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Research Article

STUDIES ON CORTISONE AND ANTIBIOTICS FOR PROMPT THERAPEUTIC CONTROL OF TYPHOID FEVER AND SCRUB TYPHUS

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Prior to the use of chloramphenicol in the treatment of patients with typhoid fever the mortality rate in this disease was almost 10 per cent and approximately one-fourth of the deaths were attributable to the toxic-febrile state (1). Chloramphenicol has been shown to control the bacteriologic manifestations of typhoid fever within a matter of hours but the toxemia has responded more slowly to the specific antibiotic (2–4). Indeed, fever and general toxemia generally have continued unabated or are even somewhat intensified (2, 3, 5) for two or three days after antibiotic therapy has been instituted. The observations of our group (6, 7) indicated that cortisone, when used either alone or along with chloramphenicol, brought prompt relief of subjective and objective acute febrile manifestations of typhoid fever. Moreover, others have made similar observations in such patients treated with ACTH and chloramphenicol (8, 9).

The present report is concerned primarily with additional studies on the use of a combined cortisone-chloramphenicol regimen in the treatment of typhoid fever patients, and, secondarily, with related studies on the use of the same therapeutic combination in the treatment of scrub typhus patients. In both of the diseases, but particularly in the former, the studies have been oriented toward attempts to understand the factors concerned with the toxic-febrile reactions displayed by acutely ill patients and the physiological mechanisms by which these may be alleviated.

MATERIALS AND METHODS

Typhoid Fever

Selection of patients: All patients included in this study were treated on the wards of the General Hospital, Kuala Lumpur, Federation of Malaya. Each exhibited pyrexia and typical manifestations of severe typhoid fever; in every instance a positive blood culture was obtained prior to treatment which was instituted between the ninth and sixteenth days of disease. The 18 patients mentioned in this report included 6 males and 12 females who ranged in age from 7 to 35 years.

Treatment: All patients received both chloramphenicol [1] and cortisone [2] orally. The regimens listed below were those given to Asian adults who weighed about 45 Kg.; children received proportionately smaller doses.

In each instance the antibiotic was administered according to a fixed schedule in two courses as follows: A first course consisting of 3.0 Gm. initially, followed by maintenance doses of 1.5 Gm. at 12-hour intervals until the patient had been afebrile for 48 hours; and a second course consisting of 1.5 Gm. every 12 hours for eight doses, beginning on the eighth day after completion of the first course.

Cortisone was administered according to several schedules in order to learn more about its effect and optimal dosage.[3] Thus, the patients were divided into five groups on the basis of the duration of cortisone treatment. The four patients in Group I received an average total dose of 10.7 mg. cortisone per Kg. of body weight during a single day of steroid therapy. For 45 Kg. adults this dose amounted to a total of 500 mg. cortisone of which 300 mg. were administered with the initial dose of chloramphenicol, and 200 mg. 12 hours later. Groups II (five patients), III (six patients), and IV (one patient) received cortisone twice daily over periods of 2, 3, and 4 days, respectively; here the amount of drug on a body weight basis was somewhat smaller (8.1 to 6.4 mg. per Kg. during the first day) than in Group I. For an average Asian adult these dosages amounted to a total of 300 mg. on the first day, 200 mg. on the second, and 100 mg. on the third and fourth days. The regimen was so arranged that the morning dose was approximately twice that given on the

[1] Supplied by Parke, Davis and Company.

[2] Supplied by Merck and Company, Incorporated.

[3] Oral administration of the 25 mg. tablets of cortisone acetate, which were employed throughout the study, was originally troublesome in stuporous patients and in children because the tablets quickly became soft and adhered to the palate or tongue. This difficulty was avoided after it was found that the tablets disintegrated readily in water to form a suspension which could then be given orally with a medicine dropper.

evenings of the first and second days, but the amounts supplied on subsequent days were divided equally between the morning and evening. The two patients in Group V, who were cared for late in the study, received smaller amounts of this drug at more frequent intervals, *i.e.*, 50 mg. doses of cortisone at 6-hour intervals until the temperature returned to normal; subsequently the hormone was given at 12-hour intervals. Full details of the treatment regimens employed with all patients are included in Appendix A.

Care of patients: Clinical and laboratory procedures employed in this study were similar to those used previously by our group in Malaya (2, 7, 10). Members of the team administered the drugs personally and took the patients' temperatures frequently during the initial response to treatment. Pyrexia in patients with typhoid fever was defined, in accordance with previous reports, as an oral temperature of 99° F. or above. Blood cultures were made during the first few days of therapy, on the two days immediately prior to the second course of chloramphenicol, and in any subsequent febrile period. Relapses of typhoid fever were treated with chloramphenicol alone, and other complications by appropriate measures. Public health regulations for release of convalescent typhoid fever patients in Malaya require that three consecutive stool and urine cultures taken at weekly intervals be free of *Salmonella typhosa*. In order to minimize the possibility that negative cultures were the result of continued antibiotic suppression instead of a bacteriological cure, collection of specimens for culture from convalescent patients awaiting discharge was not begun until five days had elapsed since the last dose of chloramphenicol. An additional stool culture was obtained from those patients who reported for a follow-up examination two weeks after discharge from the hospital.

