TREATMENT OF THE NEPHROTIC SYNDROME IN CHILDREN*

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AS SEEN IN ADULTS the nephrotic syndrome, consisting of œdema, proteinuria, hypoproteinæmia, hyperlipæmia occurs most commonly as a stage in the relentless progressive course of chronic nephritis and carries an almost hopeless prognosis. The situation in children is quite different, and the majority of children who are seen with a nephrotic syndrome follow a clinical course which resembles that of "pure lipoid nephrosis". At present, the term "nephrotic syndrome of undetermined etiology" is usually used, thus excluding a nephrotic syndrome which may occur in the course of other diseases such as lupus erythematosus, syphilis, amyloid disease involving the kidney, or as a result of renal damage from poisons such as mercury, or drugs such as trimethadione (Tridione).[1] This term also allows the inclusion of children who may have transient periods of hypertension, azotæmia and even gross hæmaturia, as it has been found that these signs do not make recovery less likely.[2] The disease is much commoner in younger than in older children or adults, and has even been described as commencing in the first month of life.[3]

Its etiology is unknown, though there is much evidence that an antigen-antibody reaction affecting chiefly the glomerular basement membrane is an important factor. What the antigen is, and why certain children react for a time in this way, are questions still to be answered.

The onset is usually a fairly rapid appearance of œdema which becomes generalized and severe, and includes ascitic and less often pleural effusions. The child becomes irritable, listless, and anorexic. Oliguria is present, and the urine will contain much protein and many casts, with or without microscopic hæmaturia. A high serum total lipid and cholesterol are found, and a low serum protein and albumin. Although spontaneous remissions may occur, the child may remain very œdematous for months at a time, with periods of anorexia, diarrhœa, vomiting, and semi-invalidism to complete invalidism because of œdema. Another distressing and dangerous aspect of the disease is the extreme susceptibility to infections, which is attributed to the abnormally low serum gamma globulin. While some infections aggravate the disease, other infections may actually lead to a remission of the disease. About 50% of the patients ultimately recover after one to three years, and they remain well thereafter. The remainder may die of infection or pass on to a stage of progressive renal destruction and insufficiency.

Until recent years, treatment of the nephrotic syndrome was purely symptomatic. In the past five years, methods of therapy have been developed which appear to attack the underlying disease itself, resulting in complete remissions. At first such remissions were usually only temporary, but ways are now being found to prolong them, with the hope that in many cases they will be permanent. Remissions may be induced by treatment with ACTH, cortisone, or nitrogen mustard.[4] We have had no personal experience in the use of nitrogen mustard, and it will not be discussed in this paper. At times treatment with hormone is inadvisable or contraindicated, and then a knowledge of the symptomatic treatment is most important. The remainder of this paper will deal with both forms of therapy.

A. GENERAL AND SYMPTOMATIC TREATMENT

1. *Rest.*—Bed rest is advisable at the onset of the disease, during infections and periods of severe œdema. At other times the children may be allowed up, but over-tiring or chilling should be avoided.

2. *Diet.*—A low-sodium normal protein diet is advised. In the presence of severe œdema the sodium intake should be as low as possible, and this can be achieved by avoiding sodium-containing foods, using salt-free bread and butter, and Lonalac* in place of milk. This is very rarely necessary, however, and most children do well on a diet in which obviously salty foods are avoided, and no salt is used in the cooking. Because large amounts of protein may be lost daily in the urine, the protein intake should be at least normal for the child's age. A multiple vitamin supplement is given, preferably one containing iodine, to make up for the lack of iodine which is normally obtained as iodized salt.

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*Lonalac is a powdered milk from which the sodium has been removed by dialysis, made by Mead Johnson and Company Limited.

3. *Infection.*—Antibiotics have greatly reduced the mortality due to infection, but infections are still dangerous to the nephrotic child, and in the past year two children have died from infection. Each was admitted to hospital in moribund condition and died within a few hours, one from peritonitis and the other from meningitis.

Mild infections should be given careful attention, with bed rest and antibiotic therapy to prevent complications. We have tried continuous antibiotic prophylaxis through the winter months but have not been able to prove it helpful. It should be considered when there are other children in the family who might bring infections from school.

