EFFECT OF CORTISONE ON ACUTE STREPTOCOCCAL INFECTIONS AND POST-STREPTOCOCCAL COMPLICATIONS [1]

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It has been established that adrenal hormones play an important role in the defense reaction of the body to stress (1). A common stress stimulus in man is that produced by infection with group A streptococci. Streptococcal infections assume especial importance because they precede acute rheumatic fever, a disease which responds favorably to treatment with the adrenal hormone, cortisone (2–4). An epidemic of streptococcal exudative tonsillitis and pharyngitis afforded the opportunity to obtain data on the effect of cortisone therapy not only on an acute bacterial infection and the immunological response of the host, but also on the subsequent occurrence of acute rheumatic fever.

DESCRIPTION OF STUDY

This study was conducted at Francis E. Warren Air Force Base, Wyoming, from February 20 to April 17, 1950. All patients entering the hospital with respiratory infections were examined within a few hours after admission. Since it was desirable to include in the study only those patients in the early phase of a streptococcal respiratory infection who would be available for follow-up examinations, the following criteria were employed: (*a*) the presence of exudate on the pharynx or tonsils, (*b*) a total leucocyte of 10,000 or greater, (*c*) an illness which began less than 31 hours before admission to the study, and (*d*) availability for follow-up studies for at least four weeks.

One hundred and seventy-four patients fulfilled the above criteria and were divided into treated and control groups on the basis of their Air Force serial number. Eighty-seven patients had numbers ending in the digits 5–9 and received treatment; 87 with numbers ending in the digits 0–4 received no specific therapy and composed the control group.

Cortisone acetate was injected intramuscularly into the gluteal region according to one of the two treatment schedules. The first 17 patients received a total of 500 mgms in 50 mgm doses. The first injection was given at the time of admission to the study and subsequent doses were administered at 12 hour intervals. The remaining 70 cases were given a total of 600 mgms in 100 mgm doses. The initial injection was given at the time of admission to the study, the second and third at 9 a.m. and 9 p.m. on the second hospital day, and the remaining three at 9 p.m. of the third, fourth and fifth days. Control patients received 0.85 per cent sodium chloride injections by the same schedules. During hospitalization no antipyretics or other medications were given except codeine for relief of severe headache.

Patients were examined daily through the sixth day of illness by one member of the professional staff who had no knowledge of the treatment being administered. Symptoms were recorded for each 12 hour period during the first two days of illness and daily thereafter. Physical signs were recorded daily. Oral temperatures were taken every four hours. Total leucocyte counts and cultures of the tonsils and pharynx were obtained each day. Sera were obtained on the first and sixth days of illness. An electrocardiogram was recorded soon after the acute symptoms had subsided.

Subsequent examinations were conducted during the third, fourth and fifth weeks following the onset of the streptococcal illness. The patients were questioned concerning post-streptococcal complications. Those with symptoms were examined and admitted to the hospital for further study. An electrocardiogram was taken approximately 21 days after onset. In addition, at each of the weekly examinations, serum and a culture of the throat were obtained.

All cultures were examined for *beta*-hemolytic streptococci which, when present, were isolated in pure culture. The first and last strains isolated during hospitalization and all strains obtained at each subsequent examination were grouped and typed according to the methods of Maxted (5, 6) and Swift, Wilson, and Lancefield (7). The acute and convalescent antistreptolysin "O" titers of all sera from each patient were determined concomitantly by a modification of the technique of Hodge and Swift (8).

RESULTS

That the patients in this study had streptococcal disease is indicated by the demonstration of a sig-

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nificant rise [3] in the antistreptolysin titer in the sera of 86 per cent of the control group. In addition, group A streptococci were isolated from the initial cultures of the tonsils and pharynx of 89 per cent of all patients and the symptoms and physical signs were characteristic of streptococcal infections (9). The data presented in Table I show that the two groups of patients were essentially comparable.

The effect of cortisone on selected symptoms and physical signs is presented in Figures 1 and 2.[4] Little or no effect on the acute illness was demonstrated. The symptom, sore throat, persisted somewhat longer in the control group, being present on the sixth day of observation in 20 per cent

TABLE I

Comparability of the 87 cases in each of the treated and control groups

	Cortisone group *per cent*	Control group *per cent*
History of tonsillectomy	26.4	31.0
Age 17–21	77.0	74.7
*Symptoms:**		
Chilliness	65.5	75.8
Feverishness	82.7	86.2
Malaise	41.3	56.3
Sore Throat	82.7	85.0
Headache	86.2	80.4
Physical signs:†		
Enlarged or tender cervical nodes	91.8	90.8
Lymphoid hyperplasia	37.9	37.9
Laboratory:		
Group A streptococci on admission	89.7	88.5
Type 14	54.0	65.5
Type 24	17.2	10.3
Type 6	9.1	9.1
Leucocyte count 12,000 or greater	91.9	86.2
Antistreptolysin titer—125 units or less on admission	68.9	67.8

* Symptoms occurring during first 12 hours of illness.
† Physical signs present on admission examination.

of the control patients and 6 per cent of the treated cases. Chilliness, headache and malaise occurred with equal frequency in the two groups. No difference was noted between the treated and control patients in the time of disappearance of physical signs.

