Corticotropin (ACTH) in Heart Disease: Its Paradoxical Effect on Sodium Excretion in Resistant Congestive Failure

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Since the spring of 1952 we have undertaken a clinical trial of corticotropin in 21 cardiac patients with resistant edema. Of these, there were eight with arteriosclerotic, eight with chronic rheumatic, and three with hypertensive heart disease, while two had cor pulmonale. Beneficial results were obtained in 17, or 81 per cent of the cases. These consisted of a spontaneous diuresis either during corticotropin administration or after its withdrawal, or an alteration of response to mercurials, the patients subsequently responding favorably, whereas they had previously been completely refractory to the mercurial diuretics.

During recent years, it has been increasingly realized that a number of edematous patients fail to respond to the usual diuretic measures now in use. The picture of truly resistant edema where diuretic measures, including vigorous use of mercurial diuretics, are entirely of no avail, or cause natriuresis with no weight loss (or even a weight gain), resulting inevitably in hyponatremia, is a frustrating one. An occasional patient responds, albeit temporarily, to simultaneous administration of salt solution and a mercurial diuretic.

Since the spring of 1952, we have obtained sufficient clinical evidence and electrolyte balance data which promise to establish corticotropin (ACTH) as the therapeutic agent par excellence for the situation just described. This is the more fascinating if one recalls that to date corticotropin has been considered contraindicated in congestive heart failure due to its sodium-retaining effect. Well aware of its known physiologic actions at the time, we nonetheless decided to start a clinical trial of corticotropin in the following categories of patients in whom there was little to lose: (1) those cardiac patients with truly resistant edema as described above, (2) heart patients with severe myocardial insufficiency (left ventricular) in whom there was severe pulmonary passive congestion and incapacitating, unreleivable paroxysms of dyspnea and (3) cardiac patients with severe, associated intrinsic bronchopulmonary disease (asthma, bronchiectasis, emphysema).

The initial trial of corticotropin in these cardiac patients was guided by the consideration that benefit might be obtained from the action of the hormone on some organ-system of the body which would offset that concern with sodium retention through increased production of desoxy cortisol-like substances by the adrenal cortices. This might possibly be in the form of improvement of the myocardium. With this thought, the clinical trial of corticotropin in heart disease was launched, but not without fear and trepidation.

Method and Material

The patients reported in this paper were all treated in the Metabolic Unit of the Deaconess Hospital. On admission, the patient's height and weight were obtained and from then on daily fasting weight in the morning was recorded on a scale which is sensitive to 100 Gm. The usual diuretic regimen as well as full digitalization or withdrawal were instituted from the time of

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admission and intractability of edema was verified by our own observations. In several instances, control periods of observation lasting for as long as 20 to 41 days (during which vigorous diuretic measures were used) were carried out prior to institution of corticotropin therapy.

The patients, selected with the criteria previously mentioned, were carefully evaluated for the existence of contraindications to corticotropin, other than congestive heart failure. The prospective candidate was then given a Thorn test to determine the responsiveness of the adrenal cortex.

In the meantime, 24-hour urine specimens were collected daily, collections being started and ended at 6:00 A.M. and their volumes recorded. The daily urinary excretion of chloride, sodium and potassium were determined in all except two patients. The morning following admission, and again immediately before corticotropin therapy, blood specimens were obtained in the fasting state for initial chemical determinations, which included plasma sodium, potassium, chloride, carbon dioxide combining power, serum proteins, blood sugar, urea nitrogen, cholesterol, blood pH, plasma specific gravity and plasma osmotic pressure. The procedures used in these analyses have been mentioned in a previous publication.1 The same set of determinations or part of it was obtained at appropriate intervals and at the end of treatment. Total eosinophil count was repeated on the fourth to sixth day of corticotropin therapy2 to insure effective dosage of corticotropin, which was given intramuscularly in doses of 10 to 25 mg. (depending on body weight) every six hours for 10 to 12 days. Two patients (C. O. and H. W.) received corticotropin intravenously over a period of nine days, the dose gradually being reduced from 15 mg. (in three divided doses) to 5 mg. daily. One patient (A. F.) received cortisone because no circulating eosinophils were found in the peripheral blood prior to corticotropin administration.

