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Effect of Cortisone upon Passive Anaphylaxis in the Guinea Pig.* (18858)

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The mechanism of action of cortisone upon diseases of allergy or hypersensitivity(1) is unknown, though the marked effect of this hormone upon tissue proliferation certainly contributes significantly to this suppressive or masking effect(2-4). The anaphylactic response of sensitized tissues, however, is independent of an inflammatory reaction or cellular proliferation, and though quantitative studies of anaphylaxis in animals sensitized by active immunization are unsatisfactory because of the tremendous variation in the ability of individual animals to produce antibodies to a similar stimulus and our inability to measure the total antibody produced by or present in an organism at a given moment, Kabat and his coworkers(5-7) have shown that quantitative studies of passive anaphylaxis are very reproducible. Although several investigators(8-13) have obtained varying effects with cortisone in anaphylaxis, the application of these quantitative technics (5-7) with challenge *in vitro* by the method of Schultz(14) and Dale(15) has brought forth further significant data.

Methods. Virginal female guinea pigs weighing 250 ± 50 g and on *ad lib.* feeding were used in all experiments. Sensitizing injections were given intravenously using the veins on the ventral surface of the hind legs. The antibody used was in the form of rabbit antisera to type III pneumococci, calibrated by the method of Heidelberger and Kendall

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(16). All animals were sacrificed by a blow to the head 48 hours following sensitization. The uterine and bowel strips were mounted in a 70 ml bath of Ringer-Locke's solution according to the technic of Dale(15). The experiments were carried out immediately following the death of the animal, except for occasional experiments in which the tissues were chilled prior to use. One uterine horn and one bowel strip were usually mounted together in the same bath and recorded simultaneously, thereby serving as controls for one another. The bowel strips were obtained from the ileum and jejunum of the guinea pigs, and no bowel strip was considered to be insensitive until at least three strips from different sections of the lower small bowel gave a negative response. All bowel and uterine strips showing a negative reaction were tested for viability with histamine at the conclusion of each experiment. The antigen, purified Specific Soluble Substance III, was shown to be non-irritating to normal muscle strips on many occasions. The average challenging dose of 20 γ was added to the bath with a pipette. The pipette was inserted to the bottom of the bath and then slowly withdrawn as the antigen was allowed to flow into the bath, thus facilitating better distribution. All contractions were recorded on revolving smoked drums. The injections of cortisone or control solutions were started two days prior to sensitization and continued until sacrifice of the animals, 2 days after sensitization. The cortisone‡ treated animals were injected with 2.5 mg of the hormone in the deep subcutaneous tissues morning and night except during some of the early experiments when only one injection each day of 5 mg was given. In 9 animals cortisone was not started until 18 hours after the sensitizing injection.

Results. Table I summarizes the effect of cortisone upon the passive sensitization of uterine smooth muscle as measured by the Schultz-Dale technic. In no animal was sensitization affected by cortisone.

Table II summarizes the rather striking effect of cortisone upon the passive sensitization of guinea pig small bowel. Of the 21 controls, 19 showed good sensitization, while only 2 failed to demonstrate sensitivity. In the cortisone treated group, two-thirds of the cases(14) showed an absence of sensitization and only one-third(7) demonstrated definite sensitivity. In 8 of 9 animals treated with cortisone 18 hours after the sensitizing injection had been given, the bowel strips demonstrated good responses to the challenging antigen.

Five of the control animals were injected twice daily with the vehicle used for suspending the cortisone solutions and 6 others simultaneously received injections of normal saline. All of these animals showed sensitization except one in the normal saline group. Six

TABLE I. Effect of Cortisone upon Passive Sensitization of Guinea Pig Uterine Muscle.

Antibody N given	Controls	Cortisone treated, 96 hr	Cortisone treated, 30 hr
25 γ			
Contracting	17	9	6
Non-contracting	0	0	0
50 γ			
Contracting	4	11	2
Non-contracting	0	0	0
100 γ			
Contracting	0	1	1
Non-contracting	0	0	0
Totals			
Contracting	21	21	9
Non-contracting	0	0	0

TABLE II. Effect of Cortisone upon Passive Sensitization of Guinea Pig Small Bowel.

Antibody N given	Controls	Cortisone treated, 96 hr	Cortisone treated, 30 hr
25 γ			
Contracting	15	2	5
Non-contracting	2	7	1
50 γ			
Contracting	4	4	2
Non-contracting	0	7	0
100 γ			
Contracting	0	1	1
Non-contracting	0	0	0
Totals			
Contracting*	19	7	8
Non-contracting*	2	14	1

* Statistical probability of this being chance variation less than 1 in 1000, as determined by the Ohi square test.

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‡ Merck brand Cortone.

other animals were given cortisone for 96 hours, but no sensitizing injection. They showed no abnormal reactions to the challenging antigen.

Both animals in the control series showing no bowel sensitization received a sensitizing dose of 25 γ of antibody N while 5 of the 7 cortisone-treated animals showing definite sensitization received at least twice this dosage of antibody, an amount never failing to sensitize control animals. Although exactly comparable amounts of antibody were not used in all experiments, it will be noted that the variations were in the direction of less antibody injected into the controls and more antibody given the cortisone-treated animals. Such variation should add further weight to the recorded figures. The amounts of antigen used for challenging were also varied in some instances, again in such a manner as to make the experimental results more significant.

Discussion. The mechanism of attachment or binding of antibody molecules to cells (or of any body protein to cells) is unknown, though it is likely that specific binding and not simple adsorption of antibody upon the cell surface is necessary for sensitization to anaphylaxis(17,18). The inability of cortisone to interfere with the anaphylactic response of bowel muscle when started 18 hours after the antibody was given and the marked sensitivity of the uterine horns in the animals showing non-sensitized bowel strips suggest that cortisone may have interfered with the association of the antibody with the smooth muscle of the gut. The data do not suggest whether such interference is a specific action upon the binding of protein molecules to the cell or whether it is merely a manifestation of altered or depressed cellular function.

The amount of antibody N used for sensitization in most of these experiments, (25 γ), was chosen because this is the amount which will consistently passively sensitize 250 g guinea pigs to fatal anaphylaxis when given 48 hours before challenge. Although this quantity of sensitizing antibody is less than that used by others, it was chosen because cortisone does not exert all or none effects, and large excesses of antibody will mask cortisone actions.

We have no data to explain the paradox of the suppressive action of cortisone upon the smooth muscle of the gut with no demonstrable effect upon the smooth muscle of the uterus. (One can only speculate on whether the uterus, an organ which meets its greatest stress during labor, a time when large amounts of cortisone-like substances are circulating, has been spared an inhibitory metabolic effect of these hormones, while the bowel, an organ put physically at rest during stress, may also be metabolically depressed). The data do, however, suggest that cortisone may so alter some tissues that although adequate antibody is present for sensitization, no sensitization is elicited.

Summary. Administration of cortisone prior to and subsequent to sensitization of the virginal female guinea pig with known quantities of antibody, inhibited the response of the smooth muscle of the small bowel to antigen, but failed to alter the sensitization of uterine smooth muscle.

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