THE NEPHROTIC SYNDROME IN CHILDREN TREATED WITH A COURSE OF PREDNISOLONE

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The nephrotic syndrome, under various names, has been recognized since the beginning of this century. In this paper we use the term "nephrotic syndrome" to imply a condition with oedema, heavy proteinuria, and hypoalbuminaemia.

Many different treatments have been tried since Potter's (1904) dietary regime of additional protein in milk. Barness *et al.* (1950) list 64 different methods of therapy in Boston between 1926 and 1948. Most were unsatisfactory until the advent of corticotrophin and the steroid hormones. These sometimes diminished, and rarely abolished, the proteinuria, but they had the drawback of producing salt and water retention. Prednisolone, however, had less salt-retaining action, and Arneil (1956) described the successful treatment of the nephrotic syndrome in five children with this substance.

This paper reports the results of treating six children with prednisolone.

Material and Treatment

Table 1 summarizes the clinical state of the six children before prednisolone treatment. These children had been under observation from one week to one year before prednisolone treatment started. Various methods of treatment, including cortisone (3 g. of cortisone in five weeks) and prednisone (100 mg. of prednisone in seven days), had been used in two children, but they did not affect the albuminuria, although oedema was often relieved. All six children were typical examples of the nephrotic syndrome. However, P. M. had a transient period of severe haematuria, and S. T. a greatly increased blood urea during an acute exacerbation when he was passing only 100-300 ml. of urine a day.

The course of treatment was planned to last 40 days, and all except one received the full course. Children weighing 40-60 lb. (18-27 kg.) received 60 mg. of prednisolone a day for 10 days; the dose was then gradually reduced over 30 days, in steps, so that they received 10 mg. a day over the last 10 days. Children weighing less than 40 lb. (18 kg.) started with 40 mg. a day. These were very large doses, being equivalent to about 300 mg. of cortisone a day. All children received potassium supplements, but were otherwise on a normal diet.

Immediate Response

All children completed the full 40-day course of treatment except K. G. (see below). In the first two to three days of treatment there was little change; then a gradually increasing diuresis and a marked fall in proteinuria occurred. In all but one case (D. C.) proteinuria disappeared by the eighth day of treatment, and the serum proteins returned to normal values two to four weeks after treatment (Figs. 1-4; Tables II and III).

All the children had a very large appetite following the diuresis, with a gradual increase in weight without the reappearance of oedema. This increase in weight has also been seen in children treated with cortisone for rheumatoid arthritis, and has not apparently been due to oedema (Geppert *et al.*, 1951).

No complications were seen in any child except K. G., who became very excitable and needed sedation with phenobarbitone. As he was thought to be incubating measles his course was shortened; he later developed measles.

Subsequent Course

Of the five children in whom proteinuria disappeared, three have had no recurrence of proteinuria or oedema for 6, 15, and 18 months respectively. One child (T. J.)

FIG. 1.—Case S. T.

FIG. 2.—Case T. J.

TABLE I.—Clinical Details before Treatment

Patient:	D. C.	P. M.	S. T.	T. J.	K. G.	L. L.
Sex	Female	Male	Male	Male	Male	Female
Age at first admission	6 years	7 years	4 years	5 years	2 10/12 years	4 years
Onset of disease	15/9/55	8/3/57	24/11/55	23/8/55	6/3/57	28/4/55
Maximal blood pressure	95/60	140/95	100/60	120/80	100/-	130/80
Average daily protein output	5-15 g.	5 g.	5-10 g.	5 g.	3 g.	4-15 g.
Presence of haematuria on admission	0	+++ no casts	0	0	+ no casts	0
Blood urea (highest and lowest value) (mg./100 ml.)	36-20	48-23	99-17	65-18	42-30	36
Oedema	Gross, + ascites	Gross, + ascites	Gross, + ascites	Gross, + ascites	Gross, + ascites	Gross, no ascites
Treatment given before prednisolone	Cortisone	None	Glucose, water, acetazolamide, ammonium chloride, paracentesis	Prednisone, mersalyl, paracentesis x 2	None	Cortisone. Ton-sillectomy

remained oedema-free, without proteinuria, for 15 months; proteinuria (2 g. a day) then returned, followed later by oedema. He was given a further course of prednisolone (0.7 g. over 20 days), followed by 5 mg. of prednisolone on alternate days. Although oedema-free, proteinuria persists (0.5-1 g. a day). K. G., who caught measles, had a return

of proteinuria and oedema three months after discharge and has responded again to a course of prednisolone (total of 1 g. in 40 days). D. C., in whom proteinuria had never disappeared, remained oedema-free for 13 months, although she continued to pass up to 2 g. of protein a day. She was readmitted, oedema-free, and given a further 40-day course of prednisolone followed by a maintenance dose of 5 mg. on alternate days, which reduced the proteinuria to a trace.

