

EFFECT OF CORTISONE UPON THE RISE OF SERUM ANTIBODY LEVEL AFTER THE INJECTION OF A SATURATING DOSE OF ANTIGEN IN RABBITS SENSITIZED TO OVALBUMIN*

B. N. HALPERN, G. MAURIC, A. HOLTZER, AND M. BRIOT, PARIS, FRANCE

THE remarkable clinical results obtained with ACTH and cortisone in the treatment of allergic conditions such as allergic rhinitis, drug allergy, allergic dermatitis, and allergic asthma¹⁻⁸ gave rise to the hypothesis that these hormones could interfere with some fundamental mechanism of the allergic state, such as the antigen-antibody reaction. Recent published data, however, have shown that these hormones cannot modify a state of acquired anaphylactic sensitivity whether it has been actively or passively acquired. They cannot protect the animal against anaphylaxis^{9, 10} or the Arthus reaction.¹¹ They cannot inhibit the Prausnitz-Küstner reaction in man.¹² These hormones, nevertheless, can exert a definite influence upon antibody production during the sensitization period. The results published by Germuth and Ottinger,¹³ who used ovalbumin as an antigen, and those reported by Bjorneboe, Fischel, and Stoerk,¹⁴ who use polyvalent pneumococcal vaccine, have shown that if ACTH or cortisone are injected during the sensitization period, the antibody level obtained in the serum was considerably smaller in the treated animals, than in the control animals.

It is difficult to understand how these hormones modify the production of antibodies. It is known that cortisone¹⁵ can inhibit the activity of tissues from which the cells which are believed to produce the antibodies are derived, e.g., the reticulo-endothelial tissues, the plasmocytes,¹⁶ or the lymphocytes.^{17, 18} It is probable that these hormones inhibit antibody synthesis by the cells themselves. On the other hand, Dougherty, Chase, and White^{19, 20} have shown that the injection of corticotrophic hormones and of hormones of the adrenal cortex can cause a certain increase of the antibody level of the blood in the immunized animal as well as an important decrease in the number of lymphocytes in the lymphatic tissues. These two sets of data seem to be contradictory and need a logical explanation.

An objection can be raised to the experiments which require a prolonged administration of hormones during the period of sensitization. It is well known that treatment over an extended period of time with these hormones, as the experiments require, usually causes a deterioration of the physiological balance

Address: Hôp. Broussais, Clin. Propédeutique, 96 rue Didot, Paris 14, France.

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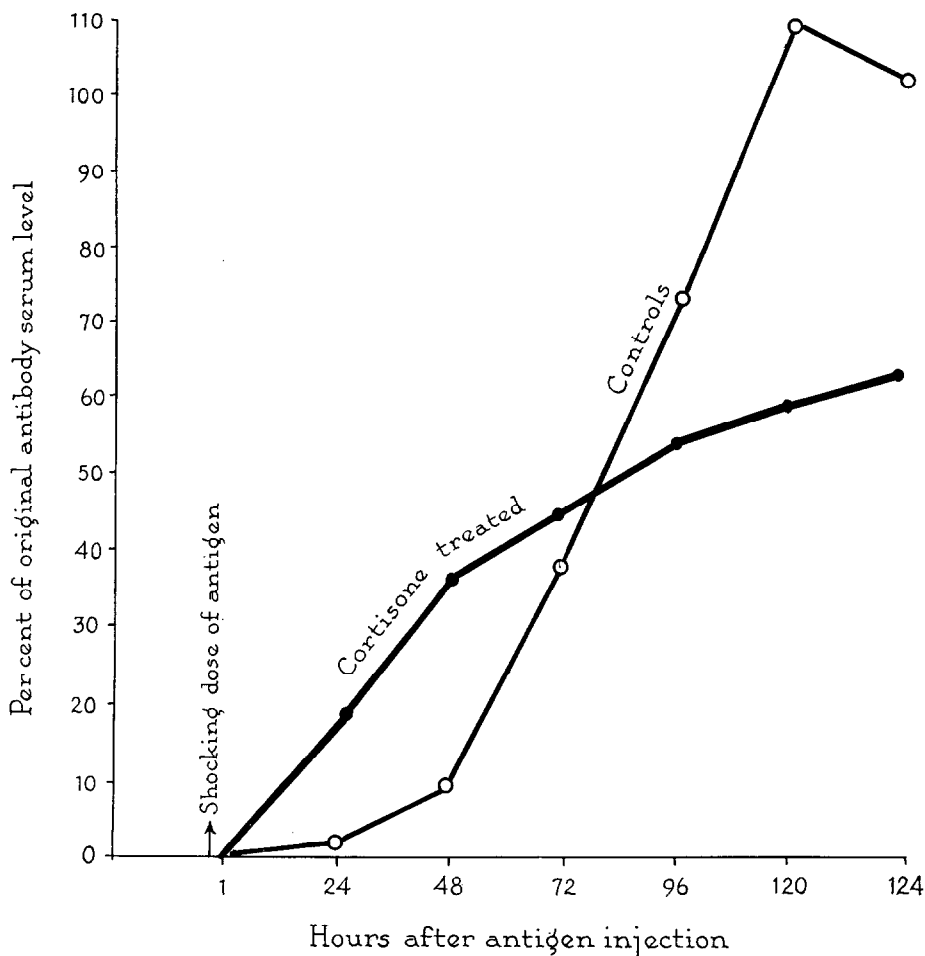


