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Treatment of Nephrotic Syndrome with Interrupted ACTH or Oral Cortisone Therapy.* (20104)

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In previous investigations(1,2) we have demonstrated that serum complement levels are persistently low in all cases of acute and subacute glomerulonephritis. We have also shown that in almost all cases with the nephrotic syndrome complement is low during the edematous phase, and that 24-48 hours prior to the onset of diuresis, serum complement rises to or toward normal. Conversely, 1 to 2 days prior to clinical relapses, complement falls below normal levels(3). This behavior of complement has been considered to be the result of a complement-binding antigen-antibody reaction *in vivo,* wherein the altered kidney and probably, more specifically, the altered basement membrane of the glomerulus, represents the antigen which provokes antibody formation in the body(1,2,3). The low serum complement levels in these diseases are apparently in no way related to urinary excretion of complement. In the nephrotic syndrome we were unable to find complement in the urine. Furthermore, the low complement levels are not related to the excretion of protein, for in spontaneous or ACTH induced remissions the degree of albuminuria often does not change significantly while complement levels rise sharply *prior* to the remission. No correlation between proteinuria and serum complement levels was demonstrated in four cases of Kimmelstiel-Wilson's Disease in which massive proteinuria and normal complement levels were found. In our determinations of serum complement, the technic of which has been reported previously(1,2), 166 normal subjects or patients with diseases other than glomerulonephritis or the nephrotic syndrome have placed the normal level of serum complement between one and 3 units. (Average, 1.78 units, standard deviation 0.587,† Fig. 1).

Complement unit. Complement was freshly prepared from commercial lyophilized guinea pig serum, diluted in steps of 5 from 1:5 to 1:50 and titration was carried out in the same manner as previously described(1) for the unknown serum. Guinea pig serum 0.1 cc was mixed with 0.1 cc inactivated human serum because guinea pig serum is known to have approximately twice the complementary activity of human serum. The dilution of

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† As the actual shape of the statistical distribution is unknown and the data are not homogeneous enough and numerous enough to determine this shape, a normal distribution function has been assumed for the sake of expedience. While comparisons between the means are not significantly affected by the shape of the distribution functions, no extrapolation beyond the range of $\pm$ one standard deviation appears permissible.

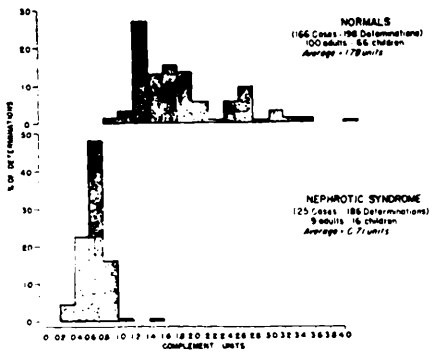

FIG. 1. Distribution of average serum complement levels in 166 normals and 25 patients with the nephrotic syndrome.

guinea pig C′ which just produced 50% hemolysis was defined as a unit of complement (usually a 1:25 dilution). The number of units in the unknown serum was expressed as a multiple of this standard. Thus if the serum under investigation produced 50% hemolysis in a 1:5 dilution its complement content was $5 \times 25 = 0.2$ units.

If the assumption is true that the complement binding antigen-antibody reaction causes a lowering of complement in the host, then depression of antibody formation should effect a rise in serum complement level. Numerous investigators have shown that ACTH and Cortisone depress antibody formation. The degree of depression depends upon the amount and strength of the antigen and the species of the host(4-7). Administration of ACTH and Cortisone does not alter the serum complement level in normal experimental animals or normal humans(8,2).

Procedure. For seven consecutive days ACTH (100 mg per day‡) was given to 16 cases (4 adults, 12 children) with the nephrotic syndrome. No differentiation was made between those patients showing and those not showing signs of underlying glomerulonephritis, for these cases apparently do not differ immunologically. All had low serum complement levels before treatment. (Average 0.71 unit, standard deviation 0.239) Fig. 1. Altogether 25 courses of ACTH therapy were given. Massive diuresis occurred following 22 of the 25 courses (88%). Each diuresis was preceded by a distinct rise in complement and in some cases there was a "rebound phenomenon" characterized by rise in complement to a very high normal level. In the 3 instances where no diuresis occurred complement rose not at all or only very slightly and never approached the normal range. Of the sixteen cases thus treated several relapsed within a few days after diuresis and a total of 11 (69%) relapsed with an associated drop in complement within a period of 12 months.