In no case was there any evidence of deterioration in renal function or of the development of hypertension.

FIG. 3.—Case K. G.

FIG. 4.—Case D. C.

TABLE II.—Response to Prednisolone

Patient:	D. C.	P. M.	S. T.	T. J.	K. G.	L. L.
Interval between onset of oedema and start of prednisolone therapy	1 yea.	1 week	6 months	9 months	9 days	1 yea.
No. of admissions to hospital before prednisolone	3	0	2	3	0	1
Date prednisolone started	20/7/56	25/3/57	4/5/56	24/4/56	15/3/57	23/6/56
Dose of prednisolone	60 mg. for 10 days 40 " " 10 " 20 " " 10 " 10 " " 10 "	60 mg. for 10 days 40 " " 10 " 20 " " 10 " 10 " " 10 "	60 mg. for 10 days 40 " " 10 " 20 " " 10 " 10 " " 10 "	60 mg. for 10 days 40 " " 10 " 20 " " 10 " 10 " " 10 "	40 mg. for 10 days 30 " " 6 " 20 " " 4 " 15 " " 5 " 10 " " 1 day 2.5 " " 7 days	60 mg. for 10 days 40 " " 10 " 20 " " 10 " 10 " " 10 "
Results at end of prednisolone therapy:						
Proteinuria	2 g./day	Absent	Absent	Absent	Absent	Absent
Oedema	Absent	Absent	Absent	Absent	Absent	Absent
Serum proteins	Normal	Normal	Normal	Normal	Normal	Normal
State in October, 1957	No oedema for 13 months. Proteinuria up to 2 g./day. Partial response to further course	No recurrence for 6 months. Passing an occasional trace of protein	No recurrence for 18 months	No proteinuria for 15 months, then relapsed. Partial response to further course	Developed measles at end of course. 3 months after discharge proteinuria recurred and persisted at 0.25-1 g./day. Responded to further course	No recurrence for 15 months. Is on small maintenance dose of prednisolone

TABLE III.—Laboratory Investigations at Intervals

Investigation	Time Before and After Start of Prednisolone Treatment	D. C.	P. M.	S. T.	T. J.	K. G.	L. L.
Serum albumin (g./100 ml.)	Before:						
	12-6 months	1	—	—	3.4	—	—
	6-3 "	—	—	<1	1.6	—	—
	3 months-0 days	1.3	2.4	<1	2.7	2.4	1.6
	After:						
	1-10 days	—	2.8	—	—	3.0	2.7
	11-20 "	—	4.9	3.8	3.8	4.8	—
	21-30 "	3.8	4.8	4.9	4.8	4.4	5.0
	31-60 "	—	—	5.0	5.0	4.4	—
	61-90 "	—	—	4.6	4.4	3.5	—
Blood urea (mg./100 ml.)	Before:						
	12-6 months	36	—	—	54	—	—
	6-3 "	—	—	99	—	—	—
	3 months-0 days	20	48	45	18	30	—
	After:						
	1-10 days	—	28	—	20	30	—
	11-20 "	—	31	25	18	42	—
	21-30 "	16	31	18	18	—	—
	31-60 "	—	—	17	20	22	—
	61-90 "	—	—	—	—	—	—

Discussion

The nephrotic syndrome in children is a fluctuating condition. It is characterized by episodes of exacerbation of proteinuria and oedema. Some children remit spontaneously, losing oedema and proteinuria permanently. Others continue to pass protein, without impairment of renal function, for long periods. A small proportion die of renal and cardiac failure or other causes. Absence of proteinuria for many months does not preclude a relapse. This makes it impossible to evaluate the results of treatment over short periods.