The number of patients with fever is recorded in Figure 3. At each four hour time period prior to treatment, the incidence of fever was the same in the two groups. Following therapy, the per

[3] A significant rise is considered to be two dilution increments when the convalescent titer is compared to the acute titer.

[4] Observations made after the development of purulent complications in four patients from the control group were not included in this analysis.

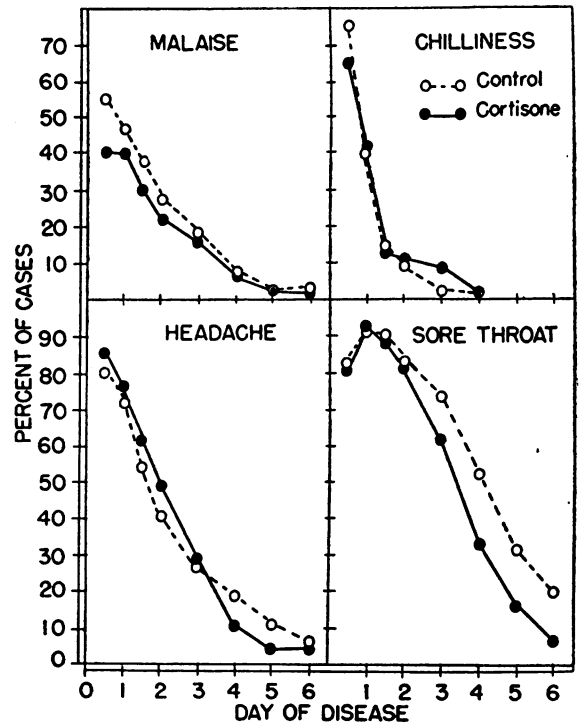

FIG. 1. EFFECT OF CORTISONE THERAPY ON THE SYMPTOMS OF STREPTOCOCCAL TONSILLITIS AND PHARYNGITIS

cent of patients with fever was greater in those who received cortisone than in the control group. This difference, evident up to the third day of treatment, was as great as 26 per cent.

There were 15 patients who developed a complication during the period of treatment with cortisone or saline injections (Table II). Two of the

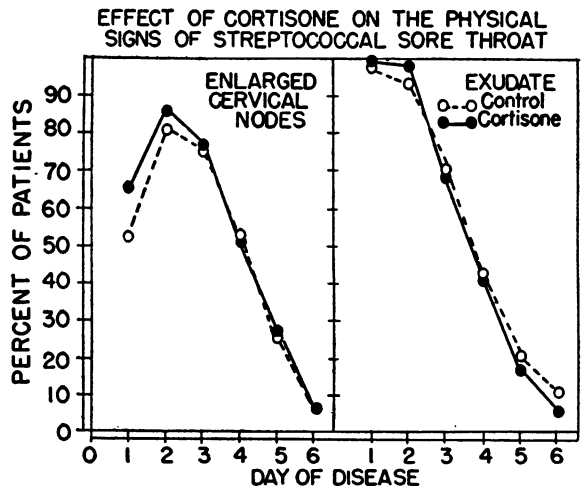

FIG. 2

TABLE II

The effect of cortisone on the complications of streptococcal sore throat

Complication	Cortisone group (87 cases)	Control group (87 cases)
Suppurative:		
A. During treatment		
1. Peritonsillar cellulitis	0	3
2. Otitis media	4	7
3. Appendicitis	1	0
B. Following treatment		
1. Exudative tonsillitis	4	3
2. Peritonsillar cellulitis	1	2
3. Otitis media	1	0
Non-suppurative:		
Rheumatic fever	2	5

three peritonsillar abscesses required incision and drainage, and in one instance of acute otitis media spontaneous rupture occurred. All three of these patients from the control group received penicillin as therapy. Symptoms of otitis media were present in six untreated and four treated patients but were not severe enough to require specific therapy. In the group treated with cortisone, one patient developed acute appendicitis, the symptoms of which began 20 hours after the initial injection. With continued administration of cortisone, abdominal tenderness and rigidity, increase in pulse rate, and an elevated leucocyte count persisted. At operation, 20 hours after the onset of abdominal symptoms, a gangrenous appendix was removed. No *beta*-hemolytic streptococci were isolated from cultures of the appendix taken at the time of operation.

