The Effects of Cortisone and ACTH on the Acute Phase of Rheumatic Fever

By Arlie R. Barnes, M.D.

MOST of the observations reported in this review will be based on study by my colleagues and me of 14 patients with rheumatic fever, 10 of whom received cortisone and 4 of whom received adrenocorticotropic hormone (ACTH). When observations of others are reported, the source of information will be given.

The results of administering cortisone or ACTH to patients with acute rheumatic fever vary with the severity of the disease but especially according to how early in the course of rheumatic fever these hormones are given. If they are given early in the acute attack, polyarticular symptoms, elevation of temperature and increased heart rates are abolished in one to five days. Prolonged P-R intervals decrease in a week and at two weeks usually are at the normal levels. Sedimentation rates begin to fall rapidly in a week and reach normal levels in from twelve to twenty-one days. In two to three weeks the values for hemoglobin rise sharply and the globulin fraction of the serum protein falls to normal levels. There is a fall in fibrinogen of the blood, which parallels the fall in the sedimentation rate.2 McEwen and his co-workers3 noted that the C-reactive protein also fell as the condition of the patient improved. The same observers reported that the antistreptolysin-O titer fell as the condition of the patient improved, but they questioned whether this fact could be attributed to the use of the hormones. When the administration of cortisone or ACTH was discontinued after four or five weeks, some or all of the acute manifestations of the disease reappeared within ten days in a majority of our patients. This phenomenon can best be illustrated by figure 1.

The response to the administration of cortisone or ACTH to patients who have been ill from several to many weeks, particularly if they have carditis, may be much less striking than in the patients treated early in an attack of rheumatic fever. If the hormones are given late in the course of the disease, fever and increased pulse rates may be restored to normal only after many weeks of therapy, and the same is true of prolongation of the P-R interval. Prolonged P-R interval associated with previous myocardial disease may be unaffected in spite of marked clinical improvement of the patient. The sedimentation rate may return slowly to normal, and sometimes it never returns completely to normal. Diminution of heart size occurs slowly if at all and may require four to five weeks for marked changes to occur.

And yet in spite of the tardy improvement in these features the patient's well-being, appetite and appearance of toxicity may be altered fairly promptly.

The reappearance of the acute manifestations of the disease after the omission of the hormones occurred with such frequency in our patients that it was concluded that they were capable of suppressing but not curing acute rheumatic fever. We have arrived at the conclusion that rheumatic fever has an inherent duration that varies from individual to individual, and we are doubtful that its duration is shortened by treatment with cortisone or ACTH. Massell and Warren,4 on the other hand, have expressed the belief that they cured...
the disease in some patients and shortened its course in others.

If our deduction is valid that these hormones do not cure rheumatic fever or shorten its duration, what value do they have in treating the disease? If they have value, then it must reside in their ability to suppress the proliferative reactions in the heart and thus diminish or forestall the subsequent reparative process which results in chronic cardiac disease. Despite the disappearance of murmurs in several of our patients (Massell and Warren\textsuperscript{4} co-workers\textsuperscript{4} showed that cortisone or ACTH, administered subcutaneously for five days before testicular hyaluronidase was injected into rats intravenously, largely inhibited the increased capillary permeability normally produced by such an injection of hyaluronidase. Dorfman and Moses\textsuperscript{5} have demonstrated that ACTH produces a marked decrease of the level of the nonspecific hyaluronidase inhibitor in the serum of patients with rheumatic fever and that this decrease parallels the drop in the sedimentation rate and the patient's clinical im-

\begin{figure}
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\includegraphics[width=\textwidth]{figure1}
\caption{Effect of administration of cortisone to a boy, 17 years of age, in his first attack of rheumatic fever. Note reappearance of acute manifestations of the disease when administration of cortisone was discontinued.}
\end{figure}

have reported a similar experience) we must remember that Aschoff bodies may persist for a long time and that murmurs appear in patients several years after apparently full recovery from an attack of rheumatic fever. For that reason these patients will have to be observed for three years or longer before it can be concluded that they have been spared permanent cardiac injury.

We must admit ignorance concerning the mechanism by which cortisone and ACTH act in bringing about improvement in patients with rheumatic fever. In a report by Adams and Dwan\textsuperscript{6} it is pointed out that there is an increase in hyaluronidase in rheumatic fever and that this substance has the property of increasing the permeability of membranes. Benditt and improvement. They suggested that this may be a reflection of an effect of the adrenal hormones to change the state of connective tissue so that it no longer reacts to the precipitative stimuli in the disease. An alternate interpretation is considered by these investigators: that the hyaluronidase inhibitor may represent some substance which is released on the destruction of connective tissue. Dougherty and Schneebeli\textsuperscript{7} found that adrenal cortical secretions produce anti-inflammatory effects on inflammation produced by an allergen. They concluded that this was an effect on the inflammatory reaction sui generis and was not due to interference with the union of antigen and antibody. These observations suggest at least that these hormones act at the tissue level and that they profoundly
alter cellular reaction and permeability of the cell membrane.

