sponse appeared to be diminished.

Additional study is required for a complete understanding of the mechanism by which endotoxin influences the delayed hypersensitivity reaction called contact sensitivity.

Summary. The data presented show that intravenous administration of bacterial endotoxin modify the delayed hypersensitivity reaction commonly called contact sensitivity. The effect on the reaction was dependent both upon timing of the injection and dose of endotoxin used.

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1. Chase, M. W., J. Allergy, 1957, v28, 30.
2. Crowle, A. J., Science, 1959, v130, 159.
3. ———, Delayed Hypersensitivity in Health and Disease, C. C Thomas Co., Springfield, Ill., 1962.
4. Crowle, A. J., Hu, C. C., J. Immunol., 1965, v94, 555.
5. Floersheim, G. L., Int. Arch. Allergy, 1965, v26, 340.
6. Guld, J., Roelsgaard, E., Bull. Wld. Hlth. Org., 1965, v33, 345.
7. Jaques, K., Immunopathol., 1958, v1, 237.
8. Karush, F., Eisen, H. N., Science, 1962, v136, 1032.
9. Lowney, E. D., J. Invest. Dermatol., 1965, v45, 378.
10. Merrit, K., Johnson, A. G., J. Immunol., 1965, v94, 416.
11. Pitkin, D. H., Proc. Soc. Exp. Biol. and Med., 1965, v120, 350.
12. Schwartz, R. S., Fed. Proc., 1966, v25, 165.
13. Speirs, R., Blood, 1963, v22, 363.

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Influence of Stress on Granuloma Formation.* (31815)

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Studies in our laboratory have shown stress to decrease susceptibility of mice to viral infections(1,2), to retard viral clearance(3) and to suppress interferon production(4). Christian and Williamson(5) showed that stress of crowding decreased significantly foreign body granuloma formation in mice. The present study was undertaken to determine the influence on foreign body granuloma formation(6) by the previously employed forms of stress(1,2,3,4).

Materials and methods. Nine-week-old male Swiss, Webster BRVS strain, mice were used. Each foreign body granuloma was produced by subcutaneous implantation of a single commercial dental cotton pellet (Richmond #4) between the scapulae. This procedure was done under ether anesthesia, and the incision was closed with a wound clip which was removed after 48 hours. Two forms of stress were employed: high intensity sound (123 db) and avoidance-learning in a shuttle box apparatus. These have been described(2,7).

The mice were divided into 3 groups: Group I was given sound stress for 5 days before implantation and avoidance-learning stress for 14 days after implantation; Group II was given sound stress for 5 days before and 14 days after; Group III received no stress. On the 14th day after implantation, the granulomas were excised, trimmed of their tissue adhesions, and weighed. They were then fixed in 10% formalin, imbedded, sectioned at 5μ thickness, stained with hematoxylin and eosin, and graded on an arbitrary scale of 1-5 on the basis of macro- and microscopic appearance of the capsule and on the degree of cellular infiltration into the cotton pellet. The following scores were used for the capsules: 1 = none, 2 = some cellular adhesion, 3 = partial thin, 4= partial thick,

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TABLE I. Granuloma Analysis in Mice Subjected to Combined and Uncombined Stresses.

Group	No. of mice	Mean wt (in mg) ± SD	% decrease in wt	p value*	Mean scale values† based on Macro capsular exam	Micro capsular exam	Cellular infiltration
I	44	34.6 ± 7.9	35.7	<.001	2.4	3.5	3.3
II	56	37.4 ± 8.7	30.5	<.001	2.7	3.4	3.6
III	57	53.8 ± 12.4	—	—	4.5	4.6	4.3

Group I: Sound and avoidance-learing stress. Group II: Sound stress only. Group III: Controls.

* p values obtained by t test as compared to controls (performed by Health Sciences Computing Facility, UCLA Medical Center).

† Based on arbitrary scale described under *Materials and methods.*

S.D.—Standard deviation.

and 5 = complete thick capsule; for the degree of cellular infiltration: 1 = none, 2 = some marginal, 3 = much marginal with some central, 4 = much throughout, and 5 = dense throughout.

Results and discussion. The results of these experiments are summarized in Table I. Highly significant decreases in mean granuloma weights were observed in both stress groups as compared to the controls. The differences between the sound and combined stress groups were insignificant. Our earlier observations on changes in susceptibility had suggested a greater response in mice subjected to combined stress(4); this was not seen in these experiments.

Histological examination also demonstrated significant differences between granulomas from stress and control mice (Fig. 1). The capsules were narrow in both stress groups with only slight cellular infiltration into the cotten pellet. Granulomas from the control animals had wide capsules which were poorly differentiated from the dense marginal cellular infiltration. In both stress groups, cotton fibers were still visible, and the centers of most of these granulomas showed very little digestion of cotton, while the centers of the control granulomas were often nearly devoid of fibers. The histologic findings are in accord with those of Smith *et al*(8) who noted a moderate repression of the inflammatory response in animals pretreated with sound stress. Toivanen *et al*(9) have also reported the retardation of wound healing in sound stressed rats. Whether or not the above noted suppression of the inflammatory response is related to changes in susceptibility of such stressed mice to viral infections(1,2) cannot be determined from these data.

