Papers and Originals

Controlled Trial of Prednisone in Adult Patients with the Nephrotic Syndrome

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Summary: A multi-centre controlled trial of steroid treatment of the nephrotic syndrome was carried out on 125 patients. Of these, 64 were controls and 61 received prednisone in a recommended dose range of 20-30 mg./24 hours. The actual initial dose averaged 29 mg./24 hours. Treatment was continued for a variable period, but not less than six months. More than 10 mg./24 hours was given on average for 12 months to all patients, and for longer periods to some. Patients were classified, on the basis of biopsy specimens, into three groups: A, minimal change; B, membranous nephropathy; and C, proliferative glomerulonephritis. In groups B and C prednisone did not have any strikingly favourable effect on proteinuria or on renal function as compared with the control group. In group A, however, prednisone reduced proteinuria to a striking and statistically significant extent. It had little if any effect on long-term renal function in any group. The death rate was higher in the combined prednisone groups (17/61) than in the control groups (12/64). This difference was not statistically significant, but there was a significantly higher number of deaths from cardiovascular disease in the prednisone group, whereas the numbers of deaths from renal failure were not significantly different in the two groups.

Patients and Methods

It has been known for many years that some patients suffering from the nephrotic syndrome enter clinical remission, with greatly diminished proteinuria, within a few days of being given steroids of the glucocorticoid group. This treatment became more widely adopted with the introduction of steroids, such as prednisone and prednisolone, which have little salt-retaining effect, so that any remission is not preceded by worsening of the oedema. Steroid-induced remission was found to occur more often in children than in adults; and in children at least the use of steroids became generally accepted as part of the treatment of the nephrotic syndrome. This was based on clinical evidence of steroid-induced remissions and also on retrospective comparison with the results in children treated without steroids. Nevertheless the fall in mortality shown by the later series of cases could well have been due, at least in part, to improvements in antibiotic and diuretic agents, which coincided with the increasing use of steroids. In adults assessment of the value of steroid therapy was even more difficult since there was in them a lower incidence of steroid-induced remissions and a higher incidence of complications such as hypertension, which might be aggravated by steroids, than among children.

At a conference held in 1962 it was agreed that, in adults at least, it was not clear whether the advantages of steroid

therapy for the nephrotic syndrome outweighed the disadvantages, and that it would therefore be justifiable to carry out a controlled trial. Its objects would be to discover whether patients in general were benefited by long-term steroid treatment; whether any benefit was related to the histology of the renal lesion; and whether the long-term benefit, if any, was sufficient to offset the risk of steroid-induced complications.

This communication is limited to the experience gained in this trial; much of the available literature has recently been reviewed by Miller *et al.* (1969).

Organization of Trial

The nephrotic syndrome was considered to be present when *all* the following criteria were met: (a) oedema—still present or recently observed; (b) proteinuria—5 g. or more per day, measured by biuret or turbidimetric method, not Esbach's method; and (c) hypoproteinaemia—serum albumin less than 3 g./100 ml. Only those patients were admitted to the trial who: (a) were aged 15 or over; (b) had suffered from the nephrotic syndrome, as defined above, for not more than one year; (c) had not been previously treated for this condition with steroids or with corticotrophin; (d) were still excreting in the urine, at the end of a preliminary period of four weeks, at least 1 g. of protein per day; (e) showed neither pathological nor strong clinical evidence of a cause for the nephrotic syndrome other than glomerulonephritis; (f) had no past history of episodes of the nephrotic syndrome except during the year immediately preceding admission to the trial; and (g) had not received steroids or corticotrophin for any condition during the past year.

A history of proteinuria extending over more than a year, without other features of the nephrotic syndrome, did not entail exclusion from the trial, nor did uraemia, hypertension, or urinary infection.

In order to obtain sufficient data within a reasonable period a multi-centre trial was necessary. A total of 125 patients who satisfied all the clinical and histological criteria for entry were admitted to the trial in 19 centres over a period of three and a half years. An almost equal number of patients suffering from the nephrotic syndrome had to be rejected for a variety of clinical reasons. Clinical information on patients admitted to the trial was recorded on a standard form, and they were observed for a month before being allocated to "steroid" or "non-steroid" groups.

