

than do any other tissues in the body. Certainly this reaction is of some importance to the animal economy. Further experimental procedures should give some clue to the function of this widespread organ system and to the fundamental importance of the lymphocyte.

*Summary.* Administration of purified ACT to the male rat produces by its action on the

adrenal cortex a striking reduction in the weight and size of the thymus gland and the cervical lymph nodes. This same effect is not manifest in the adrenalectomized animal. This finding furnishes further evidence for the existence of a definite relationship between adrenal cortex and thymus and lymph nodes. Functional interpretation of this relationship awaits further experimental and clinical study.

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## Age as a Factor in Susceptibility of Mice to the Endotoxin of Bacillary Dysentery.

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As a part of a series of studies dealing with the effects of bacterial toxins on mice,<sup>1-5</sup> experiments were set up to ascertain the susceptibility exhibited by mice of different ages, and therefore, of different body weights, to a specific endotoxin. The toxic material used in these experiments was obtained from the cell bodies of *Shigella paradysenteriae* Flexner by methods previously described.<sup>5</sup>

Three age-weight groups of normal male Rockland mice were chosen for the tests, and comprised 12-, 20-, and 35-g mice with ages of approximately 25, 50, and 350 days, respectively.\* Survival curves were obtained by injecting the endotoxin in dosages ranging from the minimal effective killing level to that causing death in nearly all the mice. All injections were of aqueous solutions by the

intraperitoneal route. Survivors were counted at the end of a 24-hour interval, experience indicating this to be an adequate period. The data from two duplicate experiments are presented graphically.

In Fig. 1 the experimental data are presented as percent survival against dosage expressed in the usual terms of grams of toxin per kilogram of body weight. The curves indicate different susceptibilities for animals of the 3 age-weight groups. This difference may be interpreted as meaning that the 35-g mice, at the 50% survival level, are about 3 times more sensitive to the lethal action of the toxin than are the 10-g mice, and somewhat less than twice as sensitive as the 20-g. It would be assumed from such an interpretation that the aging process in mice involves an increasing sensitivity to the endotoxin.

A more plausible interpretation of this type of toxication becomes apparent if percent survival is plotted against the absolute dose required to kill (Fig. 2). The curves obtained when the data are plotted in this manner appear to be almost superimposable within the limits of experimental error. This suggests that the toxic material in causing death in the mouse acts by disabling a single physiological system, and that this unit injury is to a system which is substantially independent of age or normal body weight for the range tested.

<sup>1</sup> Zahl, Paul A., Hutner, S. H., Spitz, S., Sugiura, K., and Cooper, F. S., *Am. J. Hyg.*, 1942, **36**, 224.

<sup>2</sup> Zahl, Paul A., and Hutner, S. H., *Proc. Soc. Exp. Biol. and Med.*, 1942, **51**, 285.

<sup>3</sup> Zahl, Paul A., and Hutner, S. H., *Proc. Soc. Exp. Biol. and Med.*, 1943, **52**, 116.

<sup>4</sup> Hutner, S. H., and Zahl, Paul A., *Proc. Soc. Exp. Biol. and Med.*, 1943, **52**, 364.

<sup>5</sup> Zahl, Paul A., Hutner, S. H., and Cooper, F. S., *Proc. Soc. Exp. Biol. and Med.*, 1943, in press.

\* The mice used in these experiments were of a standardized inbred strain tested at regular intervals for freedom from bacterial infections.

