Protective Effect of Cortisone on Induced Asthma in the Guinea Pig.* (19790)

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Most of the working concepts in human allergy, such as the antigen-antibody reaction and the principles of sensitization and desensitization, have had their origin in observations on anaphylaxis in animals, particularly in the guinea pig. Nevertheless, the prevention of anaphylactic death as a method of studying the value of some therapeutic procedures proposed for allergy has been unreliable. Although fever, localized infections and other stresses frequently relieve asthma and other allergies in man, preliminary experiments showed that artificially induced fever or abscesses in sensitized guinea pigs failed to inhibit anaphylactic death. Then, too, although cortisone or adrenocorticotrophic hormone relieves the symptoms of asthma and many other allergic phenomena in the majority of sufferers, virtually all investigators agree that neither of these hormones is effective in protecting against anaphylactic shock.

This discrepancy between clinical allergy and anaphylactic shock in the guinea pig might be explained either on the basis of a total difference in mechanism or on a difference in degree, such as the intensity of the phenomenon of anaphylactic shock. Certainly the severity of the manifestation of human asthma is usually far removed from the violence of the reaction pertaining in the shocked animal. Indeed, in some instances where the allergic phenomenon was very acute and severe, approaching in intensity that of anaphylaxis in the guinea pig, [allergy to ACTH(1), acute reactions from aspirin(2)], cortisone was found incapable of inhibiting it. With these considerations in mind a procedure in the laboratory animal has been developed which would more closely approach in degree and kind the symptoms encountered in clinical allergy.

Methods. Male guinea pigs of about 350 g average weight were passively sensitized by the intravenous injection of 0.5 ml/kg of guinea pig antiovalbumin serum. These were divided into two groups. After 48 hours the control animals were subjected to an aerosol of a 0.2% solution of the homologous antigen in physiological saline introduced into the chamber at 5 lb pressure. The experimental group of animals was pretreated with 50 mg of cortisone (Cortone Acetate Merck) given as two divided doses, each injected into a gluteal muscle 18 hours before exposure to the antigen by aerosol. The animals were allowed to remain in the chamber and the time of exposure required to produce obvious symptoms of asthma (marked dyspnea and cough) was noted. The animals were removed from the chamber after 10 minutes if during this period no symptoms appeared.

Results and discussion. The results of 100 determinations for each group are shown in Table I. Each series consisted of approximately 50 guinea pigs which were subjected to an identical experiment after a 2 week rest period. The protective effect of cortisone is apparent from the fact that a large number of the hormone-treated animals tolerated the

TABLE I. Effect of Cortisone on Time Required to Produce Asthma by Aerosol in Sensitized Guinea Pigs.

No. of guinea pigs	Trial 1, mean in min.	Trial 2, mean in min.
	Control	
50	2.52	2.51
Mean of total	2.51	
σ^2	1.80	
	Cortisone treated	
50	5.94	4.43
Mean of total	5.19	
σ^2	21.75	
t	5.5	

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aerosol a longer time before the symptoms of asthma occurred. It has been calculated by the method of normal variables that a significant difference exists between the means of the times of exposure of the two groups. A value of $t = 5.5$ was obtained which indicates a significant difference with a confidence limit of better than 98%.

After a further 2 week rest period the control group of guinea pigs became the experimental, hormone-treated group, and vice versa. A significant difference, $t = 4.7$, was calculated for the means of these two groups.

The amounts of antiserum and the concentration of the antigen used were determined experimentally so that the appearance of asthma would neither occur too rapidly nor too slowly in the control group. It was found that the quantity of cortisone used and the time interval allowed to elapse before challenge were important criteria. The animals showed individual variation as to the rapidity with which asthma was produced, effectiveness of hormonal treatment, etc. This variation was not necessarily consistent in a repeated trial. None of the untreated, control guinea pigs failed to show typical symptoms of asthma, however, within the ten minute time limit which was arbitrarily chosen. Most of the cortisone-treated animals which survived a 10 minute exposure failed to show any of the more typical symptoms of asthma after they were out of the chamber; an increased respiratory rate was noticed in some of these animals.

Cortisone has been reported as being effective in suppressing experimental hypersensitivity of the Arthus type(3), in inhibiting the cardiovascular and renal lesions of hypersensitivity in rabbits(4), in preventing the anaphylactoid reaction in rats(5), in protecting mice (6) and rats(7) against anaphylaxis and guinea pigs against reversed passive anaphylaxis(8). The hormone has been found to be ineffective in specific antibody-antigen reactions resulting in anaphylaxis by the usual active and passive technics. The results herein reported indicate that cortisone does play a protective role in the anaphylactic type of hypersensitivity. Preliminary results indicate that ACTH also exerts a somewhat similar effect.

Summary. In a significant percentage of sensitized guinea pigs cortisone was found to be effective in inhibiting or delaying the symptoms of asthma induced by an aerosolized antigen.

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Determination of Quaternary Ammonium Compounds Including Acetylcholine, Tetraethylammonium, and Hexamethonium.*† (19791)

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The increasing pharmacological interest in quaternary ammonium compounds (QAC) stimulated our efforts to develop a method for their determination in biological media. The methyl orange method of Brodie(1,2) and the bromcresol purple method of Woods(3) are general reactions for organic bases, and

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