There was no evidence of toxicity even in the mice fed 1000 μg of streptomycin daily for 4 to 6 months. No significant difference was apparent between the streptomycin-fed mice and controls in regard to percentage fertility; size of litters and number of mice weaned. The first litters of mice fed various levels of streptomycin showed no significant differences in weight gains but the second litters at the higher levels made greater gains as a rule than controls and those at low level intakes.

First Litters. Weight gains of first litters from mice fed streptomycin were similar to those of control mice fed stock diet.

Second Litters. The mice fed at a daily level of 1000 μg of streptomycin made greater gains than control mice and those given 50 μg daily. At the 400, 200, and 100 μg levels, the trend toward greater weight gains is evident (Table III). A possible explanation for the greater gain in weight of second litters may be that the mothers had obviously been on the streptomycin-containing diet longer, at the time of their birth than when the first litters were produced. Work is now in progress to check the influence of the 1000 μg level as well as 3000, and 6000 μg daily intake of streptomycin on weight gains of young litters of mice.

No gross pathology was evident in several mice sacrificed and autopsied from each group. Histological examination‡ of tissues from mice fed 1000 μg of streptomycin daily revealed no significant changes.

A study of the intestinal bacterial flora of mice receiving 1000 μg of streptomycin daily and of control mice is in progress.

Summary. No toxic effects were observed in albino mice fed streptomycin at daily levels of 1000, 400, 200, 100, and 50 μg for periods of one to 6 months. These levels had no significant influence on percentage fertility, litter size, number of young mice weaned, and general condition of the animals. Although no influence was evident at the various levels of streptomycin in the weight gains of first litters of mice, a greater increase in weight occurred in second litters at higher levels compared to second litters of the control and 50 μg groups.

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Histamine and Anaphylactic Shock in the Mouse.*

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Anaphylaxis may be defined as an acute and frequently damaging reaction of a sensitized animal to the specific antigen used in sensitization. This phenomenon has been studied in many animals but only recently has it been described adequately in mice.[1] The experiments cited below not only confirm that mice are susceptible to anaphylactic shock but also indicate that they are refractory to histamine shock.

White mice of an inbred *Olitsky* strain varying in age from 2 to 6 months were sensitized by intraperitoneal injection of 1 ml of egg white (diluted 1:4 with normal saline) every second day to a total of 4 ml, following the procedure of Weiser, Golub and Hamre.[1] Twelve days after the last sensitizing injection anaphylactic shock was produced by injection of 1 ml of the antigen into the tail vein.

The anaphylactic shock syndrome in the mouse was characterized by sluggishness, wobbling gait, dyspnea, cyanosis, paralysis of extremities, loss of sphincter control,

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1 Weiser, R. S., Golub, O. J., and Hamre, D. M., *J. Inf. Dis.*, 1941, **68**, 97.

struggling convulsions and death. These symptoms never appeared in less than 5 minutes and never terminated in death in less than 11 minutes, nor in more than 1 hour.

Of 53 sensitized animals given a shocking dose of the antigen, 49 showed some anaphylactic reaction and of these 14 died. These animals were tested in groups of 14, 7, 10 and 22 with death rates ranging from 20 to 28%. A minimal reaction was observed in only one of 20 nonsensitized controls which were similarly inoculated with 1 ml of the antigen.

Thirty-five mice were inoculated intravenously with 1 ml of a 1% solution of histamine diphosphate in distilled water (about 400 mg/kg body weight). None of these animals developed clinical evidence of reaction, but one was found dead of unknown cause one hour after injection. It appears questionable whether this fatality was due to histamine shock, and in any case it may be concluded that the mice used in these experiments were essentially refractory to histamine. These conclusions are not jeopardized by earlier reports[2,3] in which deaths that were attributed to histamine occurred instantaneously on injection and were, therefore, probably embolic. Furthermore, the absence of controls and the small number of animals used tend to invalidate those earlier findings.

Twenty-five mice sensitized to egg white were given intravenously 1 ml of the antigen and 5 mg of histamine in 0.25 ml of distilled water. Half the animals were injected with the egg white first, followed within 5 minutes by the histamine, this order being reversed with the others. Results in both groups did not differ significantly from those observed in the previous experiment where antigen alone was used as a shocking agent.

TABLE I.

Material injected and animals used	No. of animals	% showing at least minimal shock	% dying
Egg white in sensitized mice	53	92	26
Egg white in non-sensitized mice	20	5	0
Histamine in non-sensitized mice	34*	0	0
Egg white and histamine in sensitized mice	25	96	12

* One mouse found dead of unknown cause one hour after injection not included in this summary.

The results of these experiments are summarized in Table I.

This failure of mice to react to histamine while showing susceptibility to anaphylactic shock could not be explained by an antihistamine substance in mouse serum. Seven guinea pigs were injected intravenously with 0.5 mg of histamine diphosphate in normal saline (an experimentally determined M.L.D.), and 6 others with a similar dose of histamine in a 1:2 dilution of normal mouse serum, this mixture having stood at room temperature for 10 to 60 minutes before administration. The frequency and severity of histamine shock in these 2 groups appeared equal. Mouse serum alone had no apparent effect when injected intravenously into 3 guinea pigs.

Similarly, the difference between mice and guinea pigs in susceptibility to histamine did not appear to be explainable on the basis of an histamine-activating factor in guinea pig serum, for guinea pig serum mixed in equal parts with a 1% histamine diphosphate solution and injected intravenously into 10 mice produced no reaction.

Summary. In this series of experiments it has been suggested that the mouse is highly resistant to histamine shock although regularly susceptible to anaphylaxis; that histamine administered either immediately before or after the antigen failed to potentiate the reaction; and that mouse serum *in vitro* failed to detoxify histamine for the guinea pig while guinea pig serum *in vitro* failed to make histamine toxic for the mouse. Further studies of the pathogenesis of anaphylactic shock in the mouse are in progress.

It is therefore concluded that there is no evidence at the present time that histamine plays a direct or significant role in anaphylactic shock in the mouse.

[2] Voegtlin, C., and Dyer, H. A., *J. Pharm. and Exp. Therap.*, 1924, **24**, 101.

[3] Schmidt, G. W., and Staehlin, A., *Z. f. Immunitatsforsch.*, 1929, **60**, 222.