Management of Nephrosis

The Use of Long Continued Hormone Therapy

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• **The course of nephrosis in 36 children was evaluated. Twelve of 24 who received no treatment or short-term courses of steroids died. Eleven of the 24 had been well for six months to five years at the time of this report.**

Twelve patients received steroids by schedule over extended periods. One died and eleven had been free of signs and symptoms of nephrosis for four to eighteen months at the time of report. In only two cases was therapy discontinued. It seems evident that these patients are experiencing a better state of well-being. Whether or not the prognosis is being altered for any single patient cannot be determined.

IT IS BECOMING increasingly apparent in both adults and children that nephrosis occurs as a distinct clinical entity. It is characterized by the insidious onset of edema with or without a history of previous illness, proteinuria, hypoproteinemia and hyperlipemia. Transient azotemia, hematuria and hypertension may occur.

The usual natural course of nephrosis is marked by exacerbation and remission of the signs and symptoms for an average duration of two years. Rarely a patient recovers after a single episode of anasarca. Unfortunately, a slightly greater number show nephritic signs (hematuria, hypertension, azotemia) early in the disease which are persistent and progress unrelentingly to renal failure. Whether therapy of any kind offers relief to such patients is extremely doubtful. However, it is equally questionable that the outcome for the majority of patients between these extremes is settled at the outset and not influenced by the chronic nature of the disease. For these patients, management is directed at control of the edema and other apparent abnormalities such as proteinuria with the hope that the basic lesion may be corrected and the development of permanent renal damage prevented.

Prior to chemotherapy, approximately 50 per cent of patients with nephrosis died of infectious processes, particularly peritonitis. Observation of nephrotic patients in whom adequate chemotherapy controlled intercurrent infections indicated that approximately 50 per cent of these patients survived longer only to die in renal failure.[21,7] Regardless of the duration of the nephrotic symptoms, it is impossible to predict the outcome until signs and symptoms of progressive renal failure develop. Some observers have found early persistent hypertension indicative of a poor prognosis.[19] On the other hand, other investigators noted that hypertension present for more than a year could be relieved by adequate therapy[2] or might disappear spontaneously.[7]

Management of nephrosis has been directed at the elimination of the edema because spontaneous recovery is preceded by diuresis and because in this way the patient can be made more comfortable. A variety of means has been used—administration of agents to increase oncotic pressure, diet or ion exchange resins for control of sodium intake, diuretics or excessive water intake to increase salt and water excretion, mechanical removal of edema fluid, pyretic agents and a number of hormones, desiccated thyroid and particularly adrenal steroids. A few of these are listed in Table 1. Two hyperoncotic agents, salt-poor albumin[15] and dextran[5,20] cause diuresis of water and salt promptly after pronounced increase in plasma volume. Febrile episodes following such infections as measles[6] and malaria[2] are also followed by diuresis and remission in a significant number of cases. A recent report of Gilbertsen and Bashour[2] is especially interesting: Four of five patients with signs of chronic renal failure had complete remissions with relief of azotemia and hypertension for 11 to 20 months after therapy with malaria. It is evident from this incomplete presentation of published data that the over-all experience with adrenal hormones has been most uniform. In general, short-term courses of cortisone, hydrocortisone or corticotropin given by intramuscular or intravenous routes cause diuresis in approximately 80 per cent of patients.[4,18,22,23,25]

The almost invariable relapse after initial treatment led to the administration of repeated courses of adrenal hormones, as many as ten courses being given to a patient.[4] There is no predictability as to which course in a series in a given patient will

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TABLE 1.—*Results of Therapy with Various Agents*

Agent	Patients: Number	Patients: Per Cent with Diuresis	Investigators
Salt-poor albumin..	13	54	Luetscher, et al.
Dextran	16	37	James, et al.
	12	60	Olive, et al.
Measles	12	75	Janeway, et al.
Malaria	5	80	Gilbertsen, et al.
Steroids for edema	88	74	Rance, et al.
	64	81	Heymann, et al.
	47	81	Metcoff, et al.
	34	82	Rapoport, et al.