Scrub Typhus

Selection of patients: The patients in this study, with one exception, were healthy young adult male volunteers who had been inoculated intradermally with a few infectious units of the Karp strain of *Rickettsia tsutsugamushi* while serving as members of control groups in an investigation dealing with immunization against scrub typhus (11, 12). Each of these volunteers bears the same identifying code number here that was used in the other reports. Since these reports contain many of the details of the course of the disease of each volunteer, including laboratory proof of scrub typhus infection, only information which is pertinent to the present study will be mentioned here.

Care of patients: As the inoculated volunteers became ill they were placed alternately into two groups,[4] *i.e.*, Group A (seven patients) who received chloramphenicol alone and Group B (eight patients) who received cortisone in addition to the antibiotic. Each volunteer of both groups was given specific antibiotic therapy after approximately 48 hours of sustained fever which was regarded as an oral temperature of 100° F. or higher in the ambulant person.[5] The course of treatment with chloramphenicol consisted of an initial 3.0 Gm. oral dose followed by 1.5 Gm. amounts 12 and 24 hours later. Members of Group A were given no additional medication, but those of Group B also received a total of 500 mg. of cortisone given orally in amounts of 300 mg. and 200 mg., respectively, along with the first two doses of antibiotic. The single patient with naturally acquired scrub typhus, a British soldier hospitalized at the British Military Hospital, Kinrara, near Kuala Lumpur, was treated on the seventh day of disease with the same chloramphenicol-cortisone regimen used for the volunteers.

[4] Group A includes volunteers C-10, C-11, C-13, C-14, C-17, C-19, and C-23. Group B includes volunteers C-9, C-12, C-15, C-16, C-18, C-20, C-21, and C-22. Volunteers C-21, C-22, and C-23 were inoculated at one time with 90 mouse minimal infectious doses while the remainder were inoculated on a different day with 60 mouse minimal infectious doses.

RESULTS

Typhoid Fever

Results of the therapeutic studies are summarized in Table I and are presented in detail for each patient in Appendix A. Since all patients received essentially the same course of chloramphenicol, which usually renders typhoid patients afebrile in about four days, emphasis will be placed on the effect that different regimens of cortisone had on the course of the disease during the first few days of treatment.

Prompt control of pyrexia and toxemia by combined therapy: Rapid and dramatic defervescence was observed in all patients in the present study who received the large dose of cortisone, *i.e.*, Groups I through IV in Table I. The average time required for these patients to become afebrile after receiving the first oral dose of cortisone and

[5] Fever was defined as a sustained oral temperature above 99° F. in early studies of therapy of patients with naturally acquired scrub typhus who were first seen after some days of high fever and who were content to remain in bed or on limited activity for a reasonable period after therapy. Later, however, it was found that this criterion did not suffice to distinguish abnormal temperature in volunteers inoculated with *Rickettsia tsutsugamushi*. These persons remained ambulatory and quite active in the tropical environment during the incubation period and frequently exhibited oral temperatures above 99° F. even during the period prior to the test. Furthermore, since they were treated within 48 hours after the onset of clinical disease and, hence, experienced little or no debilitation, the volunteers refused to remain in bed for more than a few hours after therapy was instituted. Under these circumstances, an oral temperature of 100° F. or above more accurately indicates a real deviation from normal.

TABLE I

Summary of responses of typhoid fever patients to treatment with chloramphenicol and cortisone: Comparison with patients treated with chloramphenicol alone

Group	Duration cortisone Rx (*days*)	Number of patients	First normal temp. after cortisone (*hours*)*	Duration afebrile period due cortisone (*hours*)*	Duration fever after escape from cortisone (*days*)*	Perm. afebrile due therapy (*days*)*
Present study						
I	1	4	5.5	22.5	3.5	4.8
II	2	5	6.0	49.6	1.9	3.8
III	3	6	6.0	45.0†	1.8†	4.2
IV	4	1	6.0	Perm. afebrile after cortisone		0.3
Other studies						
1‡	4	4	15.5	Perm. afebrile after cortisone		0.7
2§	0	45		No cortisone given		4.0
3‖	0	500		No cortisone given		4.5

* Average value for group.
† Average of the four patients who had recrudescence of fever; two patients were permanently afebrile after cortisone.
‡ Data on intramuscular cortisone and chloramphenicol from Reference 7.
§ Combined data from References 2 and 10.
‖ From data of Reference 4.

antibiotic was six hours. The three charts in Figure 1 illustrate graphically the accelerated defervescence.

Signs and symptoms commonly attributed to toxemia decreased along with defervescence. Thus, a patient who was in a semi-stuporous febrile state at noon when therapy was begun, might be sitting up in bed, smiling and showing interest in his surroundings at 6:00 p.m. Even Patient 18, who was markedly toxic with pronounced stupor, tachycardia and incontinence of urine and feces, improved distinctly within a few hours after initiation of therapy.

