amined, there was no correlation between rate of growth and susceptibility or resistance, a result in accord with experience summarized by Clark, McClung, Pinkerton, Price and Schneider indicating that animals will tolerate severe restrictions of food over long periods of time without significant changes in susceptibility providing specific deficiencies of essential nutrients are excluded(12). In comparing the experiments reviewed by Clark, *et. al.* (12) and the recent work of Schaedler and Dubos(11), the difference in partial deprivation of food or nutrients and complete starvation must be kept in mind. Absence of direct correlation between failure to gain and susceptibility in our experiments indicates that nutritional impairment and increased susceptibility to herpes simplex were independent responses to the experimental stress.

Summary. Stress induced in mice by avoidance-learning or by restraint resulted in an increased susceptibility to infection with the virus of herpes simplex.

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Production of Hypertonic Urine in Humans in the Probable Absence of Antidiuretic Hormone (ADH). (23427)

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Shannon observed the formation of concentrated urines in severely dehydrated dogs with experimental diabetes insipidus(1). Subsequently, Homer Smith and his associates(2) suggested the presence of an "ultimate" concentrating segment (possibly the collecting tubule) where, independently of ADH, water was continuously reabsorbed without solute. In this conceptual scheme, the primary function of ADH is to allow the back diffusion of water when solute is actively reabsorbed in the "penultimate" portion of the distal tubule, permitting delivery of a small volume of isosmotic fluid to the final segment, where a hypertonic urine may be formed.

Recent animal experiments suggested that this does occur and that ADH is not essential for production of a hypertonic urine(3,4). Berliner and Davidson(3) produced "physiologic diabetes insipidus" in dogs by sustained water loading and simultaneously collected urine from each kidney. When the glomerular filtration rate was considerably reduced on one side by compression of the renal artery, urinary flow and solute excretion fell markedly while urinary solute concentration increased to a level greater than that of the plasma. Urine from the contralateral side remained hypotonic, indicating that the experimental procedure did not cause the liberation

of ADH. del Greco and de Wardener(4), in somewhat similar experiments, were also able to produce hypertonic urines following depression of the glomerular filtration rate. Finally, Wirz(5) found by micropuncture technics in the mammalian kidney, that during dehydration tubular urine obtained from the distal part of the distal convolutions was isotonic while bladder urine was very hypertonic. This indicated that the actual concentrating process occurred in the most distal segment of the nephron or actually in the collecting tubules.

However, to the authors' knowledge, the effect of acute reductions in filtration rate in humans during maximal water diuresis or in diabetes insipidus has not been described. The present experiments were undertaken to evaluate this problem.

Materials and methods. Two patients, ages 25 and 27, with known diabetes insipidus, served as subjects. In one, the diabetes insipidus was secondary to a head injury (basal skull fracture), and the other was of idiopathic origin. Neither subject showed an antidiuretic response when infused with hypertonic saline; neither was capable of forming a concentrated urine after 10-12 hours of dehydration, and one showed no antidiuretic response to rapid inhalation of 4 cigarettes (nicotine test). Both subjects had random 24-hour urinary volumes of 7 to 10 liters. On the morning of the test, one hour after a breakfast with liberal fluid intake, the subject was catheterized, put in a supine position, and hydrated with 1000 cc of water by mouth. Throughout the experiment a sustained positive water balance of 1000 cc was maintained by intravenous infusion of 2.5% glucose in water in amounts equivalent to his urinary flow. After a constant rate of urinary flow had been obtained in the horizontal position, the patient was elevated to 45 degrees, and the effect of the upright position was observed for 4 to 5, 20-minute periods. At the end of this time, hexamethonium was infused intravenously at a slow rate until a sustained lowering of blood pressure occurred. Usually 5 to 7, 20-minute periods were obtained after initiating the hexamethonium infusion, and the subject was then returned to the horizontal position and urinary collections continued for an additional 6 to 8 periods. Samples of venous blood were drawn approximately 2 minutes before the midpoint of every collection period. Blood pressures were measured at frequent intervals throughout the experiment. The osmolality of plasma and urines was determined by freezing point depression utilizing the Fiske Osmometer. Glomerular filtration rate was estimated from the clearance of inulin. The latter was analyzed in serum and urine by the method of Roe and Epstein(6).

