EFFECTIVE TREATMENT AND PREVENTION OF TYPHOID FEVER: UPDATED*

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For more than three decades, specific chemotherapy has been available for treatment and amelioration of the manifestations of acute typhoid fever. Yet, in spite of specific therapy with either chloramphenicol, ampicillin or trimethoprim-sulfamethoxazole, important problems are unsolved.

The present report describes a significant reduction of mortality in severe typhoid fever by use of high dose dexamethasone therapy and the encouraging findings that typhoid can be prevented by use of an oral, viable, attenuated vaccine.

DEXAMETHASONE/CHLORAMPHENICOL TREATMENT OF PATIENTS CRITICALLY ILL WITH TYPHOID FEVER

In 1948, it was found, virtually by accident, that a patient, thought to have scrub typhus fever (tsutsugamushi disease, tropical typhus) failed to respond to chloramphenicol treatment in the anticipated thirty hours (1). The patient, Mohammed Ali (not Cassius Clay), transferred from a rubber estate in Kuala Lumpur, Malaysia, appeared just as ill the day after initiating chemotherapy. A second patient with scrub typhus had been hospitalized with him from the Seaport Rubber Estate. This area had provided a steady flow of scrub typhus cases. The next day, after beginning antibiotic treatment for his presumed scrub typhus, Mohammed Ali was found to have a distended abdomen, diarrhea and continued toxic signs. Typhoid fever was then suspected and antibiotic treatment was continued in spite of the fact that we were involved in a prospective study to evaluate chloramphenicol in scrub typhus. Chloramphenicol was continued and in about forty-eight hours, bedside signs indicated improvement, such as the patient's appearance, pulse and blood pressure. On the following day, specific cultures of peritoneal exudate

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obtained from inoculated mice revealed gram negative motile bacilli; the rickettsial etiology of scrub typhus was now disproved. The patient became afebrile in three days with abatement of toxic manifestations.

This fortunate chance observation prompted an efficacy study of chloramphenicol in typhoid fever which proved to be favorable. In vitro studies had not suggested that chloramphenicol would be effective in typhoid patients. Hence, there was no initial plan for this study. Based on the results in ten patients, a preliminary report was published in 1948 which represented the first specific effective therapy for this ancient enteric disease (1). This report and others to follow (2–4) revealed certain limitations of therapy: 1) a period of three to three and a half days lapsed before clinical improvement and defervescence occurred; 2) the classic complications of perforation with peritonitis and intestinal hemorrhage occurred particularly when specific treatment was started late in the illness (second to third week); 3) relapse of clinical manifestations with bacteremia occurred in a significant number of patients at rates up to 20 per cent; and 4) the typhoid carrier state, which occurred previously at a rate of about 3 per cent, occurred after antibiotic treatment (2–4).

A serious limitation of antibiotic therapy was continuation of toxic signs much longer than the twenty-four to thirty-six hour response experienced in penicillin treatment of pneumococcal pneumonia. Various mechanisms to explain continued toxic manifestations were proposed (5), but none have been confirmed. During this period in early 1950, Finland, et al (6) showed the dramatic abatement of toxic signs in pneumococcal pneumonia patients treated with ACTH. We treated six typhoid patients with bacteremia using only corticosteroids (steroids) in doses of about 200 to 300 mg daily for one to three days (7, 8). We were astonished to observe the fever abate rapidly, within the first twenty-four hours of treatment with parallel improvement in the toxic signs. These dramatic responses occurred in spite of continued bacteremia with *S. typhosa* (8).

Several of these early patients were treated with large doses of cortisone combined with chloramphenicol by Lewis Flinn, of Wilmington. He telephoned about a young girl very ill with typhoid, so ill that she was admitted to a seriously ill unit with marked toxemia, severe abdominal pain and possible peritonitis. Chloramphenicol was given with large doses of cortisone (300 mg) daily which is a high dose for a 13 year old child. The next day Lew enquired, "What am I to do, the child yesterday critically ill, is now walking about the ward as if nothing is wrong." Therapy was continued and she recovered fully from typhoid fever without surgical intervention. Perforation of an intestinal ulcer had not occurred.

