A NEW THERAPEUTIC REGIMEN FOR ACUTE NEPHRITIS *

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Acute glomerulonephritis is the most common form of nephritis in children. It accounts for about 0.5 per cent of hospital admissions [1] and two - thirds of all cases occur in children under four years of age. *Etiology.* Acute diffuse glomerulonephritis is a non - suppurative proliferative inflammation in which no bacteria can be demonstrated. It is a sequela of an acute infection with group A hemolytic streptococci [2] in the upper respiratory tract, in otitis media or in scarlet fever. Most of the nephritogenic strains belong to Lancefield's type 12 although strains of types 4 and 25 may also produce nephritis. Other organisms, such as pneumococci, staphylococci and streptococci viridans have also been incriminated. [3] The spread of a nephritogenic type of group A streptococci may be responsible for an epidemic in families and small communities, but this dissemination may be prevented by the prophylactic use of penicillin. [4]

There is little doubt that acute nephritis is an allergic reaction to a preceding streptococcal infection similar to the reaction causing rheumatic fever. Clinical, pathological, biochemical and experimental evidence all points to the allergic and immunologic basis of acute nephritis : clinically, the latent period between the streptococcal infection and the renal disease; biochemically, the development of a high titer of anti - streptococcal antibodies, [5] and the low concentration of serum complement in the early phase of the disease; [6] pathologically, the resemblance of the proliferative and exudative renal lesion to the basic lesion of collagen diseases; experimentally, the work of Mellers using immunologic and microfluorescent techniques to demonstrate the immunologic basis of human glomerulonephritis. [7]

Pathology : Boyd [8] has summarized the ultramicroscopic picture of acute nephritis as follows :

1. Endothelial proliferation of glomerular capillaries with swelling and proliferation of the vascular endothelium. This is rap-

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idly followed by edema and the accumulation of mononuclear cells in the intercapillary spaces. These changes are largely responsible for capillary ischemia.

2. Proliferation and multiplication of the epithelial cells of the glomerular tufts with an exudate, composed of coagulated albumin threads and fibrin, leukocytes and red cells, accumulative in capsular spaces.

3. At the end of the third week of illness, a laying down of fibrin which will stain red with PAS and blue with aniline dyes.

There is evidence of general capillary damage in acute nephritis, the brunt of the damage being borne by the vulnerable glomeruli of the kidney, but also there is some damage to the extra renal capillaries as suggested by the early edema before cardiac failure and the high albumin content of the edema fluid at a time when the blood serum albumin is high and when the urinary output is still good.

Clinical Picture. The clinical picture may vary widely from almost unnoticed attacks to severe cases with high fever, grave constitutional symptoms, oliguria occasionally approaching anuria, hypertension with encephalopathy and cardiac failure.

Hematuria is usually the first symptom. Edema is usually slight although it may be severe. A rapid gain in weight may be the only sign of incipient edema. Hypertension is present in about 60 to 70 per cent of cases. There is cardiac enlargement in 50 per cent of cases and cardiac failure in 20 per cent.

The main clinical problems in acute nephritis are hypertension, cardiac decompensation and anuria.

Laboratory Finding. There is blood in the urine, microscopic or gross, with high specific gravity at the onset, moderate proteinuria and a variable number of casts, especially red cell casts.

The blood NPN and urea nitrogen are usually increased. The sedimentation rate is usually high and is a good guide to the progress of the disease. Serum albumin is usually slightly depressed. Acidosis occurs in some patients and an impairment of renal function is found in about 50 per cent.

Treatment. The conventional therapy in acute nephritis is largely symptomatic. A seven day course of penicillin is often recommended to eradicate any remaining streptococci; bed rest for three or four weeks; a liquid diet and, at the onset, a low salt diet is of some

importance; proteins may need to be restricted at the height of the disease. Measures to curb hypertension and encephalopathy such as magnesium sulfate and a combination of Reserpine and Aphresoline are used. Cardiac decompensation is managed by sedation and digitalization. Electrolyte balance must be carefully maintained in cases where anuria and uremia are present.

In the average case the urine presents a normal microscopic picture in about six to eight weeks. The erythrocyte sedimentation rate usually returns to normal within three months and can be used as a reliable index of improvement. [9] The prognosis under this treatment has been uncertain and the mortality rate has ranged from 1 to 5 per cent in the acute phase of the disease. The incidence of chronic nephritis has been from 5 to 10 per cent and a recurrence of the disease, before complete healing, is common with a new respiratory infection or after the removal of infected tonsils.

The conventional treatment is often life - saving but lacks the important attributes of 1. combating the renal lesion, essentially of allergic origin, and 2. minimizing the sequelae of renal pathology and possibly reversing the damage already incurred.

The introduction of corticosteroids has marked the beginning of a new era of therapy for allergic and immunologic disease. In acute nephritis, however, corticosteroids have not ordinarily been used because of the serious side effects produced by the classical steroids. Cortisone has been found to affect metabolism in such a way that sodium and water are retained while potassium is excreted leading to hypertension, edema and hypokalemia. In cases where renal function is impaired cortisone treatment may lead to growth failure, wasting and increased blood urea because of the increased metabolism of proteins and the diversion of amino acids into the carbohydrate pool with consequent nitrogen loss. It is evident that side effects such as these cannot be allowed in a disease already characterized by renal function impairment, hypertension, cardiac decompensation and edema.

Present Work. The introduction of the newer corticosteroids (including Dexamethasone and Triamcinolone, which have basic differences in relation to water and sodium metabolism and relatively fewer side effects) has, however, opened up the possibility of utilizing the powerful anti - allergic and anti - inflammatory properties of the steroids without fear of serious trouble due to side reactions.

