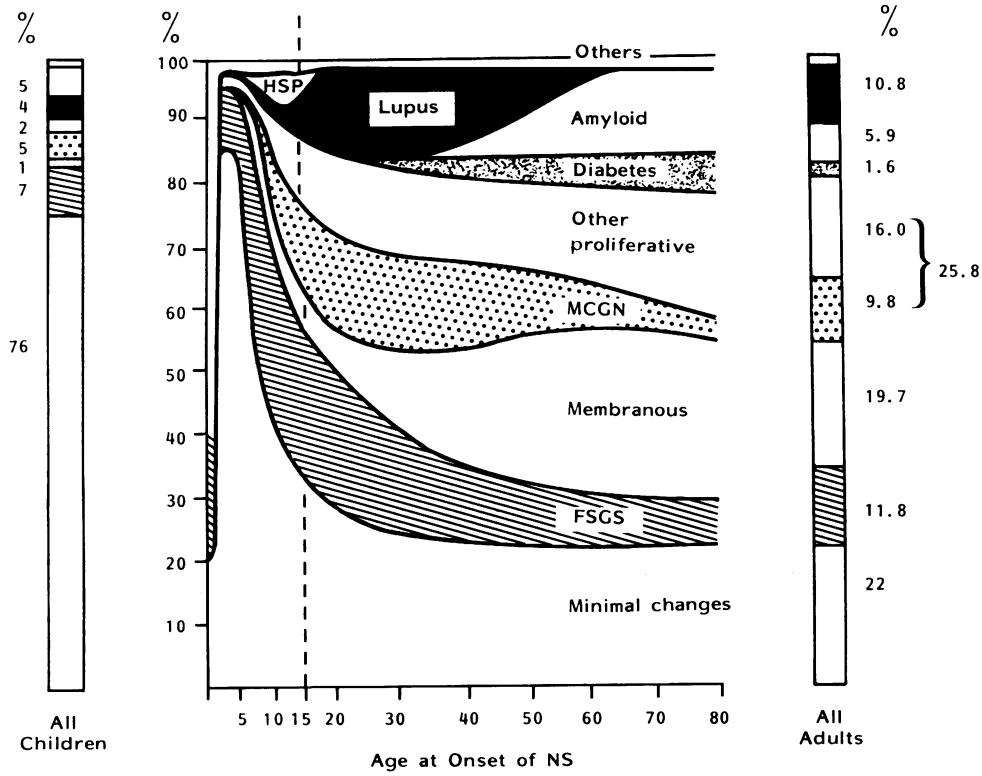

Fig. 3. The underlying glomerular histological appearances found in a series of over 700 nephrotic children and adults seen at Guy's Hospital 1963-1984. The 506 adult biopsies were taken during the whole of this period; the 200 children were all biopsied before 1970, at a time when (as is still our policy in adult nephrotics) *all* children with a nephrotic syndrome were subjected to renal biopsy.

(HSP = Henoch-Schönlein purpura; FSGS = focal segmental glomerulosclerosis; MCGN = mesangio-capillary glomerulonephritis; 'other proliferative' includes predominantly crescentic (extracapillary) forms, IgA- and IgM-associated nephropathy and other mesangial proliferative glomerulonephritides, and focal proliferative glomerulonephritis. 'Others' includes all other forms of glomerular disease not included in the above categories, e.g. the congenital (Finnish) nephrotic syndrome in infants, microscopic polyarteritis and paraproteinaemia in adults, etc.)

The reasons for this decision are evident in the diagram: under the age of 6 or so, the overwhelming number of children show the minimal change lesions of 'lipoid nephrosis' and almost all are responsive to corticosteroids, losing their proteinuria within at most 4 weeks' treatment. A further 25% of those with focal segmental glomerulosclerosis will also lose proteinuria. Thus, it is justified to give almost all young nephrotic children corticosteroids, provided their urine does not contain persistent haematuria with casts. Then in the minority, with no response by at most 4 weeks, a biopsy can be done at this point.