This ancillary form of therapy was recommended when glucocortico-

steroids became generally available. In some instances, steroid therapy alone was used in typhoid patients. This was not advised in the initial publication (7–9). Nevertheless, in spite of firm convictions, there is no convincing evidence in the published literature of the efficacy of glucocorticoid therapy in typhoid patients (10).

More recently, it became apparent that a significant death rate occurs in severely ill patients in spite of therapy with chloramphenicol, ampicillin or trimethoprim-sulfamethoxazole. This is independent of the drug resistance problem (11). Correspondence between the NAMRU-2 Medical Unit in Jakarta, Indonesia, and Baltimore (SLH and TEW) raised the suggestion of a controlled efficacy trial because of an indicated need for better treatment regimens. This was dictated by the realization of a mortality of approximately 20 per cent in severely ill typhoid patients in spite of chloramphenicol treatment. An appropriate plan of study was formulated which provided for careful selection of seriously ill patients randomly chosen and a simple test treatment regimen using chloramphenicol alone or chloramphenicol plus high dose dexamethasone therapy for two days. Conventional peer reviews by appropriate committees with approvals were followed (12).

METHODS

The study was randomized, placebo-controlled, double blind. The sample size was determined so as to detect with 99 per cent probability a real difference between postulated case fatality rate of 10 per cent and 35 per cent in the dexamethasone and placebo groups, respectively.

Case Selection and Definition of Illness: All patients with febrile illnesses admitted to the Infectious Diseases Hospital in Jakarata from April 15, 1981 to July 15, 1982, were study candidates.

Definitions:

Severe typhoid fever: A febrile patient in shock or with abnormal alertness with *S. typhi* or *S. paratyphi* in culture of blood, marrow or aspirate.

Abnormal alterness: A delirious, obtunded, stuporous or comatose patient. Delirium was typified by markedly confused thinking and speech. A drowsy patient, coaxed to respond to verbal stimuli was obtunded. A patient who failed to respond verbally to any stimuli but withdrew from cutaneous stimuli was classified as stuporous. Comatose patients failed to respond to cutaneous stimuli.

Shock: A condition with systolic blood pressure less than 90 mm Hg for adults (>12 years) and less than 80 mm Hg for children (<12 years) and evidence of *decreased organ perfusion.* The latter was defined as abnormal alterness, cold, clammy skin, constricted peripheral veins or

oliguria after rehydration (<20 ml urine output/hour). A patient with abnormal blood pressure without evidence of decreased organ perfusion but with tachycardia (>120 beats/minute) was given chloramphenicol and a fluid infusion based on assessment of hydration. If after fluid administration the patient remained hypotensive with tachycardia, shock was considered present.

Borderline shock: Included those adult patients with systolic blood pressure less than 90 mm/Hg or children less than 80 mm/Hg without decreased organ perfusion, or adults and children with systolic blood pressure of 90–99 and 80–89 mm/Hg, respectively, and evidence of decreased organ perfusion.

Antibiotic therapy: Chloramphenicol was given in doses of 50 mg/kg as an initial dose intravenously and subsequent daily, divided intravenous doses until defervescence and for approximately two weeks thereafter. When feasible, the oral route was used.

Hormone therapy: Dexamethasone was given intravenously in doses of 3 mg/kg as an initial dose and subsequent daily doses of 1 mg/kg every six hours for eight doses. The dexamethasone and normal saline placebo were indistinguishable colorless solutions presented in identical numbered boxes of ampules which were randomized before delivery to Jakarta.

General management: All patients were managed in an intensive care facility by nursing and medical workers fully trained in clinical and therapeutic practices. Intravenous fluids were administered equally to the two treatment groups and superimposed infections were specifically treated as indicated by appropriate bacterial smears and cultures. There was continuous nursing and medical coverage.

