

EFFECTS OF ADRENOCORTICOTROPIC HORMONE AND CORTISONE IN PATIENTS WITH TUBERCULOSIS^{1,2}

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INTRODUCTION

In the early reports on the administration of adrenocorticotrophic hormone and cortisone to patients with various disease states, there were described a number of effects, the reproduction of which might conceivably alter the course of infections in man. Among these effects were defervescence, decrease in edema and inflammation, change in antibody production, and alteration in the state of hypersensitivity to bacterial products. Clinical evidence of such effects was provided by Finland, Kass and Ingbar (1) who showed that adrenocorticotrophic hormone may effect striking alterations in the course of pneumococcal and primary atypical pneumonia. Moreover, equally striking changes were observed by Freeman and his co-workers in two patients with pulmonary tuberculosis (2). The modification of response to infection, by an agent which presumably acts solely upon the host, thus presents an opportunity for further evaluation of the participation of host mechanisms in tuberculous disease.

There are relatively few forms of tuberculosis in humans appropriate for such a study. A serious form of progressive disease, with a reasonably predictable course, is necessary. It is desirable to avoid reliance upon chest roentgenograms as the sole means of evaluating changes in a tuberculous lesion. In this situation, the extent of viable tissue within a lesion must be determined by a procedure which is highly subjective before proper evaluation

of subsequent changes within the lesion can be accomplished. Although the accuracy of the method is increased by having the roentgenograms interpreted independently by several competent observers, the interpretations frequently do not reflect the course of the disease as judged by other criteria (3). Such is not the case, however, when a lesion is available in which changes occurring after the introduction of a variable can be easily observed by more direct visualization. For these reasons, a special effort was made to include patients with active laryngeal tuberculosis in this study.

COMPOSITION OF CLINICAL SERIES AND METHODS OF STUDY

Seven patients with far advanced pulmonary tuberculosis were selected for study. Four of the seven had active laryngeal tuberculosis with lesions of the larynx which could be readily visualized by indirect laryngoscopy. A fifth patient had tuberculous empyema on the right side and was considered to be in a terminal phase of her illness. The strains of *M. tuberculosis* isolated in cultures of specimens of sputum from four of the seven patients were highly resistant to dihydrostreptomycin *in vitro*.

The course of tuberculous illness in each patient was evaluated prior to hormone administration from the available clinical, roentgenographic, bacteriologic and immunologic data. Whenever possible, a preliminary observation period of seven to ten days was undertaken. Each patient then received 100 mgm. of hormone intramuscularly in four equally divided doses at six hour intervals for an initial ten day period. Four of the patients received adrenocorticotrophic hormone⁴ and three received cortisone.⁴

Throughout the study all patients were maintained at rest in bed. They received diets of their own selection and an estimate was made of actual caloric and protein intake. The pulse rate and rectal temperature were recorded at two hour intervals. In addition to customary bedside

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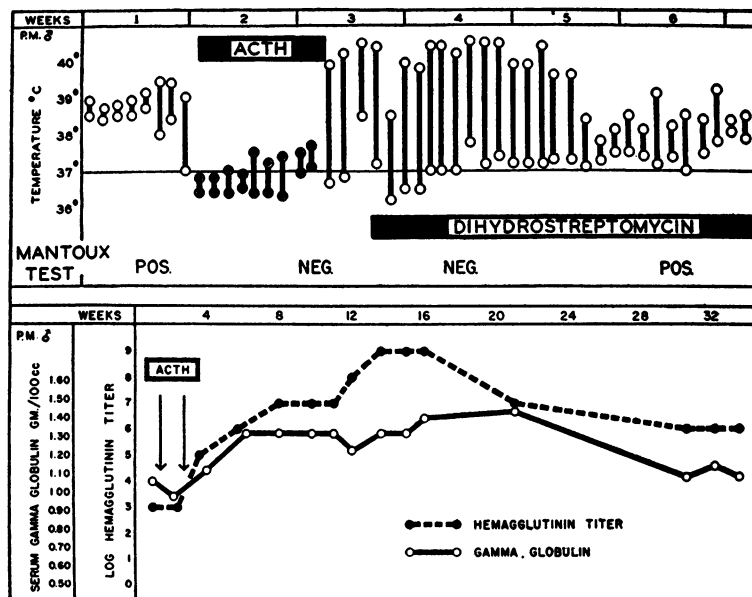


FIG. 1. PATIENT P. M., AGE 49 YRS.

In the upper portion of the chart are shown the daily range of temperature and the results of tests for cutaneous hypersensitivity to tuberculo-protein. Note the rapid defervescence following the start of ACTH administration, and the abrupt return of fever with wide fluctuations after stopping ACTH. The return of cutaneous hypersensitivity to tuberculo-protein coincides with the fall in fever while under treatment with dihydrostreptomycin. In the lower portion of the chart are shown the alterations in the values obtained for concentrations of serum gamma globulin and in the titer of hemagglutinating antibodies.

observations, indirect laryngoscopy was performed on each patient with laryngitis. Drawings were made of the laryngeal lesions as seen in the laryngeal mirror, at intervals determined by change in the appearance of the lesions. Serial chest roentgenograms, using a standardized technique, were obtained at 72 hour intervals.

