cleic acids might be a fairly general phenomenon.

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Synergistic Renal Effects of DCI and Cortisone in Mice Poisoned with Bacterial Endotoxin. (28309)

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The adrenergic blocking agent DCI or 3,4-dichloroisoproterenol provided a measure of protection against bacterial endotoxin when given subcutaneously to mice by McLean and Berry(1). Cortisone had been found to protect mice from these lipopolysaccharides by Berry *et al.*(2,3) and the handling of nitrogenous waste products was implicated(4). In the present work the influence of DCI on nitrogen excretion and its interaction with cortisone has been investigated.

Methods. Male CF1 mice were used in this study. Saline blanks were given subcutaneously as were the doses of DCI 10 mg/kg and cortisone acetate 5 mg/mouse. Difco crystalline lipopolysaccharide from *E. coli* (Code 0.27:B8, Control 118023) was the endotoxin used. An approximate LD_{50} of 0.3 mg/mouse was injected intraperitoneally. The DCI dose was given twice; 5 hours before and 1 hour before the endotoxin. The cortisone doses were given in the same way. The average weight of the mice used in these experiments was about 23 g. The micro-Kjeldahl procedure was used for determination of urinary nitrogen and blood non-protein nitrogen (NPN). Urine was collected under toluene in conical centrifuge tubes. Pairs of mice were restrained by small stainless steel screens over glass funnels. The animals were without food and water throughout the collection period, which was 17 hours (5 P.M.-10 A.M.). For determination of NPN one volume of blood (about 1 cc) was mixed with 2 volumes of 10% trichloroacetic acid, centrifuged at 3000 RPM for 3 minutes and then filtered. One cc of the filtrate was combined with 0.5 cc 36N H_2SO_4.

Results. Three separate experiments were conducted, each with 6 values per group. Two sets of values were combined to give the data presented in Fig. 1 and the final experiment, carried out some months later than the others, confirmed the earlier findings. The results are presented graphically in the Figure. DCI did not increase urinary nitrogen or urinary volume outside normal limits. Cortisone did augment these parameters and the differences were significant. In combination DCI and cortisone acetate doubled urine volume and markedly increased urinary nitrogen excretion during the 17 hours of the test. Endotoxin alone depressed urinary nitrogen elimination and blood non-protein nitrogen levels reached very high values. If the mice were pretreated

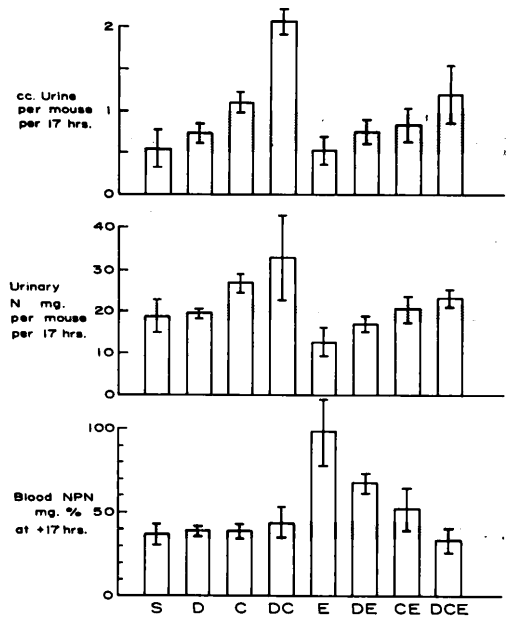

FIG. 1. Bar graph prepared for relative comparison of factors related to nitrogen excretion. Symbols on abscissa are as follows: S, saline; D, DCI; C, cortisone acetate; DC, DCI and cortisone acetate; E, endotoxin; DE, endotoxin after DCI; CE, endotoxin after cortisone acetate; DCE, endotoxin after DCI and cortisone acetate. Shaded areas represent approximate normal limits. Lines in tops of bars indicate plus and minus the standard deviations.

with DCI before the endotoxin some protection was obtained. Pretreatment with cortisone acetate provided a more effective antidote. In combination these 2 agents restored urinary nitrogen levels and blood non-protein nitrogen to normal. This factor may very well account for the protection noted by McLean and Berry when mice were treated with DCI before endotoxin administration. It is interesting to note the direct parallel between urinary volume and urinary nitrogen excretion and the inverse correlation of these factors with blood non-protein nitrogen. A cause and effect relationship is strongly suggested.

Discussion. Blood non-protein nitrogen is characteristically high in acute renal failure in man. This may result from a variety of causes including bacterial infection. Exposure of experimental animals such as the rat(5) or the dog(6) to bacterial endotoxin has been shown to produce a like effect. More recently Berry *et al.*(2-4) have clearly demonstrated the reduced urinary nitrogen output and resultant high NPN in endotoxin-poisoned mice. Cortisone and ACTH had marked effects in their experiments. Cortisone is one of the few agents which protect mice against bacterial endotoxin. DCI is another.

On the basis of chemical structure and known physiological actions it seems likely that the pronounced effect seen when DCI and cortisone were given together is the result of the addition of 2 different types of influence. Urinary nitrogen levels reflect the ability of the kidney to filter. The direct correlation between urinary nitrogen and urinary volume and the inverse relationship to blood NPN which is apparent therefore suggests a vascular or hemodynamic influence on the kidney. DCI would appear to improve the renal circulation in some way. It can affect the normal as well as the endotoxin-poisoned mouse kidney and it can act synergistically with cortisone.

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