For the calculation of electrolyte balance data, the daily dietary intake of sodium and potassium was calculated from the figures given by Bowes and Church,5 for the food actually ingested. Losses of sodium and potassium through the urine, by emesis or by any drainage (thoracentesis, paracentesis) as well as levels of plasma sodium and potassium were determined by the use of a Beckman flame photometer. Skin and fecal losses were estimated, using the figures obtained by Arn and Reimer.5

Results

To date a total of 21 cardiac patients have met our criteria warranting the use of corticotropin. Of these, eight had arteriosclerotic cardiovascular disease and three had hypertensive heart disease. Of the remaining 10 patients, 2 had cor pulmonale secondary to broncho-pulmonary disease while eight had rheumatic heart disease with chronic valvulitis. The age range for the whole series was 39 to 69 years; there were 13 males and 8 females.

The clinical data on these patients are summarized in table 1.* Seventeen (81 per cent) out of the 21 patients were definitely benefited by a course of corticotropin. Of the four failures, one patient (R. H.) died of a pneumonia which developed on the ninth day of therapy. The three other failures were all cases of chronic rheumatic valvular disease. Although they tolerated the course of corticotropin therapy well, no improvement could be discerned from the point of view of intractability of edema and incorrigible hyponatremia, even with sodium supplements (patient M. C.), or from the point of view of relief of severe left ventricular insufficiency with incapacitating paroxysms of dyspnea (patients E. S. and R. T.). One of the failures already mentioned, patient M. C., proceeded on a progressively downhill course, as she had been doing prior to corticotropin despite all the other adjuvant measures, and expired three weeks later. At autopsy a “fish-mouth” stenosis of the mitral valve was found associated with an aneurysmal dilatation of the left atrium. Two other failures mentioned above, patients E. S. and R. T., are still living, but both have suffered much in morale in the last several months, with the justifiable feeling that they have reached the stage when nothing can be done for them. The first, patient E. S., had had a “bottle baffle” operation for marked mitral valve insufficiency in Boston two and one half months previously, while the other patient, R. T., is considered unsuitable for cardiac surgery due to marked involvement of both mitral and aortic valves. She has had numerous embolic phenomena in the past, the last one to the brain, resulting in a permanent dysarthria.

The beneficial results obtained in the 17

* A quantity of corticotropin sufficient for a complete therapeutic course for 10 patients was generously supplied by Dr. G. W. Bissell of the Armour Laboratories.

* At the request of the Editor, table 1 is being omitted. This table will be furnished on request.
patients may be grouped together into the following categories:

1. Spontaneous diuresis (i.e. without the use of a mercurial diuretic) occurring during and continuing after the course of corticotropin in four patients (D. K., F. R., R. B. and C. O.), with loss of previously resistant edema. In two of these patients (D. K. and F. R.), the initial diuresis was mainly a water diuresis, with correction of a coexisting hyponatremia (no sodium supplements being given), followed by proportionate sodium and water loss until all signs of edema disappeared.

2. Diuresis occurring spontaneously after discontinuation of corticotropin, with edema weight loss and relief of intractable pulmonary passive congestion in three patients (R. D., E. M. and R. V.).

3. An altered response to mercurial diuretics, the patients responding effectively whereas they had been refractory to them previously; this change occurring either during or after the course of corticotropin therapy. This type of beneficial effect was observed in the majority of cases, as exemplified by patients R. M., C. M., R. C., B. S., A. F., W. R., H. L., R. H., C. B., and H. W.

Graphic representations of pertinent data on a few of the patients illustrate vividly the different types of beneficial results obtained with corticotropin. The graphs are self-explanatory.