Fig. 1.—Modifications of serum antibody levels in sensitized rabbits treated with cortisone during the period following the intravenous injection of a saturating dose of antigen.

of the animals, i.e., loss of weight, cachexia, spontaneous infections, etc. *Could these alterations of the health of the animals explain the weakening of the antibody production?*

It seemed interesting to us to study the action of cortisone not upon the antibody production during the course of sensitization, but upon the antibody production of the sensitized animal when all the circulating antibody has been neutralized by an intravenous injection of an adequate dose of antigen. It is well known that under these conditions the antibody level of the serum returns rapidly after four or five days to a level similar to the one which existed before the neutralizing injection of the antigen. This method avoids prolonged treatment with the hormones. The results presented in this study* afford a new approach to the problem of the action of adrenocortical hormones on the antibodies in the blood.

*This study was conducted in the Department of Research of the University Medical Clinic; Chief of the Clinic, Prof. Pasteur Vallery-Radot.

TECHNIQUE

Twenty-four rabbits were divided into two lots of twelve each. The animals were injected intravenously three times a week for three weeks with doses of crystallized ovalbumin, increasing progressively from 0.5 mg. per kilogram to 2.0 mg. per kilogram. Eight days after the last injection the antibody levels of the sera were ascertained by the precipitin method. We determined the equivalent point of antigen-antibody for each serum, taking our readings after the tubes had remained forty-eight hours in the refrigerator. We expressed the antibody level of the sera by the amount of albumin necessary for a complete saturation of the antibodies. These values varied between 150 and 650 gammas per c.c. of crystallized ovalbumin. When the level of antibody had been established we injected intravenously a calculated amount of antigen to that which was thought necessary for a complete saturation of the antibodies. We then analyzed the sera for antibody levels one hour, 24, 48, 72, 96, 120, and 144 hours later.

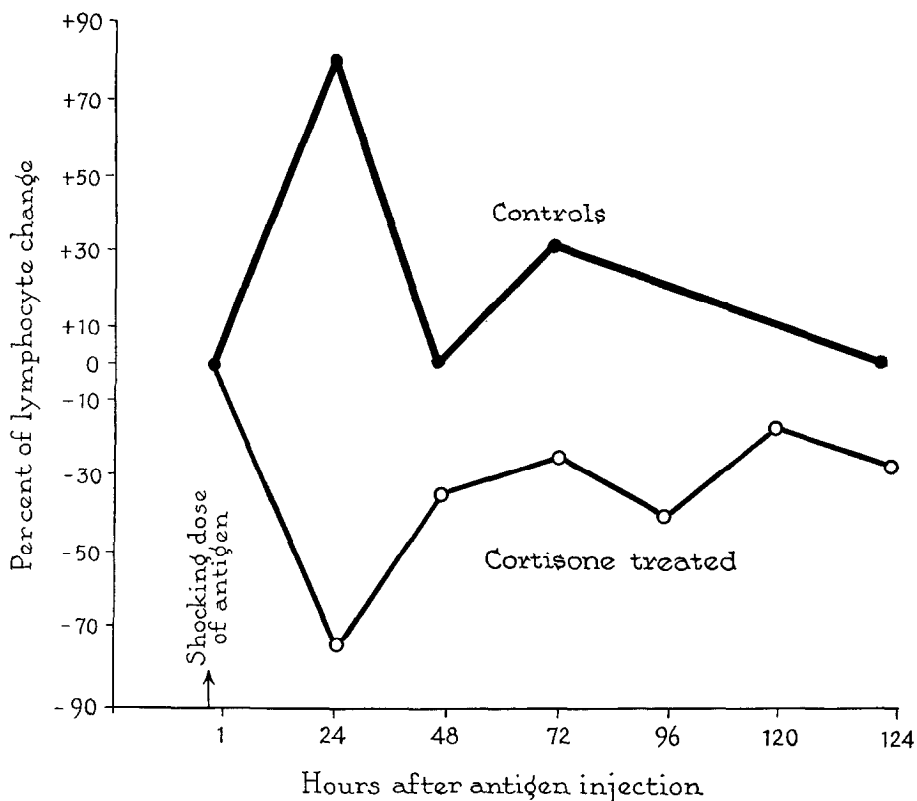


Fig. 2.—Modifications of levels of blood lymphocytes in sensitized rabbits treated with cortisone during the period following the intravenous injection of a saturating dose of antigen.