Twenty-four hour aliquots of continuous sputum collections were measured for volume and the character of the specimen noted. The aliquots were then digested, centrifuged and direct smears were made of the concentrate. Duplicate smears were stained with carbol fuchsin by the Ziehl-Nielsen technique and with Sudan black B (4). Petraghani and oleic acid-albumin media were used for cultivation of the *M. tuberculosis* from the concentrated specimens of sputum. The colonial morphology of the bacilli growing on oleic acid-albumin medium was examined for the characteristics known to be associated with various degrees of virulence (5). Organisms obtained from each patient at weekly intervals were grown in Tween⁵-albumin medium and were tested for sensitivity to dihydrostreptomycin.

Observations on the cutaneous hypersensitivity to tu-

berculin were made using an amount of tuberculo-protein, standardized individually for each patient, sufficient to obtain an unequivocally positive reaction. An initial reaction of more than 10 mm. in diameter showing erythema and definite edema was obtained in five patients using 0.00002 mgm. of Tuberculin, Purified Protein Derivative⁶ (First Test Strength). In one patient (P. M.), 0.005 mgm. of Tuberculin, Purified Protein Derivative (Second Test Strength) was required to produce a reaction of this magnitude. The reactions were examined and the outlines traced on cellophane at 48 and 96 hours after intracutaneous injection of the forearm.

Specimens of serum were obtained at frequent intervals from each patient for estimation of tuberculin hemagglutinating antibody titer as described by Middlebrook and Dubos (6) and the concentration of serum gamma globulin by the method of Kunkel (7). Bone marrow examinations with particular reference to the plasma cell count were done as described by Good and Campbell (8). Other laboratory examinations were made in each patient and gave results comparable to those reported in other studies with these compounds.

⁵ "Tween 80" is the trade name of the polyoxyethylene derivative of sorbitan monooleate, obtained from the Atlas Powder Company, Wilmington, Del.

⁶ The Tuberculin, Purified Protein Derivative used in this investigation was obtained from Parke, Davis and Co., Detroit, Mich.

RESULTS

Course of illness: In five patients the onset of hormone administration marked the inception of a series of profound changes, the first of which were evident as early as six to eight hours after the initial dose. In all patients, a strikingly rapid disappearance of the signs and symptoms of acute illness occurred and persisted throughout the period of hormone administration. Following the cessation of hormone administration, however, a quick return to the previous state of illness was observed.

In three of the four febrile patients defervescence was complete within six hours of the start of hormone administration (Figures 1-3). This process required 72 hours for completion in one patient (Figure 4). All patients remained essentially afebrile until the cessation of hormone administration. Defervescence was accompanied by a feeling of increased strength and desire for

physical activity. Appetite increased markedly with concurrent rise in the caloric and protein intake.

In the four patients with laryngitis improvement in phonation and disappearance of dysphagia were evident by the end of the initial 48 hour period of hormone administration. Thereafter, a progressive increase in the volume of the voice and improvement in its quality ensued. Discomfort from dyspnea and cough was markedly relieved although the volume of the sputum was not significantly decreased. All of the patients experienced some degree of a sense of well-being which in some amounted to euphoria.

The cessation of hormone administration was followed by abrupt return of the signs and symptoms of acute illness. The manifestations of acute illness immediately following the end of hormone administration were at least equal in severity to those present before hormone administration and

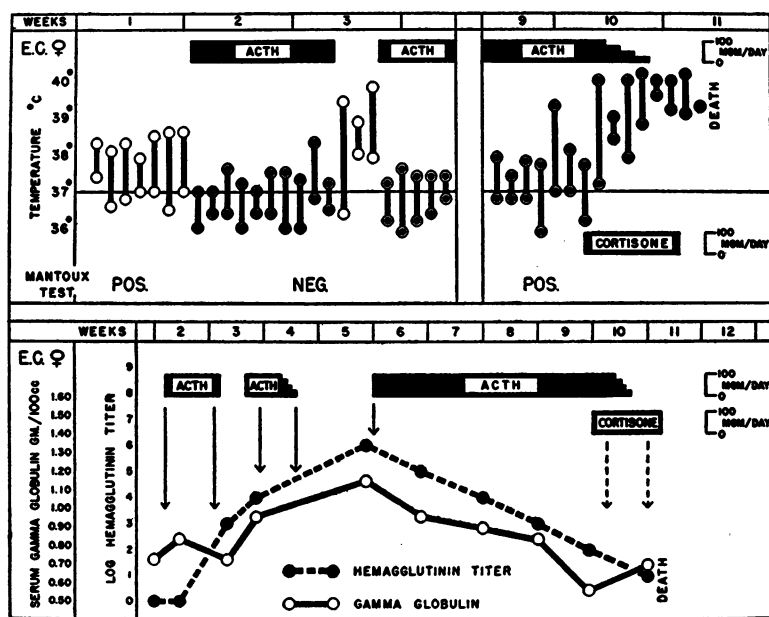


FIG. 2. PATIENT E. C., AGE 21 YRS.