The defervescence, which began shortly after therapy was instituted, was precipitous in all patients of the first four groups and in about half of these the temperature fell to hypothermic levels, *i.e.*, below 96° F. orally. During the period of marked hypothermia experienced by Patient 9, whose chart is shown in Figure 1, the rectal temperature fell to 94° F. Of the 10 patients whose temperature fell below 96° F., 4 attained a minimum between 95° and 95.9° F., and 4 between 94° and 94.9° F.; in 2 patients the minimum temperature was 93.8° F. The skin of patients with marked hypothermia was cold and clammy (sweating was profuse during defervescence). These persons responded slowly to commands and exhibited pronounced intention tremors. If asleep, they were awakened with difficulty. However, there was no evidence of cardio-vascular collapse since the pulse was slow and strong and the blood pressure normal or even slightly elevated. After a few hours the temperature rose and the signs associated with hypothermia disappeared, leaving no residual deleterious effects. Hypothermia following cortisone administration was more frequent among children than adults of this series; it occurred in seven of the nine children between 7 and 14 years of age and in three of the nine older patients. This phenomenon is not peculiar to patients treated with cortisone although it may be more pronounced in them. It may be recalled that some degree of hypothermia, at times sufficiently severe to warrant remedial measures, has been known to occur during early convalescence of untreated typhoid fever patients (13) and, more recently, in patients treated with chloramphenicol alone (3, 14).

The two patients included in Group V in Appendix A received smaller doses (50 mg.) of oral cortisone at intervals of six hours in an attempt to avoid the extremely rapid change in temperature. Despite the fact that defervescence in Patient 17 occurred somewhat more slowly than usually observed in patients in Groups I through IV,

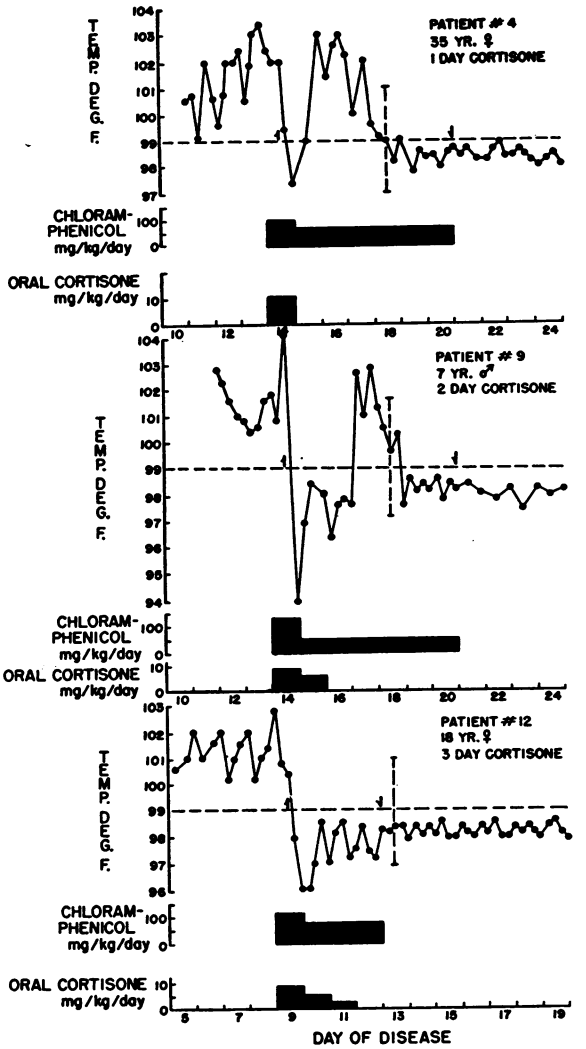

FIG. 1. FEVER CHARTS IN CHLORAMPHENICOL TREATED TYPHOID FEVER PATIENTS RECEIVING CORTISONE FOR ONE, TWO AND THREE DAYS.

Note: Interrupted vertical line on charts 4 days after institution of therapy indicates average duration of fever in patients treated only with chloramphenicol.

a minimum temperature of 95.6° F. was attained 12 hours after the initial dose. Patient 18 responded more slowly and at no time was a temperature below 97.8° F. recorded.

Duration of antipyretic effect of cortisone: In all nine of the patients in Groups I and II who received cortisone for one or two days, and in four of the six in Group III who were given the hormone for three days, fever, headache and other manifestations of toxemia reappeared within 18 to 72 hours after combined therapy was instituted. For convenience, this prompt return of the febrile-toxic state will be referred to hereafter as "escape" from cortisone effect in order to differentiate it from relapse in patients treated with chloramphenicol; the latter has been associated with return of demonstrable bacteremia and generally occurred some days after antibiotic therapy was discontinued.

The escape phenomenon became manifest in 6 to 24 hours after the last scheduled dose of cortisone had been administered to the patients in Groups I and II; the average time was 16 hours for the former and 20 for the latter. Stated differently, the durations of the afebrile periods induced by cortisone were 22.5 and 49.6 hours, respectively, for the two groups, while the average times of escape for the groups were 28 and 56 hours after the beginning of therapy, see Table I and Appendix A.

The patients in Group III presented no such consistency as regards escape. In the first place, two of the six members never displayed the phenomenon; they progressed to uneventful recovery. Among the four who suffered a return of fever and toxemia, three demonstrated these findings some hours before the last dose of hormone (Patients 10, 11, 15, see Appendix A) while the fourth (Patient 14) reacted in this manner 12 hours after the end of cortisone therapy. Several factors probably contributed to the irregularity of the phenomenon in this group of patients who received the hormone for three days. In the first place the patients were approaching the period, *i.e.*, the fourth day, when the antibiotic effect alone would have rendered them afebrile, see Table I; hence, a proportion of the group might be expected to avoid the escape phenomenon. A potential factor is the possibility that a given dose of cortisone may be less effective in controlling the febrile-toxic state on the third day than on the first day of treatment. Thus, in Patient 17, 100 mg.[6] corti-

