## COMPARATIVE STUDIES ON THE TOXICITY OF ESCHERICHIA COLI LIPOPOLYSACCHARIDE ENDOTOXIN IN VARIOUS ANIMAL SPECIES

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Recently, numerous reports have appeared on the pharmacology and pathology of the different endotoxins (2, 3), and in them, lethal doses described for one and the same species have been inconsistent, depending on the kind of endotoxin used. Since there are few comparative data on the sensitivity of various species, we are reporting our results of comparative studies on the toxicity of lipopolysaccharide (LPS) endotoxin obtained from *Escherichia coli* O78.

The endotoxin used in this experiment was extracted by the warm phenol–water method of Westphal and Lann (4) from a fermentor culture of a freshly isolated type O78 *E. coli* strain. Toxicity assay was carried out in calves, swine, dogs, cats, rabbits, guinea pigs, rats, mice, chickens, frogs, and fish (carp). The endotoxin was dissolved in an 0.9% NaCl solution and administrated by the intraperitoneal route.

TABLE I

Sensitivity to *E. coli* endotoxin of different animal species

| Species | No. animals | Body weight | Lethal dose (mg/kg) |
|---|---|---|---|
| Calf | 1 | 500 kg | 0.025 |
| | 3 | 55±10 " | |
| Rabbit | 15 | 3±1 " | 3.0 |
| Dog | 6 | 10±5 " | 4.0 |
| Swine | 12 | 10±4 " | 5.0 |
| Guinea pig | 20 | 450±50 g | 10.0 |
| Cat | 6 | 2.5±0.5 kg | 15.0 |
| Rat | 200 | 300±50 g | 20–60.0 |
| Mouse | 400 | 18±4 " | 25–60.0 |
| Chicken | 30 | 1±0.2 kg | > 50.0 |
| Frog | 70 | 40±10 g | >100.0 |
| Fish (carp) | 10 | 110±10 " | >200.0 |





Results are summarized in Table I, listed in order of endotoxin sensitivity. Determination of $LD_{50}$ not being possible in all cases, only the lethal doses have been included in the table.

The most common clinical symptoms of the endotoxin sensitive animals were fever, diarrhea, adynamia, and hemodynamic changes (hyperventillation, cyanosis, tachycardia). In cats, small doses of endotoxin produce vomiting in 1 or 2 hours after administration. Cats and also dogs reacted sometimes with bloody diarrhea. Occasionally cats developed aggressiveness and mice tetanic paralysis of the legs. Pathologically, edema and hemorrhages in various tissues were most frequently demonstrable after endotoxin shock. In mice, edema alone was found, as described previously (1). In all endotoxin sensitive species most lesions were found in the gastrointestinal tract. In rats and dogs, hemorrhages were frequently detected in the lymphatic tissues, particularly in the thymus and Payer's plaques. In dogs the endotoxin sometimes produced hemorrhagic infarcts of the spleen. In cats and swine, hemorrhages were present in the epicardium and endocardium and sometimes there was a pulmonary emphysema.

The above results are suggestive of a certain correlation of endotoxin sensitivity with the phylogenetic maturity of the species. Fish and frogs displayed an extreme resistance to endotoxin. In fish even doses as massive as 200 mg/kg endotoxin failed to produce clinical symptoms, although the bulk of the endotoxin had been most probably absorbed from their peritoneal cavity because sera taken 24 hours after toxin injection caused 100% lethality when injected into mice intraperitoneally in 0.5-ml doses. Clinical symptoms (diarrhea, adynamia, etc.) were apparent with chickens, but none of them died of endotoxin shock.

The mammalian species examined displayed a wide range of sensitivity to endotoxin. Calves were extremely sensitive, whereas rats and mice were rather resistant.

Although the clinical and pathological changes of the endotoxin shock were roughly uniform in all examined species, distinct differences in tissue reactivity were encountered.

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