Metabolic Changes Associated with Administration of Adrenocorticotropin in the Nephrotic Syndrome.* (17809)

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This study was undertaken for the purpose of determining and describing the metabolic changes associated with the activation of the adrenal cortex by adrenocorticotropin in the nephrotic syndrome. Since the mechanism and duration of such activation are still obscure in the normal as well as in the disease entity reported here, efforts were made to vary the periods of administration and to prolong the periods of observation following courses.

Eight patients were treated with adrenocorticotropin. The subjects varied in age from 3 to 37 years. Six were males. In all cases the disease had been present for over 3 months. With one exception the blood urea nitrogen was found to be above the upper limits of normal in all cases, prior to administration of adrenocorticotropin. In one patient nitrogen retention was marked; the clearance of mannitol was 7 cc/min. Papilledema and retinal hemorrhages were present and the blood pressure was consistently elevated. (See Fig. 1).

Methods. The total daily dose of ACTH varied from 40 mg to 100 mg. Armour standard, given in divided doses every 6 hours. Courses of administration were also varied in duration and in 4 instances were repeated several times. All patients were maintained on dietary salt intakes of 700 mg or less, daily. In 6 cases metabolic studies included nitrogen balances, weekly blood chemistries, frequent or daily eosinophil counts, determinations of sodium, potassium, chloride, phosphorus, creatinine, total nitrogen and protein, from 24-hour urine collections. The blood chemistries were performed according to standard procedures. Sodium and potassium determinations were done with the Beckman flame photometer. Eosinophil counts were made in the hemocytometer chamber, employing the differential stain developed by Randolph.†

Results. The majority of patients manifested a more or less marked increase in edema during the administration of ACTH. In 5, the course was followed within a period which varied from a few hours to 3 days, by a diuresis which developed to the point of dehydration and was indicated by a weight-loss of 17 lb in a 7-year-old and 40 lb in a 17-year-old. One patient failed to initiate diuresis during 2 courses but after the tenth day of the third course she regained her normal weight within 4 days while still receiving the medication. The seventh patient, a 3-year-old-boy, showed no significant diuretic response to several brief courses. When diuresis was finally established, dehydration was evident in the tissues of face and limbs, but a residuum of ascitic fluid persisted. In the eighth patient, a 37-year-old man with massive ascites, repeated experimental periods resulted in a negligible reduction in edema.

In all cases, the amounts of adrenocorticotropin administered were sufficient to suppress the circulating eosinophils.

In those patients in whom nitrogen studies were possible, the balance was consistently negative during administration of ACTH and for 3 or 4 subsequent days, after which a consistent and marked positive balance appeared. During this period the serum proteins rose substantially. Improvement in serum cholesterol tended to parallel that of the serum proteins. The blood urea nitrogen decreased in all cases. Control blood sugar levels were generally low and all values showed an increase during the experimental period.

Urinary protein diminished considerably but disappeared entirely in only one patient.

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† Randolph, T. G., Blood Studies in Allergy, I. The Direct Counting Chamber Determination of Eosinophils by Propylene Glycol Aqueous Stains, *J. Allergy*, 1949, v15, 89.