Suppurative complications, which became evident within ten days after the period of hospital observation, occurred in six patients in the treated group and in five in the control group. In the group receiving cortisone four patients with recurrences of exudative tonsillitis, one with peritonsillar cellulitis and one with acute otitis media were readmitted to the hospital. In the control group, there were readmissions for exudative tonsillitis in three cases and peritonsillar cellulitis in two patients.

A total of seven patients developed a non-suppurative sequela diagnosed as definite rheumatic fever according to a modification (10) of the classification of Jones (11). Two of the patients with rheumatic fever had received cortisone and five had received no therapy. All seven patients exhibited migrating polyarthritis, fever, and an elevated sedimentation rate. A past history of rheumatic fever was obtained in only one patient who was from the control group. The electrocardiographic abnormalities are recorded in Table III. The interval from the onset of the observed respiratory infection to the first symptom of rheumatic fever was 18 and 27 days in the treated group and 13, 19, 19, 27 and 28 days in the control patients. None of the seven patients showed bacteriological evidence of an intervening streptococcal infection, although one patient from the control group (interval 13 days) entered the hospital with peritonsillar cellulitis four days before the first symptom of rheumatic fever.

There were 15 patients who exhibited abnormalities of the P-R interval on the electrocardiogram recorded about 21 days after the onset of exudative tonsillitis or pharyngitis (Table III). Of the patients who received cortisone the P-R interval was greater than 0.21 seconds in five, and only one of these had symptoms of rheumatic fever. In the control group of patients four showed a prolongation of the P-R interval, three of whom had symptoms of rheumatic fever. In addition, there were three patients in the treated and three patients in the control group whose P-R interval increased at least 0.04 second on the 21st day as compared to the initial recording.

Of the group of eight patients who showed abnormal P-R intervals on the electrocardiogram and who showed no other evidence of rheumatic fever, four in the cortisone treated group showed bacteriological evidence of a new infection. A new type of streptococcus was isolated from the phar-

TABLE III

Effect of cortisone therapy of acute streptococcal infections on the post-streptococcal electrocardiogram

Classification	Cortisone group		Control group	
	Total cases	Cases	Total cases	Cases
Rheumatic fever:	2		5	
P-R interval greater than 0.21 second		1		3
Increase P-R interval of at least 0.04 second*		1		2
No symptoms of rheumatic fever:	85		82	
P-R interval greater than 0.21 second		4		1
Increase in P-R of at least 0.04 second*		2		1
Totals	87	8	87	7

* Exclusive of individuals showing a P-R interval of over 0.21 second.

ynx of three patients at the time of the second electrocardiogram but there was no other evidence of infection. In one patient a new type of streptococcus was isolated at the time of readmission to the hospital for exudative tonsillitis seven days after the onset of the original infection.

Total leucocyte counts were obtained daily during hospitalization in 96.6 per cent of the cases. The percentage of leucocyte counts greater than 10,000 is recorded in Table IV according to hospital day. The number of elevated leucocyte counts fell continuously in the control group. In contrast, the treated group showed a decrease in elevated counts on the second day followed by a return to a high level and then a gradual fall.

Group A streptococci were isolated at some time during hospitalization in 95.3 per cent of the cortisone treated group and 96.5 per cent of the control group. The same type of organism was

TABLE IV

Effect of cortisone therapy in streptococcal sore throat on the total leucocyte count

Group	Per cent of leucocyte counts greater than 10,000 according to hospital day				
	1	2	3	4	5
Cortisone	95.1	78.7	90.7	83.5	78.8
Control	92.9	83.5	54.7	48.2	48.1

isolated during the acute illness and throughout the follow-up period in 79.5 per cent of the treated group and 71.6 per cent of the untreated group. A new type of streptococcus was identified in 8.5 per cent of the cortisone group and 4.9 per cent of the control group. All of these changes in type, except for one instance in the control group, were demonstrated after discharge from the hospital.

The antistreptolysin titers of the sera collected on admission to the hospital and five to seven days after the onset of the disease are recorded in Figure 4. Since the distribution of the antistreptolysin titers of the acute phase sera is very similar in the two the average rise in the antibody titer during convalescence may be compared.