Histological Classification

The nephrotic syndrome has a great number of possible causes, but in any large series about three-quarters of the patients are suffering from one form of glomerulonephritis or another. Even within the category of glomerulonephritis, however, there is great histological diversity, and this is associated with differences in aetiology and probably in

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clinical outcome. Biopsies were therefore carried out, both to exclude causes other than glomerulonephritis and to determine the histological lesion of each patient admitted to the trial.

The biopsies were processed in the various participating centres. A variety of fixatives were used: formol saline, formol sublimate, Helly's fluid, and Susa. Four unstained slides, each bearing three to six serial sections, were sent to Professor D. B. Brewer. Two slides were stained with haematoxylin and eosin and two by the periodic-acid/Schiff method. After examination and classification they were sent on to Professor I. Doniach, who reported independently.

The biopsies were classified into three groups: minimal change, membranous nephropathy, and proliferative glomerulonephritis. This is, of course, a considerable oversimplification of the wide variety of appearances found in the kidney in the nephrotic syndrome, and because of this the criteria used were rather crude and arbitrary.

Minimal change includes those cases that show no definite glomerular abnormality—in particular those where there are no evidence of proliferation, no capsular adhesions, and no thickening of the glomerular basement membrane. A major difficulty in allocating cases to this group is to determine whether or not there is a slight increase in the endothelial cells (including mesangial cells), particularly when the cells are grouped about the centres of the glomerular lobules.

Membranous nephropathy is characterized by a diffuse thickening of the glomerular basement membrane. Every tuft is affected and within each tuft the basement membrane is diffusely and more or less evenly thickened. This thickening can best be judged by examining the peripheral capillary loops of the tufts. There is little or no cellular proliferation. In occasional cases it was difficult to decide whether the glomerular basement membrane was thickened or not, but this difficulty arose less often than was expected.

Proliferative glomerulonephritis.—The first two groups described are fairly homogeneous, but the last group, proliferative glomerulonephritis, is very heterogeneous. Its diagnostic feature is an increase of cells in the glomerulus. These cells may be endothelial cells (including mesangial cells), epithelial cells, polymorphonuclear leucocytes, or all of these at once. The proliferation may be diffuse or focal or may take the form of epithelial crescents.

Obviously the findings are subject to sampling variations. In both membranous nephropathy and well-developed proliferative glomerulonephritis every glomerulus is involved. However, in some cases of focal proliferative glomerulonephritis, or where the proliferation is slight or resolving, the lesions may be small and few so that it is possible, in a small biopsy including only a few glomeruli, to miss such foci of proliferation and to conclude, wrongly, that the case is one of minimal change.

Another important difficulty arises in distinguishing between diffuse endothelial cell proliferative glomerulonephritis of some duration, in which a good deal of fibrillar thickening may have developed, and membranous nephropathy. In making this distinction it is important to examine the glomerular basement membrane in the peripheral capillary loops of the tuft. For the purposes of the trial patients with proliferative changes were subclassified into four groups: (1) focal changes, (2) early endothelial proliferation, (3) late endothelial proliferation, and (4) proliferation with crescent formation. As judged by treatment response, proteinuria, and renal function, however, the first three of these groups did not differ significantly. The fourth group included only four patients, all of whom died.

When the biopsy showed a combination of clear-cut proliferative and membranous changes it was assigned, for the purpose of the trial, to the proliferative group.

The definitive classification of biopsy specimens was carried out only after entries to the trial were complete; at this stage

the pathologists had no knowledge of the clinical progress of individual patients. In all 177 biopsies were received from 173 patients. The final agreed classification was as follows:

Minimal change	..	..	..	..	..	38
Membranous nephropathy	..	..	..	..	..	25
Proliferative glomerulonephritis	..	..	..	..	..	87
Renal amyloidosis	..	..	..	..	..	6
Diagnosis uncertain	..	..	..	..	..	1
Biopsy specimen insufficient or unsuitable	..	..	..	..	..	20
						177

As already mentioned, certain of these patients whose pathological classification was acceptable had yet to be excluded on a variety of clinical grounds; the final total admitted to the trial was 125.

