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Mechanisms of Action of Cortisone in Resistance to Sequels of Anaphylaxis

By **Th. F. Dougherty**

It seems clear from the topics considered by the several speakers at this Symposium that the eventual common aim of our researches is to obtain information concerning the etiology of the connective tissue diseases. There are many possible areas of disagreement concerning the classification of such alterations and, indeed, even concerning the integration of facts at hand relating to the etiology of various diseases which we tend to incorporate under the inclusive term «connective tissue disease». Thus, it is essential to delineate clearly the frame of reference which one chooses to regard as a process common to the diverse clinical manifestations produced by changes in the structure of connective tissue. The search for a unified concept of disease leads one to consider that the inflammatory response represents the sole biological event which is common to the vast array of superficially dissimilar parenchymatous alterations. With this point-of-view in mind, debatable though it might be, it becomes evident that most connective tissue diseases are inflammatory responses to phlogogenic stimuli.

There are two general theories concerning the etiology of the connective tissue diseases. According to one point of view these alterations are due to an imbalance in the secretions of the adrenal cortex (1). On the

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other hand, it seems fairly clear that hypersensitivity (2) is a disposing factor in the development of lesions identical to those supposedly produced by hormone imbalance. A third point of view previously proposed by the author (3, 4) states that the allergic response, one fundamental etiologic mechanism in connective tissue disease, is moderated by secretions of the adrenal cortex.

In order to subject this theory to investigative procedure we have attempted to relate by quantitative methods the relative importance of secretions of the adrenal cortex and of the degree of hypersensitivity to the development of the manifestations of allergic phenomena. In all experiments independent variables such as the amount and nature of the antigen used for sensitization, species of animals sensitized, and the procedures for eliciting allergic phenomena were first standardized. Mice of the same strain, age and sex were used in all of the experiments. Since mice are virtually completely resistant to fatal anaphylactic shock (4, 5) and to localized allergic inflammation (Arthus phenomena), the mouse proved to be an ideal test animal for the quantitative determination of the roles played by various types of hormones in moderating the sequels of the antigen-antibody union.

It is apparent from the data presented in detail elsewhere (4, 6, 7, 8) that cortisone and compound F provide significant protection against both generalized fatal and localized (7, 8, 9) anaphylaxis. Desoxycorticosterone not only provided no such protection (4, 7, 8, 9), but actually minimized the anti-anaphylactic effects of the C-11 oxysteroids. It was observed that this action of desoxycorticosterone was not mediated by its pituitary-suppressing activity since it antagonized the anti-anaphylactic action of cortisone in adrenalectomized animals. By using replacement therapy in hypersensitive adrenalectomized mice, it was demonstrated that allergy whether manifested by generalized or localized anaphylaxis is not an all-or-none phenomenon. «It is, rather, a graded response which under uniform conditions of sensitization, depends upon the challenging homologous antigen dose, and upon the quantitative relation between the dose of antigen and that of the protective agent, namely secretions of the adrenal cortex» (8). In order to find the link in the chain of events where adrenal cortical steroids exert their anti-anaphylactic action, it is necessary to reiterate certain concepts.

Hypersensitivity describes a state of hyper-reactivity to a specific stimulus. Allergy, whatever its manifestation, is a response to a *specific* stimulus applied to an organism having *specific* hypersensitiveness. An allergic inflammatory response is similar in its characteristics to inflammation resulting from stimuli other than the antigen antibody union.

Allergy differs from other types of phlogistic responses in that the stimulus which may produce inflammation in non-hypersensitive animals induces a far greater response in the organism which has hypersensitiveness to the specific phlogogenic agent. Thus, it is evident that adrenal cortical hormones could exert their anti-anaphylactic effects in either one or both of two ways. They could reduce the degree of hypersensitiveness or they could act directly on the allergic response. Careful consideration of the evidence for each of these possible modes of action has resulted in the suggestion that cortisone may moderate allergy by diminishing both hypersensitiveness and the inflammatory manifestations of allergy (8). An evaluation of the relative importance of these two mechanisms of anti-anaphylactic action depends upon the quantitative interrelationships of several variables which influence the degree of the allergic response.

