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Serum Protein Regeneration Following Use of Amino Acids* in Nephritis (Nephrotic Stage).

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During the past few years the effect of administration of solutions of amino acids upon the regeneration of serum proteins in hypoproteinemic individuals has been studied in a variety of cases.[1, 2, 3] That amino acid solutions can maintain nitrogen balance is clear[4] but that regeneration of serum proteins follows their use is uncertain. In hypoproteinemia associated with the "nephrotic stage" of chronic nephritis, evidence for the regeneration of serum proteins following the use of amino acids is lacking.

Among a number of individuals with hypoproteinemia to whom intravenous amino acids were administered at this hospital, there were 2, exhibiting edema, albuminuria and elevation of blood cholesterol, in the "nephrotic stage" of chronic nephritis.

Procedure. Both patients were placed upon a 120 g protein diet, low in fat for 2 or more weeks before observations were begun. They were weighed daily. In the first case the period prior to administration of amino acids lasted 7 days, and in the second, 12. Total urinary nitrogen, serum proteins, and occasionally fecal nitrogen were determined by the micro-kjeldahl method.

Both cases had been followed closely for more than a year prior to the present studies. Despite high protein diets and frequent administration of large amounts of iron, the protein levels of the serum and the degree of anemia did not exceed the limits given (Table I). The first case was known to have suffered from nephritis for 5 years and to have exhibited the so-called "nephrotic stage" for 3. In the second case, the onset of nephritis is unknown, but marked albu-

* We are indebted to Frederick Stearns & Co. for a generous supply of amino acid solutions made by enzymatic hydrolysis of casein, approximately 80% complete. The amino acids in the hydrolysate were said to be present in the same concentration as in native casein.

1 Elman, Robert, and Weiner, D. O., *J. A. M. A.*, 1939, **112**, 796.

2 Elman, Robert, *Ann. Surg.*, 1940, **112**, 4.

3 Ravdin, I. S., Stengel, Alfred, Jr., and Prushankin, Mitchell, *J. A. M. A.*, 1940, **114**, 107.

4 Shohl, Alfred T., Butler, Allan M., Blackfan, Kenneth D., and MacLachlan, Elsie, *J. Pediat.*, 1939, **15**, 469.

TABLE I.
Comparison of Data in Two Cases of Chronic Nephritis in "Nephrotic Stage."

	Case I	Case II
Age and sex	24, female	40, male
Blood pressure (range), mm Hg	140 160 / 96 110	130 160 / 94 104
Urea clearance, % normal	30	28
Maximal specific gravity of urine	1.012	1.013
Albumin, g/24 hr in urine	7-10	6-12
Serum protein, g %	3.9-4.8	4.0-4.8
Serum cholesterol, mg%	400-1000	450-600
Hemoglobin (Sahli), g/100 cc	9-11	11
Red blood corpuscles, millions/mm³	2.75	2.75

minuria has been present for at least 2 years. Edema has always been much more marked in the first case.

In Case I 500 cc of a solution of 5% amino acids and 5% glucose were injected intravenously daily for 14 days. The injections were given slowly during a period of 3 hours. Increase in level of serum proteins did not occur (Fig. 1).

In the second case, daily intravenous injections of 180 cc of 20% solution of amino acids diluted with an equal quantity of distilled water were given for 14 days. Three hours were allowed for each

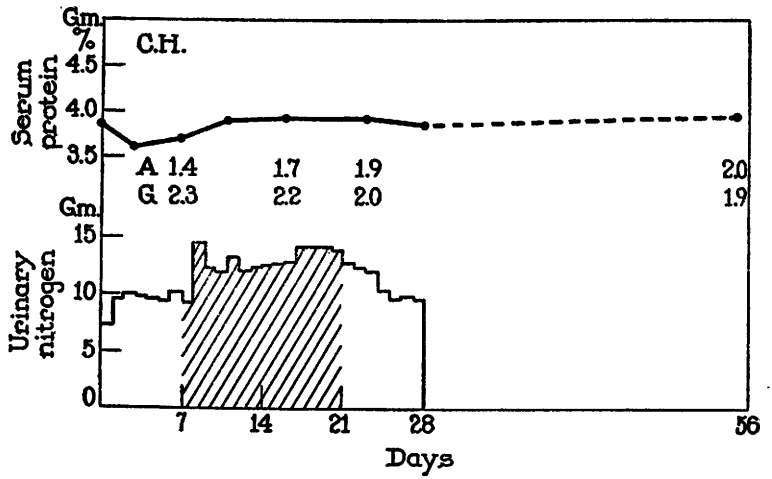

FIG. 1.

