SELECTIVITY OF PROTEINURIA IN NEPHROTIC SYNDROME

By C. H. Tay, Beatrice T. M. Chen and R. Wee

SYNOPSIS

Protein clearance study was performed in 23 patients with proven nephrotic syndrome by the method described by Cameron and Blandford (1966). The Selectivity Index obtained, was correlated with renal histology and steroid response.

Whilst there was close correlation between Selectivity Index and the responsiveness to short-term oral steroid therapy, no close relationship was obtained between the Selectivity Index and the renal histology. The arbitrary Selectivity Index obtained in this series was 0.333, a much higher index than those obtained elsewhere. In addition, the tests proved to be too expensive for routine medical uses.

INTRODUCTION

The study of proteinuria in nephrotic syndrome by measuring the clearance of various proteins in plasma and urine have been employed for more than a decade (Hardwick and Squire, 1955). However, most of the methods used were tedious, expensive and unsuitable for routine uses (Soothill, 1962 and Hardwick, 1965).

In 1966, Cameron and Blandford developed a quick, simple and cheap method of measuring the selectivity of heavy proteinuria using the clearances of two proteins, the IgG and the transferrin. They obtained good correlation between this method and that of Soothill (1962).

In this paper, we present a pilot study of proteinuria selectivity in 23 patients with proven nephrotic syndrome, based on the method described by Cameron and Blandford (1966).

MATERIAL AND METHODS

Twenty three randomly selected patients with proven nephrotic syndrome above the age of 10 in Medical Unit II, Outram Road General Hospital, Singapore, were included in this study.

All had renal biopsy done by one of us (B.T.M.C.) using the method described by Kark and Meuhrcke (1954) with minor modifications (Chen, 1971). The histological diagnosis was based on established criteria (Heptinstall, 1966).

All the patients were on maintenance steroid therapy at the time of this study. The result of the response to steroid was taken as that obtained eight weeks after the initial therapy and the criteria of response was based on those described by Cameron and Blandford (1966).

A 'good' (or YES) response to steroid was defined as loss of oedema, reduction of proteinuria and the return of blood biochemistry towards normal. A 'poor' (or NO) response, on the other hand, was associated with no change or worsening of the clinical states and the biochemical findings.

Protein clearances studies were done by one of us (R.W.). Fresh and unmodified plasma and urine were obtained from all patients. Using the method described by Cameron and Blandford (1966) the quantitative measurement of plasma and urinary IgG and transferrin were obtained by means of commercially prepared immunodiffusion plates with the appropriated incorporated antisera ("Partigen", Behringwerke, Ag. Marburg, Lahn). The standard and reference sera were also obtained from the same source.

The Selectivity Index (S.I.) of protein clearance of each patient was derived from the ratio of the clearances of IgG and transferrin, using the following formula:

$$\text{S. I.} = \frac{\text{Urinary IgG/Plasma IgG}}{\text{Urinary transferrin/Plasma transferrin}}$$

RESULTS

Table I shows the age, sex, race, renal histology, steroid response and the selectivity index (S.I.) of the 23 patients in this series. The majority were Chinese males in the second and third decades of life.

Eight patients had diffuse proliferative glomerulonephritis, of which one was severe; 7 had 'minimal' change type of glomerulonephritis; 4 had focal glomerulonephritis; 3 had Lupus nephritis and one, Membranous glomerulonephritis.

Outram Road General Hospital, Singapore.
Medical Unit III.
C.H. TAY, A.M., M.R.C.P.(G.), Physician.
Medical Unit II.
BEATRICE T. M. CHEN, A.M., M.R.A.C.P., Senior Registrar.
Department of Pathology.
R. WEE, B.Sc.(Hons.), M.Sc., Dp.Bact., Bacteriologist.

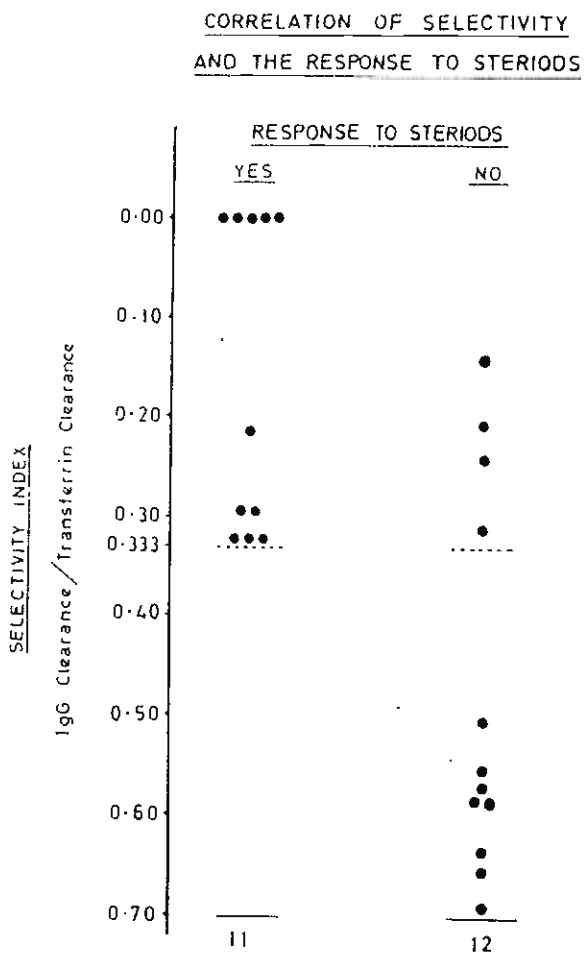

Fig. 1.