In representing sodium and potassium balance data, columns above the base line show positive balance, while those below the base line indicate negative balance.

Patient D. K., the data on whom are represented in figure 1, had had a myocardial infarction eight years previously. For two and one-half years he had been in congestive failure, the edema responding at first to the usual measures but gradually and progressively becoming intractable. He came with the history of nonresponse to various diuretic measures, including the intravenous injection of mercurial diuretics three times a week. On admission he presented the picture of anasarca with severe hepatic passive congestion (lower edge of the liver was 4 inches below the right costal margin), moderate ascites, and orthopnea with Cheyne-Stokes respiration. A trial period longer than four days on our usual regimen was not attempted on account of the rapidly worsening condition of the patient. There was persistence of marked oliguria and development of more edema, abdominal distention, persistent hiccups, and severe hyponatremia.

Corticotropin was started on the fifth hospital day, and note in figure 1 that on the fifth day of corticotropin therapy, after an initial weight gain of 3.9 Kg. and a drop of plasma sodium to 116 mEq. per liter, there started a continuing diuresis which, in the brief span of 13 days, resulted in a total edema weight loss of 17.8 Kg. Calculation of data from the fourth to the tenth day of corticotropin administration during which an edema weight loss of 8.2 Kg. occurred, shows that there should have been a negative sodium balance of 1,033 mEq. (8.2 × average plasma sodium concentration of 126 mEq. per liter). The total urinary sodium output during those six days amounted to only 4.3 mEq., and there was a positive sodium balance of 3.7 mEq. The absence of a natriuresis during the first five days of increased volume of urine output is interesting, especially since it was accompanied by a progressive rise in plasma sodium concentration. Clinical improvement went hand in hand with the rapid clearing of edema, ascites and hepatic passive congestion. The small doses of Thiomerin were subsequently given to shorten his hospital sojourn, the patient being eager to rejoin his family in Canada. We feel that the diuresis would have continued anyway, perhaps at a slower rate, had the mercurial diuretic not been given.

The data on patient R.D. are graphically represented in figure 2. This 69-year-old physician had suffered an acute myocardial infarction seven months previously and had been subsequently readmitted to the hospital twice previously for severe pulmonary passive congestion prior to these studies. For about four weeks before this admission he had been incapacitated by severe, unrelietable paroxysms of
Fig. 2. Clinical and Laboratory Data on Patient R. D., male, age 69, with arteriosclerotic coronary heart disease.

dyspnea. He manifested marked Cheyne-Stokes respiration on admission. The lower two-thirds of the lungs were full of moist rales. Peripheral edema was minimal. Nevertheless, there was a total edema weight loss of 8.5 Kg, following the discontinuation of corticotropin. As seen in figure 2, small doses of Thiomerin were given twice, on the seventh and again on the tenth day of corticotropin. There was a rather pronounced, uninterrupted natriuresis following the last day of corticotropin.

The problem in patient R. D. was not an intractable edema, but rather, the severe paroxysms of dyspnea. Following the course of corticotropin therapy he became free of respiratory distress and was able to resume part-time practice for nine months.

Patient R. M., the data on whom are graphically represented in figure 3, had severe chronic valvular disease on a rheumatic basis, involving both the aortic and the mitral valves. She had been in auricular fibrillation for at least 21 years, and in severe congestive failure for two years before she was first seen in 1949. From then on, there followed a long series of hospital admissions with a progressively intractable edema. Incidentally, she was found in 1950 to be a potassium loser and had to have daily supplements of potassium chloride.

On this admission in 1952 she was massively

Fig. 3. Clinical and Laboratory Data on Patient R. M., female, age 56, with rheumatic heart disease, chronic valvulitis.
anasarcaeous, with deep pitting edema involving the upper and lower extremities, and the lower two-thirds of the torso. There were ascites and severe passive congestion of the lungs and liver. A 41-day battle with her edema, including the use of daily potassium supplements, large and rather frequent intramuscular and intravenous doses of Thiomerin, intravenously administered sodium-poor albumen, even large oral doses of urea along with all the other adjuvant diuretic measures, accomplished little. The weight loss during the precorticotropin period was only 2.3 Kg; most of this represented tissue weight loss since the average daily food intake contained only 800 calories.