Clinical Results

The random selection of patients was satisfactory with treatment (dexamethasone-chloramphenicol) and placebo (chloramphenicol) groups comparable with respect to age, sex, days of illness preceding therapy, incidence of blood and marrow cultures, minimal inhibitory concentration of chloramphenicol for typhoid strains, pleocytosis and protein concentration of CSF, hematocrit, leukocytic and platelet counts (Table 1).

Not shown in Table 1 are the respective weights and CSF findings for each group. Weights were comparable, 38.3 kg for the steroid group and 35.8 for controls. Several patients in each group showed minimal numbers of PMN's and monocytes in the CSF not regarded as significant. CSF protein contents for each group were comparable, 41.0 and 35.0 (mg/dl), treatment vs placebo, respectively. In Table 2 is given the clinical status

TABLE 1
Comparability of Study Groups Before Therapy

Criteria	Chloramphenicol Dexamethasone	Chloramphenicol
Total Cases	20	18
Day of Illness*	12.8	13.2
Temperature C° (AV)*	39.1	39.0
Culture—Blood	15.0	15.0
Marrow	20.0	18.0
MIC (ug/ml) Chloro*	4.1	4.3
Hematocrit (%)*	35.1	34.1
Leukocyte Count Mean	5,816	5,493
Platelet Count Mean	70,000	67,000

Av. age 20, each group; 18 males, 20 females; av. wgt. comparable.
* All values as mean ± SEM (range).

TABLE 2
Clinical Status at Time of Beginning Therapy

Clinical Assessment	Chloramphenicol/Dexamethasone	Chloramphenicol
General	No. %	No. %
Toxic	13* (65)	12 (66)
Severely Toxic	6 (30)	6 (33)
Alertness		
Delirium	11 (55)	12** (67)
Delirium (obtunded)	5 (25)	3 (17)
Stupor	4 (20)	2 (11)
Circulatory Status		
Normal	14 (70)	13 (72)
Borderline shock	4 (20)	3 (17)
Shock	2 (10)	2 (11)
Chance of 24 Hour survival		
Moderate	12 (60)	16 (89)
Poor	8 (40)	2 (11)

* 1 Additional patient mildly ill
** 1 Additional patient normally alert

of the two groups at the time of initiating therapy; the data show that they were well-matched.

Response to Dexamethasone

Two of twenty patients who received dexamethasone plus chloramphenicol died and ten of eighteen patients who received chloramphenicol alone died (Table 3). The 10 per cent case fatality rate in the dexamethasone-chloramphenicol group was significantly lower than the 55.6 per cent case fatality rate in the chloramphenicol group ($p = 0.003$).

TABLE 3
Case Fatality
Chloramphenicol vs Dexamethasone/Chloramphenicol

Drug	Total Cases	Died	Lived	Case Fatality Rate Per Cent
Chloramphenicol Dexamethasone	20	2	18	10.0*
Chloramphenicol	18	10	8	56.6

* Case fatality in dexamethasone group significantly lower ($p = .003$, Fisher's exact test, one tailed)

Clinical Course and Complications in Survivors

Among surviving patients, the temperature reached normal more rapidly with dexamethasone (74.4 ± 23.9 hours, mean ± SEM) than placebo (203 ± 29.4 hours $p < 0.01$). General improvement coincided with the improved febrile response. There was no difference between groups with respect to return of alertness or total days hospitalization.

Among survivors in either group, there were no differences regarding gastrointestinal bleeding, transfusions given or presence of pneumonia, urinary tract infections or non-Salmonella bacterial sepsis occurring forty-eight hours after beginning drug therapy. No survivors developed intestinal perforation.

Comparability Re: Bacteriologic Findings, Chloramphenicol Levels and Use of Other Antimicrobials

Table 1 shows the close similarity of positive blood and marrow cultures for *S. typhi* in each group. In addition, twenty-two patients (58 per cent) showed positive rectal swab cultures, two positive urine cultures and one CSF isolate for *S. typhi*. The latter was a placebo survivor. Blood cultures for *S. typhi* were positive one day (78 per cent) and two days (28 per cent) after initiating therapy; two patients were positive on day four. The incidence of *S. typhi* bacteremia was similar in each group.

