# Cortisone and ACTH Impairment of Response to Rabies Vaccine

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CORTISONE and corticotropin have been widely and successfully used in controlling human reactions to rabies vaccination, particularly the neuroparalytic and anaphylactoid reactions induced by the rabbit brain tissue in the vaccine mixture. Although both drugs are used to control these reactions, this study may indicate that cortisone actually interferes with the production of immunity and thus defeats the objective of vaccination. ACTH, on the other hand, does not appear to significantly impair neutralizing antibody response to rabies vaccine, and would seem to be the drug of choice should the need for such treatment arise.

Interest in this problem was aroused when one worker in the Fourth U.S. Army Medical Laboratory was accidentally exposed while working with a rabid laboratory animal. He was given 11,000 units antirabies serum (refined and concentrated horse serum) and 0.5 milliliter modified Harris vaccine daily for 14 days. On the 7th day of the prophylactic regimen, urticarial and anaphylactoid reactions (dyspnea) were observed and steroid treatment was instituted as follows: oral cortisone 300 milligrams daily from the 7th through the 14th days, with a gradual reduction in dosage and ultimate discontinuance of the drug on the 24th day (total dosage 4,200 mg.); intravenously administered hydrocortisone, 100 mg. on the 7th and again on the 9th day; Acthar Gel, 80 units per day from the 9th through the 16th days and 40 units per day from the 17th through the 25th days. By the 27th day, reaction symptoms were completely alleviated and the patient was discharged.

The patient (E.G.) exhibited a high level of circulating neutralizing antibody for a period of 21 days (table 1). The titer of neutralizing antibodies then fell rapidly, and even after 116 days, no evidence of active immunity, such as might have been expected from administration of Harris vaccine, was detectable. The time-titer relationship is compatible with passive immunity conferred by the prior administration of antirabies serum.

The normal response to rabies prophylactic treatment employing 14 daily doses of 0.5 ml. of rabies vaccine (modified Harris), administered subcutaneously was investigated by collecting serum specimens from five persons reporting to the emergency room, Brooke Army Hospital, with a history of exposure to the bites of rabid animals. Their serums were obtained at frequent intervals after initiation of prophylaxis (table 1). None of the individuals received antirabies serum at the time of treatment in the emergency room and none reported having received antirabies immunization at any

*At the time of this study, the authors were working in the Fourth U.S. Army Medical Laboratory, Fort Sam Houston, Tex., where Lt. Colonel Lukeman was commanding officer and Mrs. Shelton remains as bacteriologist, Virology Division. Lt. Colonel Burns is assigned presently to the U.S. Army Chemical Warfare Laboratories, Directorate of Medical Research, Army Chemical Center, Md., and Major Grogan is now with the Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C.*

prior date. Neither ACTH nor cortisone was administered to any of this group. All five individuals demonstrated positive log neutralization indices ranging from 3.8 to 4.2 (table 1) when serums collected 18 to 21 days following initiation of therapy were compared with serums obtained before vaccination.

These results are to be expected from active immunization and strongly imply that the failure of the vaccine to immunize the first patient mentioned (E.G.) may well have been due to the concomitant administration of steroids. To investigate this possibility, animal experiments were undertaken.

### Experiments on Animals

Rabbits were selected for this experiment, because much is known of their immunophysiology (*1–5*), particularly the role of the adrenal glands in immune reactions (*6*). Mature male Flemish animals weighing 3 to 4 kilograms were obtained locally and were allowed a 2-week period of acclimatization prior to initiation of the experiment. Throughout the study they were permitted a standard diet of rabbit chow ad libitum. A 16-hour fast was imposed prior to collection of serum samples.

Rabies vaccine (modified Harris), packaged for human use with 14 individual 0.5 ml. doses per box, was used. The Harris type vaccine is a living, attenuated virus, prepared by suspending in sterile distilled water the brains of rabbits that have been infected with attenuated (fixed) rabies virus.