Note that figure 3 shows that during and after the course of corticotropin, intramuscular doses of Thiomerin were much more effective in producing both water and sodium diuresis. The urine volumes were 6700 ml. and 7100 ml. when Thiomerin was administered on the eighth day of corticotropin and the day following its discontinuation, respectively, with a corresponding urinary output of sodium of 282 mEq. and 297 mEq. The subsequent weight loss of 6.6 Kg. is more significant if one takes into account that an increase in appetite with corticotropin boosted her average daily calorie intake from 860 to 1,940 calories. There was virtual clearing of peripheral edema, with persistence of only minimal ascites.

Another patient, C. M., whose response to corticotropin was similar to that of the patient described above (fig. 3, R. M.) is worth referring to. A course of corticotropin (which was given only after a control period of 22 days during which true resistance was demonstrated), resulted in complete alteration of response to mercurial diuretics. There occurred a rapid clearing of edema; he has not required mercurial injections since his discharge from the hospital, and has remained free of edema for 28 months at the time of this report.

Discussion

The results we have had with the use of corticotropin in apparently hopeless and terminal cases of cardiac patients have so far been highly gratifying. Judging from the favorable response obtained in 81 per cent of the patients, it would seem that a new avenue of hope has been opened for such patients.

Excessive renal tubular reabsorption of sodium (and the corresponding proportionate amounts of water) is generally accepted as the ultimate mechanism of edema formation. Since this function of the renal tubules is under the control of desoxycorticosterone-like substances from the adrenal cortex, the use of corticotropin, which stimulates adrenocortical activity, has been considered contraindicated in congestive heart failure.

From theoretical considerations it would seem logical to anticipate that the use of corticotropin would cause an intensification of the congestive failure syndrome in heart disease. We have, however, demonstrated that when the regimen which is ordinarily effective in combating edema is used in conjunction with corticotropin, the theoretically deleterious effect, perhaps observed during the initial few days of its administration, becomes relegated to the background and is then overshadowed by heretofore unsuspected beneficial effects. This regimen, which has been described in detail in previous publications, is instituted from the beginning of treatment, and is maintained during and after corticotropin therapy. The patients receive an acid-residue diet which contains from 9 to 30 mEq. of sodium daily, depending on the caloric intake. Up to a certain point of dietary sodium intake, the emphasis is on the acid reaction of the diet residue rather than on strict sodium restriction. Ammonium chloride is administered daily in doses of 1.5 to 4 Gm.; it is given in loose powder form buffered with equal amounts of calcium carbonate in a capsule. The few patients who do not tolerate this are given the enteric coated form of ammonium chloride. Strict attention is paid to water intake which is kept between 2500 and 4000 ml. daily in the majority of cases. To accomplish this, oral water intake is supplemented with intravenous infusions of 5 per cent dextrose in distilled water, if necessary. Fasting weights are obtained daily in the morning. Those patients who do not diurese spontaneously by the fifth or sixth day, or who become distressed by the usually slight initial weight gain (maximum 3.9 Kg. observed in patient D. K.) are given intermittent doses of Thiomerin. Adjuvant measures such as digitalization, oxygen administration, sedation, and others are used as indicated. This regimen has shown its value in minimizing the initial antidiuretic effect of corticotropin, and later potentiating and maintaining its beneficial effect.