The total number of discrepancies originally discovered between the two pathologists' findings was 40. In nine of these cases the biopsies were small and one or other pathologist considered that the material was insufficient. If these cases are excluded the discrepancies amount to 31 out of 168 adequate biopsies (18.5%).

The first major reason for these discrepancies was the difficulty, described above, of distinguishing between proliferative glomerulonephritis and minimal change. In this respect Brewer tended to accept very slight changes as evidence of proliferation but Doniach required more definite evidence. As a result 12 biopsies were classified by Brewer as proliferative glomerulonephritis and by Doniach as minimal change. The second major difficulty lay in distinguishing between endothelial cell proliferative glomerulonephritis and membranous nephropathy. There were nine such cases that Brewer classified as proliferative glomerulonephritis and Doniach as membranous nephropathy and four more that Brewer called membranous nephropathy and Doniach proliferative glomerulonephritis.

The Patients and their Management

On the basis of the histological findings the 125 patients who qualified for the trial were classified as follows: group A (minimal change) 31 patients; group B (membranous nephropathy) 19 patients; and group C (proliferative glomerulonephritis) 75 patients.

The age and sex distributions are shown in Table I. Each of the three groups shows a distinctive pattern. Group A cases occur at all ages, with about equal numbers in each sex. Group

TABLE I.—Numbers of Patients Entering the Trial: Age and Sex Distribution

Age	Group A		Group B		Group C		Total	
	M.	F.	M.	F.	M.	F.	M.	F.
<25	5	4	2	1	10	9	17	14
25	4	2	2	—	3	5	9	7
35	3	—	3	—	8	6	14	6
45	2	5	2	—	15	—	19	5
55	1	3	6	1	11	—	18	4
≥65	2	—	1	1	7	1	10	2
Total	17	14	16	3	54	21	87	38

B cases also occur at all ages, but with a strong preponderance of males throughout. Group C cases in males occur at all ages, but especially in the second half of life; under the age of 45 cases occur with about the same frequency in females as in males, but above the age of 45 the series included only one female patient with proliferative glomerulonephritis.

At the end of the initial assessment period of one month 61 patients had been allocated to the steroid and 64 to the control group. Allocation was carried out centrally and was randomized both within the three main histological categories and within the various hospitals. Some of the initial characteristics of the two groups are shown in Table II. In general the differences are very small, but the blood cholesterol level is

TABLE II.—Characteristics of Prednisone and Control Groups before Entry to the Trial

Characteristics	Mean and S.D.	
	Prednisone (N = 61)	Control (N = 64)
Age in years	40.6 ± 16.2	41.3 ± 18.3
Body weight (kg.)	68.7 ± 10.6	65.8 ± 14.4
Blood pressure (mm. Hg)	144.4 ± 23.0	146.2 ± 22.4
	{ Systolic	{ Systolic
	{ Diastolic	{ Diastolic
Haemoglobin (g./100 ml.)	13.0 ± 2.0	12.9 ± 1.8
Proteinuria (g./24 hours)	10.2 ± 6.2	9.8 ± 5.3
Plasma albumin (g./100 ml.)	1.9 ± 0.54	2.1 ± 0.64
Plasma cholesterol (mg./100 ml.)	494 ± 197	417 ± 126
Plasma creatinine (mg./100 ml.)	1.69 ± 1.65	1.42 ± 1.00
Blood urea (mg./100 ml.)	49.5 ± 25.8	48.5 ± 30.4
Creatinine clearance rate (ml./min.)	84.7 ± 53.3	93.4 ± 44.9

higher in the steroid group and the difference is unexpectedly large ($0.02 > P > 0.01$). The allocation and reporting procedures were such that this could not be anything but a chance result; moreover, cholesterol level did not appear to be related to progress or outcome in the series as a whole.

Patients in the steroid group were given prednisone. The dosage in the first three weeks was not less than 20 mg./day, the precise dose being left to the discretion of the physician. Thereafter the prednisone was continued for at least six months, but the dose range was now limited so far as possible to 20–30 mg. daily. The protocol allowed for the dosage to be altered if necessary in the patient's interest, but this "escape clause" was used only once in the initial six-month period and five times thereafter (four of these patients were in the minimal change group). Prednisone could also be given to control patients who were not progressing satisfactorily, but this need arose in only six cases (five minimal change and one proliferative). The mean dosage levels given at various stages of the trial are included in Table III.

