TABLE III. Lethality in Pertussis-Treated Mice of Endotoxin Reacted *in vitro* with Extracts of Spleen from Pertussis-Treated Mice Pretreated with Hydrocortisone.

Dose of endotoxin, μg	Not given hydrocortisone	Given hydrocortisone*
50	10/10	10/10
25	9/10	10/10
12.5	10/10	9/10
6.2	8/10	7/10
3.1	5/10	4/10
1.6	0/10	0/10

* 2 mg hydrocortisone intraperitoneally 2 hr before exsanguination.

(7) and anaphylactic shock(8), do not explain it. This study suggests that hypersensitivity is a result of the loss of endotoxin-detoxifying activity in the RES. This view is confirmed by the further observation that the recovery of normal resistance to endotoxin is concurrent with recovery of normal detoxifying power of the spleen and liver, which occurs about 6 weeks after injecting the vaccine.

In the light of other data showing that the lethal action of endotoxin is mediated *via* the nervous system(9), the anti-endotoxic effect of hydrocortisone appears to be achieved by blocking the interaction of endotoxin with nerve tissue. This hypothesis is being studied.

Conclusion. Pertussis vaccine produces hypersensitivity to endotoxin in mice by reducing the potency of the endotoxin-detoxifying component in the reticulo-endothelial system.

1. Kind, L. S., *J. Immunol.*, 1953, v70, 411.
2. Smith, E. E., Rutenburg, S. H., Rutenburg, A. M., Fine, J., PROC. SOC. EXP. BIOL. AND MED., 1963, v113, 781.
3. Rutenburg, S. H., Rutenburg, A. M., Smith, E. E., Fine, J., *On the nature of tolerance of endotoxin.* Symposium on endotoxin, Rutgers Univ. Press, 1964.
4. Kind, L. S., Woods, E. F., PROC. SOC. EXP. BIOL. AND MED., 1954, v84, 601.
5. Kind, L. S., *J. Allergy,* 1953, v24, 52.
6. Parfentjev, I. A., Goodline, M. A., *J. Pharmacol. Exp. Therap.,* 1948, v92, 411.
7. Munoz, J., PROC. SOC. EXP. BIOL. AND MED., 1957, v95, 200.
8. Malkiel, S., Hargis, B. J., *ibid.,* 1952, v80, 122.
9. Palmerio, C., Zetterstrom, B. E. M., Shammash, J., Euchbaum, E., Frank, E. D., Fine, J., *N. Engl. J. Med.,* 1963, v269, 709.

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Supersensitivity to Barium in the Denervated Nictitating Membrane of the Spinal Cat.* (29564)

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Recent research with the nictitating membrane of the cat indicates that the supersensitivity produced in that organ by denervation involves two or more independent mechanisms(1-3). The supersensitivity which follows decentralization or reserpine is moderate in degree and relatively nonspecific since the sensitivity is increased to an equal degree to both norepinephrine and acetylcholine(3,4). The mechanism involved in this nonspecific supersensitivity apparently is identical to one of the mechanisms of denervation supersensitivity(3). The purpose of this communication is to demonstrate that this nonspecific supersensitivity is extended to a third substance, barium, in addition to norepinephrine and acetylcholine.

Methods. Cats of 1.5 to 3.0 kg body weight and of either sex were used. The cats were pithed under ether anesthesia using the spinal method of Burn(5). Following this operation the animals were maintained on artificial respiration and ether discontinued. The responses of the right nictitating membrane were recorded isometrically with a

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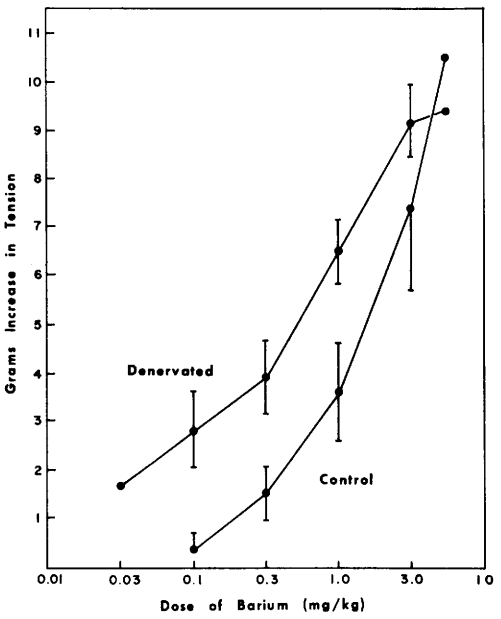

FIG. 1. Mean dose-response curves in denervated and control nictitating membranes of spinal cats. Vertical bars represent standard errors of means.

Grass strain gauge and polygraph. Resting tension was maintained at 7.5 ± 0.5 g and responses were measured as increases in tension above this level. The carotid arterial pressure was also recorded. Injections of barium were given intraarterially through the central end of the lingual artery into the external carotid artery(4), such that high concentrations could be delivered directly to the nictitating membrane without marked systemic effects. No injection was given until the nictitating membrane and blood pressure had recovered from the effects of the preceding injection. The volume of injection (0.1 ml) was constant for all injections. In 5 cats, the nictitating membrane was denervated by surgical removal of the right superior cervical ganglion 12 to 13 days before the experiment. Seven unoperated cats served as controls. Doses of barium chloride are recorded as free barium ion. The statistical significance of the results was determined using Student's t test.

Results and discussion. Fig. 1 presents the mean dose-response curves of nictitating membranes to barium in control and chronically denervated preparations. The curve representing responses of the denervated membranes lies to the left of the control curve, indicating that supersensitivity to barium developed following denervation. The differences in mean response were significant ($P<0.05$) at the 1.0 mg/kg dose and all lower doses. The differences at the 3.0 and 5.0 mg/kg doses were not significant ($P>0.2$).

Denervation supersensitivity in the nictitating membrane of the cat is characterized by a remarkable degree of nonspecificity. Chronic denervation of the organ has been shown to result in supersensitivity to the following diverse group of agents: catecholamines(2), acetylcholine(3,4), 5-hydroxytryptamine(6), tryptamine(6) and now barium. Any theory which attempts to explain the mechanism of chronic supersensitivity of the nictitating membrane must take into account the striking degree of nonspecificity.

Summary. A study of the response of the nictitating membrane of the spinal cat to barium, administered by close intraarterial injection, has demonstrated that chronic denervation produces supersensitivity to barium. These results accentuate the very nonspecific nature of chronic supersensitivity in this preparation.

1. Trendelenburg, U., Muskus, A., Fleming, W. W., Gomez Alonzo de la Sierra, B., *J. Pharmacol. exp. Therap.*, 1962, v138, 181.

2. Trendelenburg, U., *Pharmacol. Rev.*, 1963, v15, 225.

3. Fleming, W. W., *J. Pharmacol. exp. Therap.*, 1963, v141, 173.

4. Trendelenburg, U., Weiner, N., *ibid.*, 1962, v136, 152.

5. Burn, J. H., *Practical Pharmacology*, Blackwell, Oxford, 1952.

6. Schaeppi, U., *J. Pharmacol. exp. Therap.*, 1963, v139, 330.

Received June 22, 1964. P.S.E.B.M., 1964, v117.