The use of Dexamethasone has obviated the problem of sodium retention since the drug has no sodium retaining effect. [10] Other side

effects including hypertension are lessened although weight increase and edema occasionally occur. [11,12] Triamcinolone on the other hand, although not devoid of low - grade side effects, is characterized by a definite natruretic effect. If edema is present and if it has been caused by other steroids it readily disappears with the use of Triamcinolone.[13] No hypertension has been recorded in connection with this drug. It was therefore felt that it would be logical to try a combination of Dexamethasone and Triamcinolone to obtain a possible neutralizing effect from the point of view of water balance.

The program we developed can be summarized as follows :

1. Use of Dexamethasone and Triamcinolone in combination, the usual dose being 2 - 3 mg. of Dexamethasone and 4 - 8 mg. of Triamcinolone. This has the following advantages :

   a. it combats the allergic mechanism responsible for the disease,

   b. it diminishes capillary damage and the permeability present in acute nephritis, and,

   c. it reduces the occurrence of fibrosis and lessens the possibility of chronicity.

2. Usual symptomatic treatment.

3. Use of anabolic drugs whenever blood urea has a tendency to rise. These drugs have the following advantages :

   a. they lower the blood urea,

   b. they counteract the anti - metabolic effect of the corticosteroids, thus preventing increases in blood urea and body weight, and

   c. they minimize the wasting so often noticed in the course of this disease.

This therapeutic regimen has been tried in 10 cases of acute nephritis and the results have been compared with those in 8 control cases treated in the conventional manner.

All 10 of our cases showed a prompt response characterized by the disappearance of edema, the lowering of blood pressure, improved general well - being and an increase in urine output. Laboratory results showed a parallel improvement with normalization of the urine and improved renal function tests. The erythrocyte sedimentation rate promptly became, and remained, normal. In no case were we forced to stop using the new steroids because of bad side effects.

Discussion

The criteria of comparison between cases treated with the new regimen and cases treated by the conventional method were :

1. *General Condition* as gauged by lowering of fever, disappearance of malaise, improved appetite, subsidence of edema, normal cardiac findings and normal blood pressure.

2. *Urinary Findings* based on the amount of urine, its specific gravity and microscopic examination of sediment.

3. *Sedimentation rate.*

The general condition of the patients in the first group improved more rapidly than did that of the control group. Edema disappeared on the average in one week. Blood pressure showed no increase under treatment but rather a drop concomitant with the general improvement. Most impressive was the improvement in appetite and sense of well - being in the first group as compared with the controls. The urinary output increased markedly in the first group within five or six days while it took two weeks for the controls to show improvement. The microscopic picture returned to normal in an average period of 2 - 3 weeks for the first group, 6 - 8 weeks for the second. The sedimentation rate showed a prompt normalization under the new treatment. It returned to normal on the average in four weeks and remained normal after use of steroids had ceased.

In no case were we obliged to stop treatment because of untoward effects and in only one case did symptoms recur during treatment. This followed a fresh upper respiratory tract infection and responded promptly to antibiotic treatment without stoppage of the steroids.

In all our cases the doses of steroids were tapered slowly over a 7 - 10 day period and the average duration of therapy was 2 - 3 weeks. We found it advisable in two cases to give a course of anabolic drugs because of initial high blood urea, the dose being 25 mg. of Durabolin twice weekly. Both cases responded favorably to the new therapy and were cured completely.

Some of the patients in the first group were followed for a period of nine months and all displayed consistently normal urinary findings and sedimentation rate. No case in the first group entered into the chronic phase whereas in the second group one case showed evidence of chronicity with persistent abnormal urinary findings.

The author feels that this new therapeutic regimen has been successful and is worthy of trial on a larger scale.

TABLE 1

GROUP TREATED WITH NEW THERAPY

Case No.	Age	Oliguria	Blood Pressure at Onset	Heart Failure	Blood Urea mg./100 ml.	Normalization of Urine	Normalization of E.S.R.	Remarks
1	3 yrs.	+	120/75	+	36	3 weeks	4 weeks	
2	2½ yrs.	+	110/70	+	28	4 »	4 »	
3	3 »	+	120/70	—	30	5 »		
4	5 »	++	120/70	+	40	4 »	5 »	
5	4 »	++	110/70	—	90	4 »	5 »	Durabolin given
6	6 »	—	100/65	—	36	3 »	4 »	
7	3 »	+	90/60	+	40	2 »	3 »	
8	4 »	+	110/70	—	60	3 »	4 »	Durabolin given
9	3½ »	+	90/60	—	30		3 »	
10	5 »	+	110/70	+	38	3 »	4 »	

TABLE 2

GROUP OF CONTROL CASES

Case No.	Age	Oliguria	Blood Pressure at Onset	Heart Failure	Blood Urea mg./100 ml.	Normalization of Urine	Normalization of E.S.R.	Remarks
1	3 yrs.	+	110/70	+	30	6 weeks	8 weeks	
2	5 »	+	110/60	+	36	8 »	10 »	
3	6 »	++	120/70	++	40	10 »	12 »	
4	4 »	—	90/60	—	28	5 »	8 »	
5	2½ »	+	100/70	—	40	6 »	12 »	
6	5 »	+	110/65	—	32	Still abnormal after 16 weeks	Abnormal after 16 weeks	Merged into chronic stage
7	6 »	—	110/70	—	36	10 weeks	12 weeks	
8	7 »	+	110/60	—	26	8 »	10 »	

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