CONTINUOUS INTRAVENOUS ADMINISTRATION OF ACTH

BY

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Shortly after treatment with adrenocorticotrophic hormone by intramuscular injections had been started, it was found that the total daily amount was therapeutically much more effective when administered in small divided doses every 4 to 6 hours. This increased effectiveness was evident by a more rapid clinical improvement, as well as by the laboratory criteria of adrenal response.

Sayers et al. (1949) found that, following the intravenous administration of 100 mg. ACTH, the hormone concentration in the blood dropped to its former level 2 hours after the injection. It was also found that the incubation of the hormone in vitro with plasma, or with liver, kidney or muscle tissue, resulted in its rapid inactivation.

That the continuous administration of ACTH by intravenous drip is a more effective way of supplying the hormone to the organism has been shown experimentally by Ingle (1951), and clinically by Gordon (1950), Querido (1951) and Jelliffe et al. (1951). Gordon et al. showed a twenty-fold increase in response to ACTH when a given dose was administered intravenously over a period of 12 hours, as compared with the administration of an equal amount by a single intramuscular in-
<table>
<thead>
<tr>
<th>Case</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Disease</th>
<th>Duration of disease</th>
<th>Total ACTH mg</th>
<th>No. of days of treatment</th>
<th>Date of treatment until complete</th>
<th>Average daily dose of ACTH mg</th>
<th>Side effects</th>
<th>Duration of remission</th>
<th>Remarks</th>
<th>Complications</th>
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<tbody>
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<td>1</td>
<td>V. A.</td>
<td>54</td>
<td>F</td>
<td>R. A.</td>
<td>20 yrs</td>
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<td>80</td>
<td>18</td>
<td>18</td>
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<td>Cont. Cortisone</td>
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<td>3</td>
<td>M. L.</td>
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<td>2 mths</td>
<td>117</td>
<td>37</td>
<td>37</td>
<td>3.2</td>
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<td>Flushing, moon face, abd. swelling</td>
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<td>47</td>
<td>F</td>
<td>4 yrs</td>
<td>33</td>
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<td>20 days</td>
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<td>R. S.</td>
<td>33</td>
<td>F</td>
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<td>73</td>
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<tr>
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<td>F. S.</td>
<td>72</td>
<td>F</td>
<td>2 yrs</td>
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<td>15</td>
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<td>20 days</td>
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<td>G. S.</td>
<td>56</td>
<td>F</td>
<td>B. A.</td>
<td>12 yrs</td>
<td>60</td>
<td>8</td>
<td>8</td>
<td>7.5</td>
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<td>Thromboephlebitis</td>
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<td>6</td>
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<td>Flushing, moon face</td>
<td>21 days</td>
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<td>7</td>
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<td>--</td>
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<td>T. P.</td>
<td>52</td>
<td>F</td>
<td>2 mths</td>
<td>16</td>
<td>11</td>
<td>1</td>
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<td></td>
<td>--</td>
<td>7 days</td>
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<tr>
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<td>M. L.</td>
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<td>R. D.</td>
<td>40</td>
<td>M</td>
<td>Urt.</td>
<td>14</td>
<td>8</td>
<td>5</td>
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<td>42</td>
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<td>2 mths</td>
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<td>1.5</td>
<td></td>
<td>--</td>
<td>3 months ***</td>
<td>Post Penicillin</td>
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</table>

B. A. = Bronchial Asthma    R. A. = Rheumatoid Arthritis    Urt. = Urticaria

*) No complete relief  **) Case could not be followed  ***) Complete remission at time of writing
jection. Mandel et al. (1951) and his co-workers state that their therapeutic results were as good as or better when using only 1/10 to 1/20 of the dosage previously employed by intermittent intramuscular injections. Their average daily dose was between 5 and 10 mg. given by continuous intravenous drip over a period of 8 to 20 hours. Renold (1951) and his colleagues gave an average daily dose of 20 mg., while Jelliffe et al. (1951) administered 25 to 50 mg. by intravenous drip on alternate days.

Following these reports, we administered the hormone by continuous intravenous drip to patients suffering from various diseases known to respond to ACTH treatment. The first few patients were given the dosage recommended by Mandel. It was soon noticed that in some patients receiving 10 mg. daily (cases 1, 2 and 3), the original symptoms of the disease were exacerbated during the administration of the hormone, although on discontinuation of the drip there was an immediate and considerable improvement. Furthermore, undesirable side effects occurred in these patients, such as flushing, epigastric fullness and rounding of the facial contours. In consequence, the amount of ACTH given daily was gradually diminished, and finally we were led to the conclusion that 1 to 3 mg. ACTH per diem may be therapeutically as effective as larger doses administered by the same method.

**METHOD OF ADMINISTRATION**

In our study all patients were hospitalized, and the routine clinical and laboratory examinations for assessing the degree of progress were performed at frequent intervals. The range of active and passive movements was determined in patients suffering from rheumatoid arthritis. All patients were on a diet containing not more than 2 gm. sodium chloride per diem. The ACTH (ACTHAR Armour) was administered daily by continuous intravenous infusion in 500 to 1000 ml. of a solution of 5 per cent glucose with the addition of 0.2 per cent potassium chloride. The rate of the drip was from 12 to 16
drops per minute. If a tendency to clotting was observed at the site of the venipuncture, 3 to 4 drops of a one per cent solution of heparin were added to the infusion.

CASE REPORTS

The following is a report on 7 cases of rheumatoid arthritis, 9 cases of bronchial asthma in a state of acute exacerbation and 2 cases of giant urticaria. The findings are summarized in the accompanying table; three illustrative cases are described in detail (cases 7, 15 and 18).