The cortisone-treated group received, 70 minutes after the injections of antigen and every day afterward, either 10 mg. or 25 mg. per kilogram of cortisone daily in two injections. The antibody levels were determined in these

animals in the same way as in the control group, and the histologic appearance of lymphatic tissues and the number of lymphocytes in the blood were studied as well in both groups of animals.

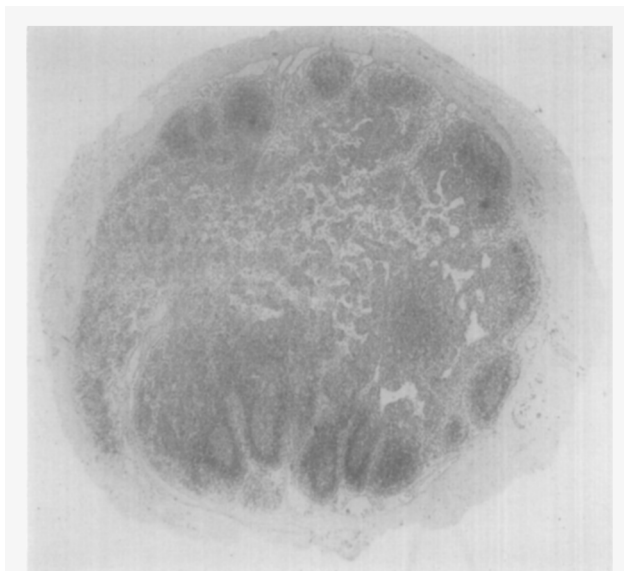


Fig. 3.—Normal lymph node: Under the capsule the lymph follicles with their paler germinative center and the crown of lymphocytes on the periphery. The lymphatic cords separated by the lymphatic sinuses converge toward the center of the node.

RESULTS

Changes in the Antibody Levels in the Control Animals After the Neutralizing Injection of Antigen.—As can be seen in Fig. 1, after the injection of a dose of antigen calculated to be theoretically saturating, the antibody level fell to the extent that there were no precipitins in the sera taken one hour after the injection. In the control animals, the antibody levels remained close to zero for 24 hours; after 48 hours, the level of precipitins came normally to about 8 per cent of the original amount, the level increased then rapidly to 79 per cent of the original amount after 4 days and after 6 days to more or less 100 per cent of the original amount.

Effect of Cortisone Upon the Increase of the Serum Antibody Level After the Neutralizing Injection of Antigen.—The results obtained were similar, whether the animals received 10 or 25 mg. of cortisone a day. As can be seen in Fig. 1, the results obtained with the rabbits treated with cortisone showed a great difference from those obtained with the control animals. After 24 hours the treated animals showed a serum level of 17.2 per cent of the original amount of precipitin, while the control animals showed a level of 0.9 per cent of the original amount of precipitin. After 48 hours, the treated animals had recovered on an average an antibody serum level of 36.6 per cent of the original amount, while the control animals had gained only 9 per cent. The third day, the two curves met and crossed each other at the 45 per cent level of recovery. But after the third day the antibody levels in the treated animals compared

to the control animals began to lag decisively and consistently. When the control animals had completely recovered their original level of antibody, generally after the fifth day, the treated animals showed only a level of precipitins of 56.4 per cent of the original amount.