Among these variables are the extent of hypersensitiveness, the amount and nature of the specific allergen, the duration of the hypersensitive state and the amount of cortisone available. As we have pointed out in numerous publications, the results of our investigations suggest that cortisone has a general antiphlogogenic action (4, 9). Therefore, the anti-allergic effect of this hormone is not considered to be a specialized function of cortisone, but rather, it is simply a manifestation of the capacity of this hormone to moderate the inflammatory response regardless of the inflaming stimulus. By means of a method by which the degree of in-

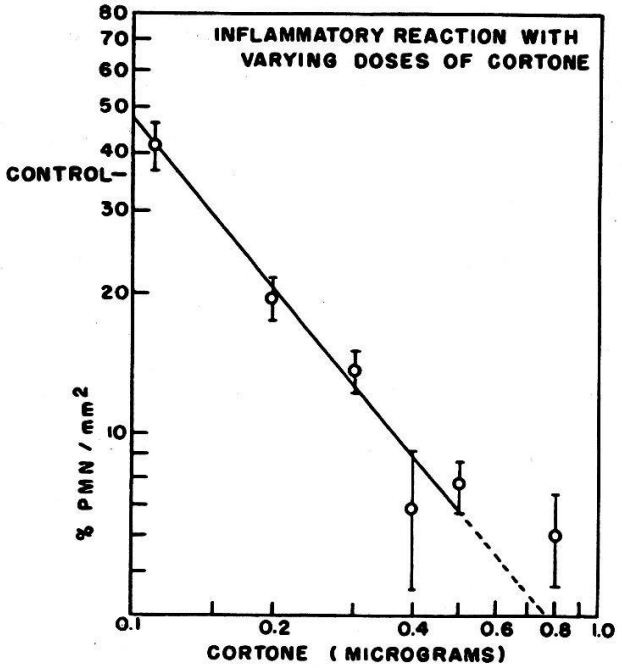

Fig. 1. Log of the percent of PMN's/mm² plotted against log of graded doses of Cortone Eighty-four animals were used in the experiment. Mean values were obtained from a minimum of fourteen separate experiments. Vertical bars indicate one standard error.

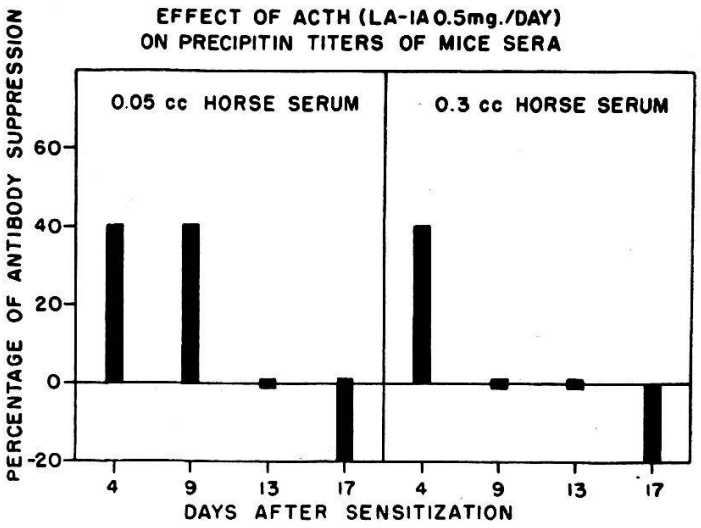

Fig. 2 and 3. Suppression of antibody synthesis in immunized mice given ACTH. Antibody suppression is indicated by percentage of immunized ACTH-treated animals having no circulating antibody as compared to equal numbers of immunized non-ACTH treated animals. At least twenty hormone-treated animals were used in each experiment. Equal numbers of control animals were employed.

flammation is assayed according to the percentage distribution of PMN's/mm of inflamed loose connective tissue following local application of a standard inflaming stimulus in the presence or absence of hormones of the adrenal cortex, we have been able to assay the antiphlogistic potency of various adrenal cortical hormones (8, 10, 11). With the aid of this antiphlogistic test it was observed that different agents (traumatic [9], chemical [9, 10], bacterial [7], bacterial toxins [12], and anaphylotoxins [9]) stimulate the entrance of different numbers of nonautocthonous cells into inflamed areolar tissue at various standardized times following topical administration of the different inflaming agents. When the type and amount of phlogogenic stimulus is held constant, adrenalectomy increases and cortisone and compound F profoundly decrease the cellular manifestations of inflammation (9). The inhibitory effect of cortisone involves both the alterative and the infiltrative stages of inflammation (9). Thus, local fibroblasts are protected from damage in the early stages. Desoxycorticosterone exerted no antiphlogogenic action when any of the above mentioned stimuli were used. Indeed, as was the case in the experiments concerning hormone protection against anaphylactic shock, DCA displays an anticortisone effect.