[6] The temperatures of three patients (numbers 10, 11, and 15) in Group III, *i.e.*, those who received the 3-day cortisone regimen, showed a distinct upward trend on the third day of steroid therapy and experienced the onset of the escape phenomenon just before or shortly after the last dose of cortisone. This suggested that the amount of hormone given the patients on the third day was inadequate; hence, the two patients in Group V were given smaller doses at 6-hour intervals in the initial phase of therapy in the attempt to prevent the abrupt defervescence

TABLE II

Duration of bacteremia in typhoid fever patients after institution of combined cortisone-chloramphenicol therapy

Time of culture	No. patients cultured	No. patients with positive cultures
2 hours before Rx begun	18	9
24 hours after Rx begun	14	3
48 hours after Rx begun	11	0
72 hours after Rx begun	13	1*

* Not cultured at 48 hours.

sone produced a rapid defervescence from 103.2° F. to 95.6° F. on the first day of therapy while on the third day the same dose was followed instead by a rise in temperature from 98.6° F. to 100.2° F.

The data presented in Table I and the charts in Figure 1 show that the patients in the present study who escaped from the effects of cortisone progressed to recovery along courses essentially indistinguishable from those of patients in earlier studies who were treated with chloramphenicol alone. The former became permanently afebrile in about the same length of time from the start of therapy as did the latter patients.

Laboratory studies: Table II summarizes the results of blood cultures taken during the first 72 hours after institution of therapy. With one exception, blood cultures were negative after the first 24 hours of therapy. The single culture which yielded *S. typhosa* at 72 hours was from Patient 9, the youngest of this series, who later suffered a relapse. None of the blood cultures taken immediately prior to the second course of chloramphenicol was positive, a finding of considerable interest since earlier studies (10) had shown that this time marked the beginning of the period in which relapses with recurrence of bacteremia were most prone to occur.

Stool cultures in five patients were positive for *S. typhosa* on one or more occasions after therapy was begun. In two cases the pathogen was found on the second and fourth days, respectively, of the initial course of chloramphenicol; and in another, on the day following the last dose of the first course. One patient had three positive stool cultures immediately prior to the second course of antibiotic but subsequent cultures were negative. The feces of two patients, one of whom had a positive stool culture on the fourth day of the initial course of therapy, were positive on a single occasion after completion of second courses of antibiotic. The chronic carrier state did not develop in any of the patients during the period of observation, an average of 31 days after the last dose of chloramphenicol.

Total eosinophil counts were of no value in estimating the hormonal response since 12 of the 18 patients had no demonstrable eosinophils prior to the first dose of cortisone. The counts of the remaining six patients were 22, 22, 37, 121, 275, and 300 eosinophils per cu. mm. at the time therapy was begun, and dropped sharply after the first dose of cortisone. Since eosinophil counts are generally low in typhoid fever (15) and since such tests were employed here in an attempt to evaluate the initial cortisone effect, they were not extended beyond the first few days of observation.

Complications and relapse: There was no instance of overt intestinal hemorrhage in this series of cases. Only in the case of Patient 18 did symptoms and signs suggest a small intestinal perforation. This occurred on the 45th day while the patient was receiving chloramphenicol for a relapse of typhoid fever. The signs and symptoms disappeared with continued administration of chloramphenicol alone. Pneumonitis was present when treatment was begun in two cases, both of whom received penicillin in addition to antityphoid therapy. One other patient exhibited a marked bronchitis which improved without additional therapy. Acute cholecystitis complicated the convalescence of Patient 2 with symptoms beginning on the 59th day of disease. A stool culture positive for *S. typhosa* just four days prior to onset of symptoms suggested the possibility of typhoidal etiology in this complication.

Bradycardia was common during the first few days of convalescence. This can hardly be classed as a complication since the older literature on typhoid fever states that true bradycardia, in contrast to the relative bradycardia early in the disease, was not uncommon during early convalescence of un-

and 1.5 to 2 times as much steroid on the third day as on the first in the attempt to prevent escape. It is of interest that the smaller more frequent doses of the drug produced, on the first day, rapid defervescence in one patient of Group V; but in the other patient, by far the most severe case in this series, the action was less rapid. Furthermore, the large dose on the third day was inadequate to prevent escape.

treated cases (13). It is of interest that premature convalescence induced by chemotherapy may also be accompanied by the marked slowing of the heart rate.

Irregularity of the pulse was noted in four patients one to three days after initiation of therapy. It was the clinician's impression that the irregularity in all four cases resulted from dropped beats. Indeed, an electrocardiographic tracing obtained from a patient showing this sign demonstrated second degree heart block in the form of a typical Wenckebach's phenomenon. This condition disappeared spontaneously in the four patients in from one to nine days after onset. Cardiac irregularities were by no means rare in typhoid fever patients before the era of specific therapy; irregularity and intermittency (16, 17), heart block and changes in the ventricular complexes in the electrocardiogram (18), and a high incidence of prolongation of the P–R interval (19, 20) were all described. Furthermore, arrhythmias have been noted recently in typhoid fever patients treated with chloramphenicol alone (21). Since the electrocardiographic changes encountered in cases before the days of antibiotics were more frequent during the second and third weeks of disease, it would be difficult to ascribe the cardiac irregularities noted in the present series, which occurred at a corresponding period, to the effects of therapy alone. On the other hand, the possibility that some animal tissues may exhibit unusual responses to bacterial products while under the influence of the cortisone must be admitted (22).