Fortunately, contraindications to the administration of corticotropin in cardiac patients warranting its use have not been encountered.
with frequency in our series. When known contraindications (other than congestive failure) coexist, careful clinical judgment has to be exercised between possible catastrophe and anticipated beneficial results. Using proper precautions, no condition has been considered as an absolute deterrent to the use of corticotropin when faced with a desperate situation. Such was the case with one of the patients, F. R., (severe hypertension for 10 years; acute pulmonary edema before admission) whose condition rapidly deteriorated within a week following admission. This patient had had a chronic duodenal ulcer with a flare-up only two weeks previously, had developed an infection (pleuropericarditis) and had become markedly agitated and mentally confused, but a course of corticotropin therapy was decided on nevertheless, on account of a rapidly failing myocardium, as manifested by severe paroxysmal dyspnea with Cheyne-Stokes respiration of a marked degree, acute dilatation of the left ventricle (demonstrated by serial chest roentgenograms), marked fall in blood pressure, and finally right-sided failure with generalized edema. Precautionary measures taken included the following: daily red cell counts and hemoglobin determinations and daily examination of the stools for occult blood were done while blood was held in readiness for emergency transfusion; Probanthine was administered intramuscularly in 15 mg. doses every five hours; adequate protective doses of penicillin, streptomycin and erythromycin were given; and to combat agitation, he was sedated with intravenous doses of sodium amytal for 36 hours. The gamble taken with the use of corticotropin was richly rewarded in this case, with recovery from acute myocardial failure and since then, freedom from congestive failure and from respiratory embarrassment for seven months at the time of writing.

The clinical and laboratory detection of rheumatic activity in chronic cases of rheumatic heart disease is admittedly a difficult one. However, the absence of fever, and the other cardinal signs of activity (joint manifestations, chorea, subcutaneous nodules, and other signs), the normal sedimentation rate, the nonprolonged P–R interval by electrocardiograph, and the absence of leukocytosis all lead us to conclude with some certainty that we were not dealing with rheumatic carditis in the eight patients with rheumatic heart disease in this series. This point is brought up because of the well-known fact that cardiac decompensation from active rheumatic carditis may be corrected by corticotropin or cortisone, whereas the value of these hormones in congestive failure from the mechanical effects of chronically deformed valves has not until now been carefully evaluated. Interestingly enough, three of the four failures in this series of 21 patients were cases with chronic rheumatic heart disease.

Potassium chloride was administered orally or intravenously to some of these patients receiving corticotropin in whom negative potassium balance became manifest from increased urinary excretion of the electrolyte or from a dropping level of plasma potassium concentration. Two of the patients, R. M. (fig. 3) and R. T. had previously been known to be inordinate potassium losers, and they received daily supplementary doses of potassium chloride throughout the period of treatment. Liddle, Bennet and Forsham have demonstrated that sodium retention induced by corticotropin may be corrected by the administration of large doses (200 mEq. or more) of potassium salts. They found that potassium salts in large doses consistently cause sodium diuresis, even in subjects not receiving corticotropin, although the natriuretic effect of potassium was much less in the latter than in those undergoing corticotropin therapy. Although the supplementary doses of potassium chloride in some of our patients undoubtedly contributed to their general well-being, it is unlikely that natriuresis was induced by its administration. The dose of potassium chloride was usually 40 mEq., and did not exceed 80 mEq. daily in any of our patients, a dose much smaller than that shown to produce natriuresis by the above mentioned workers. In patient R. M., potassium chloride had been given daily prior to corticotropin in the same dosage as during and after corticotropin yet the intractability of edema had persisted, and no effective natriuresis could be obtained even with vigorous use of diuretic measures until after the course of corticotropin therapy. Potassium
supplements were not given to patient D. K. (fig. 1) until the last day of corticotropin administration at which time he had already lost 13.1 Kg. of edema weight and had had sodium diuresis. There was no definite correlation between potassium administration and the start of natriuresis in the other patients studied in this series, hence it may be safely assumed that the small doses of potassium chloride administered did not play a major role in inducing natriuresis.