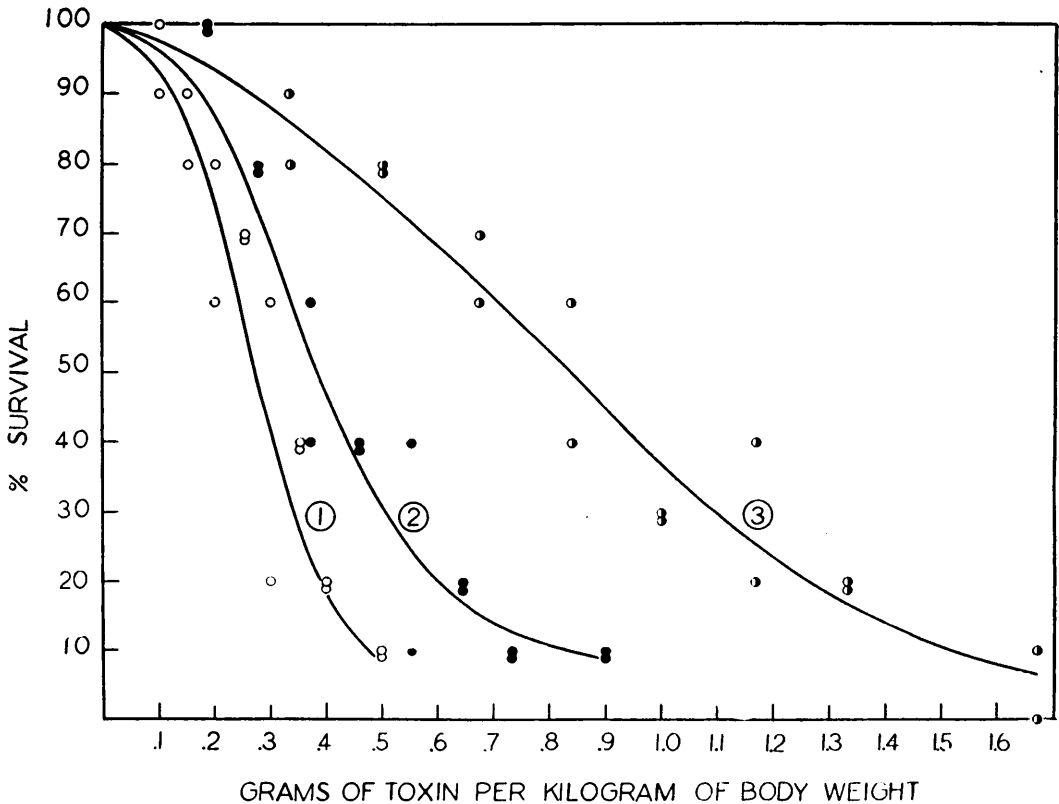


FIG. 1.

Survival curves of mice receiving intraperitoneal injections of *Shigella* endotoxin, computed on the basis of grams of dry toxic material per kilogram of body weight. (1) 35 g mice; (2) 20 g mice; (3) 12 g mice. Each point plotted refers to 10 animals.

It appears probable that the unit injury in this case is direct vascular damage. This view is supported by the current belief that the somatic O antigens of gram-negative bacteria exert their toxicity primarily on the vascular system, particularly the capillary endothelium.<sup>6-11</sup> Dennis presents this point of view perhaps most clearly in generalizing from his studies on the typhoid endotoxin: "The puri-

fied somatic antigen complex is a vascular poison. The toxic manifestations and histopathology are entirely attributable to extensive capillary hemorrhage."

The toxicity of the preparation used here is referable in almost full measure to the somatic O antigen, the strain being smooth and virulent for mice. That this kind of vascular damage is characteristic of the endotoxins of gram-negative bacteria has been demonstrated by the uniform production of hemorrhage in transplanted tumors following the injection of the endotoxins of almost any gram-negative bacterium.<sup>1,4</sup> This property is lacking in gram-positive bacteria, which do not possess chemically similar somatic antigens. One would suppose from the uniform pattern of vascular damage produced by gram-negative endotoxins that the results reported here for *Shigella* would be obtained with the endotoxins of other gram-negative bacteria, whether

<sup>6</sup> Cameron, G. R., Delafield, M. E., and Wilson, J., *J. Path. and Bact.*, 1940, **51**, 223.

<sup>7</sup> Dennis, E. W., *Proc. Third Internat. Cong. Microbiol.*, New York, 1940, 797.

<sup>8</sup> Kourilsky, R., Kourilsky, S., and Bablet, J., *C. R. Soc. Biol.*, 1941, **135**, 18.

<sup>9</sup> Penner, A., and Bernheim, A. I., *J. Exp. Med.*, 1942, **76**, 271.

<sup>10</sup> Morgan, Herbert R., *Am. J. Path.*, 1943, **19**, 135.