Ten of twenty-six survivors in either group developed non-Salmonella bacteremia forty-eight hours or more after beginning therapy. The bacteria isolated were *Pseudomonas aeruginosa* (six patients), and *Klebsiella pneumoniae*, *Flavobacterium*, *Actinobacter* in one each. There was no significant difference in superimposed infections in either group. Other conventional antibiotics, devoid of an anti-typhoid effect were given to help control these infections.

All chloramphenicol concentrations including trough levels measured at 11, 17 or 23 hours after the first dose of chloramphenicol were

comparable; they were 13.6 ± 0.5 μg/ml (mean ± SEM) in twelve dexamethasone treated patients and not significantly different from the level of 12.3 ± 0.9 μg/ml in thirteen placebo patients.

Follow-up: Twenty-two of twenty-six convalescent patients were examined from seventeen days to sixteen months after hospital discharge. All survivors including eighteen in the dexamethasone group remained in good health without relapse or intestinal bleeding, and no rectal swab cultures were positive for *S. typhi*. Four patients moved their residence from Jakarta, three of whom are known to be well.

Mechanism of Dexamethasone Activity

The mechanism by which dexamethasone reduced mortality is unknown. Since tolerance develops rapidly, circulating endotoxin does not appear to be the major factor responsible for the sustained pyrexia and toxemia of typhoid fever. It could account for acute exacerbations of illness, including shock, since patients were found hyperreactive to the initial injection of *S. typhi* endotoxin given intravenously (13). In addition locally released endotoxin can enhance the local inflammatory response and possibly thereby contribute to pathogenesis. In the current study, many patients had endotoxin in their plasma and cerebrospinal fluid (unpublished data). It is true that corticosteroids ameliorate the clinical effects of bacterial endotoxin (13).

Perhaps the explanation resides in a blocking mechanism of toxic products of macrophages which are induced by *S. typhi*. Lipopolysaccharides such as endotoxin stimulate macrophages to produce monokines, arachidonic acid and its metabolites, and free oxygen species (14–17). Such factors cause fever, initiation of the clotting mechanism, vascular instability and cytotoxicity, all features of severe typhoid fever (15–21). Corticosteroids reduce production of arachidonic acid and its metabolites and act an antioxidants (22–26). They reduce levels of macrophage-derived lysosomal enzymes and render normal macrophages unresponsive to lymphokines (27, 28). Evidence for suppression of one monokine, endogenous pyrogen, has been summarized previously (29).

It is suggested that products of macrophages released consequent to interaction of *S. typhi* endotoxin with these cells are responsible for the significant manifestations of typhoid fever and that dexamethasone reduces the levels or the physiological effects (or both) of these products and hence, reduced mortality. The sequential relationship, sites of production, release and stages of inhibition remain to be determined.

Status of Typhoid Immunization

There has been controversy regarding efficacy of typhoid vaccine which was reviewed briefly and reported to the Association in 1966 (30).

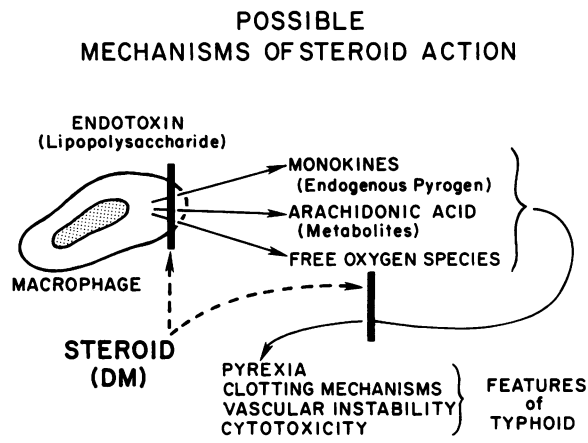

FIG. 1. Suggested mechanisms of action of dexamethasone: (A) decreases or impedes production of toxic macrophage products, or (B) reduces physiologic effects of such products.