Case 7. A female, 72 years old, was admitted with a history of pains and swellings in the joints for the past two years. Both large and small joints were affected, and the disability increased gradually until she became bedridden 6 months ago. She had suffered for the past 25 years from palpitations and from loose bowel movements. On admission her temperature was 38° C., pulse rate 110. There was limitation of movement in almost all her joints. In addition to the severe rheumatoid arthritis, the patient showed signs and symptoms of thyrotoxicosis. She was started on 2 mg. ACTH by continuous intravenous drip. At the end of 24 hours the pain was very much alleviated. The following day the swellings of the joints regressed and she was able to straighten her knees completely. After 10 days of daily treatment, during which time she had received a total amount of 13 mg. ACTH, she was able to get out of bed and walk a few steps. At this time her ESR was 25 mm. during the first hour, whilst her circulating eosinophil count had dropped from 73 to nil. The daily 17 Ketosteroid excretion in the urine rose from 4.5 mg. to 9 mg. Treatment was continued for a total of 21 days, during which time she received a total of 30 mgs ACTH. When she left hospital she was walking freely and did not complain of any pains in the joints.

Case 15. A male schoolteacher, 24 years old, who has been suffering from asthmatic attacks for the past 6 years. During the past few months the attacks had increased both in frequency and severity, and for the three days prior to hospitalization he was in a status asthmaticus. He was given 1 mg. ACTH daily by continuous intravenous drip for 6 days. Immediately following the first day of treatment the patient was conscious of a definite improvement in his chest condition, although broncho-spasm still persisted. On the second day the dyspnoea completely disappeared and the patient no
longer had any feeling of constriction in his chest. On the third
day he was free from all symptoms of the disease.

Case 18. A male, 42 years old, had been under treatment with pe-
nicillin for a chronic leg ulcer, and had developed giant urticaria
which persisted for two months after the antibiotic was discontinued
and was resistant to all the usual forms of treatment, including anti-
lhistaminics. On admission, the patient's temperature was 38° C., he
looked extremely ill and oedematous and appeared to be in great
distress. Practically the whole of his body was covered with urti-
caria. The patient was given 2 mg. ACTH by intravenous drip. About
8 hours after the commencement of treatment the patient's dis-
comfort was very much alleviated and his urticaria started to recede.
The following day his urticaria had completely disappeared and he
received a further milligram of ACTH intravenously. At the time of
writing, three months after his discharge from hospital, the urticaria
has not reappeared. During his stay in hospital, whilst receiving
treatment with ACTH, there was a coincident and marked improve-
ment in the state of the ulcer.

RESULTS

In all our cases there was an appreciable clinical response
to intravenous treatment with ACTH on the first or second
day, and the effects of adrenocortical stimulation were also
evident from the laboratory findings. Temperature, whenever
elevated, dropped to normal during the first few days of treat-
ment. Diuresis was satisfactory in spite of the additional fluid
introduced intravenously in the infusions. There was no sud-
den increase in body weight, nor any retention of sodium
chloride, in contrast to our previous experience when ACTH
had been given intramuscularly or intravenously with higher
doses (cases 1, 2 and 3). None of the patients treated with
small amounts of ACTH showed any rise in blood pressure,
not even those with a pre-existing high blood pressure. On the
other hand, one case of hypertension (case 1) treated with a
larger dose (10 mg. per diem) did show a rise in arterial ten-
sion, necessitating a temporary cessation of treatment; re-
sumption of treatment with smaller quantities (1 to 3 mg.)
did not bring about a renewed rise in blood pressure and was
sufficient to induce further clinical improvement. In patients
with a high erythrocyte sedimentation rate a decrease of the E. S. R. was noticed during the first week of treatment. In cases who first received the larger dosage (10 mg. per diem), and later the smaller dosage (1 to 3 mg. per diem), the rate of slowing of the E. S. R. was equally sustained during both periods. As with the intramuscular administration, no complete normalization of the E. S. R. was obtained. The circulating eosinophil count dropped rapidly to a low level, sometimes to zero, though we preferred not to obtain an absolute aneosinophilia. As already mentioned, the few cases who received initial large doses of ACTH (10 mg.) intravenously, displayed such features as face flushing, abdominal distension, rounding of the facial contours and fluid retention; on reducing the dosage of ACTH these symptoms and signs disappeared, although clinical improvement continued. One patient receiving 5 mg. ACTH per diem (case 8) complained of severe epigastric pain; on reduction of the dose to 1 to 2 mg. daily the pain disappeared and did not recur. Apart from occasional slight flushing during the administration of the drip, none of the patients in the series receiving small doses of ACTH showed any of the above-mentioned undesirable side effects. A few cases showed slight euphoria. No reactions of protein shock type, as described by Wilson (1951), were observed in our series.

COMMENT

In spite of the excellent immediate effects of therapy, the remissions achieved were short, from 1 to 3 weeks on the average, except in the cases of urticaria in which the condition cleared up completely.

The immediate and favourable response to small doses of ACTH given intravenously with almost a complete absence of undesirable side effects, coupled with the economy in the use of the drug, are, in our opinion, the great advantages of this method of treatment. Fundamentally, however, the essential problem — i. e. the maintenance of the therapeutic re-
suits achieved — remains unsolved as is the case with other methods of administration of the hormone. Furthermore, this method has its own technical limitations common to all prolonged continuous intravenous treatment (thrombosis at site of injection, thrombophlebitis, etc.).

SUMMARY

Seven cases of rheumatoid arthritis, nine cases of bronchial asthma and two cases of urticaria were treated with small daily doses of ACTH given by intravenous drip over a period of 12 to 20 hours. It was found that a dosage of 1 to 3 mg. resulted in satisfactory clinical improvement. No unfavourable side reactions were encountered with this dosage. Remissions were of the same duration as those achieved with other methods of administration.

ACKNOWLEDGEMENT

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REFERENCES