In two of our cases moderate doses of cortisone and prednisone did not affect the proteinuria, while a course of prednisolone produced a marked reduction. As Arneil (1956) and Lennard-Jones (1957) have also shown, prednisolone is the only form of treatment that consistently reduces or abolishes proteinuria in children. Proteinuria may recur many months after successful prednisolone treatment—as occurred in two of our children; however, these children responded to a further course. It is suggested that prolonged treatment with small doses of prednisolone—for example, 5 mg. on alternate days—may prevent relapse.

Summary

Six cases of the nephrotic syndrome in children have been treated with large doses of prednisolone and followed for periods of up to 18 months. Five cases lost their proteinuria, and three of these are protein-free at 6, 15, and 18 months after treatment. Two developed proteinuria and oedema after 3 and 15 months. Both were treated again with a course of prednisolone, with disappearance of oedema and reduction in proteinuria. One further case has continued to pass a decreased amount of protein, which was further decreased after another course of prednisolone.

ADDENDUM, August, 1958.—Since October, 1957, three of ten children—D. C., S. T., and T. J.—have had no relapses. P. M. and L. L., when last seen, some months ago, were also well. K. G. has had two more relapses; each has responded to further short courses of prednisolone (0.5 g. in two weeks). Two other cases have been treated and followed up for nine and six months respectively. Each responded to the initial course, and was kept on a maintenance dose. One of these had to be readmitted six months after his initial course, but responded to a short course of prednisolone (0.5 g. in two weeks). The latter remains well, but continues to have proteinuria, despite maintenance therapy.

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The Public Health (Preservatives, etc., in Food) Regulations, 1925–1953, permit the importation of citrus fruit in wrappers impregnated with diphenyl to the extent of not more than 40 mg. per 100 sq. in. Exporting countries now employ other methods of preservation—for example, the impregnation of the container with diphenyl or the inclusion of impregnated pads or spacers in the container—and the regulations have been amended to permit the importation and sale of citrus fruit which contains diphenyl or orthophenylphenol or admixtures of the two substances within prescribed limits.

D

EXOPHTHALMOS IN CUSHING'S SYNDROME

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Cushing (1932), in his original description of the syndrome that now bears his name, recorded several instances of mild-to-moderate exophthalmos. Subsequent reports have confirmed this finding. Although there does not appear to be any example of severe exophthalmos, some degree of proptosis was found in 8% of 189 patients with Cushing's syndrome reviewed by Plotz *et al.* (1952).

The following case appears worthy of record because of the unusual course of the disease in which the appearance of malignant exophthalmos preceded the evolution of severe Cushing's syndrome.

Case History

A woman of 39 was admitted to the London Hospital on July 11, 1956. She had been agitated and depressed for the six weeks before admission, and for the previous three days had been very excitable, unable to converse intelligently, and was quoting odd phrases from the Bible.

Her ankles had been swollen four weeks before admission, the oedema being dispersed by acetazolamide. Her eyes had been slightly prominent for as long as her relatives could remember, but for the previous 18 months they had been sore and watering, although no increase in prominence had been noted.

On examination she was found to be obviously psychotic. Bilateral proptosis was present in marked degree, with severe conjunctivitis and slight ptosis on the right. Thyrotoxicosis was looked for particularly, but no sign other than her exophthalmos was found. A provisional diagnosis of an intracranial tumour was made.

During the first night in hospital she made an attempt at suicide by cutting her wrists with pieces of a broken spectacle lens. Consequently on July 13 she was transferred to Warley Hospital, where she was found to be mentally inaccessible, with delusions and hallucinations. Physical examination revealed obesity and male distribution of body hair, together with a severe proptosis. Her blood pressure was 120/90.

By July 16 her exophthalmos had increased to such an extent that orbital decompression was considered. Two days later electric convulsion therapy was started and a course of seven electroplexies completed on July 27. A considerable improvement in her mental condition had occurred and her exophthalmos had diminished.

On August 16 her mental condition relapsed, her eyes became more prominent, but a further course of seven electroplexies improved her condition. Up to this time menstruation had been normal, but she then developed amenorrhoea, which persisted until December. On September 3 her blood pressure was 180/130. Another relapse necessitated a further course of electric convulsion therapy, but by October 21 she had so improved that she could be discharged. She was then referred to one of us (A. S. M.), and on this occasion volunteered the fact that she thought her face was changing and that some fat was