If suppression of the acute manifestations of the disease is a desideratum, it seems important that treatment be started early in the course of the disease and that as complete and continuous suppression as possible be maintained until the acute rheumatic state has reached the end of its natural duration. Figure 2 illustrates our conception of a rational program for the administration of these hormones.

The work of Adams and Dwan is of especial interest with respect to indexes of continued secretion. They consider that treatment is inadequate unless the number of circulating eosinophils drops practically to zero and that a satisfactory therapeutic response consists of a rise during treatment. They found that a fall in circulating eosinophils below the normal range after discontinuation of therapy may indicate the necessity for readministration of ACTH.

The physiologic effects of cortisone and ACTH are many. As Sprague, Power and Mason have pointed out, "some of these effects have favorable therapeutic implications, others

![Figure 2](http://circ.ahajournals.org/)

**FIG. 2.** Adequate, continuous suppression of the acute manifestations of acute rheumatic fever in a woman 24 years of age who received cortisone in her first attack of the disease.

activity of rheumatic fever. They observed that the administration of cortisone and ACTH to patients with acute rheumatic fever caused a fall in hyaluronidase which paralleled the fall in the sedimentation rate. Mucoprotein values did not fall correspondingly. If administration of these hormones was discontinued when the sedimentation rate had returned to normal but while the mucoproteins were still elevated, the acute manifestations of rheumatic fever reappeared. They concluded that a study of the mucoprotein values was a much more accurate index of the persistence of the tissue reactivity in rheumatic fever than was the sedimentation rate. Wilson and Helper regard the count of the circulating eosinophils as probably the most useful guide to therapy with cortical hormone

are relatively unimportant, while still others may impose hazard upon the patient." These effects may be discussed under the following headings:

**Effects on Carbohydrate Metabolism**

In the patients of Sprague, Power and Mason, doses of cortisone and ACTH were small relative to body weight; and, though slight increases in the level of the fasting blood sugar were sometimes observed, the values have not usually exceeded the normal range. None of our patients with rheumatic fever receiving cortisone or ACTH showed significant elevation of the values of blood sugar.

However, exaggerated diabetogenic effects have been reported by several observers in
patients receiving cortisone and ACTH. This possibility must be borne in mind, and the urine of both diabetic and nondiabetic persons receiving these hormones should be tested for sugar at intervals.

**Effects on Protein Metabolism**

Large doses of cortisone (200 mg. daily) and of ACTH (105 mg. daily) have been observed to result in a rather decided loss of nitrogen from the body.9

**Effects on Fat Metabolism**

There is some evidence that cortisone and ACTH may mobilize fat stores for conversion into glucose. In several of our patients receiving these hormones pronounced rounding of the facial contour has developed, and there is good evidence that this is a result of deposition of fat in the cheeks. This phenomenon disappeared in a few weeks after administration of these hormones was discontinued.

**Effects on Metabolism of Water and Electrolytes**

The effect of cortisone and ACTH on the metabolism of water and sodium chloride is variable. In some instances these hormones may cause the retention of salt and water to the point of the production of edema. In none of our patients with acute rheumatic fever did heart failure or an accentuation of previously existing heart failure develop while the patients were receiving these hormones. However, other investigators have observed this to occur while patients were receiving cortisone or ACTH for rheumatic fever. When this occurs, mercurial diuretics must be employed and in some instances administration of the hormone must be discontinued temporarily. These hormones must be administered with unusual caution in patients who have heart failure. In such cases a diet containing not more than 0.5 Gm. of sodium is important in order to avoid the production or accentuation of heart failure.

Hypochloremic, hypopotassemic alkalosis may follow the administration of cortisone in a dose of 200 mg. daily and of ACTH in a dose of 100 mg. daily. The loss of potassium and chlorides from the body may be counteracted by the administration of 2 to 4 Gm. of potassium chloride daily. In none of our patients who received these hormones for acute rheumatic fever did potassium values drop to dangerously low levels.1

**Androgenic Effects**

Mild hirsutism in women was the only androgenic effect observed in our patients receiving cortisone or ACTH.

**Effects on Menstrual Function**

Menstrual function usually ceased in our patients who received cortisone or ACTH for acute rheumatic fever. These patients all were young, and there is evidence that menstrual function is interrupted much less commonly when these hormones are given to women with long-established menstrual function. In our patients normal menses were resumed within a few months after administration of the hormones was discontinued.

**Effects on the Psyche**

Along with prompt improvement in appetite and rapid gain in weight many of our patients exhibited marked improvement in feeling and morale. No patient exhibited depression or psychotic behavior. Massell and Warren observed rather severe mental depression in 1 of 20 patients receiving ACTH. We have not observed withdrawal symptoms of asthenia in our patients with rheumatic fever after administration of cortisone or ACTH had been discontinued.