Results. Fig. 1 and 2 illustrate the essential changes observed in both experiments. During initial control periods both subjects demonstrated large volumes of very hypotonic urine (50 and 75 mOs./L., respectively) characteristic of water-loaded and/or diabetes insipidus subjects. On elevation to 45 degrees, filtration rates declined gradually and urinary flows fell progressively. Urinary osmolality increased slightly in both cases (to 80 and 103 mOs./L.). Hexamethonium administration produced marked and sustained reductions in both systolic and diastolic pressures. Almost simultaneously with the sustained hypotension, glomerular filtration rates decreased precipitously to less than 10 cc/minute, and urinary flows decreased to less than 0.5 cc/minute. In both subjects, urinary osmolalities rose promptly and strikingly to hypertonic levels (573 and 763 mOs./L., respectively). As blood pressures began to rise subsequent to termination of the infusion of hexamethonium, and particularly after the patients returned to the reclining position, the glomerular filtration rates rose progressively. In one subject (Fig. 1), urinary osmolality fell rapidly to the previously hypotonic level, while in the other a more gradual return was noted (Fig. 2). Urinary flows increased progressively, but total solute excretions and rates of flow were still substantially below the control reclining periods.

Discussion. It is apparent that in both cases blood pressures were reduced to levels barely consistent with continued glomerular perfusion and filtration. Tubular, pelvic, and ureteral urinary flows obviously were rapidly changing in velocity, therefore errors in rate of

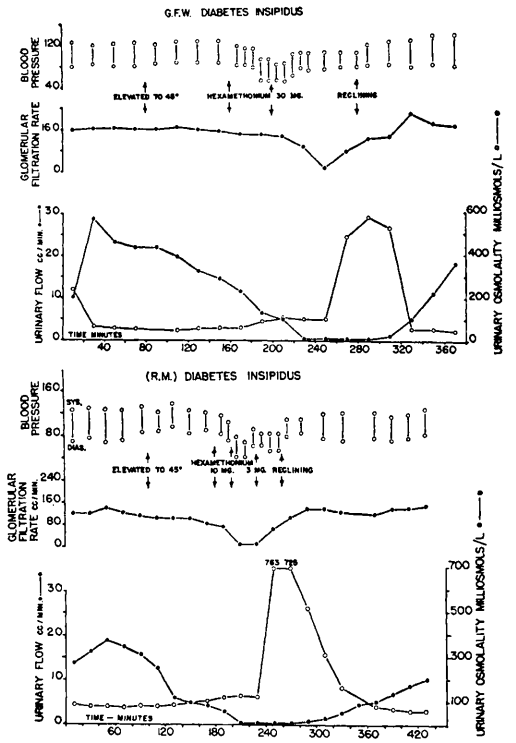

FIG. 1 (top) and 2 (bottom). Effect of acute reduction in blood pressure on filtration rate, urinary flow, and osmolality of patients with diabetes insipidus.

flow and solute concentration due to delay time and residual volumes in the urinary dead space were certainly introduced. These would best explain the slight time lag between the minimal calculated filtration rates and the maximal urinary osmolalities. Similarly, while glomerular filtration was probably reduced to 10 to 15% of normal in both cases, the absolute values shown must be considered only an approximation.

The results of these 2 studies in humans with diabetes insipidus appear to confirm animal experiments of Berliner and Davidson (3) and del Greco and de Wardener(4) that even in the absence of ADH, if the volume of fluid delivered to the concentrating or "ultimate" segment of the renal tubule is small enough, a definitely hypertonic urine can be formed. Although both patients were typical cases of diabetes insipidus, however, it cannot be stated with absolute certainty that the profound reduction in blood pressure did not cause the release of some "residual" ADH in spite of the sustained water load and hypotonicity of the body fluids. This criticism, however, cannot be directed at the experiments of Berliner and Davidson(3), and it seems clear that in the present 2 cases the severe reduction in filtration rate played a fundamental role in the production of the hypertonic urines. Recently a statistical evaluation in humans(7) of the non-hormonal factors affecting characteristics of maximal water diuresis has suggested that glomerular filtration rate varies inversely with the concentration of the urine.

Although reduction in solute excretion was extreme, particularly during the oliguric period, this *per se* is not the cause of the hypertonic urine as suggested by del Greco and de Wardener(4). If glomerular filtration rates are maintained while total solute excretion is reduced by low protein, low salt diets, the normal water-loaded subject excretes a more *dilute,* not a more *concentrated* urine(7).

Summary. The effect of profound reduction of glomerular filtration rate on urinary osmolality of 2 subjects with diabetes insipidus was investigated. In both, reduction in filtration rate was associated with production of a significantly hypertonic urine. These observations support the animal experiments which suggest that ADH is not essential for the production of a hypertonic urine.

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