Relapses, with proven bacteremia in each instance, occurred in 3 of the 18 patients; these episodes began 8, 9, and 21 days, respectively, after completion of the second course of chloramphenicol. Response to readministration of chloramphenicol was prompt. This incidence of relapse does not represent a significant deviation from the combined relapse rates observed by previous groups using chloramphenicol alone (23) and is intermediate between the relapse rates noted by John and Vinayagam (24) for continuous and for intermittent schedules of chloramphenicol therapy. Marmion (3), on the other hand, recently observed relapses in 41 of 97 patients treated on a very similar schedule of interrupted antibiotic therapy. In contrast, there was only one relapse among the 21 patients of Marmion who received a 10-day course of typhoid vaccine concurrent with the interrupted antibiotic regimen. This author calls attention to the higher relapse rate among patients treated early in the disease as compared with those treated late but does not indicate the exact day of disease upon which therapy was begun in his large series of cases. One suspects that his patients, military personnel, were hospitalized and treated at an earlier stage of the disease than were the civilians of the present study in whom therapy was begun, on the average, on the 12th day of disease. Observations on patients with scrub typhus clearly indicate that relapses are common in those treated within the first few days of illness but rare in those treated during the second week (25); it is possible that an analogous phenomenon may be found in typhoid fever.

Scrub Typhus

The response of patients with scrub typhus to combined therapy with cortisone and chloramphenicol is compared with the response to chloramphenicol alone in summary form in Table III. The febrile-toxic state terminated in the usual rapid manner in the volunteers treated only with antibiotic; but those who were given supplementary cortisone experienced even more rapid alleviation of their illness. Thus, volunteers of Group A, who received chloramphenicol, were afebrile in an average of 21.7 hours while those of Group B, who received the combined cortisone-chloramphenicol regimen, were afebrile in an average of 6.7 hours. The charts of selected volunteers are presented in Figure 2. Marked symptomatic improvement accompanied the fall in temperature and within a few hours after institution of therapy it was difficult to persuade most of these volunteers to stay in bed. In a few patients, however,

TABLE III

Comparison of combined cortisone-chloramphenicol regimen with chloramphenicol alone in the treatment of volunteers infected with the Karp strain of scrub typhus

Group	Number of patients	Treatment: Cortisone (*mg.*)	Treatment: Chloramphenicol (*Gm.*)	Response to treatment: 1st normal temperature after Rx (*hours*): Average	Response to treatment: 1st normal temperature after Rx (*hours*): Range	Number of relapses
A	7	0	6	21.7	13–40	1
B	8	500	6	6.7	4–14	4

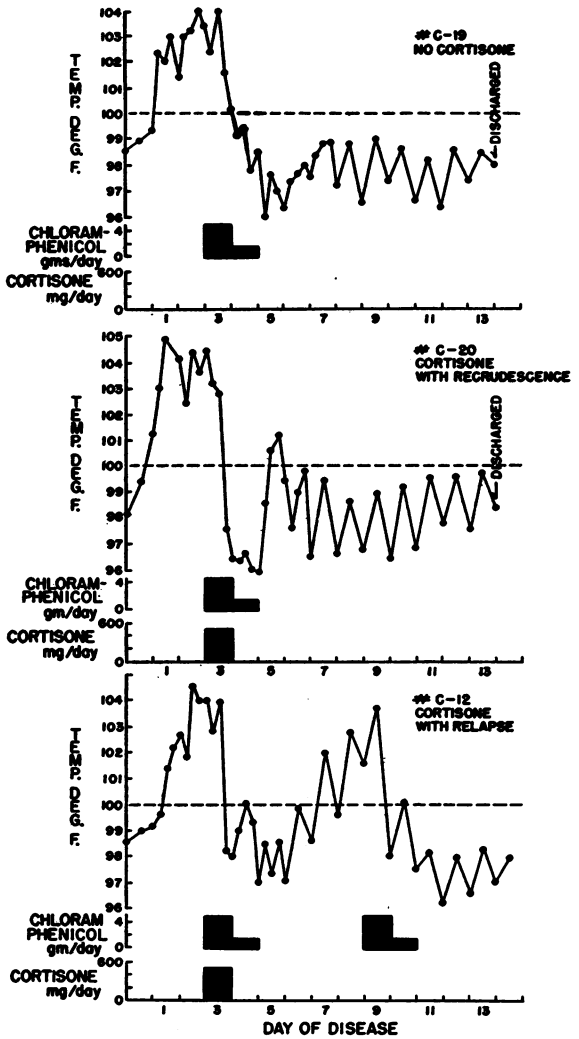

FIG. 2. FEVER CHARTS OF PATIENTS WITH SCRUB TYPHUS, SELECTED TO ILLUSTRATE (a) HYPOTHERMIC RESPONSE TO CHLORAMPHENICOL THERAPY ALONE, (b) POSSIBLE ESCAPE PHENOMENON, AND (c) RELAPSE

regression of headache was not quite as rapid as defervescence.

None of these patients experienced such marked hypothermia as did some of the typhoid fever patients. Almost half of the scrub typhus patients treated with antibiotic alone exhibited an oral temperature as low as 96° F. for a short time after therapy; this is illustrated by the temperature curve of volunteer C-19 in Figure 2. The chart of volunteer C-20 (Figure 2) was selected for presentation partly because it demonstrated a minimum temperature as low as that attained in any of the cortisone-treated group.