TABLE 2.—*Physiologic Changes Following Steroid-Induced Diuresis*

1. Improvement in renal function.
   (a) Increase in glomerular filtration rate.
   (b) Decrease in clearance of albumin.
2. Metabolic alterations.
   (a) Decrease in urinary excretion of aldosterone.
   (b) Increase in serum proteins with improvement in electrophoretic pattern.
   (c) Decrease in circulating antidiuretic hormone.
3. Influence on basic lesion.
   (a) Return of serum complement to normal levels.

produce favorable results. Observations made during the course of diuresis brought about by adrenal hormones soon indicated that profound physiological alterations were occurring in addition to loss of excess salt and water. In Table 2 are listed some of the significant changes. Renal function improves[1,11] and the abnormal serum electrolytes, protein[27] and lipids revert toward normal. There is a decrease in the elevated, circulating antidiuretic hormone[12] and in the urinary excretion of the salt-retaining hormone, aldosterone.[14] The rise in serum complement merits an additional word. Lange[10] interpreted the rise of serum complement as indicative of cessation of the disease process. He considered nephrosis a disease of "complement-binding" antigen-antibody reaction and expressed belief that cortisone and corticotropin act by the depression of certain antibodies. In experimental work on rats with the nephrotic syndrome this theory was demonstrated very nicely.[3] Unfortunately, the cause of the human disease remains obscure.

Cognizant that adrenal hormones were doing more than producing diuresis, Kramer and co-workers[8] began to treat nonedematous patients. A second course of corticotropin was given a week or two after hormone-induced diuresis. Continued improvement with frequent return to normal of proteins and lipids and pronounced extension of the period of remission were observed.

Long-term courses of hormone therapy followed. Lange and co-workers[9] induced diuresis with corticotropin, 100 units to 200 units per day given for ten days. If diuresis did not occur, treatment was repeated with a larger dosage. After diuresis occurred, cortisone was given by mouth, 100 mg. every eight hours for three consecutive days each week. If the patient weighed more than 40 pounds, 400 mg. per day was given. The intermittent therapy was continued for one year. Discontinuing the hormone was done by increasing the interval between the courses rather than by diminution of the dosage. Of 29 patients, 28 were edema-free after three to 40 months of therapy, 14 of 23 patients did not have proteinuria.[10]

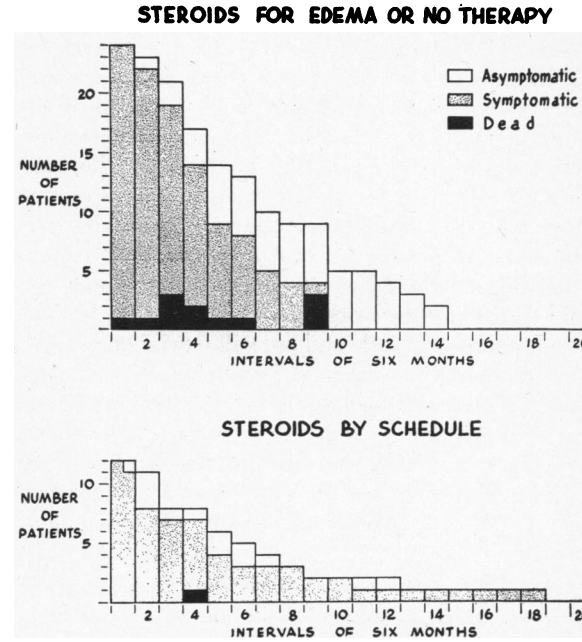

Chart 1.—Summary of course of nephrosis in 36 children, plotted in six-month intervals of disease.

Merrill[17] recommended daily administration of corticotropin-gel, 1 unit per pound of body weight until edema and proteinuria were eliminated. The same dose was continued for two additional weeks then halved by giving it every other day for two weeks. Gradual reduction of the dosage followed for the next 12 weeks. If the patient remained free of proteinuria, the injections were given only twice weekly for an additional four weeks. Of 26 patients, 24 were free of edema and proteinuria. Nine of them had had no treatment in 18 months. This type of management is recommended only for children, as the large doses are not well tolerated by adults.

It is apparent that success of treatment can only be established after many years of following great numbers of patients. However, Riley[26] attempted to evaluate, in a statistically acceptable method, various types of therapy in fluctuating clinic populations on a yearly basis. The course of nephrosis in 533 pa-

tients, as determined by records collected from many hospitals, was analyzed. No difference in mortality rate was observed as between patients receiving no therapy and those receiving steroids for edema only. However, a pronounced decrease in mortality was noted in patients treated with steroids by schedule. Obviously, as Riley emphasized, the data are not suitable for statistical analysis. However, the evidence seemed to suggest that giving steroids by schedule prolongs life in childhood nephrosis.