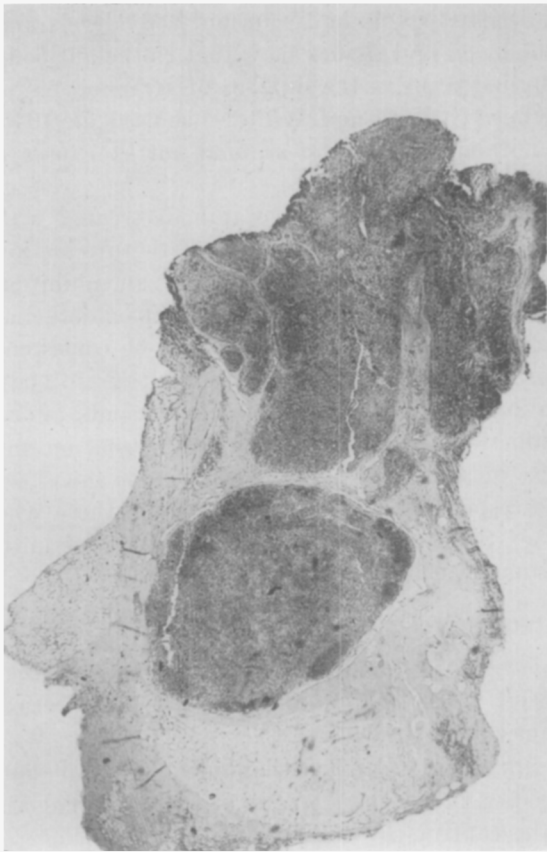


Fig. 4.

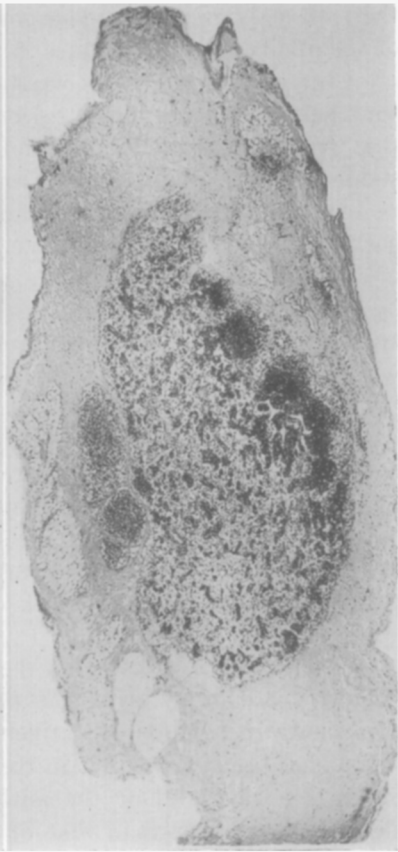


Fig. 5.

Fig. 4.—Lymph node of a rabbit one hour after the challenging dose of antigen. Decrease of the number of free cells associated with hyper-reticulosis. The lymph follicles and the lymphatic cords are not distinct.

Fig. 5.—Lymph node of a rabbit after six days of treatment with cortisone; considerable atrophy of the lymphatic elements. The lymph follicles and cords have almost completely disappeared. The lymphatic sinuses are empty and wide.

DISCUSSION

It is very clear that treatment with cortisone modifies definitely the pattern of recovery of the serum antibody level in the sensitized rabbit after the injection of a neutralizing dose of antigen. Two distinct modifications from the normal should be noted in the animals treated with cortisone. In the first 48 hours after the injection of the antigen, the antibody level is found to be consistently and significantly higher than in the control. But after the third day, there is a serious lag in the recovery of the serum antibody level in the treated animals compared with the controls.

How could we explain this seemingly paradoxical behaviour of the animals treated with cortisone? We believe that the remarkable increase in the serum antibody level which is observed in the first 48 hours, is due to the release of antibodies under the stimulation of the hormones, from the lymphatic tissues. Indeed, we have been able to observe a considerable lysis of lymphocytes in these animals (Fig. 2). The parallel studies of the serum antibody levels and of the number of lymphocytes in the blood and tissues show that as the antibody level increases, there is a corresponding drop in the number of lymphocytes in the blood and lymph nodes. Dougherty, Chase, and White^{5, 6} showed, in 1945, that treatment with ACTH and hormones from the adrenal cortex causes a sudden release of antibodies from the lymphocytes.

On the other hand, the modifications observed in the animals treated with cortisone, after the third day, i.e., the decrease after that date of the production of antibodies as compared with the controls, could be explained by an inhibition by the hormone of antibody production by the cells of the reticulo-endothelial system which produce them normally. This interpretation would be consistent with the data reported by other workers on the effect of cortisone upon antibody production during active sensitization. The results of our experiments afford a possible explanation for the conflicting findings of the authors who, on the one hand, have observed an increase of antibodies in the blood under the effect of cortisone during the anamnestic response, and on the other hand, those who have reported a depressing effect of this hormone on the production of antibodies when administered during the sensitization period.

SUMMARY

The effect of cortisone on the level of serum-antibodies in rabbits sensitized against ovalbumin during the period which follows the challenging injection of a neutralizing dose of antigen has been studied.

It has been found that in the first forty-eight hours following the injection of antigen the level of the antibodies in the sera of the treated animals is significantly higher than that of the control.

After the third day, on the contrary, the production of antibodies of the treated animals is found to be much lower than that of the control.

An explanation of these facts is suggested.

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