It was predictable that inactivated vaccines would be of limited effectiveness because even the immunity following untreated typhoid fever is incomplete; relapses occurred in about 10 per cent of patients in the pre-antibiotic era. Evidence of failure to develop resistance to typhoid was revealed in Marmion's 1953 report of second attacks of illness in British Air Force troops in Egypt; fifty-four men became reinfected during a second epidemic which occurred within five months after the first. Attack rates were similar regardless of whether chloramphenicol was given in the initial outbreak (31).

Controlled field trials using phenol (L) or acetone (K) inactivated typhoid vaccine were carried out under World Health Organization sponsorship in British Guinea, Poland and Yugoslavia. Each vaccine appeared to be protective particularly in vaccinees of school age (32–34). Trials in British Guinea were evaluated over six years and protection was said not to have waned.

From early 1950 until 1966, parallel studies were performed in volunteers using K (acetone inactivated) and L (phenol inactivated) typhoid vaccines to determine efficacy under field conditions. After subcutaneous inoculation, the efficacy of protection was similar and showed about a 70 per cent protection rate provided the infecting dose of typhoid bacilli was low, ie, 10^5 viable bacteria (100,000 typhoid bacilli). Such infections might occur in nature after ingestion of contaminated water in contrast to heavier infections which follow ingestion of contaminated food (13, 35).

The volunteer studies using phenol or acetone inactivated vaccines correlated with the WHO field trials and suggested that vaccine induced

resistance by the subcutaneous route would not be protective against infection by heavily contaminated foods (13, 35).

In 1968, our focus in volunteers turned to oral immunization to stimulate resistance of intestinal barriers such as copro-antibody or cellular immune factors in the lamina propria. Several types of oral vaccine which contained killed typhoid bacilli in keratinized tablets were evaluated. These included Typhoral (Behring Co., Somerville, N. J.), containing inactivated *S. typhi* and paratyphoid A and B bacilli and Taboral (Swiss Serum and Vaccine Institute, Bern, Switzerland), a monovalent vaccine with 100×10^9 acetone-killed *S. typhi* (strain Ty 2). Ingestion of these tablets stimulated increases of circulating O, H, and Vi antibodies in various vaccinees not exceeding 50 per cent. Following ingestion of a 25 per cent infectious dose (100,000 viable typhoid bacilli), volunteers showed some resistance to infection comparable to those vaccinated by the parenteral route (13).

Biopsy specimens of the upper intestine taken during the incubation period of typhoid fever in volunteers showed mild enteritis and granuloma formation in the lamina propria specifically in those who ultimately developed active illness (36). The assumption was made that active stimulation of antibody-producing cells in the lamina propria or elsewhere must occur before resistance to infection is established.

Logic suggested that greater resistance might be promoted in the intestinal tract with a vaccine containing viable *S. typhi*. A streptomycin-dependent mutant strain of *S. typhi* (S 27) showed efficacy in mice (37). In volunteers, an orally vaccinated group showed a much better protection rate than that observed in other trials (38) and fewer *S. typhi* were isolated from stool specimens in the viable *S. typhi* vaccine group, when compared with controls. Unfortunately, the lyophilization process, necessary to produce the vaccine commercially, resulted in significant reduction of protective efficacy.

Germanier, et al. developed a Ty 21a attenuated mutant strain which given orally caused no significant side effects in volunteers and resulted in an 87 per cent protection rate after a standard infectious dose of pathogenic *S. typhi*; typhoid fever occurred in 53 per cent of control volunteers. The vaccine regimen was five to eight doses (3×10^{10}) of living, attenuated, mutant organisms (39).