TABLE III.—Mean Prednisone Dosage (mg./day)

Interval (Months) from Entry	Group A	Group B	Group C
0–	26	32	29
1–	27	21	24
3–	23	20	18
6–	18	20	13
12–	11	14	11
18–	5	7	10
24–	5	3	9
30–	4	0	7
36–	1	0	8
42–8	0	0	4

Patients in both groups were given similar treatment in other respects; this included diuretics, hypotensive drugs, and antibiotics, but not immunosuppressive agents.

Results

At the time of analysis all patients had been in the trial for at least two years. Beyond this point follow-up information was available for diminishing numbers. Mortality was initially followed by sequential analysis of the two groups (Fig. 1), so that participating physicians could be told of any clear-cut advantage of either the "steroid" or the "non-steroid" regimen. Other forms of analysis were applied to the degree of proteinuria, the blood pressure level, the creatinine and blood urea levels, and similar indices.

Proteinuria

Among prednisone-treated group A patients there was generally an early and dramatic decrease in proteinuria. The mean protein loss in these patients was reduced during the first month of treatment from 10.1 to 3.8 g./24 hours, as compared with a fall from 10.1 to 9.3 g./24 hours among control patients ($t=2.583$, 23 D.F., $0.02 > P > 0.01$). Excluding two early deaths, only three patients in the treated group failed to show a large fall in proteinuria within two months of starting

FIG. 1.—Sequential analysis of deaths and patients on chronic haemodialysis.

FIG. 2.—Group A patients (minimal change). Proportion of patients with proteinuria of more than 1 g./24 hours expressed as a percentage of those alive and in the trial (numbers of patients in trial after two years in parentheses).

prednisone; these three continued to show heavy protein loss throughout the period of observation and two of them died. Fig. 2 illustrates the contrasting trends in proteinuria between the prednisone and control groups. In the original control group four patients were later given prednisone, and three responded. The remaining control patients showed a tendency to recover, though far more slowly, and it was only in the first few months of treatment that the prednisone group showed a significantly faster recovery rate.

Of the 75 patients finally classified as group C (proliferative) 18 had been classified initially by one of the pathologists as group A (minimal change). Of those given prednisone none showed a convincing steroid response in the first six months; but, regardless of treatment group, these patients were much more likely than those with agreed proliferative change to lose their proteinuria; after two years just over half of them had 1 g. or less of protein in the urine per 24 hours. They also tended to have higher creatinine clearance rates.

Following the decrease in proteinuria, the prednisone-treated group A patients attained lower levels of plasma cholesterol and higher levels of plasma albumin than their controls. The advantage in respect of plasma albumin was greatest during the second and third months (3.8 against 1.9 g./100 ml., $P < 0.01$). Thereafter it diminished and by two and a half years the difference had gone. Similarly, half of the prednisone-treated patients were free of oedema within a month, as compared with only 14% of control patients; but the difference gradually diminished, and had disappeared

after two years. The reduced incidence of oedema in the prednisone-treated patients in group A was not reflected in any improvement in the proportion who were able to return to work. During the first three months this proportion was in fact somewhat higher for the control patients. During the rest of the trial differences were very small.

In group B (membranous) and group C (proliferative) the early response to prednisone seen in group A was completely lacking (Figs. 3 and 4). There was, however, one control patient with proliferative change who was given steroid after 18 months, and who then showed a fall in proteinuria from 12 to less than 1 g./24 hours. From the second year onwards the prednisone-treated patients were at some advantage with regard to proteinuria, but at no point did the differences approach statistical significance. In both group B and group C proteinuria tended to be much more persistent than in group A (regardless of treatment group).

Plasma albumin level and oedema showed very similar trends in prednisone-treated and control patients in both group B and group C. There was no notable difference in the proportion of patients who were able to return to work.

FIG. 3.—Group B patients (membranous change only). Proportion of patients with proteinuria of more than 1 g./24 hours expressed as a percentage of those alive and in the trial (numbers of patients in trial after two years in parentheses).