**Dosage**

Our experience to date indicates that cortisone should be administered intramuscularly.* Cortisone under the trade name Cortone has been found effective when given orally in the treatment of rheumatoid arthritis. We have not used Cortone orally in the treatment of rheumatic fever, but it would be anticipated that it would be effective. It is suggested that 300 mg. of cortisone be given on the first day and 200 mg. on subsequent days until the acute manifestations of rheumatic fever have been suppressed. The dose can then be reduced to an amount sufficient to maintain suppression of the acute manifestations of the disease. Cortone given by mouth should be given in divided doses (two to four times a day).
in initial doses of 200 mg. daily in the treatment of acute rheumatic fever. This dosage should be maintained for seven to fourteen days or until it is clearly evident that the acute manifestations of rheumatic fever have been largely suppressed. The dose then may be diminished to 100 mg. daily for an additional two to four weeks. This dosage schedule may then be further reduced to 75 mg. daily or 100 mg. on alternate days. When it seems likely that the rheumatic infection is at an end, administration of cortisone may be discontinued. A sharp rise in sedimentation rate coupled with increased duration of the P-R interval, or with manifestations in the joints or both, is probably an indication for resumption of the administration of cortisone. Reappearance of a slight rise in sedimentation and heart rates and a minor rise in temperature may subside without the further use of cortisone. But under those circumstances the patient must be observed closely for evidence of reappearance of gallop rhythm, intensification of murmurs, or prolongation of the P-R interval, in which case the use of cortisone should be resumed promptly. Further study of the count of circulating eosinophils and of levels of mucoproteins in the blood as guides to adequate therapy with cortisone or ACTH deserves very careful investigation.

Initial daily doses of 45 to 60 mg. of ACTH have proved satisfactory in our experience. However, in patients critically ill with acute rheumatic fever, doses of 80 to 100 mg. daily may be desirable for a few days. The program for reducing the dosage paralleling that outlined for cortisone may be followed. Maintenance doses of 25 to 40 mg. daily usually will suffice. The daily dose should be given in divided portions three or four times daily by intramuscular injection.

It does not seem necessary to give much importance to the patient’s age and weight in determining the dosage of cortisone or ACTH. A safer guide is the severity of the disease. A patient with severe pancarditis received 2,000 mg. of cortisone in divided doses in the first forty-eight hours of administration, 200 mg. the third day and 100 mg. daily for six days with striking benefit and without untoward effects. While doses of such size are not recommended, this case illustrates the degree to which the drug may be tolerated.

**Results**

The effect of cortisone or ACTH on rheumatic fever seems to depend on several factors. The most important consideration appears to be the promptness with which the treatment is instituted after the onset of the acute attack of the disease. If the disease has existed for some considerable time (three weeks or more), murmurs may be present which are not abolished by the treatment. On the other hand, in patients treated after a short duration of the disease systolic and diastolic murmurs may develop which disappear during the course of administration of cortisone or ACTH. Similarly, rheumatic carditis treated early in its incipiency responds much more dramatically than it does when treatment is instituted after carditis has existed for many weeks or months.

Ten of our patients in their first attack of rheumatic fever and 1 in a recurrent attack received cortisone or ACTH. Six of these patients, when re-examined at periods of 1 to 18 months after their dismissal from the hospital, had no cardiac murmurs or evidence of cardiac enlargement. Two of these patients subsequently have had recurrent attacks of rheumatic fever with reappearance of murmurs and cardiac enlargement.

Five of our patients who received cortisone were considered to have carditis. In 3 patients, in whom the duration of acute rheumatic fever was 15, 16 and 40 days respectively at the time when treatment was started, carditis was improved strikingly after two weeks of treatment. In a fourth patient whose treatment was begun after a recurrence of acute rheumatic fever had existed for 43 days, a marked reduction in heart size and a marked fall in venous pressure were observed after cortisone had been given for one month. In the fifth patient with carditis, in whom treatment was started on the forty-eighth day of the disease, the effect of cortisone on the acute manifestations of rheumatic fever was not pronounced, but there did result a striking improvement in the patient’s
appetite, morale and cooperation. Cortisone was administered for one month. A roentgenogram of the thorax made with a portable apparatus six days after administration of cortisone had been discontinued showed a striking reduction in heart size, though the cardiac size still was greater than normal.

McEwen and his co-workers reported a striking benefit in one of their patients with carditis. Massell and Warren considered that ACTH suppressed rheumatic carditis in several of their patients. They considered evidence of this to be the rapid disappearance of signs of pericarditis, regression and disappearance of significant murmurs, and diminished severity of congestive failure. Wilson and Helper treated 11 patients who had carditis with ACTH. Termination of symptoms and disappearance of signs of progressive carditis occurred in every case. They concluded from their experience that the early treatment of acute carditis with adequate amounts of ACTH should shorten the course of the disease, result in minimal residual cardiac damage, and prevent death due to progressive carditis and resultant congestive failure.

This review of our experience and the experience of others of the effects of cortisone and ACTH on acute rheumatic fever leads to the conviction that these hormones are promising weapons in the treatment of the disease. This reviewer believes that the institution of treatment with cortisone or ACTH at the earliest possible time after the onset of the disease is of the utmost importance, and that the course of treatment should be so planned as to maintain suppression of the acute manifestations of rheumatic fever until the disease has reached the end of its natural duration.

Much longer observation of patients treated with these hormones will be required before the ultimate effect of the hormones on rheumatic heart disease can be adequately assessed.

REFERENCES


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