The Ty 21a oral vaccine tested in Alexandria, Egypt showed striking protective efficacy (40). Three doses of the mutant strain, each dose containing $1\text{–}8 \times 10^9$ live bacteria, were given to school children at two-day intervals preceded by sweetened, aromatized sodium bicarbonate to neutralize gastric acidity. The placebo, grossly indistinguishable from the vaccine, was prepared from a sterilized powdered milk and sugar solution. Diarrhea did not occur; mild abdominal pain, nausea and vomiting

occurred in a very few children. Other reactions such as fever were minimal. There were no isolates of the vaccine strain from a large number of stool specimens examined two and fourteen days after the third vaccine dose. Spread of the vaccine strain to other children was not detected.

Analysis of findings after three years observation in 16,486 children given the attenuated strain (initial age, 6 to 7 years) showed striking results. The attack rate of typhoid fever was 0.2 per 10,000 children per year (one confirmed case) in contrast to five cases per 10,000 children per year (22 cases) in the control group of 15,902 children.

A group of 25,628 children not given vaccine or placebo were simultaneously evaluated; the observed attack rate was five cases per 10,000 children per year (38 confirmed cases): Wahdan, et al. (40) reported a protection rate afforded by the vaccine of 95 per cent for *three* years, a remarkable achievement (41).

Further trials of the Ty 21a strain using a two dose, enteric coated vaccine, without preliminary bicarbonate ingestion are under evaluation in Chile. For nine months following immunization, the protection rate exceeded 70 per cent. When re-evaluated after two years, there was no evidence of resistance to typhoid in the vaccines (42). This raises the question of the need to neutralize gastric acid with bicarbonate. Also, it is possible that the mechanism of immunity to typhoid fever involves local intestinal factors such as coproantibody (IgA) as occurs in Asiatic cholera. Such protection after immunization for chlorea is of short duration. Our working concept is that living attenuated *S. typhi* given orally stimulate cellular immune mechanisms via the lamina propria. Results of other field trials are awaited.

Conclusions

Seriously ill patients with typhoid fever who have delirium and shock generally recover following the combined use of high dose dexamethasone and chloramphenicol therapy whereas chloramphenicol used alone is much less effective. Steroids are unnecessary for treatment of the mild to moderately ill typhoid patient.

Typhoid fever may be effectively prevented by the oral administration of living, attenuated, mutant strains of *Salmonella typhosa* given by capsule preceded by sodium bicarbonate to neutralize gastric acidity. Protection is much better than that resulting from the subcutaneous injection of inactivated vaccines.

Addendum

During the past year, an additional ninety seriously ill typhoid patients have been treated with the combined treatment regimens. There have

been three deaths, one occurred postoperatively after laparotomy for intestinal perforation and peritonitis.

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DISCUSSION

Flinn (Wilmington): Thank you, Ted, for recalling that 13 year old patient. I've had great success since then because I've not seen a case of Typhoid. I had not the opportunity for medical travels as you have and I know I would not have had the expertise which you always exhibit and have on this occasion of developing a most interesting and valuable piece of clinical work. Thank you.

Hook (Charlottesville): Dr. Woodward, I would like to thank you also for this very nice review and the interesting new observations relating to the beneficial effect of corticosteroids. I would like to ask you to comment further on this latter observation. You seem to be drawing certain analogies between typhoid fever and the clinical state often referred to as "gram-negative sepsis" in which endotoxin is thought to play an important role in pathogenesis. It has been exceedingly difficult to show—at least to document—a beneficial effect of corticosteroids in the usual type of gram-negative sepsis. Your observations are striking in showing a beneficial effect of corticosteroids in reducing mortality in patients with severe typhoid fever. I wonder if this suggests different mechanisms in the pathogenesis of the toxemic state in typhoid as compared to sepsis with conventional gram-negative bacilli. Would you please comment.