Some patients experienced a recurrence of fever, toxemia and rickettsemia shortly after termination of therapy. Such a sequence of events, which is interpreted here as relapse, is illustrated by Volunteer C-12 in Figure 2; he showed a characteristic step-wise increase in fever over a period of several days. One of the seven patients treated with chloramphenicol and four of the eight volunteers who received cortisone in addition to antibiotic showed relapse of this type. The observed relapse rate in the cortisone-treated group was numerically greater than that of the group treated only with chloramphenicol. However, in this small series, the difference was not statistically significant; nor was the rate greater than that of another group of volunteers similarly infected with a different strain of scrub typhus rickettsiae the previous year and treated with the short course of antibiotic, but without cortisone (26).

A picture exactly analogous to the escape from cortisone exhibited by some of the typhoid fever patients was not observed among the scrub typhus patients, possibly because the rapid response to antibiotic therapy itself in scrub typhus leaves little time for such occurrences. Volunteer C-20 (Figure 2) and the patient with naturally acquired scrub typhus (Figure 3) were the only instances in which escape may have occurred. However, it should be pointed out that the occasional patient treated with the short course of antibiotic alone may show a similar brief return of fever after cessation of therapy.

Rickettsemia has been observed by previous groups to persist for as long as 48 hours after institution of specific antibiotic therapy; the introduction of cortisone to the therapeutic regimen did not alter this phenomenon.

The single case of naturally acquired scrub typhus treated with the combined cortisone-chloramphenicol regimen was a 20-year-old British soldier with full-blown disease of seven days duration. A graphic summary of this case appears in Figure 3. Defervescence occurred as promptly in this individual as in the patients who had been febrile for only 48 hours when treated. Moreover, the minimum temperature attained was no lower than in those treated early.

DISCUSSION

The practical need for control of toxemia in typhoid fever is emphasized by the experience of

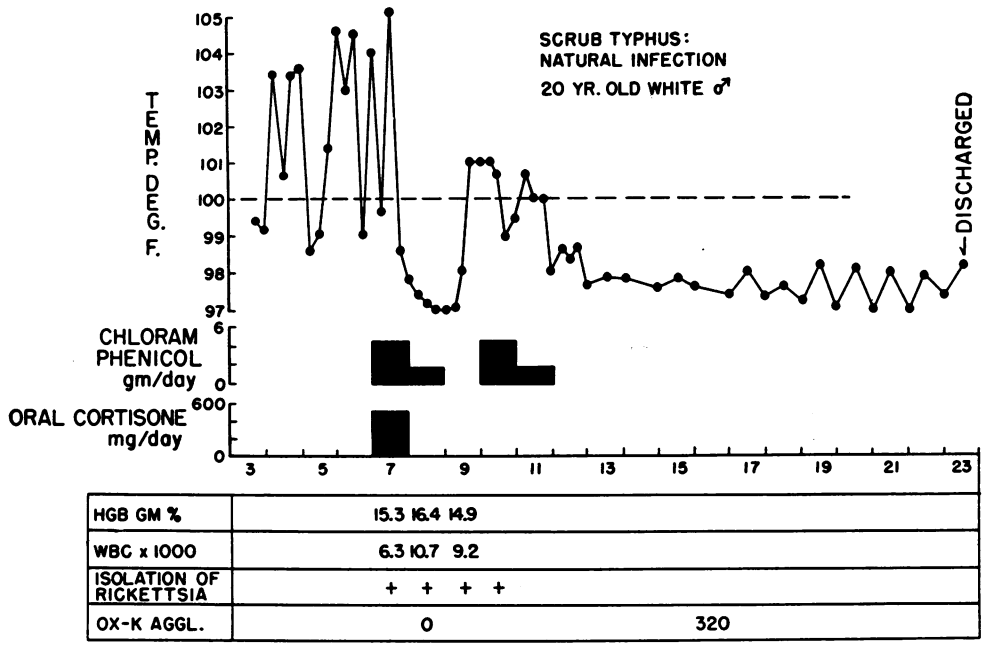

FIG. 3. CLINICAL RESPONSE OF SCRUB TYPHUS PATIENT TREATED WITH CHLORAMPHENICOL AND CORTISONE IN SEVENTH DAY OF NATURALLY ACQUIRED DISEASE

Stuart and Pullen (1), who found it a major cause of death in patients given only non-specific supportive treatment, and by the continued reports of some deaths associated with toxemia despite chloramphenicol therapy (3, 5, 27). The results of the present study confirm the earlier findings (6, 7), *i.e.*, that administration of cortisone in the initial phases of chloramphenicol therapy induced, within a few hours, a rapid and dramatic regression of the clinical manifestations of the febrile-toxic state in typhoid fever. Indeed, the oral preparation of hormone employed in the current investigation produced its effects with greater rapidity than did the intramuscular preparation used in the earlier studies. The prompt clinical improvement induced by cortisone without interference with the bacteriologic control afforded by chloramphenicol suggests that this hormone may be administered profitably to those typhoid fever patients who are so ill at the time antibiotic therapy is begun that the physician may anticipate death of the patient in the three or four days that separate initiation of antiobiotic therapy from the defervescence and detoxification that ordinarily follow this treatment. The combined experiences of our groups in over 30 patients treated with a cortisone-chloramphenicol regimen provide the background for our opinion that it is desirable to shorten the toxic-febrile state in so far as possible in the critically ill typhoid patient. These patients stand in contrast to those with disease of mild to moderate severity who respond satisfactorily to antibiotic therapy alone.

