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CORTISONE PARTIALLY PROTECTS GUINEA PIGS FROM ANAPHYLACTIC SHOCK

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The mechanism of cortisone action in allergy and anaphylaxis is still obscure. The facts established by numerous investigations are that it does not interfere with histamine action or with antigen-antibody union. Our knowledge of its influence on the formation of antibody is still scanty. We have tried to investigate this question.

METHOD

In active sensitization of the guinea pig antibody is formed from the time of the sensitizing injection until it reaches an approximately steady level after 21 days or a little later. We have used egg albumen (0.7-0.8 cc of a 5 % solution of dried albumen were injected intramuscularly) in guinea pigs of 300-400 g weight. After the end of the sensitization period the animals were shocked by egg albumin aerosol and the preconvulsion time measured. The method is described elsewhere (Herxheimer, 1952).

The preconvulsion time is the maximum period for which a sensitized guinea pig can be exposed to (the shock of) an antigen aerosol without the occurrence of convulsions. The preconvulsion time can be increased by shortening the interval between shock exposures—partial desensitization by reducing the

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amount of antibodies present—or decreased by lengthening the interval—partial resensitization by re-formation of antibodies. It varies with the severity of the anaphylactic shock: if the shock is more severe, the preconvulsion time is shorter. A preconvulsion time of 150 sec. or less is normal for a guinea pig sensitized actively 21 days beforehand. It denotes that the normal amount of antibody is present. If the preconvulsion time is prolonged, sensitization has not taken place in the normal way, and some factor or factors must have interfered with it.

Four series of experiments were carried out.

I. Series. Thirty eight guinea pigs were sensitized. Of these 12 were controls. Of the remaining 26 four received cortisons or ACTH from one day before the sensitizing injection until the shock was administered. Four other animals received cortisone or ACTH from the day of sensitization through the whole period. Four others received it for 4 days, 2 for eight days, 4 for 12 days and 4 for 17 days, starting on the day before sensitization. Three others received it from the 17th to the 21st day, when all animals were shocked. The amount of cortisone given was 1.5 mg of cortisone acetate, that of ACTH 3 mg. These doses were injected subcutaneously 3 times in 24 hours.

II. Series. Twenty animals were sensitized, of which 6 were controls. The remainder received 2.2 mg of cortisone acetate twice in 24 hours from 4 days before the sensitizing injection until they were shocked on the 21st day after sensitization. Originally 27 animals were used in this series, but 7 died during the 21 day period.

III. Series. Twenty four animals were sensitized, 7 of them as controls. The remainder received 1.5 mg of cortisone acetate 3 times in 24 hours from 4 days before sensitization until 24 days after sensitization, when they were shocked.

IV. Series. Two groups of 6 and 5 sensitized animals in which a normal preconvulsion time had been developed, were given an injection of 5 mg and 25 mg respectively of corti-

sone 4 hours before the preconvulsion time was determined. After the appropriate interval the preconvulsion time was again determined.

RESULTS

Series I. Of the 12 controls all animals were sensitized except one which neither at the 21st day nor later exhibited any reaction. This animal was the only one not sensitized in the whole series. The others had normal preconvulsion times of 150 seconds and less, or times near the normal, between 150 and 200 seconds. There was one exception (420 sec.). Of the 8 animals which had cortisone during the whole period of sensitization one did not become dyspnoic and, therefore, was completely protected; four had abnormally long preconvulsion times—743, 655, 510 and 370 seconds. The other 3 were normal. Of all the other groups in which the animals had cortisone or ACTH only during a part of the sensitization period, the times were normal except in 2 cases (265 sec. and 414 sec.). The latter time occurred in the group which had cortisone for the first 17 days of the 21 day period.

There was no difference between the effects of cortisone and ACTH. It should be noted that the long preconvulsion times of the five animals in the groups which had cortisone during the whole period became very short, when they were shocked again one week after the first shock, (i.e. on the 28th day) after the cortisone protection had ceased.

This result indicated that cortisone and ACTH failed to give any protection unless they were injected during the *whole* period of sensitization. Of the eight animals which were given cortisone during the whole period, five showed definite partial protection. As this group was too small to serve as satisfactory evidence, it was decided to repeat the experiment in a second series.

Series II. This experiment miscarried, mainly because the sensitization did not "take" in the usual way. Only 2 of the controls and 3 of the cortisone animals had normal preconvulsion times. Three of the controls had very long times, and

most of the cortisone animals had times over 200 sec. The variations were considerable, and no significant difference could be seen between the 2 groups. Apart from the failure of the sensitization this may be due to the fact that cortisone was given only twice in 24 hours, and its action may therefore not have been continuous.

Series III. This series had an unequivocal result. The controls all had normal times (average 108 sec.) and of the cortisone animals (average 298 sec.) only 2 fell into the normal range. In most of the cortisone animals the times shortened appreciably during the subsequent weeks when no more cortisone was given. The figures are included in Table 1.