Woodward: Thank you, Ed. Dr. Hook has, of course, put his finger on a very important point and it is difficult or impossible to extrapolate clinical results from one illness to another; typhoid fever differs in many ways from other gram negative infections. The clinical manifestations and responses to treatment differ. No, Ed, we do not wish to generalize and propose that because there appears to be a rather clear-cut therapeutic response in typhoid, it is necessarily so in other important gram negative infections. If this were true in other gram negative infections, it would be clear from other published reports and that is not the situation. We fail to understand fully the mechanisms of illness in typhoid. An arbitrary period of 48 hours was selected to administer corticosteroids. Perhaps one day is adequate, but it is doubtful whether another controlled experiment will be performed. It is unknown whether such a high dose of dexamethasone is needed; lower doses might be adequate. This decision was derived from experience in gram negative infections. In animals, the work of investigators show that high doses of steroids benefit animals overwhelmingly infected with gram negative bacteria. Dr. Hook has made a very important point. We have presented data which we believe to be correct; statisticians have examined the data using all variables and reach valid conclusions each time. Dr. Hook is correct in not extrapolating these results to gram negative infections other than typhoid fever.

Moser (Philadelphia): Ted, in either of those series were there any relapses? I don't know how long the study went.

Woodward: One year. There were several relapses and treatment was with chloramphenicol in each treated group. To our knowledge, there were no permanent carriers; patients were checked by rectal swab examinations. Follow-up in the 38 patients extended over 17 days from time of hospital discharge to a year and a half. Only about three patients could not be reached in a year, but there was correspondence which indicated everyone was well. There were no patients in either of the two study groups who perforated the intestine. There were some superimposed infections which were equally distributed in either group. The complications of pneumonia and urinary tract infections were similar in either group.

Moser (Philadelphia): Dr. Flinn, your patient who got up and started running around

on cortisone alone reminds me that when cortisone first became available as an investigative drug, Dr. Bill Dordy and I decided to treat rats infected wtih group A streptococci with cortisone alone and for the first 24–36 hours they did wonderfully. They raced around the cage and looked better than the controls, but I remember that when we came back on the second day, they were all out deader than a doornail. It was very clear that they didn't seem to suffer at all for a while but the bactemeria was obviously going on at a great rate, so the addition of an effective antibiotic, is, I think, a very healthy thing to do.

Woodward: In 1950, I was apprehensive when six typhoid patients were treated with corticosteroids and not given antibiotics. Dr. Greisman and I have had some interesting discussions recently. He is an expert on many things including endotoxins and gram negative infections. Several days ago, I said, "Shelly, it is my belief that in patients who are late in their illness with Rocky Mountain spotted fever (a disease characterized by vasculitis) and in late cases of typhoid, it may be possible to aim at the host by giving steroids rather than at the rickettsia or the typhoid bacillus by giving an antibiotic." This sounds like heresy, but it could be true.

Christy (Brooklyn): I know of no other data which demonstrate a clear cut positive effect on outcome achieved by the addition of corticosteroids to an antimicrobial regimen in the treatment of infectious disease. Results reported previously by others have all been negative or equivocal, or, if positive, only somewhat positive and in the end unconvincing. My own interest in this topic arises from the endocrinologist's curiosity about how adrenocortical steroid hormones work. What is their mode of action on the host that might improve the defensive response to infection? Dr. Woodward has been appropriately dispassionate in the way he presented his inferences, that is, by offering at least two possibilities as to mode of hormonal action. His results also bring to mind Lewis Thomas's repeatedly stated apprehensions about the seeming excess, the enormity of the host response to infection, a response which is in many respects deleterious to the host.

Billings (Nashville): I wonder, Ted, if there is any relationship to the Waterhouse-Friderichsen syndrome in the people with typhoid where the adrenal cortex might have been impaired and where the cortisone or the dexamethazone might have been a factor in improving them.

Woodward: I don't think that this type of toxic reaction is a major factor but it has been thought of in various parts of the world. This was reported years ago in Italy in antibiotic-treated typhoid patients. It was conceived that the antibiotic action helped release endotoxin which could lead to shock. The antitoxemic action of steriods was the reason we first used them in typhoid. I am not aware of a Waterhouse-Friderichsen type reaction in typhoid patients treated with steroids.