A saline suspension of cortisone acetate (11-dehydro-17-OH-corticosterone-21-acetate) and corticotropin, ACTH (adrenocorticotropic hormone, lyophilized), 40 international units per vial, reconstituted with 1.0 ml. of physiological saline on the day of injection, were employed.

#### *Method*

Thirty rabbits were divided into five groups of six each (table 2). Therapy was admin-

**Table 1. Serum neutralization studies on human subjects receiving rabies vaccine**

| Treatment | Patient designation | Days after start of immunization | Log $LD_{50}$ | Log neutralization index |
|---|---|---|---|---|
| Antirabies serum (horse) plus 14 daily doses rabies vaccine plus cortisone and ACTH. | E.G. | 0 | 5.8 | 0.0 |
| | | 10 | 2.3 | 3.5 |
| | | 14 | 2.5 | 3.3 |
| | | 17 | 3.0 | 2.8 |
| | | 21 | 3.8 | 2.0 |
| | | 24 | 5.1 | .7 |
| | | 30 | 5.5 | .3 |
| | | 59 | 5.7 | .1 |
| | | 81 | 5.8 | .0 |
| | | 116 | 5.7 | .1 |
| Rabies vaccine alone | S.W. | 0 | 5.8 | .0 |
| | | 10 | 4.0 | 1.8 |
| | | 21 | 2.0 | 3.8 |
| | D.D. | 0 | 6.2 | .0 |
| | | 10 | 3.7 | 2.5 |
| | | 18 | 2.0 | 4.2 |
| | J.P. | 0 | 5.8 | .0 |
| | | 21 | 1.8 | 4.0 |
| | | 53 | 1.7 | 4.1 |
| | J.J. | 0 | 5.8 | .0 |
| | | 15 | 2.8 | 3.0 |
| | | 21 | 2.0 | 3.8 |
| | O.D. | 0 | 5.8 | .0 |
| | | 10 | 2.0 | 3.8 |
| | | 20 | 2.0 | 3.8 |
| Controls | D.V.M. | Positive | 1.0 | 4.8 |
| | J.D. | Negative | 5.8 | .0 |

istered to each group as follows: group 1, rabies vaccine; group 2, rabies vaccine and cortisone; group 3, rabies vaccine and ACTH; group 4, cortisone; and group 5, ACTH. Two additional rabbits, designated as group 6 received no injections.

Groups 1, 2, and 3 received 14 daily doses of 0.5 ml. of a 1:10 dilution of the rabies vaccine. Injections were made subcutaneously in the cervical and scapular area. In view of the fact that the usual 20 percent Harris vaccine is given to adult and child alike in the same amount (0.5 ml.) and for the same number of scheduled doses (14), this dilution for rabbits is approximately proportional by weight to an appropriate dose for an 80-pound child.

Cortisone acetate was given in 14 daily doses of 5.0 mg. each by intramuscular injection in the gluteal region. This dose is comparable to that given therapeutically to a 165-pound man. ACTH (20 I.U.), representing 50 percent of the minimal dosage recommended for control of drug sensitivities in adults, was given in the same manner. The ACTH dosage employed, although not pharmacologically equal to the cortisone dosage, is in excess of the physiological dose recommended for the rabbit.

All animals were weighed and bled from the

**Table 2. Individual neutralization titers of rabbits receiving rabies vaccine (modified Harris) with and without simultaneous cortisone or ACTH**