The level of serum proteins and urinary nitrogen output are shown before, during and after administration of amino acids (Case I). The urinary nitrogen is shown in blocks representing the amount in grams during one 24-hour period. The cross-hatched area indicates the period during which 500 cc of 5% amino acid solution was injected daily. The figures beneath the graph of the serum proteins represent the amounts of albumin (A) and globulin (G). Change in level of proteins did not occur.

injection. After the series of injections was completed, a small but definite rise in serum proteins took place. The level continued to rise and reached a peak of 5.5% 36 days later. The increase occurred chiefly in the albumin fraction. During the next 3 months, the serum proteins fell slowly to the previous level. Four months later the subject was restudied under the same conditions. On this occasion, larger amounts, 300 cc of 15% solution of amino acids, were given daily for 16 days in 2 injections each lasting 3 hours. Untoward reactions have not been noticed following injections in the amounts used so far. During the first week of administration a perceptible rise in plasma proteins was noticed (Fig. 2). The level continued to rise and a peak of 5.9% was reached 12 days following cessation of therapy. The increase in serum protein again took place in the albumin fraction. An effort is now being made to maintain this level by oral administration.

Both weight curves remained fairly constant and although blood volumes were not measured, it seems unlikely that they changed materially since the hematocrit figures remained relatively constant. Throughout there was no alteration in output of nitrogen derived from urinary albumin. The entire diet was regularly consumed by the first subject but irregularities due mainly to morphine addiction occurred in the second.

Discussion. Although it was impossible to carry out total nitrogen balance studies, we have calculated from the approximate nitro-

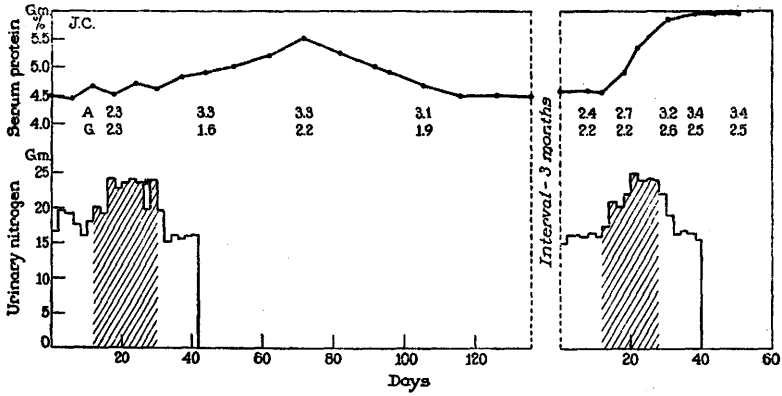

FIG. 2.

The level of serum proteins and urinary nitrogen output are shown before, during and after administration of amino acids (Case II). The urinary nitrogen is in blocks representing the amount in grams during two 24-hour periods. The cross-hatched areas indicate the periods during which amino acid solutions were given. During the first period, 180 cc of a 20% amino acid solution were given; during the second, 300 cc of 15% solution. *During this 2-day period, administration of amino acids was omitted. Note sharp drop in urinary nitrogen.

gen intake, and from the output of nitrogen in the urine, that probably less than 5% of the amino acids were retained, except perhaps during the first few days of administration. It seems clear that in the second case, the intravenous administration of amino acids initiated regeneration of plasma protein. Evidently sufficient amounts were retained to form new plasma protein. Farr and MacFadyen[5] have shown in careful nitrogen balance studies that nephrotic children are able to utilize intravenously administered amino acids but do not build plasma proteins. According to Whipple's[6] concept of protein storage, it is likely that the amino acids replenish depleted protein stores.

Conclusion. In one of 2 hypoproteinemic individuals exhibiting the "nephrotic stage" of chronic nephritis, intravenous administration of amino acids was, on two occasions, followed by a well marked rise in the level of the serum proteins. The rise occurred in the albumin fraction. The other subject failed to respond.

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Production of *Cl. welchii* Toxin in Peptone-free Medium.

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Clostridium welchii is customarily cultivated in glucose-peptone beef-infusion broth for toxin production. Many workers have found highly variable yields of toxin, which is usually due to the variation in different lots of peptone. Reed and his coworkers[1] have grown various strains of *Clostridia* in a medium consisting of 5% gelatin and 1% peptone with maximal hemotoxin production by

[5] Farr, Lee E., and MacFadyen, Douglas A., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 444.

[6] Whipple, George H., *Am. J. Med. Sc.*, 1938, **196**, 609.

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[1] Reed, G. B., Orr, J. H., and Baker, Mary C., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 620.