FIG. 4.—Group C patients (proliferative change). Proportions of patients with proteinuria of more than 1 g./24 hours expressed as a percentage of those alive and in the trial (numbers of patients in trial after two years in parentheses).

Blood Pressure

The blood pressure levels of the prednisone and control groups are set out in Table IV. Differences are very small, so there is no evidence of any important hypertensive effect of prednisone therapy in the dosage used. At the same time a

TABLE IV.—Blood Pressure Trends (All Pathological Groups Combined)

Interval (Months) from Entry	Mean Pressure (mm. Hg)			
	Systolic		Diastolic	
	Prednisone	Control	Prednisone	Control
0—	149	148	91	91
1—	148	149	91	89
3—	149	146	93	88
6—	147	141	91	85
12—	144	144	88	87
18—	147	143	90	87
24—	147	146	90	88
30—	143	145	88	88
36—	149	141	90	87
42—8	141	154	85	96

small effect might have been concealed by the greater mortality (see below) among hypertensive patients treated with prednisone, which would tend to reduce the mean blood pressure in the group of survivors. The number of patients given hypotensive agents (other than diuretics) during the first two years of the trial was 15 in the prednisone group and 10 in the control group.

Renal Function

Renal function was measured by blood urea, creatinine clearance rate, and plasma creatinine. Fortunately, the mean levels of these three indices indicated somewhat poorer renal function at the start of the trial among group A prednisone patients than among group A controls. Thereafter, however, there were no statistically significant differences between prednisone patients and controls at any stage. After the first three months renal function was consistently better among prednisone-treated patients than among controls, but the differences were throughout within chance limits. The trend in group A patients was similar to that in the remainder. The pattern for plasma creatinine is illustrated in Figs. 5 and 6.

Mortality was related to renal function, so that the early deaths of those with poorer function mean that the trends shown in Figs. 5 and 6 underestimate the real rate of deterioration. The comparisons between the prednisone and control groups, however, have not been significantly biased in this way.

Mortality and Steroid Complications*

Some characteristics of the deaths occurring in the trial are listed in Table V. During the first two years of the trial there were 16 deaths among prednisone-treated patients. In the control group there were 11 deaths in this period. Beyond the two-year point the follow-up is incomplete. Up to the present time there have been two further deaths in the prednisone group and four further deaths in the control group. All four group A deaths have occurred in prednisone-treated patients. None of these figures represents a statistically significant difference.

Examination of the causes of death listed in Table V shows that renal failure leading to death or to long-term haemodialysis occurred during the first two years of the trial in five prednisone-treated patients and seven controls. Beyond that period there have been up to the present time one more such case in a prednisone-treated patient and four in controls, making totals of 6 and 11 respectively (not a statistically significant difference).

Death from causes other than renal failure has occurred so far in 11 prednisone-treated patients, but in only one control. This difference is unlikely to be due to chance ($\chi^2=8.114$, 1

* In the general assessment of results the need to institute long-term haemodialysis has been regarded as the equivalent of renal failure sufficient to cause death.

FIG. 5.—Plasma creatinine levels in prednisone-treated and control patients for all three pathological groups combined.

FIG. 6.—Plasma creatinine levels in prednisone-treated and control patients for patients with minimum change histology.

D.F., $0.01 > P > 0.001$). Among the 11 prednisone-treated patients in this group, only one was under the age of 45. Of the 11 deaths, seven were due to various cardiovascular diseases; two were from infection, one was from a bleeding gastric ulcer, and one from cancer. The difference in cardiovascular mortality rates between the two groups (11% and 2%) is significant at the 5% level. The seven who died from cardiovascular causes had a mean initial blood pressure of 164/96 mm.Hg as compared with 144/89 mm.Hg for the prednisone group as a whole, but their mean initial plasma cholesterol level (433 mg./100 ml.) was lower than that for the whole group (494 mg./100 ml.). The additional mortality risk attributable to prednisone appeared to occur mainly (though not exclusively) in the early months of treatment.

On each follow-up report participants were asked to record any non-fatal steroid side-effects or complications. Mooning of the face, striae, and bruising were noted frequently. Of the more serious complications, there were six instances of peptic ulcer (three with bleeding), two of depression and two of other psychoses, one of tuberculosis, two of candidiasis, one of pneumonia, and one of cerebrovascular accident. No illness in any of these categories was recorded in patients not receiving prednisone, but the possibility of some underrecording cannot be excluded. One control patient who was later given prednisone developed a duodenal ulcer and pulmonary embolism.