Note the rapid defervescence and abrupt return of fever at the onset and end, respectively, of the initial course of ACTH administration. Following reinstitution of ACTH administration prompt defervescence occurred. Escape from the controlling effects of ACTH occurred later with return of fever and cutaneous hypersensitivity to tuberculo-protein despite the addition of cortisone. In the lower panel are shown the rises in serum gamma globulin values and in titer of tuberculin hemagglutinating antibodies following the initial course of administration of ACTH. Note the progressive decline of both serum gamma globulin values and hemagglutinin titer during prolonged ACTH administration.

in four patients (P. M., E. C., S. H., and T. B.), were more severe. Fever occurred within 18 hours after the last dose of adrenocorticotrophic hormone. Following the cessation of cortisone administration, however, fever occurred on the second and sixth day (Figures 4 and 5) or was not a prominent feature in the post-hormone course (Figure 6).

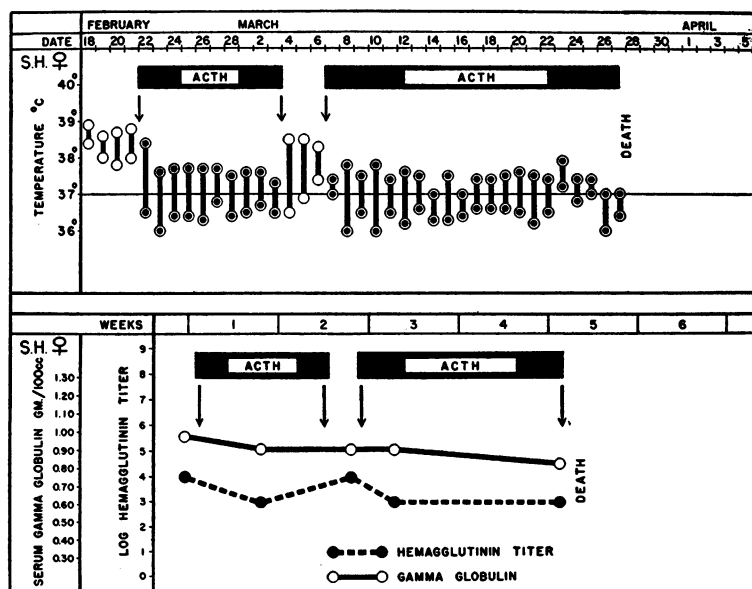
The fever following the end of hormone administration was self-limited in two patients who were essentially afebrile prior to hormone administration (Figures 5 and 7). In one patient (Figure 1) despite the institution of dihydrostreptomycin therapy soon after stopping adrenocorticotrophic hormone, fever continued for four weeks. It may be noted here that in this patient, subsidence of fever coincided with the return of cutaneous hypersensitivity to tuberculin. Significant defervescence was not observed during dihydrostreptomycin administration in another patient (Figure 4). Subsequently, the strain of *M. tuberculosis* isolated from cultures of the sputum of

this patient was found to be resistant *in vitro* to dihydrostreptomycin.

Laryngeal lesions: Observations of the changes in the laryngeal lesion was made by daily indirect laryngoscopic examination in the four patients with tuberculous laryngitis. In all patients a similar sequence of changes was observed. The changes noted in the laryngeal lesion of one patient (P. M.) are depicted in Figure 8 and may be considered as characteristic of the changes observed in all patients studied.

In this patient, initial examination of the left side of the larynx demonstrated ulceration with partial replacement by granulation tissue of the lateral portion of the arytenoid tubercle, aryepiglottic fold and true vocal cord, in addition to absence of one-half of the epiglottis. The entire right half of the larynx was edematous with marked inflammation and both true vocal cords were irregular.

Forty-eight hours after the beginning of hormone administration, edema and inflammation had subsided almost completely. In the ulcerated le-



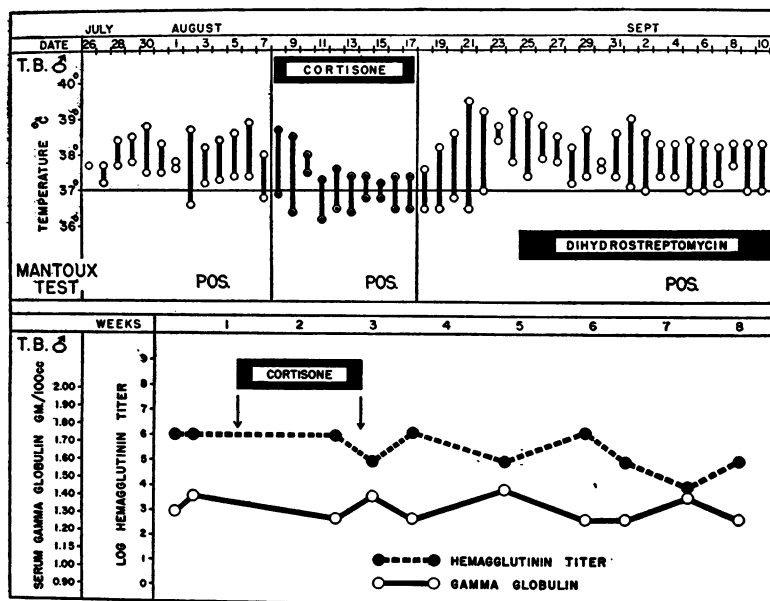


FIG. 4. PATIENT T. B., AGE 40 YRS.