The author's limited experience in this regard is presented in Chart 1. Of 24 children who received no therapy or steroids for edema only, 12 are dead and one was lost to follow-up after two years of active disease. The remaining 11, after having disease for six months to four and a half years, had been well for six months to five years of observation at the time of this report. Patients who continued to have active disease are among the 12 children who have been treated with scheduled steroids. One was seen after two years of disease, received continuous therapy for two months with no response, and died in renal failure. Four patients received continuous steroid therapy at the beginning of the disease, became symptomless promptly and are still receiving therapy. Two completed courses of scheduled steroids and have been free of symptoms for approximately one year. The remaining four, ill for three to nine years, have been receiving steroids for the last 15 to 16 months. Two are free of symptoms; the other two have continuing proteinuria and one is also hypertensive.

The usual course of therapy followed for these patients, which is somewhat similar to that of Merrill, is illustrated in Chart 2. The patient, the case shown in Chart 2, a two-year-old boy, was hospitalized with a history of edema and proteinuria of nine days' duration. After a diagnosis of nephrosis was established, corticotropin-gel was given, 1 unit per pound of body weight daily for three weeks. Diuresis had begun and proteinuria had already abated at the time therapy was started. At the end of three weeks the patient was discharged from the hospital, still receiving corticotropin-gel in dosage of 1 unit per pound of body weight every other day, prophylactic doses of tetracycline, extra potassium, and with moderate salt restriction. The mother gave the injections of steroid at home and tested daily samples of urine for protein with 20 per cent sulfosalicylic acid. The patient was seen by a physician weekly until December 1955 and monthly thereafter. In these 12 months he had two episodes of proteinuria associated with infection. Both times the corticotropin was increased and was given daily, in addition to adequate chemotherapy.

Data on the more complicated case are shown in Chart 3. The patient, a two-year-old boy, had symp-

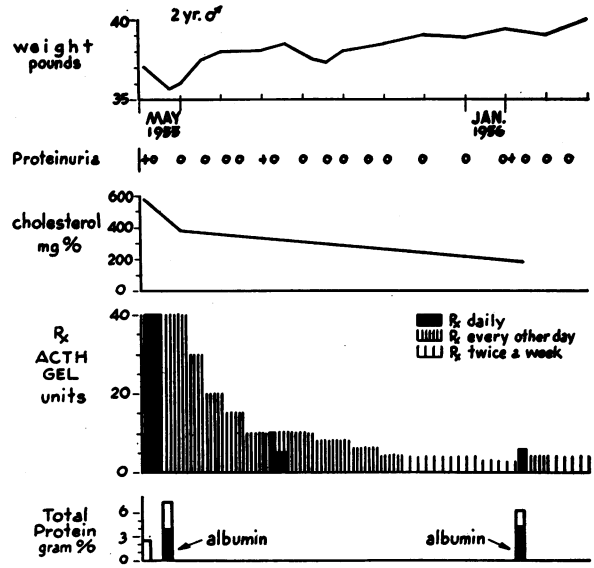

Chart 2.—Data on steroid therapy in a 2-year-old boy with nephrosis of recent onset.

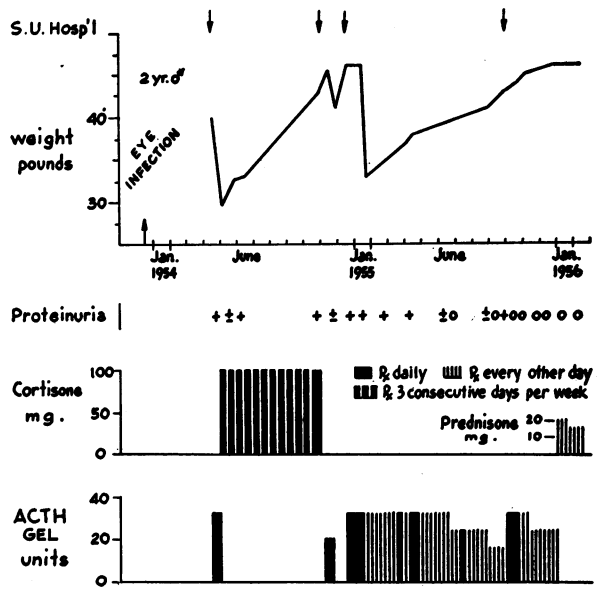

Chart 3.—Data on steroid therapy in a 2-year-old boy with nephrosis of four months' duration.