When histamine diphosphate (0.2 mg in 0.2 cm^3 saline) mixed with graded amounts of cortisone (0.25 μg to 50 μg) was injected subcutaneously, the degree of inflammation was markedly reduced. If the dose of histamine is held constant and graded amounts of cortisone (0.125 μg to 0.5 μg) are also given it may be seen that six hours after local injection

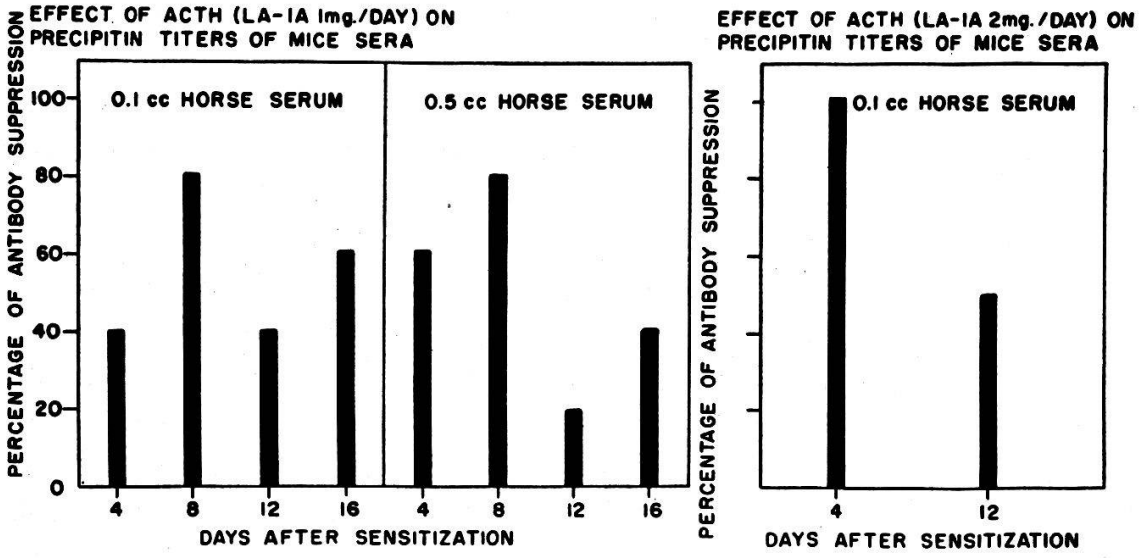

Fig. 3.

of this mixture to adrenalectomized mice, there is an inverse relationship between the percentage of PMN's in the inflamed tissue and the amount of cortisone employed (fig. 1). It should be emphasized that this dose response relationship exists only over a small range of dosages. Larger amounts of hormone (25 μg to 50 μg) tended to allow the degree of inflammation to return to control values (7, 8). This observation should be taken into consideration in clinical application of cortisone therapy.

In summary, it is concluded that the degree to which cortisone and compound F moderate inflammation is determined by two reciprocally interrelated factors: first, the strength of the inflaming stimulus, and second, the amount of cortisone or compound F available at the site of inflammation.

The antiphlogistic action of cortisone may explain the immediate anti-anaphylactic effects of this hormone. However, when one considers the quantitative nature of the antiphlogistic action of cortisone it is apparent that the degree of hypersensitivity must directly influence the amount of cortisone required to moderate allergic inflammation. In view of the fact that several authors have reported that ACTH and cortisone suppress the production of antibodies (12, 13, 14) it seemed possible that secretions of the adrenal cortex might be playing a dual role in reducing allergic inflammation by decreasing hypersensitiveness as well as exerting an antiphlogistic action.