Following the onset of cortisone administration, defervescence required 72 hours for completion. Fever slowly recurred following cessation of cortisone administration and persisted despite dihydrostreptomycin therapy. Subsequently the strain of *M. tuberculosis* isolated from culture of the sputum was found to be resistant to dihydrostreptomycin. Reversal of cutaneous hypersensitivity to tuberculo-protein was not observed in this patient. No significant alterations occurred in serum gamma globulin values or in titer of the tuberculin hemagglutinating antibodies.

sions, a border of epithelium could be visualized progressing from the edges of the ulcerated area as the granulation tissue subsided. By the ninth day of hormone administration, the epidermization had covered approximately 85 per cent of the previously ulcerated area.

Within 48 hours after completion of hormone administration, edema and inflammation had returned although no regression of epithelium was observed. Subsequently, no significant alterations in the appearance of the laryngeal lesion attributable to hormone effect were observed.

Complete healing with scarring occurred following the institution of dihydrostreptomycin therapy in two patients whose sputum contained strains of *M. tuberculosis* found to be sensitive to the drug *in vitro*.

Lung lesions: Serial roentgenograms, interpreted independently by several observers, revealed definite changes in the appearance of the lung lesions. These changes formed a consistent pattern in five of the seven patients. A representa-

tive example of the changes is shown in Figure 9 portraying enlarged segments of chest roentgenograms from one of the patients (P. M.).

In general, during the administration of adrenocorticotrophic hormone the appearance of lung lesions became more translucent with better delineation of the individual lesions. Within 48 hours after cessation of hormone administration definite increase in the density of the lesions was apparent. No patient in this series has been observed without additional therapeutic measures for a sufficient time beyond this point to evaluate the roentgenographic changes which might result solely from hormone administration.

Dihydrostreptomycin therapy was instituted in this patient (P. M.) and continued for 111 days. The increase in density reached a maximum in the fourth week, the lesions thereafter became more translucent. It is of interest that in this patient the onset of defervescence and the return of cutaneous hypersensitivity to tuberculo-protein also occurred during the fourth week after the end of

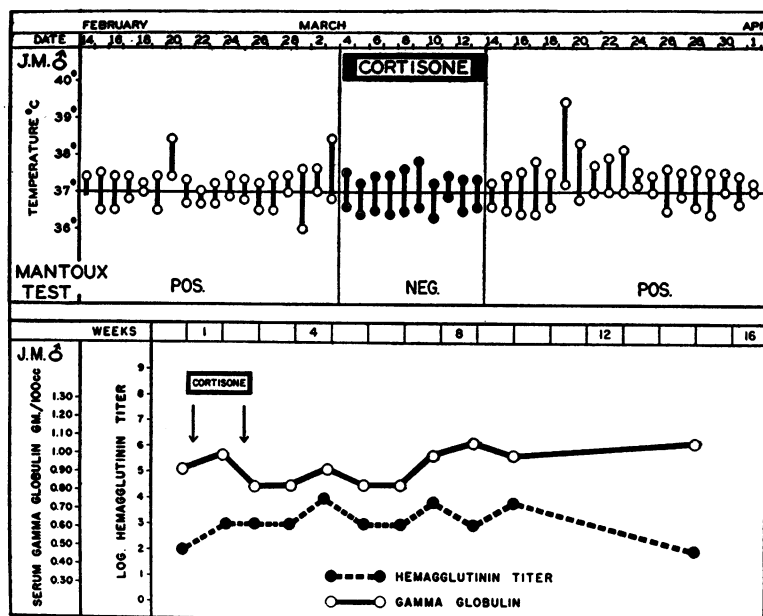


FIG. 5. PATIENT J. M., AGE 51 YRS.

Fever occurred on the sixth day after cessation of cortisone administration and gradually subsided over a 48 hour period. Reversal of cutaneous hypersensitivity to tuberculin is illustrated in the upper panel. No significant alterations in serum gamma globulin values or in titer of tuberculin hemagglutinating antibodies occurred in this patient.

hormone administration. Progressive decrease in the size and density of the roentgenographic appearance of the lung lesions ensued, marked clearing being noted seven months after hormone administration (Figure 9).

Resorption of a small purulent intrapleural exudate was observed in one patient during the administration of adrenocorticotrophic hormone. As this patient (S. H.) was in the terminal phase of her illness, prolonged observation after hormone administration was impossible. No well-defined changes in the roentgenographic appearance of the lung lesions occurred in two patients, one receiving adrenocorticotrophic hormone (A. R.) and the other cortisone (J. M.).

Roentgenographic evidence of dissemination of the tuberculous process was not obtained in any patient.

Skin hypersensitivity to tuberculin: Repeated observations on the skin hypersensitivity to tuberculin were made. In each of the six patients tested an amount of tuberculin (Purified Protein Derivative) was used sufficient to elicit an unequivocally positive reaction prior to the ad-

ministration of hormone. Reversal of cutaneous hypersensitivity to this individually standardized amount of tuberculin was observed during hormone administration in three of the six patients tested. This reversal of a previously positive response was maintained for three to four weeks after the cessation of hormone administration in the two patients followed from this standpoint. In three patients (Figures 4, 6 and 7) negative reactions were not obtained.