It has been suggested that after the cessation of ACTH therapy, antibodies are formed at pretreatment rate(6) and clinical relapses occur. On this basis, immediately following diuresis 2 of our cases were given continuous "maintenance" therapy of 25 mg of ACTH daily. In both cases relapse, preceded by lowering of complement, occurred while the patient was on "maintenance" therapy because this dosage is apparently insufficient to depress antibody formation satisfactorily. To obviate untoward effects of sustained high levels of ACTH or Cortisone therapy, but at the same time to obtain sufficient depression of antibody formation as documented by normal complement levels, the following interrupted treatment schedule was devised: Six children with the nephrotic syndrome were treated with a course of 100 mg of ACTH daily for 7 days (25 mg q 6 h.) Diuresis occurred in all cases between the 9th and 12th days. Five to 7 days after ACTH therapy, the following interrupted schedule of treatment was instituted: 100

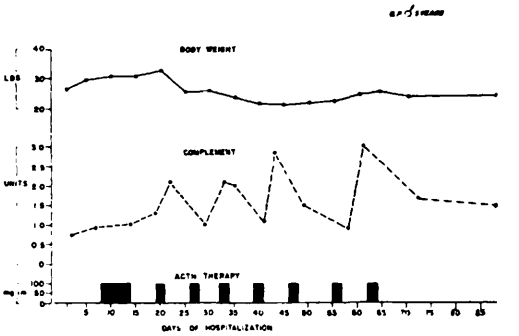

FIG. 2. Complement and body weight in a child with the nephrotic syndrome under ACTH treatment followed by 7 maintenance courses.

‡ We wish to thank Drs. A. H. Holland and G. W. Bissell of the Armour Laboratories for supplying us with ACTH.

mg ACTH daily for 3 consecutive days to be repeated weekly on the same days of the week for 5 to 8 weeks (Fig. 2). Five patients thus treated have not relapsed to date (6-26 mos. after therapy). One child reaccumulated edema 4 days after the onset of a severe purulent otitis media, but this edema promptly disappeared after one additional 7 day course of ACTH and has not reappeared. In all patients, serum complement has remained within the normal range. Three patients have lost all laboratory evidence of the disease (albuminuria, hypoproteinemia and hyperlipemia) while the others still show chemical alterations in urine and blood.

During the past 4 months, we have treated 3 patients with the nephrotic syndrome with ACTH and then interrupted Cortisone therapy. The initial week of ACTH therapy (100 mg per day) was given, and diuresis preceded by rise of complement to normal occurred on the 9th, 10th and 11th days, respectively. 5 to 7 days after ACTH therapy, oral Cortisone§ (100 mg q.i.d.) was given for 3 successive days and then repeated weekly on the same days of the week for 5 additional weeks in one case and 6 additional weeks in the other two cases until serum complement was stabilized at average normal level or higher (Fig. 2). All cases are free of edema and serum complement has remained normal. The urine of one patient is free of abnormal constituents, the other two show a marked decrease in albuminuria. All 3 patients have returned to normal cholesterol levels and the blood proteins are well within the range of normal with a return of the previously inverted A/G ratio to normal. These changes occurred within 4 weeks from the start of Cortisone therapy.

§ We wish to thank Dr. S. Fromer and Dr. E. Alpert of Merck & Co. for supplying us with liberal amounts of Cortisone.

It is too early to predict that this type of interrupted treatment will permanently relieve the nephrotic syndrome. We are reporting our results, however, so that other groups may evaluate an apparently promising therapeutic regime based on the effect of ACTH and Cortisone on the underlying immunologic process.

Summary. 1. Lowering of serum complement during the edematous phase of the nephrotic syndrome is apparently the result of an antigen-antibody reaction. 24 to 48 hours preceding spontaneous or ACTH induced diuresis, serum complement rises significantly to or toward normal. 2. ACTH, given for 7 days, effects clinical remissions which are only temporary in most cases. When the initial week of ACTH is followed by interrupted courses of ACTH given on 3 successive days of each week for 5 to 8 weeks, remissions have been long-lasting. Courses of interrupted therapy were continued until the complement level stabilized at average normal or high levels. Recent work suggests that if the initial treatment with ACTH is followed by interrupted courses of oral Cortisone, similar favorable results may be obtained.

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