toms of nephrosis for four months before he received steroid therapy. First he received cortisone, 100 mg. daily for three weeks. Diuresis occurred and proteinuria abated, and the patient then was given a maintenance dosage of cortisone, 100 mg. daily for three consecutive days of each week. However, as Lange emphasized,[9] this dose is inadequate. Three months later, while still receiving the prescribed therapy, he had a relapse and was given cortisone daily by a private physician. Due to parental anxiety, he was returned to Stanford Hospital where cortisone was given daily for a total of 14 days. After five days without treatment, as there was no response, corti-

cotropin-gel was given, 25 units daily for 14 days. After this there was increased urination but not complete diuresis, possibly because of an intercurrent infection. The patient went home for a while, then returned in four weeks and again was given corticotropin-gel, 1 unit per pound per day. Abrupt diuresis occurred on the 23rd day of therapy. During this period of rapid loss of weight, the patient had generalized convulsions for 48 hours. Blood pressure and the potassium, bicarbonate, calcium, phosphate and urea contents of the serum were normal. As in similar cases reported in the literature,[4] no cause was immediately evident. For the next eight months, therapy was determined by an effort to control proteinuria. The patient was discharged from the hospital on corticotropin-gel, 40 units every other day. He received this in the pediatric clinic where he was observed by one physician. After a two-to-four-week interval of no proteinuria, the dosage was lowered or the interval increased to twice a week. Repeated infections accompanied by return of proteinuria made reducing the amount of steroid a slow process. After nine months of therapy, in September 1955, a relapse occurred with edema in addition to proteinuria. The patient was hospitalized and given corticotropin-gel, 40 units daily. Immediately the slight edema disappeared and the urine became protein-free. A change to prednisone by mouth then was made, and at last report the patient had remained free of symptoms for four months.

Questions as to amount and duration of steroid therapy cannot be answered. Rapoport and McCrory[24] divided 42 patients with nephrosis into two groups, one group made up of those who became free of proteinuria in four to eight weeks of intensive cortisone therapy; the other of those who did not. All patients in the group who continued to have proteinuria for two years became chronic nephritics, and the ultimate fatal outcome was not influenced by steroid therapy. On the basis of their observations, these investigators considered the determination of clearance of protein a very useful prognostic tool.[16] They seriously questioned the advisability and need of prolonged steroid therapy in patients who rapidly became free of proteinuria.

Nevertheless, from observations of the small group of patients reported upon herein and the many reported upon in the literature it seems evident that with intensive steroid therapy nephrotic children are maintained in better health, that the edema which makes them so susceptible to infections is controlled and that perhaps mortality is lowered.

A discussion of intensive steroid therapy is not complete without emphasis on the dangers of such treatment. Categories of disturbances which require watching are listed in Table 3. During intensive steroid therapy, the glomerular filtration rate may

TABLE 3.—*Complications of Steroid Therapy*

1. Renal Failure.
2. Derangement of serum electrolytes.
3. Infection.
4. Thrombosis.

be lowered, and edema, serum potassium and urea may increase. For these reasons, it is exceedingly ill-advised to give potassium by mouth at this stage unless a need has been demonstrated. Blood pressure may increase with accompanying encephalopathy. Hyponatremia, hypokalemia or excessive dehydration may occur during diuresis.[13] In a patient receiving steroid therapy, signs of infections may be masked and the infection spread rapidly. Thrombotic phenomena that may occur in nephrosis may be precipitated by hormone therapy. It seems evident that treatment with steroids must be individualized for each nephrotic patient and the patient diligently watched.

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REFERENCES

1. Barnett, H. L., Forman, C. W., McNamara, H., McCrory, W. W., Rapoport, M., Michie, A. J., and Barbero, G.: The effect of adrenocorticotropic hormone on children with the nephrotic syndrome: II. Physiologic observations on discrete kidney functions and plasma volume, J. Clin. Invest., 30:227-235, Feb. 1951.

2. Gilbertsen, A. S., and Bashour, F.: Use of malaria therapy in the nephrotic syndrome, J.A.M.A., 160:25-30, Jan. 7, 1956.

3. Heymann, W., and Lund, H. Z.: Nephrotic syndrome in rats, Pediatrics, 7:691-706, May 1951.

4. Heymann, W., Spector, S., Matthews, L. W., and Shapiro, D. J.: Treatment of the nephrotic syndrome with corticotropin (ACTH) and cortisone, Am. J. Dis. Child., 90:22-27, July 1955.

5. James, J., Gordillo, G., and Metcoff, J.: Effects of infusion of hyperoncotic dextran in children with the nephrotic syndrome, J. Clin. Invest., 33:1346-1357, Oct. 1954.