Histological Follow-up

In 23 patients further kidney tissue, obtained either by biopsy or by necropsy, was available for examination at intervals of from 14 to 35 months after the initial biopsy.

In eight patients renal damage progressed considerably towards glomerular sclerosis. These included five cases of

proliferative glomerulonephritis (three mild, one moderately diffuse, and one focal) and three cases classified with some reservations as minimal change. Of the eight patients five had received steroids.

In nine patients where the initial biopsies had shown no abnormality, or only very slight abnormalities, second biopsies (and in one case a necropsy) revealed little progression of the renal lesion. Seven of these nine patients had received steroids.

In six patients the original lesion was a severe one and further material (three biopsies and four necropsies) showed no change.

TABLE V.—Characteristics of Patients Dying or Requiring Long-term Haemodialysis

Interval (Months) from Entry to Death or Haemodialysis	Age (at Entry)	Sex	Path. Group	Cause of Death (Where Applicable) or Haemodialysis
(a) Prednisone Group				
1	59	M.	C	Myocardial infarction
2	49	F.	A	Pulmonary embolism
2	56	M.	C	Pulmonary embolism (femoral vein thrombosis)
2	66	M.	A	Renal failure
3	53	M.	C	Congestive cardiac failure: coronary heart disease
3	20	M.	C	Septicaemia, agranulocytosis, thrombocytopenia
3	58	F.	A	(Renal failure—haemodialysis)
6	69	M.	C	Staphylococcal
7	21	F.	C	bronchopneumonia
7	55	M.	A	Subarachnoid haemorrhage
12	55	M.	C	Renal failure
15	57	M.	C	Bronchial carcinoma
17	43	M.	C	Renal failure
21	16	M.	C	Sudden death: ? coronary heart disease
24	61	M.	C	(Renal failure—haemodialysis)
28	45	M.	C	Bleeding gastric ulcer, haemothorax
43	37	F.	C	Cerebral haemorrhage
				Myocardial infarction
				(Renal failure—haemodialysis)
(b) Control Group				
1	47	M.	C	Renal failure
2	35	M.	C	(Renal failure—haemodialysis, followed 27 months later by death)
7	72	M.	C	?Cerebral thrombosis
14	60	M.	C	Renal failure
18	57	M.	C	Renal failure
20	21	M.	C	(Renal failure—haemodialysis, followed 5 months later by death)
20	17	F.	C	(Renal failure—haemodialysis)
24	17	F.	C	Renal failure
30	41	M.	C	Renal failure, pulmonary oedema
30	52	M.	C	Renal failure
33	61	F.	B	Renal failure, bacterial endocarditis
50	20	F.	C	(Renal failure—haemodialysis)

Note on a possible limitation of sequential analysis illustrated in this trial.—Table V shows a clear preponderance in the prednisone group of deaths occurring within three months of entry into the trial. If (as seems likely) these early deaths occur in "poor-risk" patients, they will leave a group of "better-risk" patients, while the control group has not been denuded of "poor-risk" patients by exposure to the added risks of steroid treatment. This effect could introduce bias into the longer-term comparison, to the apparent disadvantage of the control group. Sequential analysis may be misleading in a situation in which the risks or benefits of a long-term treatment vary greatly with time. In this particular trial the early disadvantage of giving prednisone just failed to reach statistical significance at the 5% level. The discrepancy in mortality did not increase later in the trial (Fig. 1).

Conclusions

The results suggest that in adult patients with the nephrotic syndrome based on glomerulonephritis the risks of giving continuous steroids routinely in the dose and duration described may well outweigh the possible benefits. In patients with minimal glomerular change treated with steroids, however, there was an earlier improvement, as compared with control patients, in respect of proteinuria, hypoproteinaemia and oedema. There was also a suggestion, not reaching the level of statistical significance, that renal function might be maintained at a higher level in the patients treated with steroids.

