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TECT LEAD-SENSITIZED RATS AGAINST
ENDOTOXIN

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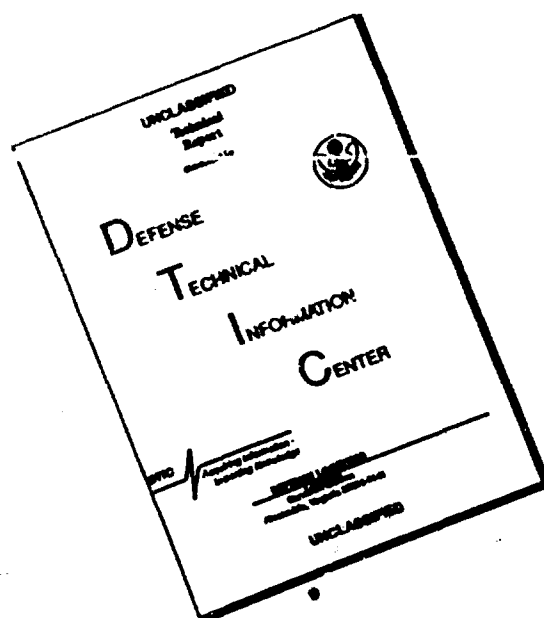
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Corticosteroids, in doses that protect normal rats against lead poisoning, had no effect in lead-sensitized rats.		

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Failure of Methylprednisolone to Protect Lead-Sensitized Rats Against Endotoxin

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Methylprednisolone, in doses that protect normal rats against endotoxin, has no effect in lead-sensitized rats.

The administration of lead acetate (PbAc_2) sensitizes both rats (7) and subhuman primates (4) to minute amounts of bacterial endotoxin. The mechanism of this sensitization has not been defined, although it has been suggested that alterations in either the degradation of endotoxin (8), or in carbohydrate metabolism (3, 4), may be important.

Glucocorticoids are demonstrably effective in protecting normal animals against endotoxin (1, 5). The purpose of the present investigation was to determine if this was also the case in lead-sensitized animals.

Under light ether anesthesia, femoral cut-downs were performed on male Sprague-Dawley rats weighing 180 to 220 g, and an intravenous injection of 20 mg of PbAc_2 dissolved in 0.5 ml of deionized water given. This was immediately followed by an injection of 0.5 ml of *Serratia marcescens* endotoxin (Difco Laboratories) suspended in 0.15 M NaCl buffered to pH 7.4 with 0.02 M sodium phosphate (PBS), after which 9.5 mg of methylprednisolone (Upjohn Co.) dissolved in 0.5 ml of PBS was also given. Deionized water was used as a control for the PbAc_2 injections in these experiments. However, other investigators have used sodium acetate with no effect on endotoxin induced mortality (2). PBS was used as a control for the endotoxin and methylprednisolone injections.

The animals were observed for 72 h, although most died within the first 12 h. The mean lethal dose was determined for each group according to the method of Litchfield and Wilcoxon (6). No deaths out of 16 were observed in control animals which received only PbAc_2 , or only methylprednisolone. Two deaths occurred in the 16 animals which received both PbAc_2 and methylprednisolone, but no endotoxin.

As can be seen from Table 1, methylprednisolone was quite effective in protecting non-lead-treated rats, a single injection causing a fivefold

TABLE 1. Effect of lead acetate and methylprednisolone on endotoxin lethality in rats

Lead acetate (100 mg/kg ^a)	Methylprednisolone (50 mg/kg ^a)	No. of animals	Endotoxin LD ₅₀ ^b (mg/kg ^c)
-	-	65	16.5 (11.6-23.6) ^c
-	+	64	82.7 (66.4-102.9)
+	-	152	0.45×10^{-3} (0.34×10^{-3} to 0.58×10^{-3})
+	+	178	0.38×10^{-3} (0.31×10^{-3} to 0.46×10^{-3})

^a Body weight.

^b Abbreviation: LD₅₀, mean lethal dose.

^c Numbers in parenthesis are the 95% confidence limits for each LD₅₀.

increase in the mean lethal dose. However, in the lead-treated rats, which were approximately 37,000 times more sensitive to endotoxin, the methylprednisolone was without any effect.

This failure of a potent glucocorticoid to protect lead-sensitized rats against endotoxin suggests that lead may produce important qualitative, as well as quantitative, differences in the response of an animal to endotoxin. Furthermore, it would seem to indicate that under certain circumstances the efficacy of steroids in the treatment of septic shock may be a function of other, seemingly unrelated, factors.

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