It is of considerable interest that despite the continued absence of cutaneous hypersensitivity to the test dose of tuberculin the acute manifestations of tuberculous illness reappeared following cessation of hormone administration in the three patients in whom reversal of the tuberculin skin test was obtained.

Serum gamma globulin and tuberculin hemagglutinating antibodies: The substantially elevated serum gamma globulin values initially present in one patient (Figure 7) decreased toward the normal range during and immediately following adrenocorticotrophic hormone administration. Subsequently, the values rose, reaching the high level

present initially by the end of four weeks, and rose even further thereafter. Aside from this instance, significant variations in the serum gamma globulin values did not occur during the ten day period of hormone administration. Likewise, the titers of the tuberculin hemagglutinating antibody were not significantly changed during this period.

Within three weeks after completion of hormone administration, however, three patients had significant increases both in the concentration of serum gamma globulin and in the titer of the tuberculin hemagglutinating antibodies (Figures 1, 2 and 6). The rises were sustained in one patient (P. M.) in whom the values reached a maximum between the 14th and 16th weeks and declined thereafter. Although significant increases in both serum components were noted in another patient (R. R.) immediately following cessation of cortisone administration, the evolution of the changes has been observed for only a short period of time. In the third patient (E. C.) reinstitution of adrenocorticotrophic hormone at the

peak of the rise in serum gamma globulin and hemagglutinating antibody titer was followed by progressive decline toward the original values.

Prolonged hormone administration: Two of the most critically ill patients (E. C. and S. H.) received additional adrenocorticotrophic hormone to relieve the extreme prostration which accompanied the return of fever. The strains of *M. tuberculosis* recovered in cultures of the sputum of both were highly resistant to dihydrostreptomycin *in vitro*. Upon reinstitution of 100 mgm. per day of adrenocorticotrophic hormone, the onset of defervescence was again rapid and complete and the signs and symptoms of acute illness disappeared promptly.

In one of these patients (E. C.) an unsuccessful attempt was made to decrease the severity of the post-hormone manifestations of illness by gradual reduction of the amount of hormone administered over a four day period. Subsequently, reinstitution of adrenocorticotrophic hormone was necessary to alleviate the manifestations of acute illness. During the fourth consecutive week of hormone

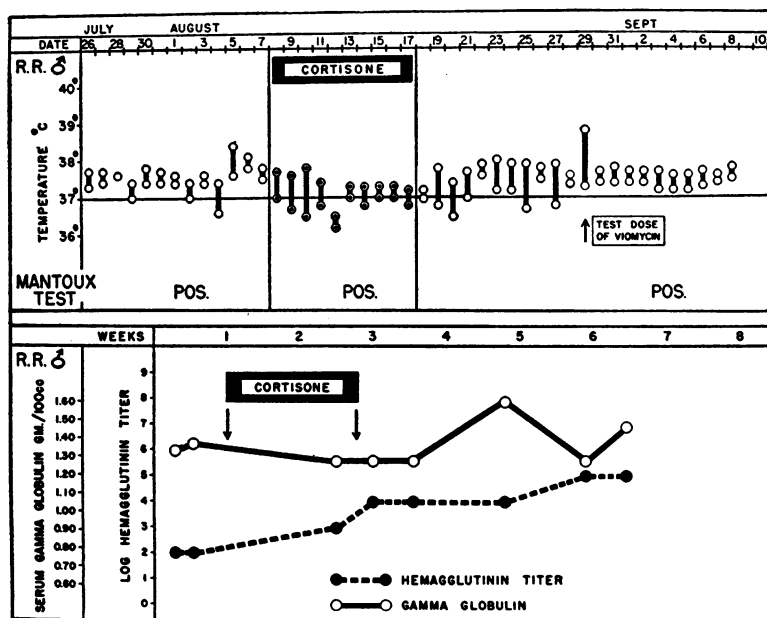


FIG. 6. PATIENT R. R., AGE 25 YRS.

Slight decrease in the daily temperature range during cortisone administration is shown in the upper panel. No post-hormone fever attributable to the cessation of cortisone administration occurred in this patient. Reversal of cutaneous hypersensitivity to tuberculoprotein was not observed. Significant increases in both serum gamma globulin values and in titer of hemagglutinating antibodies immediately following cessation of cortisone administration are shown.

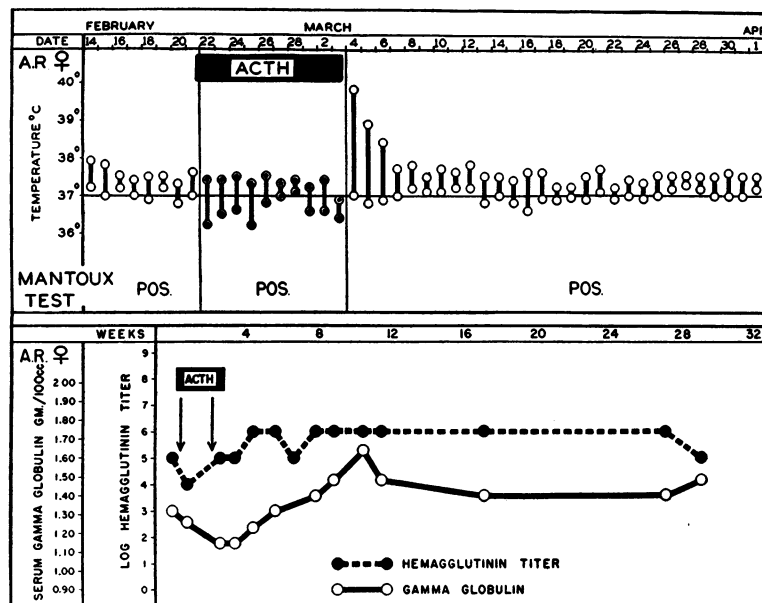


FIG. 7. PATIENT A. R., AGE 39 YRS.