At the end of the first week of illness the sera of the control group showed an average rise of 0.770 dilutions (Table V) as compared to a rise of 0.541 in the cortisone treated patients. During

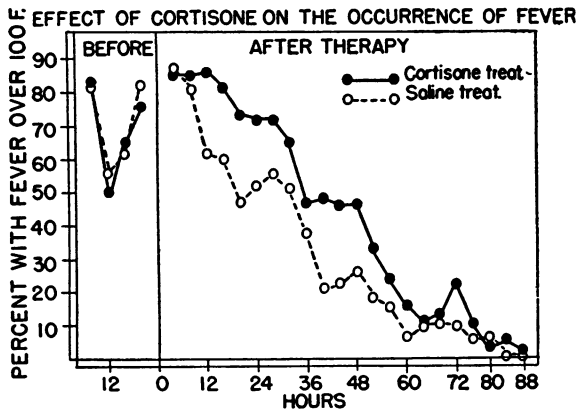

FIG. 3

the subsequent three weeks the average increase in antibody was somewhat greater in the treated group than in the patients who received no therapy. These differences were 0.175, 0.181, and 0.332 dilution increments at the second, third and fourth weeks, respectively.[5]

[5] In the treated series, those patients who gave a history of tonsillectomy had a higher antistreptolysin response than those with no such history. The average dilution increment in those without tonsils at the end of two, three and four weeks was 4.454, 5.173, and 5.173, respectively, as compared to 3.350, 3.650, and 3.542 in the patients with tonsils. No difference was noted in the control group.

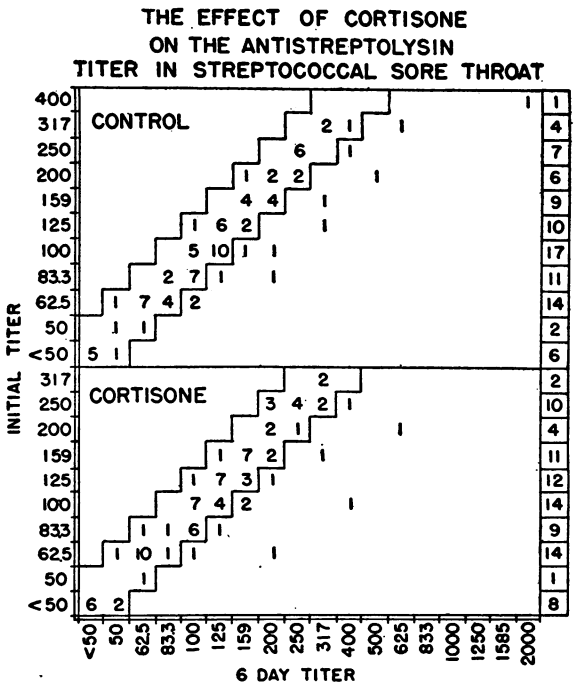

FIG. 4

TABLE V

*The effect of cortisone on the antistreptolysin titer**

Group	Days after onset of illness	Number of sera	Average dilution increase in antistreptolysin titer†
Cortisone	5–7	84	0.541
Control		84	0.770
Cortisone	14–18	79	3.607
Control		81	3.432
Cortisone	20–25	78	4.012
Control		83	3.831
Cortisone	27–32	75	3.973
Control		78	3.641

* The three patients who received penicillin therapy are excluded.

† The initial dilutions of sera employed in the tests are recorded in Figure 4. Each change in titer of one dilution is assigned a value of one (plus or minus). All changes in titer are related back to the titer of the serum specimen obtained during the first 31 hours of illness.

The only untoward effect noted during cortisone therapy was soreness around the area of injection in all patients. The soreness was most marked during the first 48 hours of therapy and diminished somewhat by the time of the last injection.

DISCUSSION

Adrenocorticotrophic hormone (ACTH) and adrenal cortical extracts have been used in studies designed to determine the effect of these hormones on acute bacterial infections. Perla and Marmorston (12) treated 17 cases of bronchopneumonia, one case of induced malaria, and six severe "grippal" infections with adrenal cortical extract. These authors report that such therapy was beneficial in that it shortened the convalescent period. Jacobs (13) treated non-immunized children who had whooping cough with adrenal cortical extract and reported the mildest course in this group when compared to other similar groups receiving pertussis antigens or triple typhoid vaccine. More recently, Finland, Kass, and Ingbar (14) used ACTH in the treatment of one case of pneumococcal pneumonia and one patient with virus pneumonia. These patients showed rapid symptomatic improvement.

In contrast to the above studies, the data presented here show that the adrenal hormone, cortisone, in the doses used, had no effect on the symptoms or physical signs of acute streptococcal sore throat. Furthermore, fever appeared to be prolonged in those patients receiving cortisone.