The mechanisms by which cortisone produces its effects in typhoid fever remain essentially unknown. Of some interest, however, is the escape phenomenon noted in patients in whom cortisone administration was discontinued a day or so before the anticipated occurrence of the defervescence induced by the antibiotic. The alleviatory effect of cortisone on typhoid pyrexia is transient and appears to dissipate itself within a day after the last oral dose of hormone. The short duration of the cortisone effect is in general agreement with published studies (28) of the duration of cortisone-induced eosinopenia in normal subjects. The present observations indicate that cortisone does not eradicate the cause of the toxic state and suggest that it exerts no direct neutralizing action on the typhoidal toxins; the latter is in accord with results of animal experiments (29). Furthermore, the persistence of bacteremia in patients treated with cortisone alone (6), despite clinical improvement, has shown that there is no suppression of

the growth of the organism by the hormone. The observed effects would appear, then, to be brought about by an action on the host through physiological mechanisms. It is worth re-emphasizing that neither the antibiotic nor the hormone "cure" the patient; they merely buy time for him to develop the immune mechanisms necessary for permanent recovery and to repair the pathologic injuries of disease.

The toxic typhoid patient does not display the signs of a patient suffering from acute adrenal cortical insufficiency, except possibly for the rare occurrence of a state resembling the Waterhouse-Friderichsen syndrome (30). Moreover, the defervescence observed in typhoid fever patients in response to administration of ACTH (8, 9, 31) suggests a reasonable degree of adrenal cortical reserve function even in these severely ill patients. It is, therefore, unlikely that administered cortisone produces the observed effects by simple replacement therapy according to the customary connotation of this term.

The eosinopenia noted in the majority of the 18 patients in the present series, though suggestive of adequate adrenal function, is difficult to assess, since bacterial pyrogens are known to produce leukopenia, eosinopenia and subsequent leukocytosis ("alarm reaction" blood picture) in adrenalectomized dogs (32).

There is an increasing number of reports, recently reviewed by Thomas (33), of spontaneous infections arising in the course of cortisone therapy and of the enhancement and dissemination of experimental infections under the influence of this steroid. The exact nature and relative importance of the factors involved in the cortisone-altered host response to infection remain ill-defined. Thus, rapidly spreading and widely disseminated infections, with bacteremia, are produced in animals by organisms which normally cause only localized infections (34, 35), yet the polymorphonuclear leukocytes present are still capable of phagocytosis and some of the blood-clearing mechanisms apparently continue to operate (34–36). In contrast to such bacterial infections, Aikawa and Harrell (37) observed that cortisone had a life-prolonging effect in guinea pigs infected with *R. rickettsii;* however, the ultimate mortality rates were the same in the treated and control groups. Contradictory reports have been forth-coming on antibody production (33–35, 38), but the reaction of antibodies with antigens is not prevented and previously immunized animals continue to show some degree of resistance to infection while under the influence of this steroid (33, 35). It is worth noting that the enhancement of infection in experimental animals, which are not given the benefit of specific antimicrobial measures, is usually greatest when cortisone is given over relatively long periods of time and when administered prior to the introduction of the infectious agent (33). Relatively little work has been reported which deals with experimental infection in animals treated concurrently with cortisone and antibiotics. Therefore, the observations of Glaser and Loeb (39) are of particular interest in connection with the present study. These authors observed that rats with streptococcal pneumonia had less severe disease when given cortisone and penicillin than did infected animals which received only penicillin.

In the typhoid fever patient adequately treated with chloramphenicol, multiplication and spread of the invading micro-organism are quickly controlled (2, 10, 23). The experience gained in the earlier studies (6, 7), and in the present investigation indicates that the addition of cortisone to the antibiotic regimen does not interfere with the rapid disappearance of *S. typhosa* from the blood.

Protection against death from bacterial toxins which is afforded by cortisone is rather striking in the case of experiments with adrenalectomized animals (40, 41). On the other hand, a similar protective effect is not so readily observed in animals with normal adrenals to whom extra cortisone is given (29). Although these animal experiments are of considerable interest, they do not help to clarify our understanding of the relief of the clinical manifestations of the toxic-febrile state elicited in man by cortisone.

The febrile-toxic state of scrub typhus was relieved as rapidly by cortisone administered in conjunction with chloramphenicol as was the similar state in typhoid fever. However, since the response of scrub typhus to specific chemotherapy is usually very rapid, the cortisone effect in this disease is primarily of academic interest. Recently, similar findings have been reported (42) in patients with another rickettsial disease, *i.e.,* Rocky Mountain spotted fever, which generally responds more slowly to antibiotic therapy than does scrub typhus.

SUMMARY

Eighteen typhoid fever patients were treated between the 9th and 16th days of their disease with chloramphenicol and with different schedules of oral cortisone in order to learn more about the effects of the steroid in this disease. In addition, the responses of eight scrub typhus patients treated with a uniform regimen of combined cortisone-chloramphenicol therapy were compared with those of a comparable group of seven patients who received antibiotic therapy alone.