In 1952 Andrus and his co-workers reported two patients with severe mitral stenosis in whom corticotropin therapy produced a striking improvement of respiratory function with clearing of pulmonary congestion. The depression of respiratory function seen initially in those patients was of such severity as to render mitral valvuloplasty hazardous, but following improvement with corticotropin, they stood mitral valve surgery well, and were greatly benefited thereby. No comment was made on the effects of corticotropin on peripheral edema, although it was stated that the patients did gain weight in the course of corticotropin therapy. Their studies centered mainly on the effect of corticotropin on some of the pulmonary complications of mitral stenosis, one of their main findings being a reduction of the abnormally high pulmonary artery pressure. No electrolyte studies were mentioned.

The mode of action by which corticotropin produces the salutary effects described in our report is worthy of speculation. Earle and his co-workers found in normal subjects an increase in urinary sodium excretion (after an initial decrease from control values) occurring sometime between the tenth and fifteenth days of corticotropin administration. They attribute this phenomenon, at least in part, to the observed concomitant increase in glomerular filtration rate. No attempt was made in our series of patients to compare glomerular filtration rates before, during and after the course of corticotropin therapy. However, it would seem from theoretical considerations alone that such variations in glomerular filtrate volume would not cause variations in the amount of urinary sodium excreted, for, after all, the distal tubules, which have the capacity to alter their reabsorptive power within a wide range, are the final arbiters of the quantity of sodium excreted. Clinically this is borne out by the observation that nephritic patients in the nephrotic stage with massive edema may have near-normal glomerular filtrate volumes, but the daily urinary excretion of sodium may be reduced to only a fraction of a milliequivalent. Conversely, nephritic patients with moderate impairment of glomerular function may have no trouble keeping free of edema even on a diet with no salt restriction. The renal tubules do not reabsorb sodium excessively, and sodium balance is maintained.

Furthermore, Earle and his co-workers point out that the rapidity with which changes occurred either on corticotropin administration or withdrawal suggest that the observed alterations in filtration rate and renal plasma flow were the result of functional (i.e., constriction of the efferent arterioles of the glomeruli, associated with dilatation of afferents) rather than morphological changes. Certainly then, the remissions observed in our patients, lasting in several instances as long as nine months, and in one instance 28 months, cannot be explained on the basis of temporary changes in renal hemodynamics induced by corticotropin.

It may be mentioned in passing that Metcalf and co-workers in a careful study of renal function in nephrotic children in whom diuresis was induced by corticotropin, came to the conclusion that altered renal hemodynamics may be the result rather than the cause of favorable response.

Thus, the explanation for the beneficial effects of corticotropin in heart disease has to be sought along different lines. There is the possibility that corticotropin may stimulate the adrenocortical production of a hormone that has an action antagonistic to that of desoxycorticosterone, thus inducing diuresis not only after, but even during the course of corticotropin therapy. An effect such as this has been reported with the use of cortisone in normal subjects and nephrotics. Luetscher and Deming have emphasized that with cortisone in nephrotics, the sodium diuresis occurs mainly after withdrawal of the hormone. They attribute this phenomenon to temporary inhibition of endogenous adrenal production of de-
soxycorticosterone as a part of the overall diminution in adrenal cortical activity, induced by the administration of cortisone. Of interest is the suggestion that cortisone prevents the rise in levels of antidiuretic substance levels in the blood of adrenalectomized rats, although it does not reduce the amounts present in normal nonadrenalectomized animals. To explain the initial water diuresis observed in patients D. K. and F. R. with corticotropin, therefore, one would have to assume a pre-existing adrenal insufficiency with little or no production of endogenous cortisone, a condition which was presumably corrected by the administration of corticotropin.

The above explanation for the beneficent effects observed with corticotropin in congestive failure is an attractive one. It will need confirmation by further trials using cortisone. The possibility remains that corticotropin may mediate its beneficial action through other still undiscovered hormones produced by the adrenal cortex. Differences have been reported between the actions of cortisone and those of corticotropin in nephrotic patients. According to Luetscher’s observations, corticotropin in general is followed by an earlier and more profuse elimination of water and sometimes of sodium during treatment. The diuresis at the end of corticotropin administration is generally more abrupt and profuse than that seen after cortisone.