6. Janeway, C. A., Moll, G. H., Armstrong, H. Jr., Wallace, W. M., Hallman, N., and Barness, L. S.; Diuresis in children with nephrosis; comparison of response to injection of normal serum albumin and to infection, particularly measles, Tr. A. Am. Physicians, 61:108-111, 1948.

7. Kohn, J. L., and Obrinsky, W.: Lipid nephrosis in children, Am. J. Dis. Child., 84:587-600, Nov. 1952.

8. Kramer, B., Goldman, H., and Cason, L.: The treatment of the nonedematous nephrotic child with ACTH, J. Ped., 41: 792-803, Dec. 1952.

9. Lange, K., Slobody, L., and Strang, R.: Prolonged intermittent ACTH and cortisone therapy in the nephrotic syndrome, immunologic basis and results, Pediatrics, 15:156-168, Feb. 1955.

10. Lange, K., Strang, R., Slobody, L. B., Friedman, E. A., Jr., and Wenk, E. J.: Prolonged intermittent steroid therapy for the nephrotic syndrome, Scientific Exhibit, Am. Acad. Ped., Chicago, Oct. 1955.

11. Lauson, H. D., Forman, C. W., McNamara, H., Mattar, G., and Barnett, H. L.: The effect of corticotropin (ACTH) on glomerular permeability in children with the nephrotic syndrome, J. Clin. Invest., 33:657-664, April 1954.

12. Lauson, H. D., Forman, C. W., McNamara, H., Mattar, G., and Barnett, H. L.: The effect of ACTH on glomerular permeability to albumin and on blood antidiuretic hormone concentration in children with the nephrotic syndrome, Am. J. Dis. Child., 83:87-88, Jan. 1952.

13. Luetscher, J. A., Jr.: Problems of electrolyte and water balance in the nephrotic syndrome, Arch. Int. Med., 95:380-384, March 1955.

14. Luetscher, J. A., Jr., and Deming, Q. B.: Treatment of nephrosis with cortisone, J. Clin. Invest., 29:1576-1587, Dec. 1950.

15. Luetscher, J. A., Jr., Hall, A. D., and Kremer, V. L.: Treatment of nephrosis with concentrated human serum albumin. I. Effects on the proteins of body fluids, J. Clin. Invest., 28:700-712, 1949.

16. McCrory, W. W., Liu, C., and Rapoport, M.: The mechanism and significance of proteinuria in nephritis and nephrosis, Am. J. Dis. Child., 90:608-609, Nov. 1955.

17. Merrill, A.: Therapy of the nephrotic syndrome, Sixth Ann. Conf. on the Nephrotic Syndrome, pp. 224-227, Nov. 1954.

18. Metcoff, J., Rance, C. P., Kelsey, W. M., Nakasone, N., and Janeway, C. A.: Adrenocorticotropic hormone (ACTH) therapy of the nephrotic syndrome in children, Pediatrics, 10: 543-566, Nov. 1952.

19. O'Hora, B. A.: Recent therapy of nephrosis, Henry Ford Hospital Med. Bull., 1:21-23, Sept. 1953.

20. Olive, J. T., Mills, S. D., and Lundy, J. S.: Dextran for nephrotic edema: Clinical experience, Staff Meetings of the Mayo Clinic, 28:199-204, April 8, 1953.

21. Philips, I., Calvin, J. K., and Kagan, B. M.: Nephrotic syndrome in children, A. J. Dis. Child., 85:451-461, April 1953.

22. Rance, C. P., and Chute, A. L.: Treatment of the nephrotic syndrome in children, Canad. M. A. J., 73:959-964, Dec. 15, 1955.

23. Rapoport, M., McCrory, W. W., Barbero, G., Barnett, H. L., Forman, C. W., and McNamara, H.: Effect of corticotropin (ACTH) on children with the nephrotic syndrome, J.A.M.A., 147:1101-1106, Nov. 17, 1951.

24. Rapoport, M.: Therapy of the nephrotic syndrome, Sixth Ann. Conf. on the Nephrotic Syndrome, pp. 211-224, Nov. 1954.

25. Riley, C. M., Corticotropin and cortisone in management of the nephrotic syndrome in children, J.A.M.A., 150: 1288-1291, Nov. 29, 1952.

26. Riley, C. M.: Therapy of the nephrotic syndrome, Sixth Ann. Conf. on the Nephrotic Syndrome, pp. 261-262, Nov. 1954.

27. Stickler, G. B., Burke, E. C., and McKenzie, B. F.: Electrophoretic studies of the nephrotic syndrome in children: Preliminary report, Staff Meetings of the Mayo Clinic, 29:555-561, Oct. 13, 1954.