Special mention might be made of two serious infections which are particularly common in nephrotic children. The first is peritonitis, which may occur when ascites is present. There is a rapid onset of fever, vomiting and abdominal pain. The entire abdomen is tender, but it is not rigid. The white cell count is elevated, and a blood culture may reveal the pathogen. *E. coli* is the commonest cause, but pneumococci or other organisms may be found. Laparotomy is rarely necessary, but if there is localized tenderness in the right lower quadrant it is safer to operate and remove a normal appendix than to wait and have an inflamed one perforate. We have used combined intramuscular penicillin and streptomycin in the past few years, and find it quite successful in relieving pain and fever within 24-48 hours.

The second common severe infection is a cellulitis of the skin and subcutaneous tissue. This, too, starts suddenly with fever and vomiting, and on examination a tender red area of skin will be found, usually over the lower abdomen, flank or thigh. The inflamed area has a sharp but not a raised margin, and may spread rapidly till it covers a wide area. Again a positive blood culture may be found, and the infection responds well to combined intramuscular penicillin and streptomycin.

4. *Œdema.*—In most nephrotic children now, œdema is cleared coincidentally with hormone therapy which has been aimed at the disease itself. However, when hormone treatment is contraindicated or ineffective, œdema may be so severe that it causes striæ in the skin, through which œdema fluid may leak or bacteria enter. Localized collections of fluid, such as large peritoneal, pleural or scrotal effusions, may also require immediate treatment.

With severe œdema the child should be kept at rest and on a strict low-sodium diet. Fluids may be restricted to known losses plus estimated insensible water loss.

When severe ascites is present there are at least three dangers: (1) peritonitis; (2) elevation of diaphragm with collapse of lung bases; (3) interference with renal function. A good site for abdominal paracentesis is in the midline halfway between umbilicus and pubis. There is little danger of touching the bladder, though the child should be asked to void if he can before the procedure is started. Then about 2/3 the estimated volume of ascitic fluid should be withdrawn, and a sterile dressing pad and a tight abdominal binder applied to prevent too sudden release of pressure. With this method there is frequently a continuing loss of fluid through the opening, and much œdema fluid may be mobilized from the peripheral tissues and lost. Occasionally a true diuresis follows relief of a tense ascites. Antibiotic prophylaxis is given as long as drainage continues.

A large pleural effusion may embarrass respirations and heart action. It may diminish when the accompanying ascites is drained, but if necessary a thoracentesis should be done.

Scrotal swelling may be extreme and cause great discomfort. Some help is provided by supporting the scrotum with a pad or sling between the legs. We have found application of dressings of saturated solution of magnesium sulphate in glycerin to be effective in relieving the swelling.

Another way to relieve œdema is to attack one of the most important causes, the low serum osmotic pressure due to low serum albumin. Infusions of salt-poor albumin can be given, but are expensive and require to be repeated almost daily, as the albumin is rapidly lost in the urine. Since the last war, dextran has become available, and has been standardized so that it has a molecular weight near that of albumin.

We have used a 6% salt-free dextran solution in six children with varying effect. The most successful result was obtained in a 2-year-old child with massive œdema, weeping areas of skin, and hypertension. He was given 150 c.c. dextran one day, and three days later 200 c.c. Within a few hours of the first injection a diuresis commenced, and in six days he lost most of his œdema. He was then treated with cortisone and had a com-

plete remission of his nephrotic syndrome. A 5½-year-old girl had a good result when dextran was first given, but the œdema returned at once and was not relieved by later infusions of dextran. A 4½-month-old infant received two infusions of 50 c.c. dextran six days apart, but as her tense ascites obliged us to do two abdominal paracenteses, through which much fluid drained, it was impossible to say how much of her loss of œdema could be attributed to dextran.

Two other children had no benefit from dextran, even though in one a blood dextran level of 2.0 g. % was reached. A sixth child, an 8-year-old boy, suddenly went into a state of anaphylactic shock after receiving a few cubic centimetres of his first infusion of dextran. He was revived with adrenaline and artificial respiration, was given no further dextran, and subsequently lost all his œdema following a course of ACTH. Some authors have reported more successful results with dextran,[5] but it would seem to have the greatest value in a severely œdematous child in whom hormone treatment as described below may be contraindicated or ineffective.

5. *Immunization.*—We have seen the disease commence shortly after a smallpox vaccination, and in two children who were in remission there was a flare-up of the disease immediately following a diphtheria toxoid injection. An exacerbation occurred in another child following an injection of anti-tetanus serum. Hence it is safer to defer such immunizations till the child has been well for a year or more.

