

On the Nature of the Nonspecific Nephropathy Attributed to Mannitol. (27653)

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The pathological changes of osmotic nephropathy are characterized by swelling and lacy vacuolization of the tubular epithelium of the kidney and are most prominent in the proximal tubules and descending limb of the loops of Henle. Lamay(1) first described these changes after infusion of sucrose in 1906 and Helmholtz(2,3) later observed them after infusion of other hypertonic solutions including urea, glucose and inulin. We observed identical changes in the kidneys of patients who received infusion of 20% mannitol in water in an attempt to prevent the occurrence of acute organic renal failure. The purpose of the present study was to compare the severity of the renal changes induced by infusion of 20% mannitol with those induced by 5% glucose. The latter substance was selected because of its universal acceptance as a clinically useful and nontoxic agent.

Method. Twelve adult dogs weighing between 10.4 and 16.3 kg underwent laparotomy and dissection of the right renal artery between its origin from the aorta and its bifurcation or trifurcation at the renal hilus. A control renal biopsy was then obtained with a Vim-Silverman needle. Four dogs then received injection of 35 cc of 20% mannitol in water (7 g) directly into the main stem of the right renal artery *via* a 25-gauge needle (Group 1). Four other dogs received intra-arterial injection of 35 cc of 5% glucose in water (1.75 g) in the same manner and in addition received 20 cc/kg of 5% glucose in water (1 g/kg) intravenously immediately prior to obtaining the control biopsy (Group 2). In an effort to distinguish between renal changes due to the agents *per se* and the attendant operative manipulations, 4 additional dogs underwent all operative manipulations but received neither intravenous nor intra-arterial injection of any fluid (Group 3). Additional needle biopsies were obtained at 15,

30, 60 and 120 minutes after intra-arterial injection of 20% mannitol or 5% glucose (Groups 1 and 2) and at the same intervals after manipulation only (Group 3). All microscopical sections were fixed in 10% formalin and stained with hematoxylin and eosin and submitted to a pathologist for study in addition to being viewed by one of us (RCD). The observers were not informed which dogs had received mannitol, which had received glucose, and which had received neither agent. The changes were graded on the following basis: 0: No evidence of osmotic nephrosis, 1+: Minimal cloudy swelling of the tubular epithelium, 2+: Severe cloudy swelling with minimal vacuolization of the tubular epithelium, 3+: Severe cloudy swelling with severe vacuolization of the tubular epithelium.

Results. The two observers graded the changes according to the system proposed and differed by more than a grade of one plus on only 4 of the sections examined. Results are shown in Fig. 1 which is a composite of the grades given each section by both observers. The grades assigned to the control sections and those obtained 15 minutes after injection

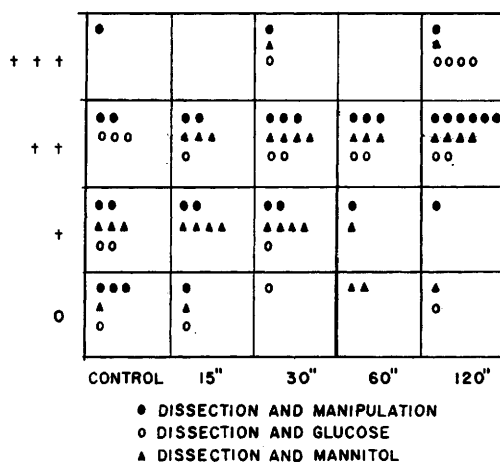


FIG. 1. Composite graph of grades given each microscopical section by 2 observers.

of either mannitol or glucose or after manipulation only were with but one exception distributed rather evenly between 0 and 2+. The grades assigned to the sections obtained 30 minutes after injection of either mannitol or glucose or after manipulation only were predominantly 1+ and 2+ while the sections obtained 60 minutes after injection of either mannitol or glucose or after manipulation only were most frequently graded 2+. Two hours after injection of either mannitol or glucose or after manipulation only the overwhelming majority of the sections were graded 2+ and 3+. Typical changes ob-



FIG. 2. Typical changes observed in canine kidney 2 hr after infusion of 20% mannitol into renal artery.

FIG. 3. Typical changes observed in canine kidney 2 hr after infusion of 5% glucose into renal artery.

served after infusion of mannitol and glucose are shown in Fig. 2 and 3. Thus the data indicated that under the experimental conditions the degree of osmotic nephropathy induced by 20% mannitol was essentially the same as that induced by 5% glucose.

Discussion. The data must be interpreted with caution. That the technic of renal artery dissection and repeated needle biopsy was not innocuous was shown by the grades assigned to the biopsies obtained from the dogs which had only dissection and manipulation but not injection into the renal artery. Then, too, the final biopsy was obtained only 2 hours after injection or manipulation of the renal artery. Perhaps a difference between the changes produced by the 2 agents would have been apparent had the biopsies been obtained at more prolonged intervals after injection. Finally, these experiments did not give any direct information as to duration of the changes or functional status of the kidney. Since, however, the degrees of change produced by the 2 agents were remarkably similar and since 5% glucose has never been implicated as a renal toxin, there appeared to be no anatomic evidence of any serious functional impairment of the mannitolized kidney.

Summary. Serial needle biopsies of the canine kidney were obtained before and periodically after injection of 20% mannitol or 5% glucose into the dissected renal artery. Similar biopsies were obtained from a series of animals which had undergone only dissection and manipulation but not injection of the renal artery. The severity of the nonspecific nephropathy induced by either 20% mannitol, 5% glucose or repeated trauma of needle biopsy was not significantly different.

1. Lamay, H., Mayer, A., Rathery, F., *J. de physiol. et de path. gén.*, 1906, v8, 624.

2. Helmholtz, H. F., *J. Pediat.*, 1933, v3, 144.

3. Allen, A. C., *The Kidney. Medical and Surgical Diseases*, Grune and Stratton, New York, 1951.

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