Recently, it has been suggested that a similar policy be adopted for adult nephrotic patients,[75, 76] on the grounds that the extra information gained from this invasive procedure does not justify the risk. The calculations used involve some rather uncertain data or assumptions, but the idea falls down on two other accounts. First, how long in an *adult* with minimal change disease must corticosteroids be given to achieve a good chance of remission? An analysis of our own adult series of patients with minimal change nephrotic syndrome, shortly to be published,[77] shows that adults take much longer to respond to steroids than children: treatment for at least 16 weeks, not 4 weeks, would be necessary to identify the non-responders — who would be some 70% of the total, not 10%. The risks of a longer course such as this to the majority who would not benefit almost certainly exceeds the dangers of renal biopsy, especially in older patients. That this difference between adults and children is not simply the result of using relatively lower doses of corticosteroids in the adults is suggested by the observation that their response to an identical dose of cyclophosphamide on a bodyweight basis (3 mg/kg/ideal weight for height for 8 weeks) is similarly retarded.

Also, there are very few clinical pointers which will indicate either an early response to treatment with corticosteroids, or a good prognosis in the long run (Table III). Surprisingly, renal function at presentation is little or no guide to the degree of underlying irreversible renal damage, since the haemodynamic events of the nephrotic syndrome override the effects of the underlying type of glomerular disease. Obviously the age at onset, as indicated in Figure 3, gives some clue as to what the likely cause may be. Hypertension also is of little help in

TABLE III

Prognostic factors in the nephrotic syndrome

Observation	Effect on prognosis
At onset:	
Persistent haematuria	Often bad
Hypertension	Sometimes bad
Diminished renal function	Useless
Persistent hypocomplementaemia	Usually bad
During subsequent course:	
Loss of proteinuria to corticosteroids	Good
Spontaneous remission of proteinuria	Good
Failure to lose proteinuria on steroids	Sometimes bad
Persisting nephrotic syndrome > 2 years	Usually bad

adults with nephrotic syndromes; patients with minimal change disease are hypertensive surprisingly often at onset,[13-15] which remits with the proteinuria; and we have made the same observations in some childhood nephrotics; presumably this is the result of volume contraction and renin secretion. A low serum complement is of use principally because of its association with mesangiocapillary glomerulonephritis (MCGN), which in general has a poor prognosis. However, above all, it is those nephrotics with persistent microscopic haematuria as well as profuse proteinuria who in general do badly, since this is a characteristic of most of the progressive forms of glomerular damage. In the longer term, persistence of the proteinuria at nephrotic levels is a poor prognostic sign. Long-term studies in our unit show that, in most patients who will ultimately heal, the proteinuria rarely remains in the nephrotic range more than a year or two. Conversely, the serum creatinine is almost always raised permanently in those with progressive disease after only 2-4 years of evolution. Essentially all patients who lose their proteinuria maintain their renal function, unless hypertension has developed and is inadequately treated.

Another interesting observation we have made recently[49, 77, 78] is that the frequency and rate of relapses in minimal change nephritis patients declines steadily with increasing age at onset of the disease. In children. all those who ran very long-term relapsing courses had an onset less than six years of age, and the average number of relapses declined steadily from 1-15 years of age. Amongst adults, the same gradient with age is evident: although as high a proportion of adults have at least one relapse as in childhood (about 70%), overall the total number of relapses is much less; that is, fewer adults become frequent relapsers. This is particularly noticeable in the older patients: over 60 years of age, relapses are rare, although the initial nephrotic episode in these old patients may be devastating and some may die in the acute phase.

For a much more extended account of the history of the nephrotic syndrome, the reader is referred to Chapters 1 and 2, by JS Cameron and RJ Glassock, and RM Kark respectively, in the forthcoming book *The nephrotic syndrome,* edited by JS Cameron and RJ Glassock (New York: Marcel Dekker), now in preparation.

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