Note the occurrence of fever immediately following cessation of ACTH administration in this patient who was essentially afebrile prior to hormone administration. Reversal of cutaneous hypersensitivity to tuberculin was not observed. Decrease in serum gamma globulin values occurred during and immediately after cessation of ACTH administration, and subsequently rose to values higher than the initial level.

administration, in the ninth week of study, hallucinations and delusions appeared abruptly. The following week fever recurred with gradual return of malaise, cough, and increasing prostration; cutaneous hypersensitivity to the test dose of tuberculin also reappeared (Figure 2). The patient's condition rapidly became worse, despite continuation of adrenocorticotrophic hormone and the addition of 100 mgm. per day of cortisone. Gradual reduction and cessation of adrenocorticotrophic hormone administration failed to produce evidence of improvement. Cortisone administration was maintained for four days without apparent change in the patient's clinical condition and was discontinued in the fifth consecutive week of hormone administration. Thirty-six hours following cessation of cortisone administration, this patient expired.

Reinstitution of adrenocorticotrophic hormone in another patient (Figure 3) was followed by a succession of events similar to those described above, although less pronounced. Marked symptomatic improvement and defervescence were gradually

supplanted by euphoria and general weakness. Death occurred on the 21st consecutive day of hormone administration in the fifth week of study without recurrence of prostration or fever.

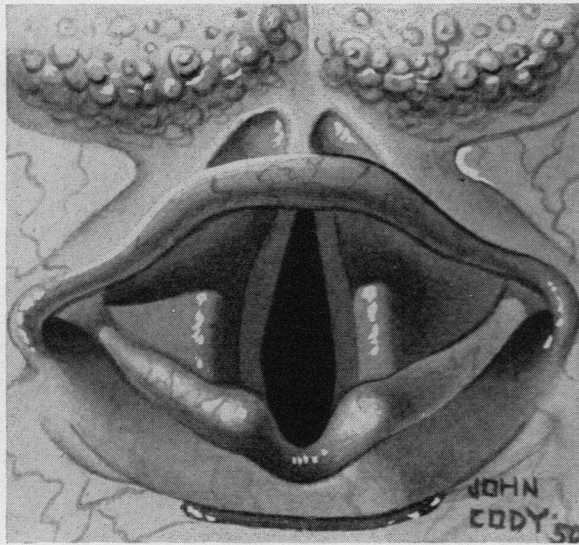
Post-mortem examination revealed no evidence of recent dissemination of the tuberculous process or significant alteration in the histopathology of the tuberculous process in either patient. The adrenal cortices of both patients were uniformly thickened and the glands were increased in weight. It is of interest that a small nodule of caseation necrosis was found at the surface of the right adrenal gland in one patient (S. H.).

Subsequent course: Two of the patients (P. M. and J. M.) have shown steady, favorable progress following the institution of dihydrostreptomycin and para-amino-salicylic acid administration. Sputum concentrates and cultures no longer show the presence of *M. tuberculosis*. Marked clearing in the chest roentgenogram of P. M. has occurred as previously noted. The activity of his tuberculous process being considered arrested, J. M. has been discharged from the hospital.

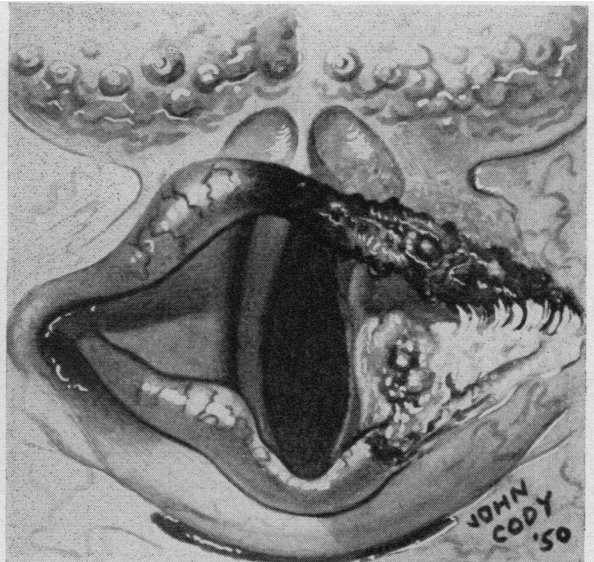
One of the patients (A. R.) whose sputum contained a strain of *M. tuberculosis* found to be resistant to dihydrostreptomycin *in vitro*, has been observed for ten months while receiving pneumoperitoneum therapy and bed rest. Her clinical status, though not conspicuously changed, has shown slight improvement. No significant alteration of her laryngeal lesion has been observed

since the changes noted immediately after cessation of adrenocorticotrophic hormone administration.