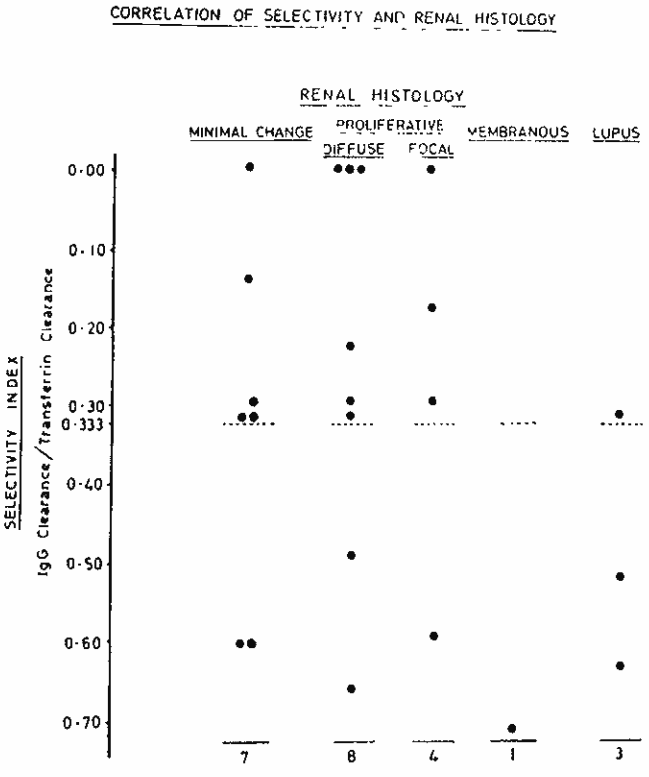

Fig. 2.

TABLE I

Case No.	Age	Sex	Race	Renal Histology	Steroid Response	Selectivity Index
1	24	M	Ch	Minimal	Yes	0·162
2	22	M	Ma	Minimal	Yes	0·333
3	45	M	Ch	Focal	Yes	0·277
4	26	M	Ch	Prolif	Yes	0·236
5	12	M	Ch	Minimal	No	0·600
6	14	M	Ch	Minimal	Yes	0·308
7	10	M	Ch	Prolif	No	0·500
8	14	F	Ch	Minimal	Yes	0·333
9	31	F	Ch	Prolif	Yes	0·326
10	25	F	Ch	Prolif	Yes	0·308
11	15	M	Ch	Focal	No	0·595
12	22	M	Ch	Prolif	Yes	0·000
13	52	F	Ch	Minimal	No	0·600
14	44	F	Ch	Focal	Yes	0·000
15	60	M	Ch	Membranous	No	0·740
16	13	M	Ch	Minimal	Yes	0·000
17	12	M	Ch	Prolif	No	0·673
18	18	F	Ch	Prolif	Yes	0·000
19	18	M	Ch	Prolif	Yes	0·000
20	20	F	Ch	Lupus	No	0·335
21	22	F	Ch	Lupus	No	0·548
22	41	M	Ch	Lupus	No	0·650
23	15	M	Ch	Focal	No	0·202

Key:

M	—Male
F	—Female
Ch	—Chinese
Ma	—Malay
Yes	—Responded to Steroid
No	—Not Responded to Steroid
Minimal	—"Minimal change" type of proliferative glomerulonephritis
Prolif	—Diffuse proliferative glomerulonephritis
Focal	—Focal glomerulonephritis
Membranous	—Membranous glomerulonephritis
Lupus	—Lupus nephritis

$$\text{Selectivity Index} = \frac{\text{Urinary IgG/Plasma IgG}}{\text{Urinary transferrin/Plasma transferrin}}$$

Details of proteinuria study are summarized in Table II. Mild to moderate degrees of proteinuria were found in this series and in 5 patients, the urinary IgG and transferrin were not readily detected in the unconcentrated urine.

The relationships between Selectivity Index, renal histology and response to steroid are demonstrated in Figs. 1 and 2.

An arbitrary point can be made at the Selectivity Index (S.I.) of 0·333 which divides the 'good' (YES) responses to steroid group from the 'poor' (NO) responses group (Fig. 2). No close correlation, however, was found between the S.I. and the renal lesions in this series (Fig. 1).