Whether cortisone therapy affects the development of complications can not be determined from the data obtained. There were ten such complications which developed in the control group during the period of treatment with saline and five in the cortisone treated group. There was one patient treated with cortisone who exhibited abdominal tenderness and rigidity, rapid pulse rate, fever and leucocytosis. This is in contrast to the report of Beck, Browne, Johnson, Kennedy and Mackenzie (15) who observed two patients who developed peritonitis during treatment with ACTH but who failed to exhibit the classical features of this disease.

Leucocytosis during the course of cortisone therapy as demonstrated in this study has been noted previously (16–19). The decrease in percentage of treated patients having leucocyte counts greater than 10,000 on the second day (Table IV) can possibly be explained by the fact that on this day most of the determinations were made about one hour after treatment. This drop in total leucocyte count immediately following the injection of ACTH and adrenal cortical extracts has been described (1, 20, 21). The remaining counts were taken about 13 hours following the previous injection.

A number of investigators have studied the relationship between adrenal hormones (22–30) and antibody production. Chase, White, and Dougherty (22) report that the administration of adrenal cortical extracts to animals receiving injections of staphylococcal toxin, horse serum, egg albumin or sheep cells results in higher antibody titers than obtained in control animals which received no adrenal extract. Mirick (23), however, reports that in man the administration of ACTH or cortisone does not alter the antibody response to immunization with pneumococcal polysaccharides. Finland, Kass, and Ingbar (14) observed that in one patient with pneumococcal pneumonia treated with ACTH antibodies appeared in the serum at about the expected time.

In contrast to the above reports, Fischel (24) demonstrated an inhibition of antibody formation in rabbits given ACTH during immunization with

formalinized pneumococci. Germuth and Ottinger (25) report that ACTH and cortisone administration markedly suppressed the formation of antibody to egg albumin in rabbits. In these experiments 10 mgms of cortisone were administered daily for 18 days to rabbits weighing 2 kgms. Such therapy completely inhibited antibody formation to egg albumin. It is to be noted, however, that antibody was not measured several weeks after the experimental period was completed. The relative doses of cortisone employed in these rabbits were greater than those used in the present study.

Antibodies to various products of group A streptococci are especially high in patients with rheumatic fever (31, 32). Recently it has been demonstrated that the attack rate of rheumatic fever following streptococcal pharyngitis is related, in part, to the magnitude of the antibody response (33). Procedures which alter this antibody response may also alter the incidence of subsequent rheumatic fever. Thus penicillin therapy of acute streptococcal pharyngitis inhibits the formation of antibody presumably because of the eradication of the antigen (streptococci) from the throat and at the same time such treatment markedly decreases the incidence of acute rheumatic fever (10).

Cortisone therapy as employed in the present study failed to alter appreciably the antistreptolysin response to streptococcal infections. Because the sera of the treated group showed a somewhat lower antibody titer at six days than the sera of the control group there may have been a slight inhibition of antibody formation. It should be emphasized, however, that the increase in antibody was somewhat greater in the treated group than in the control patients two, three and four weeks after the onset of illness. This may be due to the fact that cortisone is not antibacterial, so that when treatment was discontinued the antigenic stimulus was still effective.

The effect of cortisone therapy on acute streptococcal infections is of especial interest not only because of the above considerations, but also because the compound also exerts a remarkable effect when administered to patients with rheumatic fever (2–4). Acute rheumatic fever was not prevented by cortisone therapy. Although there were only two cases in the treated group and five cases among the control patients, this distribution could have occurred by chance. Since the incidence of abnormal electrocardiograms was equal in the treated and control group of patients, cortisone therapy had no effect on these signs which are frequently associated with rheumatic fever. Since there may have been a slight inhibition of antibody formation during the period of therapy, it is entirely possible that larger doses of cortisone administered for a longer period of time may inhibit antibody production and reduce the incidence of rheumatic fever.

SUMMARY

Eighty-seven treated and 87 control patients were studied to determine the effect of cortisone on the clinical and immunological response to streptococcal respiratory infections. Cortisone therapy, in the dosages employed, exerted no effect on the symptoms or physical signs of this infection. Patients who received cortisone exhibited fever for a longer period of time than the control patients. Suppurative complications developed during the period of cortisone or saline injections in one of the treated patients and in three of the control subjects.

Rheumatic fever was diagnosed in two treated and five control subjects. The P-R interval recorded approximately three weeks after the onset of illness was greater than 0.21 second in a total of five of the treated and four of the control group.

The increase in the antistreptolysin titer was somewhat less in the sera of the treated group than in the control patients one week after the onset of the infection, but at two, three and four weeks the formation of antibody was slightly greater in treated than in the control patients.

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