| Group | Rabbit No. | Log $LD_{50}$ of serum vs CVS rabies virus | Log neutralization index of serum vs CVS rabies virus | | |
|---|---|---|---|---|---|
| | | Collection days | | | |
| | | 0 | 15 | 30 | 53 |
| Group 1, rabies vaccine | 1 | 5.4 | 1.8 | 2.4 | 2.3 |
| | 2 | 5.7 | 3.5 | 2.9 | 3.1 |
| | 3 | 5.4 | 1.5 | 3.2 | 3.0 |
| | 4 | 5.1 | 3.1 | 3.6 | 3.5 |
| | 5 | 5.7 | 2.1 | 3.2 | 2.0 |
| | 6 | 5.4 | 2.8 | 3.9 | 3.8 |
| Group 2, rabies vaccine plus cortisone | 7 | 5.2 | .0 | .0 | .7 |
| | 8 | 5.8 | .4 | .5 | .5 |
| | 10 | 5.0 | .6 | 2.0 | 1.5 |
| | 11 | 5.4 | .0 | .4 | .0 |
| | 12 | 5.3 | .1 | .0 | .8 |
| Group 3, rabies vaccine plus ACTH | 13 | 5.5 | 1.3 | 2.8 | 2.7 |
| | 14 | 5.6 | 2.1 | 2.8 | 2.0 |
| | 15 | 5.2 | 1.6 | 1.0 | 2.7 |
| | 16 | 5.4 | .2 | 2.1 | 1.5 |
| | 18 | 5.5 | 1.9 | 3.1 | 2.9 |
| Group 4, cortisone | 20 | 5.9 | .1 | .1 | .0 |
| | 21 | 6.2 | .8 | .9 | .5 |
| | 22 | 5.4 | .0 | .0 | .0 |
| | 23 | 5.7 | .0 | .0 | .0 |
| | 24 | 6.2 | .1 | .2 | .7 |
| Group 5, ACTH | 25 | 5.3 | .0 | .0 | .0 |
| | 27 | 5.4 | .0 | .0 | .0 |
| | 32 | 5.3 | .1 | .0 | .0 |
| | 35 | 5.6 | .0 | .0 | .0 |
| Group 6, uninoculated | 31 | 5.4 | .0 | .0 | .0 |
| | 34 | 5.5 | .1 | .0 | .3 |
| Controls: | | | | | |
| Positive [1] | ---------- | 1.3 | 4.1 | ---------- | ---------- |
| Negative | ---------- | 5.4— | .0 | ---------- | ---------- |

[1] Lederle antirabies serum (rabbit) refined and concentrated.

heart prior to inoculation and 15, 30, and 53 days after initiation of therapy. Neutralization tests were conducted according to the method recommended by the Commission on Viral Infections, Armed Forces Epidemiological Board, as quoted from Paul (7), with the exception that the second hour of incubation of the serum-virus mixtures was accomplished at 4° C. The neutralizing capacity of each serum was expressed as the log neutralization index, or the difference in log $LD_{50}$ end points of a given serum-virus mixture as compared with the appropriate pre-inoculation serum.

A serum was regarded as positive if the log neutralization index was 1.7 or greater. Those less than 1.0 were reported as negative, and results between 1.0 and 1.7 were considered equivocal. Rabies Challenge Virus Standard (CVS) was employed as the test virus. The rabies-fixed virus was supplied by Lederle Laboratories. Known positive and negative serums were included with each test for control purposes.

*Results*

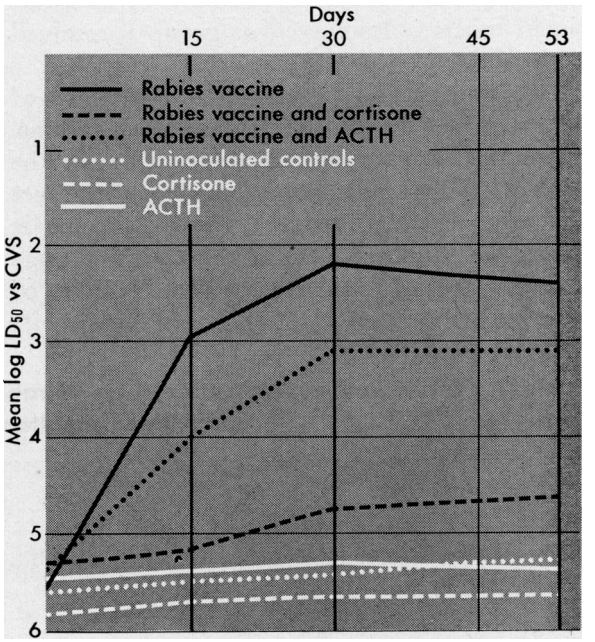
Twenty-seven of the 32 rabbits used in this study survived an observation period of 53 days, and were included for serum neutralization studies.