B. Treatment with ACTH and Cortisone

In the Hospital for Sick Children, an investigation into the use of ACTH and cortisone in the treatment of children with the nephrotic syndrome was begun by one of us (A.L.C.) in 1950 and continued to March 1954, under a grant from the National Research Council. During this time 88 children with the disease were treated. Used initially in short courses (4-6 days) because it was known that a sodium diuresis occurred on withdrawal, it was found that a remission might be produced, and that diuresis might commence even while the hormone was being given. A summary of our experience with this group of children follows.

Children were observed for a control period of several days, to ensure that they were free of infection and hypertension, as these are considered contraindications to hormone therapy. Also no child was treated who was thought to have entered the progressive irreversible stage of the disease. Daily weight and blood pressure readings were made, and the blood non-protein nitrogen, creatinine, sodium, potassium, chloride, cholesterol and serum protein levels and albumin/globulin ratio were determined. The chemical determinations were repeated weekly or more often when indicated. The blood hæmoglobin value, white cell count and erythrocyte sedimentation rate were taken before, during and after therapy. The children were kept in bed, on a diet of normal protein content, but with sodium chloride intake restricted to about 0.5 g. a day.

ACTH (Connaught Laboratories) was given intramuscularly 6 hourly in daily dosage of 20-50 mg., the dosage being adjusted so as to keep the total eosinophil count at or near zero. In older children, ACTH was given intravenously, 10-20 mg. daily in 5% glucose in distilled water, over a period of at least 8 hours.* Cortisone was given either by mouth or intramuscularly 6 hourly in daily dosage of 100-300 mg. Blood pressure readings were made before each dose, and if hypertension developed the daily dose was lowered. Mild infections were treated with antibiotics, but if a severe infection occurred the hormone was stopped.

The treatment was continued for 2-4 weeks. Frequently, diuresis commenced while therapy was still in progress, in which case treatment was continued until proteinuria disappeared or until further improvement ceased. If there was no loss in weight, therapy was stopped after two weeks, and often diuresis commenced within a few days.

When it was observed that some children had an apparently complete remission following treatment, i.e. complete disappearance of œdema and proteinuria and return to normal values for the serum proteins and cholesterol, it was concluded that the hormones had a beneficial effect on the disease itself, whatever its nature might be. This led us to try the effect of the hormones on children in whom proteinuria had recurred but who were free of œdema, and good results were again obtained.

*We have lately used a long-acting form of ACTH, Duracton (Nordic Biochemicals Limited) and find 0.50-1.5 c.c. (10-30 units) once daily is effective.

COMPLICATIONS OF HORMONE THERAPY

The commonest complication has been hypertension, which was accompanied in a few cases by convulsions. There was less tendency to hypertension when using cortisone than with ACTH.

The next most serious complication is infection, to which these children have an even greater susceptibility while under therapy. On several occasions we have felt obliged to stop hormone treatment because of the development of bronchitis, pneumonia, peritonitis, cellulitis or severe diarrhœa. Infections have developed even in children who were being given prophylactic antibiotics.

The third complication is a disturbance of acid-base and electrolyte balance, most frequently a low serum potassium with metabolic alkalosis or a low serum sodium. Clinically one observes weakness, listlessness, and cardiac irregularities, and certain changes in the electrocardiogram may be found. We have not given a potassium salt as a routine measure to every child on hormone therapy, because in some oliguric children the serum potassium tends to rise. The safest procedure is to determine the serum electrolytes once or twice a week, or whenever any suggestive signs appear, and to give sodium or potassium salt as indicated.

There have been two deaths attributable to therapy. One patient, a five-year-old girl, developed hypertension, convulsions, low serum sodium and potassium, thrush, enteritis, and cellulitis, and died 17 days after treatment was stopped. The other, a 19-month-old boy, died suddenly after five days of treatment, no cause of death being evident at autopsy, although considerable hydrothorax was found.

RESULTS

1. *Remissions resulting from ACTH and cortisone*

The 88 children treated in this series were given 164 courses of hormone (142 ACTH and 22 cortisone). Each child received from 1 to 6 courses of treatment and, as each child may have had different results from different courses, we have shown the results in terms of individual courses. In Table I the patients have been divided into 5 groups, according to whether they were œdematous (groups 1-3) or free of œdema (groups 4 and 5) before treatment, and according to the results obtained.