DISCUSSION

In the last decade, protein clearance had been widely used as an index of glomerular permeability in renal diseases particularly in nephrotic

TABLE II

PROTEIN CLEARANCES STUDY

Case No.	IgG (mg. per 100 ml.)		Transferrin (mg. per 100 ml.)		Urine Clearance for IgG (IgG U/P)	Urine Clearance for Transferrin (Transferrin U/P)	Selectivity Index
	Plasma	Urine	Plasma	Urine			
1	1184	80	130	50	1/14·8	1/2·6	0·162
2	1032	80	214	50	1/12·9	1/4·3	0·333
3	1184	80	198	48	1/14·8	1/4·1	0·277
4	1184	80	168	48	1/14·8	1/3·5	0·236
5	1108	85	183	45	1/13·0	1/4·0	0·308
6	1008	184	144	43	1/5·5	1/3·3	0·600
7	768	216	114	63	1/3·6	1/1·8	0·500
8	954	184	146	87	1/5·1	1/1·7	0·333
9	792	92	144	51	1/8·6	1/2·8	0·326
10	1168	224	132	85	1/5·2	1/1·6	0·308
11	1088	292	140	63	1/3·7	1/2·2	0·595
12	1120	0	140	0	0	0	0·000
13	640	320	134	108	1/2·0	1/1·2	0·600
14	1040	0	230	0	0	0	0·000
15	1050	210	198	54	1/5·0	1/3·7	0·740
16	1160	0	200	0	0	0	0·000
17	869	158	166	45	1/5·5	1/3·7	0·673
18	1040	0	194	0	0	0	0·000
19	956	0	132	0	0	0	0·000
20	964	190	165	99	1/5·07	1/1·7	0·335
21	816	194	160	71	1/4·2	1/2·3	0·548
22	884	221	166	83	1/4·0	1/2·6	0·650
23	1184	92	220	85	1/12·9	1/2·6	0·202

syndrome. Based largely on the concept of glomerulus as a molecular sieve (Wallerenius, 1954), the selectivity of proteinuria has been found to correlate closely with the clearance of any plasma proteins and their molecular weight (Hardwick and Squire, 1955 and Hardwick and Soothill, 1961). Patients with 'high' selectivity of proteinuria were found to excrete little or no large-molecular weight proteins in their urine whereas those with 'poor' selectivity had significant proportion of large-molecular proteins in their urine (Blainey *et al*, 1960 and Joachim *et al*, 1964). The selectivity pattern has been used to pre-determine the nature of renal lesions as well as the effectiveness of short term oral steroids therapy in patients with nephrotic syndrome. A Selectivity Index (S.I.) of 0·20 and less ('high selectivity') is often associated with 'minimal change' type of glomerulonephritis, milder forms of proliferative glomerulonephritis and a good response to a 8-week course of oral corticosteroids. A selectivity index of above 0·20 ('poor' selectivity), on the other hand, are usually found in patients with severe and diffuse proliferative glomerulonephritis, membranous nephropathy, and a poor response to steroid (Blainey *et al*, 1960; Cameron and Blandford, 1966; Cameron and White, 1965 and Cameron, 1966 and 1968).

In this series, the proteinuria observed were relatively mild and in 5 patients, the urinary IgG and transferrin were barely detectable by the immunodiffusion method. These findings could be due to the fact that our patients were already on maintenance steroid therapy during the proteinuria study and that the urine was not suitably concentrated. In this series, the selectivity index (S.I.) which was found to separate the steroid responsive group from the steroid non-responsive group was 0·333, a much higher value than the S.I. of 0·20 obtained by Cameron and Blandford (1966). But this same index (0·333) could not be used to pre-determine the nature of renal histology in this series of nephrotic syndrome (Fig. 1). Thus our study confirms the findings of other workers that patients with 'high' proteinuria selectivity (that is, S.I. of 0·333 or less, in this series) had good responses to steroid therapy (Cameron and Blandford, 1966; Joachim *et al*, 1964; Blainey *et al*, 1960 and Cameron, 1968), but there was no correlation of S.I. to renal histology as observed by these workers. However, Barcelo and

Pollak (1966) in another study also found no such correlation between S.I. and the renal lesions of nephrotic syndrome in their series.

The light proteinuria in our patients might have been due to the exhibition of steroids before the study was carried out, and thus treatment might have modified the selectivity index in this series. This observation is in contrast to the findings of other workers who found that the S.I. remains unaltered over a prolonged period, in spontaneous remission, with treatment by drugs, and it is not influenced by the quantity of proteinuria (Blainey *et al.* 1960; Vere and Walduck, 1966 and Cameron and Blandford, 1966).

Although Cameron's method (Cameron and Blandford, 1966) was employed in this study, we obtained a higher S.I. arbitrary value of 0·333 instead of the S.I. of 0·20 found elsewhere. Apart for possible differences in techniques used during the quantitative estimation of the proteins, we are unable to explain this discrepancy.

Heavy expenses were incurred for the purchase of immunoplates used in this study and it was estimated that each set of duplicate test cost about S$21/- per patient. The usefulness of employing proteinuria selectivity by this method is thus limited and we do not recommend it as a routine investigation for nephrotic syndrome in this country.

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