First of all, experiments were performed which were designed to ascertain the degree of hypersensitivity produced by graded amounts of antigen and graded doses of ACTH. The degree of antibody suppression

was estimated by a quantal response technique; instead of attempting to establish the amount of circulating antibody in each of the experimental animals, the degree of suppression was evaluated by ascertaining the percentage of ACTH, treated immunized animals as compared with control non-treated immunized mice which displayed a precipitin reaction in 1:1 dilutions of antigen and blood sera. Thus, for all practical purposes the degree of suppression was expressed as the percentage of animals in which there was an all-or-none suppression of circulating antibody. Single injections of graded amounts of antigen were administered intravenously and graded amounts of ACTH were given subcutaneously to the experimental groups. The data obtained from these investigations indicate that the degree of suppression of antibody formation is dependent upon the amount of antigen and ACTH administered (figs. 2, 3). The more antigen that is used to immunize, the more ACTH is required to suppress antibody synthesis (8, 14). Further, it was found that in spite of continuous hormone treatment the degree of suppression diminished as the time interval of antibody formation was prolonged. Although there was almost complete suppression of antibody synthesis as judged by the amount of circulating antibody when large doses of ACTH were given, it was found that these animals were as susceptible to anaphylactic shock as non-hormone treated immunized mice (8). This indicates that although the synthesis of antibody was markedly diminished it was not altogether suppressed since there was sufficient antibody present in the tissue to allow anaphylactic shock to occur.

Although the evidence to date suggests that cortisone does not prevent the antigen antibody union directly either *in vivo* or *in vitro* (8), it is able by suppressing antibody production to accomplish a similar result. By reducing the concentration of one of the participants in the antigen antibody union, and thereby the potentiality for allergic inflammation, less hormone would be required to inhibit the immediate phenomena of acute inflammation. The conflicting reports concerning the capacities of ACTH or cortisone to inhibit the Arthus phenomenon may be resolved by taking into account the facts reported here, i.e. that both the antiphlogistic and antibody suppressing actions of these hormones are dose response phenomena. The implications of these conclusions are legion. For example, in order to explain the etiology of connective tissue diseases it is not necessary to assume that the adrenal cortex elaborates a hormone which is antagonistic to either of the two above mentioned functions of cortisone-like compounds. Although such hormones may be part of the secretions of the adrenal cortex and an imbalance in the proportion of these antagonistic hormones may occur

in patients having connective tissue disease, it should be stressed that such antagonistic hormones have not been isolated from adrenal cortical secretions in either healthy or diseased individuals. Whether or not connective tissue disease occurs when an imbalance of hormones exists, we are still faced with the fact that connective tissue diseases are essentially inflammatory phenomena and that cortisone moderates the inflammatory response but does not eliminate the inflaming stimulus.

1. *Selye, H.:* Brit. med. J. **1949,** 1129. – 2. *Rich, A. R.,* and *Gregory, T. E.:* Bull. Hopkins Hosp., Baltim. **72,** 65 (1943). – 3. *Dougherty, T. F.:* Anat. Rec. (Am.) **103,** 3 (1949). – 4. *Dougherty, T. F.:* Amer. Acad. of Science. Symposium on Pituitary-Adrenal Function, 1950, p. 79. – 5. *Mayer, R. L.,* and *Brousseau, D.:* Proc. Soc. exper. Biol. a. Med. (Am.) **63,** 187 (1946). – 6. *Dougherty, T. F.,* and *Dougherty, J. H.:* Abstr. Anat. Rec. (Am.) **106,** 2 (1950). – 7. *Dougherty, T. F., Josiah Macey, Jr. Foundation:* Trans. Adrenal Cortex. New York, 1951, p. 88. – 8. *Dougherty, T. F.:* Recent Advances in Hormone Research (in press). – 9. *Dougherty, T. F.,* and *Schneebeli, G. L.:* Proc. Soc. exper. Biol. a. Med. (Am.) **75,** 854 (1950). – 10. *Dougherty, T. F.:* Fed. Proc. **10,** 1 (1951). – 11. *Schneebeli, G. L.,* and *Dougherty, T. F.:* Amer. Physiol. Soc. (in press). – 12. *Bjørneboe, M., Fischel, E. E.,* and *Stoerck, H. C.:* J. exper. Med. **93,** 37 (1951). – 13. *Germuth, F. G., Jr., Oyama, T.,* and *Ottinger, B.:* J. exper. Med. **94,** 2 (1951). – 14. *Hayes, S. P.,* and *Dougherty, T. F.:* Abstr. Amer. Physiol. Soc., 1951.