TABLE I.

ACTH AND CORTISONE THERAPY OF NEPHROTIC SYNDROME IN CHILDREN.
SUMMARY OF RESULTS OF INDIVIDUAL COURSES.

	Clinical classification of patients		*Courses of ACTH*	*Courses of cortisone*	*Total courses*
Group	*Before therapy*	*After therapy*			
1	Œdematous	Œd-free, Prot-free*	44	5	49
2	Œdematous	Œd-free	31	7	38
3	Œdematous	Unchanged	34	9	43
4	Œd-free	Prot-free	25	1	26
5	Œd-free	Unchanged	8	0	8
	Total courses		142	22	164

*Œd-free means complete absence of œdema.
Prot-free means absence of proteinuria by qualitative tests.

In the children who were œdematous before treatment, 68% of the courses resulted in loss of œdema. If the courses shorter than 8 days are excluded (Fig. 1) 74% of courses resulted in loss of œdema. In the 34 courses given to children who were free of œdema 74% resulted in loss of proteinuria.

In children who were given more than one course of hormone, the results from the later courses were not quite as good as for the first, averaging 65% good results (i.e. loss of œdema or proteinuria or both) as compared with 73%, but of the four children who had 6 courses, three had a good result from the 6th course.

In the entire series of 88 children, 70 (80%) had a good result from at least one course of hormone, and the remaining 20% failed to react favourably to one or more courses.

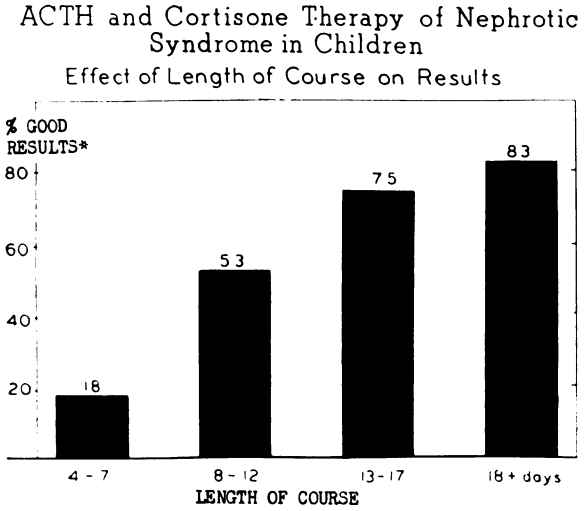

Fig. 1

2. *Effect of length of course on result*

This is shown graphically in Fig. 1. Courses of less than eight days' duration were almost useless and the best results were obtained when treatment continued for more than 12 days.

3. *Biochemical effects*

The improvement in serum protein and cholesterol values is shown in Table II. It may be noted that the biochemical changes at the commencement of treatment varied with the severity of the disease. Thus, in groups 4 and 5, in which there was no œdema before therapy, the serum cholesterol was lower and the serum protein higher than in the œdematous children. It was found that the better the clinical result, the closer to normal were the serum cholesterol and protein values after treatment.

The rise in total serum protein is seen to be due almost entirely to a rise in the albumin fraction. We have observed that the "critical" level of serum albumin is about 1.0 g. %, most children with a lower level being œdematous, and with a higher level being free of œdema.

Maintenance Hormone Therapy

Very soon after it was found that ACTH and cortisone might produce a remission of the disease, it was learned that unfortunately such remissions were seldom permanent, and that œdema might return immediately, or weeks or months later. Our longest remission followed by a recurrence is in a boy who was free of œdema and proteinuria for three years and eight months, when an exacerbation occurred after an infection. (However, in some children there has been no recurrence and they are apparently well more than two years later. Nine of 53 children treated before June 1952, are still well 2½-4 years after therapy.)

The next logical step was to give hormone over a prolonged period after the initial course. When only short-acting ACTH was available it was not practical to give frequent injections at home, but cortisone could be given by mouth and we then tried giving daily doses of cortisone at home following hormone-induced remission.

The first seven children so treated were given small doses of cortisone, 10-25 mg. daily. Four of them had longer remissions than they had had after earlier courses of ACTH, and one is still well. (He was given 12.5 mg. cortisone daily for 16 months, and it was stopped 9 months ago.) The other three children had a recurrence of the disease after a few weeks.