The clinical manifestations of the febrile-toxic state in typhoid fever and in scrub typhus disappear in about six hours after initiation of such a combined therapeutic regimen. In both diseases defervescence is accompanied by a general sense of well-being and an improved appetite which simplifies maintenance of an adequate liquid and caloric intake during the acute phases of the diseases.

Control of bacteremia was prompt in typhoid fever treated with the combined regimen and was comparable in all respects to cases treated with chloramphenicol alone. The incidences of relapse and of complications did not appear to be influenced by the inclusion of cortisone in the therapeutic regimen.

The antipyretic effect of a single dose of oral cortisone was temporary and fever recurred in typhoid patients unless administration of this hormone was continued. Experience with the different dosage schedules of cortisone in patients with this disease who were receiving uniform antibiotic therapy indicated that, in order to avoid recrudescence of symptoms, administration of the steroid must be continued for a period of time which corresponds to that required for patients to become afebrile with a regimen consisting solely of chloramphenicol, *i.e.*, about four days.

Since the response of scrub typhus to antibiotic therapy is generally very prompt, the accelerated defervescence afforded by cortisone in this disease is primarily of theoretical interest. On the other hand, selected severe cases of typhoid fever may benefit by the administration of cortisone during the period normally required for the patient to become afebrile from the antibiotic therapy. The importance of adequate control of infection by simultaneous specific chemotherapy is emphasized in patients receiving cortisone.

The mechanisms by which cortisone controls the toxic-febrile state in these diseases remain unknown; however, the observations of others with animals are discussed in the light of our clinical experience with men.

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APPENDIX A.

CHLORAMPHENICOL COMBINED WITH DIFFERENT SCHEDULES OF ADMINISTRATION OF ORAL CORTISONE IN TYPHOID FEVER

GROUP	PATIENT				TREATMENT								RESPONSE TO TREATMENT					SEROLOGY	
	NO.	AGE	SEX	WT. KG.	DAY OF DISEASE BEGUN	CORTISONE MG./KG. ON DAY				CHLORAMPHENICOL FIRST COURSE		TOTAL DRUG GM.**	CORTISONE EFFECT BEGAN, HR AFTER FIRST R_x	CORTISONE EFFECT ENDED, HR. AFTER FIRST R_x	LAST DAY FEBRILE DAYS AFTER FIRST R_x	COMPLICATIONS* TYPE	COMPLICATIONS* ONSET DAY OF DISEASE	TYPHOID "O" AGGLUTININ TITER† ACUTE	TYPHOID "O" AGGLUTININ TITER† CONV.
						1	2	3	4	DAYS	GM.								
I	1	15	F	33	10	10.1				7	15	36	4	18	5	R	49	40	80
	2	16	F	54	11	9.3				16	49.5	61.5	4	28	6	B,C	17,59	1280	640
	3	32	M	41	13	12.2				6	19.5	31.5	6	34	4			40	20
	4	35	F	45	14	11.1				7	22.5	34.5	8	32	4	H		<10	320
	AVERAGE				12	10.7							5.5	28	4.8				
II	5	10	F	24	12	8.3	6.3			7	17	25	6	54	4	H		2560	160
	6	25	M	56	13	5.4	3.6			7	22.5	34.5	4	60	4	H		160	160
	7	10	M	22	16	9.1	3.4			4	7	13	4	60	3	I,H	19	160	80
	8	10	F	23	10	8.7	6.5			7	17	25	8	48	4			80	160
	9	7	M	17	14	8.8	5.9			7	11.3	22.5	8	56	4	R,H	39	80	320
	AVERAGE				13	8.1	5.1						6.0	56	3.8				
III	10	28	F	33	12	6.7	4.5	2.3		7	22.5	34.5	8	32	6			80	160
	11	16	F	45	10	4.4	2.2	1.7		7	22.5	34.5	8	48	4	H		160	320
	12	18	F	40	9	7.5	5.0	2.5		4	13.5	35.5	6	–	<1			80	80
	13	11	M	29	15	6.9	4.3	2.6		5	13.0	21.0	4	–	<1	H		20	80
	14	11	F	26	11	7.7	4.8	2.9		6	15.0	23.0	4	72	3	H		2560	1280
	15	9	F	17	14	8.8	5.9	1.5		7	8.8	14.8	8	56	4	I,H	15	160	80
	AVERAGE				11.8	7.0	4.4	2.3					6.3	52‡	2.9				
IV	16	21	M	47	11	6.4	4.3	2.1	2.1	4	13.5	25.5	6	–	<1	I	13	40	80
V	17	14	F	25	10	6.0	4.0	8.0		7	11.8	17.8	8	60	4	B,H	10	160	320
	18	14	F	33	12	4.5	6.1	9.1		8	17	38.5	48	72	4	BIRP	11,14,39,45	80	160

* KEY TO COMPLICATIONS: R = RELAPSE; B = BRONCHOPNEUMONIA; C = CHOLECYSTITIS; I = CARDIAC IRREGULARITY; P = INTESTINAL PERFORATION; H = HYPOTHERMIA.

** SUM OF DRUG GIVEN IN FIRST AND SECOND COURSE AND IN RELAPSE.

† RECIPROCAL DILUTION.

‡ AVERAGE OF THE FOUR PATIENTS WHO ESCAPED FROM CORTISONE.