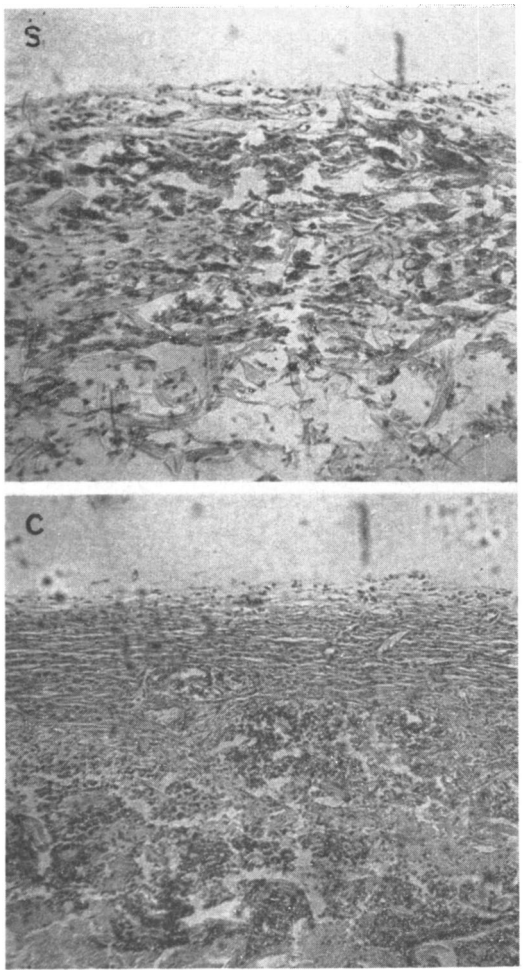

FIG. 1. Histological appearance of capsule and marginal area of granulomas which were removed after 14 days from stressed (S) and control (C) mice. Magnification: 50 ×.

Summary. Mice subjected to sound stress or a combination of avoidance-learning stress and sound stress showed a highly significant decrease in their ability to produce foreign body granulomas against subcutaneously-implanted cotton pellets. Granulomas in stressed mice were smaller with a general inhibition of capsule formation and cellular infiltration as compared to control mice.

1. Jensen, M. M., Rasmussen, A. F., Jr., J. Immunol., 1963, v90, 21.

2. Rasmussen, A. F., Jr., Marsh, J. T., Brill, N. Q., Proc. Soc. Exp. Biol. and Med., 1957, v96, 183.

3. Yamada, A., Jensen, M. M., Rasmussen, A. F., Jr., ibid., 1964, v116, 677.

4. Chang, S. S., Rasmussen, A. F., Jr., Nature, 1965, v205, 623.

5. Christian, J. J., Williamson, H. O., Proc. Soc. Exp. Biol. and Med., 1958, v99, 385.

6. Meier, R., Schuler, W., Desaulles, P., Experientia, 1950, v6, 469.

7. Jensen, M. M., Rasmussen, A. F., Jr., J. Immunol., 1963, v90, 17.

8. Smith, L. W., Molomut, N., Gottfried, B., Proc. Soc. Exp. Biol. and Med., 1960, v103, 370.

9. Toivanen, P., Hulkko, S., Naatanen, E., Ann. Med. Exp. Fenn., 1960, v38, 343.

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The Potentiation of Pressor Responses to Tyramine by a Number of Amphetamine-Like Compounds. (31816)

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Eble and Rudzik(1) found that both amphetamine and reserpine enhance the acute pressor response to tyramine in the anesthetized dog. However, when amphetamine and reserpine were both given, in either order, the pressor response to tyramine was diminished (Eble and Rudzik(2)). Results of experiments designed to determine the structural requirements of compounds producing such a potentiation of tyramine and an antagonism of tyramine when these compounds are given in combination with reserpine are reported here.

Methods. Mongrel dogs weighing between 10 and 21 kg, unselected as to sex and anesthetized with sodium pentobarbital (32 mg/kg, i.v.), were used for these studies. Supplemental doses of 3.2 mg/kg were given as needed. Blood pressure from the carotid or femoral arteries was measured with a Statham transducer (Model P-23AC).

Drug injections were made *via* a polyethylene tube passed 3 to 5 cm into a femoral vein. The following compounds were used: tyramine hydrochloride, *d*-amphetamine sulfate, *l*-amphetamine sulfate, *p-cl*-amphetamine, phentermine hydrochloride, propylhexedrine, methamphetamine hydrochloride, prenylamine acetate, chlorphentermine hydrochloride, phenylpropylmethlamine, β-phenylpropyl amine, phenylpropanolamine, hydroxyamphetamine, and reserpine.

Results. The effects of a series of compounds, structurally related to amphetamine, on the pressor response to tyramine before and after reserpine are shown in Table I. The pressor response to tyramine was potentiated by all the compounds tested with the exception of prenylamine (Compound XI).

The administration of reserpine (1 mg/kg i.v.) after the test compound either potentiated the pressor response to tyramine further, antagonized it or had little or no effect on it. In our experiments the tyramine was administered 30-90 minutes after the reserpine, allowing for base blood pressure to return to pre-reserpine levels. Reserpine administered by itself markedly potentiated the pressor response to tyramine (Compound I). After either the *d*- or *l*-isomer of amphetamine (Compounds II and III) and reserpine the pressor response to tyramine was markedly reduced. Compounds substituted on the phenyl ring (Compound IV) or with an additional methyl group on the α-carbon (Compound V) also caused a decrease in the response to tyramine after reserpine. However,