This difference was small—for example, the mean difference between the blood urea of treated and control patients was less than 10 mg./100 ml.; but it was common to all the histological groups. As against these limited advantages there must be set a higher mortality in the group treated with steroids. In the first two years the number of

patients dying from renal failure, or maintained on regular haemodialysis, was similar in the steroid and control groups; the excess mortality in the steroid group was accounted for by other causes, some of which are recognized as dangers of steroid treatment—for example, infection, bleeding peptic ulcer, vascular accidents. The dilemma is perhaps seen most sharply in the minimal change group, which showed the advantage of prompt clinical remission on steroids. The mortality of the control group was nil, while in the steroid group there were four deaths. One of these, however, was due to bronchial neoplasm, and occurred at a late stage, but the other three deaths occurred at 2, 2½, and 3 months after the start of treatment, so that even a short trial of steroid treatment is not without risk.

Perhaps consideration should be given to excluding from steroid treatment patients who might be thought to form a "high-risk group" because of their age or raised blood pressure. The trial has shown that steroids should not be used for long periods in patients who do not show a clinical remission. It has produced no evidence on the optimum duration of steroid treatment in those patients who have a remission. Steroids given in larger doses might of course have influenced the disease process more decisively; but any such gain might well have been offset by more frequent and more severe complications. Nephrotic children, with their high incidence of minimal change histology, are more likely to experience clinical remission with steroids; moreover, their youth and normal blood pressure are great assets in withstanding the dangers of steroid treatment. While to say that childhood nephrotic syndrome differs from adult nephrotic syndrome is not to deny that these findings have some relevance to paediatric practice, nevertheless it must be stressed that they can be applied directly to adult patients only. For such patients it is concluded that:

(1) When adequate facilities are available for the study of material, renal biopsy should be carried out in patients with the nephrotic syndrome, particularly in order to: (a) reveal conditions other than glomerulonephritis, and (b) distinguish patients with established glomerular changes (who are unlikely to derive benefit from steroid treatment) from those with minimal glomerular changes (who have a good chance of prompt remission if given steroid treatment).

(2) In the absence of adequate biopsy facilities, steroids in conventional dosage should be given only when the syndrome is at a relatively early stage and should not be continued for longer than six weeks if there is no demonstrable effect on proteinuria.

(3) The risks of steroid treatment are greater in older patients, especially those with raised blood pressure.

(4) There are strong arguments for referring all patients suffering from the nephrotic syndrome to a renal centre with adequate facilities for assessment.

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REFERENCE

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Addendum

Since the completion of the above report further follow-up results have become available. All patients have now been followed for two years and some for up to four years. There have been eight further deaths, four in the prednisone group (one from renal failure) and three in the control group (one from renal failure); two other control patients are now receiving long-term haemodialysis.

In the groups with "minimal change," the findings among survivors have been as follows:

	Months							
	24–		30–		36–		42–48	
	Pred.	Con.	Pred.	Con.	Pred.	Con.	Pred.	Con.
No. alive and in trial	11	15	10	13	10	12	9	11
Proteinuria (g./24 hours)	2.7	2.4	0	2.7	0	2.2	0*	0.6*
Plasma creatinine (mg./100 ml.)	1.0	1.3	1.1	1.7	1.1	2.0	1.0	1.3

*0.1 > P > 0.05.

The numbers are small, but it is striking that no proteinuria was recorded in any of the 10 patients in the prednisone group after two and a half years. During the fourth year of the trial only three of these patients received any steroid treatment. A tendency to lower creatinine levels appeared consistently throughout, but was well within chance limits.

The following have been the corresponding findings among survivors with "proliferative change":

	Months							
	24–		30–		36–		42–48	
	Pred.	Con.	Pred.	Con.	Pred.	Con.	Pred.	Con.
No. alive and in trial	23	29	22	24	19	20	16	20
Proteinuria (g./24 hours)	3.2	6.0	2.4	4.1	2.2	3.2	1.9	3.4
Plasma creatinine (mg./100 ml.)	1.9	2.4	2.5	3.0	2.8	2.6	1.7	2.3

Patients in both the treated and the control groups showed a progressive fall in proteinuria, the levels at each point being consistently lower in the prednisone group. The differences between the groups did not, however, approach statistical significance. There is no consistent pattern in plasma creatinine levels.