It was at this time that Lange's first report appeared on the use of high doses of cortisone given intermittently.[6] His reasoning, based on serum complement studies, was that the hormones depress antibody production and so stop the antigen-antibody reaction which is damaging the kidney. By following serum complement levels, he found that they rose before diuresis occurred and fell before an exacerbation. He gave 400 mg. cortisone daily for three consecutive days a week and found that serum complement remained normal and remissions continued. In a recent paper[7] he reported that this method had been successful in 16 of 18 patients who received intermittent cortisone for 6-30 weeks after an ACTH-induced remission. One patient died from a septic condition, but apart from this he reports no serious side-effects.

We had felt it would be better to start with smaller doses, increasing them gradually as necessary, largely because we had been impressed by the serious complications which may occur under continuous hormone therapy. We hoped that for each child a dosage schedule might be found which would be sufficient to maintain the remission but not so high as to cause complications. We have started maintenance therapy with cortisone at 75-150 mg. per day for three consecutive days a week. Sixteen children have been treated this way for periods up to one year. Eight are still free of œdema and proteinuria, 3-14 months after starting

TABLE II.

ACTH AND CORTISONE THERAPY OF NEPHROTIC SYNDROME IN CHILDREN.
CHANGES IN SERUM CHOLESTEROL AND PROTEINS RESULTING FROM THERAPY.

Group	Clinical classification of patients: Before therapy	After therapy	Serum cholesterol, mg.%: Before therapy	After therapy	Serum protein, g.%: Before therapy: Total	Before therapy: Albumin	After therapy: Total	After therapy: Albumin
1	Œdematous	Œd-free, Prot-free*	565	285	3.82	0.85	5.67	2.74
2	Œdematous	Œd-free	613	340	3.75	0.75	5.40	2.22
3	Œdematous	Unchanged	666	527	3.72	1.03	3.80	1.07
4	Œd-free	Prot-free	433	310	5.19	1.91	6.12	3.20
5	Œd-free	Unchanged	414	366	5.06	1.66	5.19	2.14

*See footnote to Table I.

maintenance cortisone. The other eight had recurrences in from one week to four months, and four have since improved on a higher dosage. One child died suddenly and unexpectedly. She was a 2-year-old girl in whom the disease had been present for three months. She had lost her œdema during a course of ACTH and was sent home on 75 mg. cortisone a day for three consecutive days a week. After the fourth week she developed abdominal pain and vomiting, was brought back to hospital, and suddenly died while sitting up on the examining table. Postmortem examination showed no cause for death, though some cerebral and pulmonary œdema was present.

In summary, our present plan of hormone therapy is to give ACTH in hospital early in the disease to produce a remission, then to give intermittent cortisone at home for several months in the hope of preventing a return of the disease.

Although this method seems successful in many children, and there is hope that with greater experience better dosage schedules may be worked out, our optimism must remaim guarded for the following reasons:

1. Some children never respond to the hormones and progress relentlessly to renal destruction, uræmia and death.

2. Rarely a child may die as a result of hormone treatment, from known or unknown cause, either during the initial course or during maintenance therapy.

3. A nephrotic child may still die of uncontrolled infection.

4. Some danger may result from the prolonged suppression of adrenal cortical activity by cortisone.

As far as the effects of such hormone therapy on the child's chances for ultimate cure are concerned, we cannot draw any conclusions for some years yet, until we know that children so treated are still well after 3 or 4 years, and that a significantly higher percentage recover than with other forms of treatment. This is presented, then, not as the final form of treatment for a child with the nephrotic syndrome, but rather as the current stage reached in working toward the ultimate ideal, the cure of the disease.

SUMMARY

1. The clinical course of the nephrotic syndrome in children has been briefly presented.

2. Symptomatic treatment of the disease is outlined, with emphasis on treatment of infections and relief of œdema.

3. Infusions of 6% salt-free dextran were given to six children with variable results.

4. Our experience in treating 88 nephrotic children with ACTH and cortisone is described. Seventy-four per cent of œdematous children lost their œdema, and when non-œdematous children with proteinuria were treated, 74% showed clearing of the urine.

5. Poor results were obtained when hormone treatment was given for less than eight days, and the best results followed courses of 12 days or longer.

6. Maintenance treatment with intermittent cortisone is now being tried in the hope of prolonging remissions, and our results in 16 children are briefly described.

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