<sup>11</sup> Olitzki, L., Bendersky, J., and Koch, P. K., *J. Immunol.*, 1943, **46**, 71.

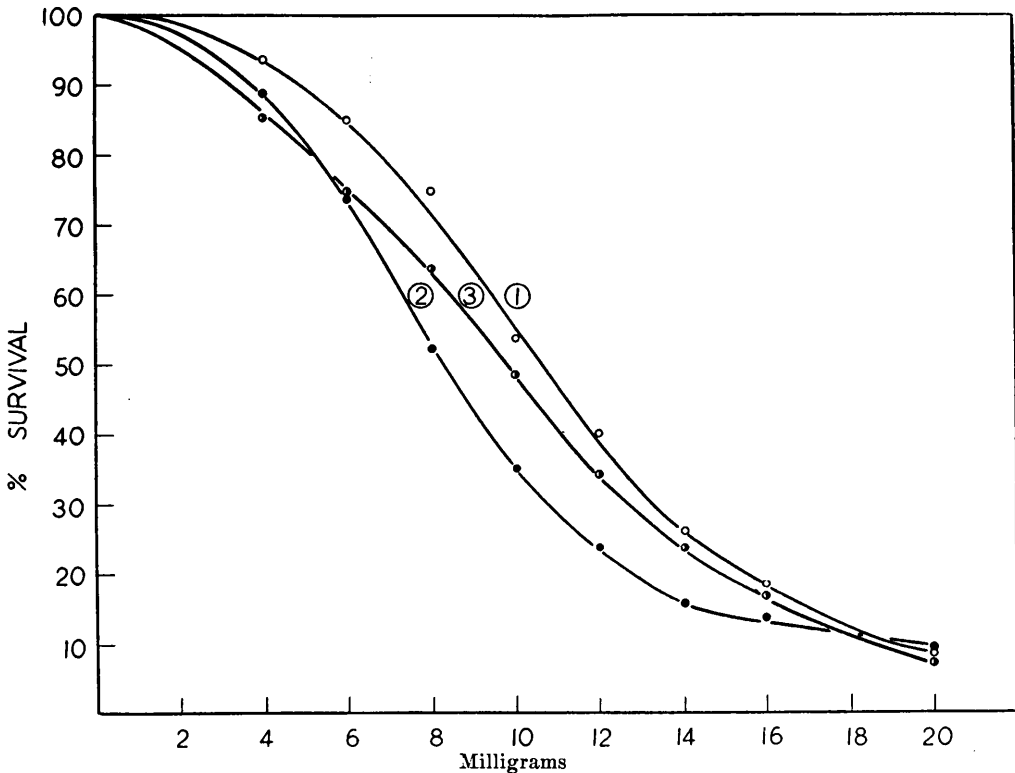


FIG. 2.

Survival curves of mice receiving intraperitoneal injections of *Shigella* endotoxin, computed on the basis of absolute amounts of dry toxic material injected. (1) 35 g mice; (2) 20 g mice; (3) 12 g mice.

the endotoxins were administered as bacterial extracts or liberated in the course of an infection by living bacteria.

The range of weights and ages covered by our data does not include the extreme limits of the life cycle where vascular susceptibilities might be expected to differ markedly.

It seems profitless to attempt a comparison of this type of toxication with those reported in the literature dealing with the results of administration of organic and inorganic poisons. In a number of studies mature rats have been described to be more sensitive than young rats to certain poisons, and equally or less sensitive to others.<sup>12</sup> Such results make

to appear almost certain that different toxication mechanisms are involved.

**Summary.** Dose-survival curves obtained by injecting the endotoxin of *Shigella paradysenteriae* Flexner into 12-, 20-, and 35-g mice indicate that such mice are killed by approximately the same minimal amounts of toxin, and that this effect is not considerably modified within the limits of age or normal weight indicated. This effect is interpreted as injury to a single system, most probably the vascular system.

<sup>12</sup> Holek, H. G. O., *The Rat in Laboratory Investigation*, J. B. Lippincott Co., Philadelphia, Pa., 1942, p. 302.