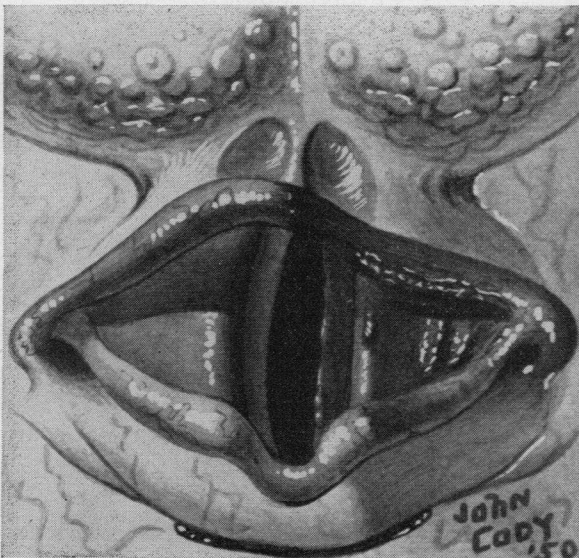
The two remaining patients (T. B. and R. R.) have not been observed for a sufficient period of time following the administration of cortisone to permit final evaluation of the influence of the hormone on the course of the infection. No dele-



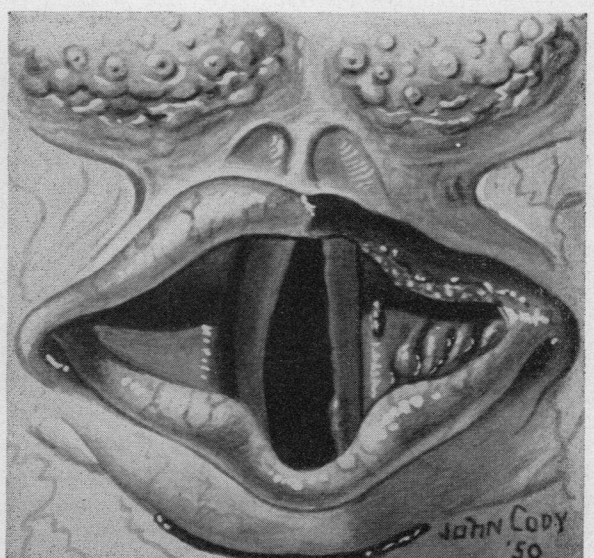
a) Normal larynx as seen in a laryngeal mirror.



b) P. M.—Larynx before ACTH.



c) P. M.—Larynx after nine days of ACTH.



d) P. M.—Larynx two days after cessation of ACTH.

FIG. 8. PATIENT P. M. CHANGES IN THE LARYNGEAL LESIONS

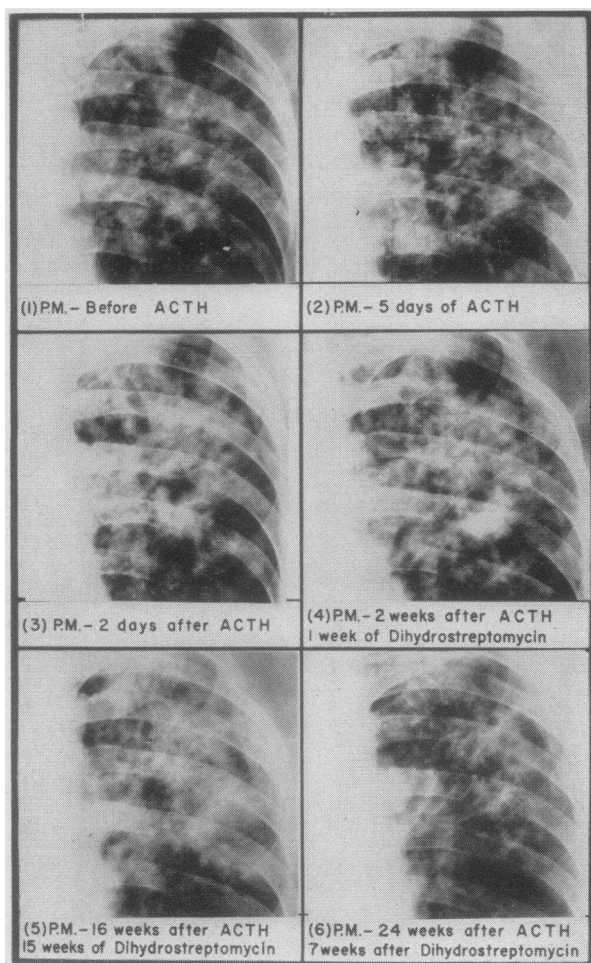


FIG. 9. PATIENT P. M. CHANGES IN THE ROENTGENOGRAPHIC APPEARANCE OF THE LUNG LESIONS

(1) An enlarged segment of the initial chest roentgenogram. (2) Note slight decrease in density of the lung lesions. (3), (4) Note marked increase in density in the appearance of the lung lesions. (5), (6) Marked clearing of lung lesions after dihydrostreptomycin.

terious effect of cortisone administration, however, has been noted during the four month period of observation.