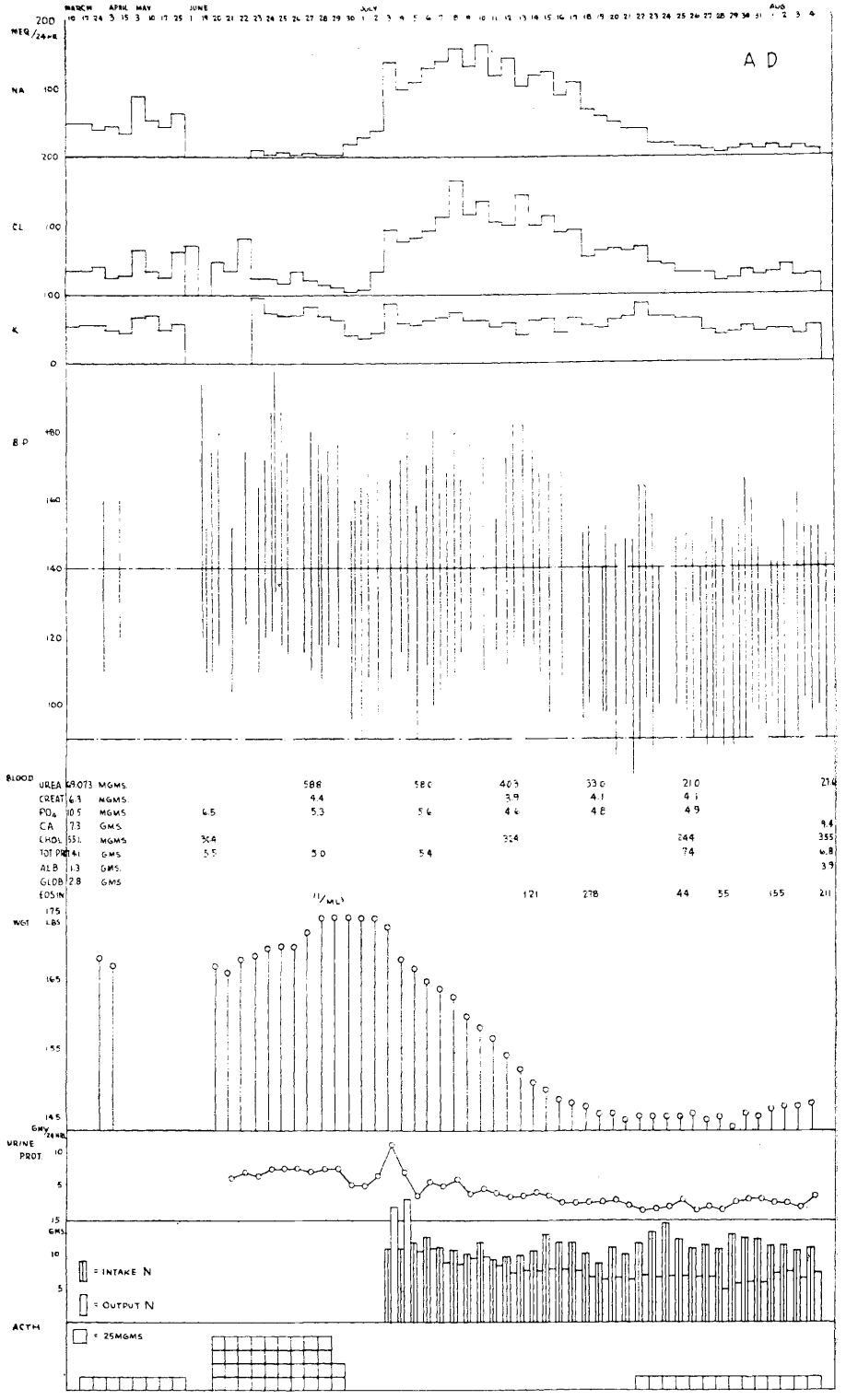

FIG. 1.
Administration of ACTH in a patient with nephrosis, azotemia, and hypertension.

Potassium output showed only inconspicuous fluctuations. In one patient the daily excretion of phosphorus was liberally increased during treatment.

Attempts were made to maintain 3 of the group by the daily administration of ACTH, 25 mg, or by weekly administration of 100 mg in divided doses. With both systems, fairly satisfactory control was secured for intervals of 6-8 weeks. Three to 4 weeks after discontinuation of medication, indications of relapse began to appear. In one instance, later repeated courses of ACTH failed to bring about diuresis, a decrease in serum cholesterol or an increase in serum proteins. The second patient has had no further treatment since Oct. 6; he shows no evidence of salt and water retention; the blood urea is at the control level. The serum cholesterol is 294 mg% and the total protein is 6.6 g% with an albumin value of 3.4 g%. Prior to treatment the total protein was 4.0 g %; the albumin 1.1 g %. The third patient discontinued treatment on the same date. He showed no tendency to redevelop edema until 3 months later, at which time the serum proteins diminished sharply.

Conclusions. It is concluded that an appropriate stimulus to the adrenal cortex by the administration of adrenocorticotropin is capable of producing marked modifications in the nephrotic syndrome. These modifications include reduction in serum cholesterol and urine protein, increase in serum proteins and profound diuresis. With one exception the diuresis occurred after discontinuance of ACTH, and the improvement in nitrogen balance and serum values continued for several weeks.

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Effect of Penicillin Dosage Schedule on Treatment of Experimental Typhoid Infections in Mice. (17810)

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It has been reported by Zubrod(1) and by White and his co-workers(2) that, for the treatment of experimental streptococcal infections in mice, the total amount of penicillin required does not vary over a fairly wide range of dosage schedules. Since it is our opinion that the major problems of penicillin therapy are now centering around the management of infections caused by organisms of high penicillin resistance, we have studied the relationship between dosage schedules and the amount of this antibiotic agent required to protect mice infected with the Panama No. 58 strain of *Salmonella typhosa*. This organism has been selected because it is quite resistant to the action of penicillin in comparison with the highly susceptible streptococci used by the above mentioned workers. When *Salmonella typhosa* was used as the infecting agent, it was found that there were marked differences in the amount of penicillin required for therapy depending upon the number and frequency of the doses employed.

These data, which can be obtained with adequate precision only from animal experimentation, are being presented because it is believed that the findings have important application to the use of penicillin in the treatment of infections in human patients, where it is desired to use the antibiotic agent with maximum efficiency and economy.

1. Zubrod, Charles G., *Bull. of the Johns Hopkins Hospital*, 1947, v81, 400.

2. White, H. J., Baker, M. J., and Jackson, E. R., PROC. SOC. EXP. BIOL. AND MED., 1948, v67, 199.