Lastly, one may add the possibility that corticotropin, directly or through some adrenocortical hormone, may produce an improvement of the failing myocardium primarily, thus striking at the root of the cause for the existence of an increased volume of extracellular fluid. The long duration of remissions from congestive failure in several cases, and in other instances the marked and dramatic relief of paroxysmal dyspnea and Cheyne-Stokes respiration (due to left ventricular insufficiency) seem to favor this speculation. The case of patient F. R. who was rescued from an episode of acute cardiac failure and in whom serial roentgenological chest films showed a return of myocardial tone (following acute dilatation of the left ventricle) with corticotropin affords strong circumstantial evidence which cannot be slightly put aside.

Be that as it may, it is hoped that this report will not only encourage further clinical trial of corticotropin in the manner described, but also stimulate more research in basic cardiac physiology with special reference to the pituitary and adrenocortical hormones.

Summary and Conclusions

A clinical trial of corticotropin, with detailed electrolyte and water balance studies, has been underway since the spring of 1952 in apparently hopeless and terminal cardiac patients falling into the following categories: (1) Cardiac patients with truly resistant edema in whom previous vigorous diuretic measures in our hands had produced no results, and in whom hypotension, hypokalemia and other electrolyte disturbances had developed with the usual methods of treatment, (2) heart patients with severe myocardial insufficiency (left ventricular) in whom there was severe pulmonary passive congestion and incapacitating, unreliable paroxysms of dyspnea and, (3) cardiac patients with severe associated intrinsic bronchopulmonary disease (asthma, bronchiectasis, emphysema).

Of the 21 cardiac patients (eight arteriosclerotic, three hypertensive, eight chronic rheumatic, and two cor pulmonale) who thus far have met our criteria warranting the use of corticotropin, 17 (or 81 per cent) were definitely benefited by the hormone. The salutary effects may be grouped into the following types of response: (1) Spontaneous diuresis (i.e., without the use of a mercurial diuretic), occurring during (usually fourth to sixth day of treatment) and continuing after the course of corticotropin therapy with loss of previously resistant edema. This was observed in 4 cases. (2) Diuresis occurring spontaneously after discontinuation of corticotropin, with edema weight loss and relief of intractable pulmonary passive congestion, was seen in three patients. (3) An altered response to mercurial diuretics, the patients responding effectively whereas they had been refractory to them previously, this change occurring either during or after the course of corticotropin therapy. This type of response was observed in 10 patients.
CORTICOTROPIN (ACTH) IN HEART DISEASE

Of the four failures, three had chronic valvular disease on a rheumatic basis, and one suffered from arteriosclerotic heart disease.

Five of the patients with chronic rheumatic valvular heart disease who responded favorably to corticotropin showed no clinical nor laboratory evidence of active rheumatic carditis prior to therapy.

The initial increase in edema with the use of corticotropin is minimized by the adjuvant use of a diuretic regimen which is reviewed in brief. Continued use of the same regimen after the course of corticotropin maintains and potentiates the beneficial effects of this hormone.

Speculations on the possible mode of action of corticotropin, based on our observations and studies of other investigators, lead to the tentative conclusion that cortisone or some other still undiscovered adrenal hormone, produced in response to corticotropin stimulation, may overcome by antagonistic action on the renal tubules the sodium-retaining effect of deoxycorticosterone-like substances which are also presumably produced by the adrenal cortex in response to corticotropin administration. The possibility remains, based on clinical observations, that corticotropin may, directly or through some other adrenocortical hormone, produce an improvement of the failing myocardium.

Further clinical trial of corticotropin in such patients will be carried out, while awaiting explanation of its rationale from basic research in cardiorenal physiology.

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