Tubercle bacilli: Tubercle bacilli were discharged in the sputum of all patients without significant fluctuations in number throughout the period of observation. Retention by the tubercle bacilli of initial staining properties with carbol fuchsin and Sudan black B and of initial *in vitro* sensitivity to dihydrostreptomycin was observed. Colonies grown on oleic acid-albumin attained the morphologic characteristics attributed to virulent organisms by Middlebrook, Dubos, and Pierce

(5) in all specimens examined. Therefore, no bacteriologic evidence of alteration in the tubercle bacilli isolated from sputum or empyema was obtained.

COMMENT

From the observations reported above, it appears that abrupt and profound changes in the course of tuberculous illness may be brought about by the introduction of hormones which presumably affect only the host.

During the period of administration of these hormones, rapid amelioration and subsequent disappearance of the constitutional manifestations of acute illness were witnessed. Complete defervescence was accompanied by a seemingly improved state wherein increase in strength, appetite, and desire for activity occurred. It is of particular interest to note that the onset of the seemingly improved state was equally evident in two patients (J. M. and A. R.) who were essentially afebrile prior to hormone administration. Improvement in phonation and disappearance of dysphagia was striking as was the recession and subsequent quiescent appearance of the laryngeal lesions. Decrease in density of the lung lesions seen on chest roentgenogram was noted in five patients. Reversal of cutaneous hypersensitivity to an arbitrarily selected amount of tuberculo-protein was observed in three of the six patients tested.

The termination of the state of apparent improvement following the withdrawal of hormone administration was equally evident. The signs and symptoms of acute illness which had been alleviated, reappeared abruptly, and were equal to or even more severe than those present before hormone administration. The return of edema and inflammation in the laryngeal lesions also occurred promptly as did the increase in density of lung lesions seen on chest roentgenograms. The swift return of the manifestations of acute illness contrasted sharply with the relatively slow return of cutaneous hypersensitivity to tuberculo-protein and rise in the titer of the tuberculin hemagglutinating antibodies observed several weeks after cessation of hormone administration.

The abrupt disappearance of the manifestations of illness induced by adrenocorticotrophic hormone and cortisone is of considerable interest in regard to the nature of the toxicity of tuberculosis. The

mechanisms by which this infection produces fever and other manifestations of illness are not completely understood. It has been generally believed that the tissue damage and the clinical illness are, in large part, consequences of the interaction of previously sensitized tissue and the absorbed products from tubercle bacilli (9a). *In vitro* studies have been demonstrated that cells of the hypersensitive body are damaged and killed by amounts of tuberculo-protein that are harmless to cells in the absence of hypersensitivity (9b). Whether the living tubercle bacillus exerts a primary toxic effect upon host tissue is not definitely established (10). Diminution in the manifestations of illness might be expected if, by alteration in the reactivity of host tissue, some degree of desensitization to the products of infection was obtained. Conversely, upon reappearance of the effects of hypersensitization their return would not be surprising.

From the observations reported here, it seems clear that reactivity of host tissues sufficient to cause severe symptoms of tuberculous illness may be present without the presence of a positive Mantoux test. Moreover, distinct symptomatic improvement was observed after the start of hormone therapy in those patients whose Mantoux test remained positive. The inability to utilize clinical quantitation and subsequent correlation of local and systemic tissue hypersensitivity to tuberculo-protein makes speculation on this aspect inadvisable.

The sudden suppression of the clinical evidence of toxicity observed to occur at the start of hormone administration may be compared to the similar state observed in patients with tuberculosis under treatment with streptomycin. Loss of so-called "toxemic" symptoms may occur in both situations and although improvement following the initiation of streptomycin therapy may be observed as early as the third day of therapy, it has not been observed to be as rapid in onset nor does its speed approach that of the changes occurring in the patients reported above. Thus the same phenomenon, sudden suppression of the clinical evidences of toxicity, may be produced on the one hand, by actions exerted principally upon the parasite and on the other, by action exerted solely through the host.

The course of the two patients who expired suggests that the changes effected by a fixed amount

of adrenocorticotrophic hormone are temporary and cannot be sustained, even with continued administration. Whether modification of the amount of hormone administered, alteration in the frequency of administration, or the combination with other agents will alter this situation is yet to be determined.

SUMMARY

The effects of adrenocorticotrophic hormone and cortisone on the course of tuberculous illness has been studied in seven patients with far advanced pulmonary tuberculosis. It was found that abrupt and profound changes in the course of the illness were brought about by administration of these hormones. These changes were in the nature of defervescence, improvements in the sense of well-being, increased strength, improvement in appetite, as well as decrease in the edema and in the amount of exudate in the local lesions of the larynx. In all patients the improved state was temporary and, as might be anticipated, could not be indefinitely maintained by further administration of the hormones.

Observations were also made on the changes in cutaneous hypersensitivity to tuberculo-protein, in concentration of serum gamma globulin and in the titer of tuberculin hemagglutinating antibodies. Reversal of cutaneous hypersensitivity to an arbitrarily selected amount of tuberculo-protein during hormone administration was observed in three of the six patients tested. Within three weeks after completion of hormone administration significant increases both in concentration of serum gamma globulin and in the titer of tuberculin hemagglutinating antibodies were noted in three of the seven patients.

Interpretation of these temporary alterations in the disease state in terms of ultimate effect in such a chronic infection must await further study.

ACKNOWLEDGMENTS

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