All six of the rabbits receiving rabies vaccine alone (group 1) exhibited positive log neutralization indices (table 2). Of the six that received rabies vaccine and cortisone (group 2), five survived; four showed no significant immunity at the end of the observation period as measured by the neutralization test, and one had an equivocal neutralization index.

In contrast to these negative findings when cortisone was administered concomitantly with rabies vaccine, four of the five surviving rabbits that received ACTH and rabies vaccine (group 3) yielded positive antibody responses, while one was equivocal.

All rabbits that received cortisone or ACTH alone, as well as those not inoculated, exhibited no change in their immunological status. Mean log $LD_{50}$ titers for each treatment group indicate the depressing effect of simultaneous administration of cortisone with rabies vaccine and the minimal interference by ACTH, at the dosage employed (see chart). The antibody

**Mean log $LD_{50}$ compared with CVS titers of rabbits receiving rabies vaccine (modified Harris) with and without simultaneous cortisone or ACTH**




response in the group which received vaccine alone and that given vaccine along with ACTH falls in the positive category of criteria set forth by the Commission on Viral Infections.

## Discussion

Since steroid therapy is often indicated clinically to offset the various allergic and paralytic reactions rising from the administration of rabies vaccine, the question herein is of considerable practical importance. As indicated by observation of one human case and by animal experimentation, our results strongly imply that cortisone should be avoided when rabies vaccine is being administered, since it apparently interferes with the production of neutralizing antibodies.

The impairing effects of ACTH, on the other hand, appear relatively less harmful, at least in the doses employed in our experiments, and probably do not adversely affect developing immunity. According to our studies, ACTH does result in a somewhat lower titer of neutralizing antibodies than when vaccine alone is employed (group 3 compared with group 1), but four of five animals receiving this drug nevertheless de-

veloped sufficiently high antibody titers to fall into the positive category.

Kass and associates (*8–10*) were able to show that rabbits ordinarily produce corticosterone as the predominant secretion of the adrenal gland and, as ACTH is given, there is a progressive shift toward cortisol production by the adrenal. Thus, at varying dose levels of ACTH these authors were able to get different effects on the production of antibodies, correlating roughly with the expected production of cortisol. They were led, therefore, to postulate that corticosterone has less effect on resistance to infection and on antibody response than does cortisone.

Although direct extrapolation of the results from rabbits to man should not be made because of the alteration in endogenous steroid output after the use of exogenous steroids in rabbits (*11*), there is, nevertheless, a definite indication of the need for conservative use of cortisone in humans when administered simultaneously with rabies vaccine for control of allergic manifestations.

While cortisone and, to a certain extent, ACTH interfere with the immunizing properties of rabies vaccine, neither drug appears to affect passive immunity adversely. The persistence of rabies neutralizing antibody in circulation for as long as 21 days seems to indicate that neither ACTH nor cortisone therapy caused early destruction of the administered passive immunity.

There is no reason to believe that the suppression of formation of rabies-neutralizing antibodies by cortisone in these experiments was a specific or selective effect. Previous experiments in rabbits (*12*) have shown that such results represent a general depression of protein anabolism and hence of antibody formation. The present observations are probably explainable on the same basis.


## Summary

The concomitant administration of cortisone and ACTH to a patient who was receiving rabies vaccine appeared to prevent the production of active immunity.

Further studies on rabbits showed that cortisone interferes with the active immunity ordinarily resulting from rabies vaccine. ACTH, on the other hand, while slightly depressing titers, does not prevent the formation of neutralizing antibodies.

It would appear, therefore, that for allergic reactions requiring steroid treatment arising during the course of administration of rabies vaccine, ACTH is the drug of choice and that cortisone is contraindicated.

In the single human case studied, neither drug affected adversely the passive immunity conferred by the injection of antirabies serum.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