Series IV. This experiment had been carried out as a preliminary to Series I-III. There was no change in the pre-convulsion time after a single cortisone injection.

DISCUSSION

The mechanism of cortisone action has been closely investigated during recent years. Its action does not interfere with the union of antigen and antibody: the immediate skin wealing reaction to the specific antigen has remained positive during cortisone treatment even when the condition of the patient had greatly improved (Feinberg et al., 1951, Rappaport et al., 1951, Zeller et al., 1950). The anaphylactic reaction in guinea pigs was also not influenced, if only a single cortisone injection was given, as Leger et al. (1949), Landau et al. (1951) and Arbesman et al. (1951) have shown. Our own experiments (IV. Series) confirm this. Cortisone is equally without influence on the effects of histamine (Friedlaender and Friedlaender, 1950). In these cases antibody must be presumed to have been present in the humans and animals under investigation, and the antigen was added in the presence of cortisone. The failure of cortisone to effect the antigen-antibody union is the more puzzling, as strong evidence has been brought forward for the excellent action of cortisone in chronic asthma. The cases reported in the

TABLE I
Preconvulsion times, series III.

No. of animals	Cortisone animals															Control animals								
	236	237	238	239	240	242	243	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272
Preconv. times (sec.) when shocked, the first time (17.3.52)	530	265	300	240	255	855	135	395	250	200	160	240	210	362	420	195	85	155	85	115	70	85	100	155
7 days later	80	90	165	70	165	700	90	400	120	210	90	240	130	250	240	124	105							
14 days later	185		190		125	220		180		60		100		85	110	70	70	70	125	155	65	70	95	75

literature must now number more than 500, and the high percentage of radical improvement justifies the assumption that every type of asthma is benefited. If we believe that the vast majority of asthma cases have an at least partly allergic aetiology, we should think it likely that cortisone interferes with the allergic mechanism. Yet, if in such cases a direct test of the nasal mucosa with the antigen in graded dilution was made (Feinberg et al., 1951), these tests remained positive although the asthma of the patient had greatly improved under cortisone.

This is difficult to understand. Our present results show that if cortisone is given during the whole period of sensitization, when normally the antibody titre increases steeply, the shock is of a definitely smaller intensity. The assumption may therefore be made that at the moment of the shock less antibody was present in our cortisone animals than would have been expected normally. If we assume that cortisone restricts the formation of antibodies, we should expect that after omission of cortisone antibody formation increases to its usual degree. This assumption is supported by the subsequent increase in sensitivity: one week after omission of the cortisone shock of much greater, and often of normal, severity could be elicited in most of our cortisone animals.

A decreased formation of antibody under the influence of cortisone has also been found by direct determination. Børneboe et al. (1951), Germuth and Ottinger (1950) and Halpern et al. (1951) have observed this result under the influence of cortisone or ACTH, whilst other authors did not find such an increase (Hahn et al., 1951, Mirrick, 1951, Larson and Tomlinson, 1951).

In the present state of our knowledge it is impossible to decide whether a decrease in the antibody as found by others and assumed by us could explain the clinical improvement in asthma. One observation points to this possibility. The cortisone effect in asthma does not appear before the second day, and reaches its peak, measured by objective methods, between the 3rd and the 5th day of treatment. Similarly, after omis-

sion of the cortisone, at least 3 days elapse before the asthma creeps back. We should assume that the production of antibodies takes place continuously in an allergic asthmatic and that the asthma is kept in existence by the continued union of antigen and antibody. As this leads to a reduction in the amount of antibody, a cortisone-caused restriction in antibody re-formation would make itself felt only after some time, namely when the amount of old antibody present at the start of cortisone treatment is used up and when less new antibody is available to replace it. The reverse process would take place after omission of cortisone.

Such an explanation however, even if it were correct, would not help us to understand the mechanism of cortisone action in reducing antibody production. It has recently been shown (Ebert and Wisser, 1951) that cortisone has a profound influence on certain blood vessels. A non-specific influence on the circulation in the organs concerned with antibody production must therefore be regarded as possible. It has also been shown (Teilum et al., 1950, Vaughan, 1951) that the gamma globulins decrease under the influence of cortisone, and that it has a strong influence on plasma cells and reticuloendothelial elements. So far no conclusive evidence for the mechanism of cortisone action is available.

SUMMARY

1. In active guinea pig anaphylaxis the preconvulsion time which indicates the severity of the anaphylactic shock, is much prolonged if cortisone is given during the whole period of sensitization. Soon after cortisone is omitted the preconvulsion time becomes shorter and eventually normal.
2. If cortisone is given only for a part of the sensitization period, the preconvulsion time remains normal.
3. This protective effect of cortisone is assumed to be due

to its restricting influence on the formation of antibody. The bearing of this assumption on the clinical effect of cortisone in asthma is discussed.

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