Acute Improvement in Exacerbating Multiple Sclerosis Produced by Intravenous Administration of Mannitol

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The mode of action of adrenocorticotropic hormone (ACTH) treatment in exacerbating multiple sclerosis was studied by short-term infusions of agents that mimic specific and limited pharmacological actions of ACTH and observing for temporally phase-locked clinical changes. The study was double blinded, and agents were administered while the patients were being treated with a standard course of 10-day intramuscular ACTH therapy (40 U twice daily). Antiedema, alkalotic–hypocalcemic, extraadrenal, and sodium-retaining actions were studied using infusions of mannitol, sodium bicarbonate, ACTH, and sodium chloride, respectively. Seven of 8 patients receiving placebo infusions (2.5% glucose) showed no significant clinical change and 1 exhibited an equivocal improvement. Five of 9 patients receiving mannitol showed definite signs of clinical improvement phase-locked to drug administration, with subsequent gradual reversal to baseline. Similar improvements occurred with infusions of $NaHCO_3$ in 5 of 8 patients and of ACTH in 4 of 8 patients. Three of 7 patients given NaCl infusion showed possible mild improvements. The results indicate that mannitol and $NaHCO_3$ induced transient acute improvement in signs at the 95% confidence level in patients with exacerbating multiple sclerosis, with ACTH having a similar effect at the 90% confidence level. These agents mimic some of the known effects of ACTH, which may be important in the therapeutic action of ACTH in multiple sclerosis. A possible role for mannitol and high-dose ACTH in the treatment of demyelinating disease warrants further study.

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Adrenocorticotropic hormone (ACTH) has been shown in a double-blind controlled study to shorten the duration of acute exacerbations in multiple sclerosis (MS) [9]. Although the effect is generally attributed to glucocorticoid release by the stimulated adrenal gland, there has not been universal agreement that ACTH and oral glucocorticoid treatments are equivalent in benefit [4, 7]. Alexander and Cass [1] reported that ACTH was superior to oral glucocorticoids in treating MS and suggested the importance of the adrenal release of hormones other than glucocorticoids. Arnason [2] has also postulated an extraadrenal or direct effect of ACTH on neural function.

ACTH stimulates the adrenal cortex to release a very rich mixture of glucocorticoids, mineralocorticoids, and weak androgens. It is possible that one or more of these hormones together with an extraadrenal action might act additively or synergistically in producing the therapeutic effect of ACTH in MS. In the present double-blind placebo-controlled study we attempted to address some of these possibilities by treating patients with MS in exacerbation with short-term intravenous infusions of agents that mimic specific and limited pharmacological actions selected from the ACTH spectrum and looking for temporally phase-locked clinical changes. This report focuses on pharmacological effects that can be acutely induced and observed over several hours. These include the antiedema, sodium-retaining, alkalotic–hypocalcemic, and extraadrenal actions of ACTH. Androgenic and other effects that cannot be acutely induced require a different protocol, but are also under study.

Methods

Patient Selection and Study Design

Thirty-four patients with definite MS, ranging in age from 19 to 47 years, who were hospitalized for treatment of acute exacerbations were selected. The severity of neurological deficit (acute and chronic) varied among patients, and the duration of the disease ranged from 6 months to 27 years. None had been treated with either steroids or ACTH for at least 3 months before their participation in this study. Newly developed or recently worsened signs of neurological deficit of 2 to 4 weeks' duration were the criteria used in defining

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acute exacerbations. No patients with other medical illnesses were included, and all participants gave informed consent.

The agents investigated were administered intravenously over the short term while the patients were also receiving ACTH, or, in the instance of isolated acute optic neuritis, receiving oral prednisolone therapy. The treatment regimen for ACTH was 40 U intramuscularly twice daily for 10 days. Oral prednisolone was begun at a total dose of 80 mg/day and was gradually tapered off after 10 days. These will be referred to as "standard treatments" in subsequent discussions.

Forty trials were carried out in 34 patients on the first or second day of the standard treatment regimen. We studied the antiedema, alkalotic–hypocalcemic, extraadrenal, and sodium-retaining effects with 20% mannitol (450 ml/hour), 7.5% $NaHCO_3$ (450 ml/30 minutes), ACTH (70 U in 250 ml of 5% dextrose/hour), and 5% NaCl (1,000 ml/3 hours), respectively. The placebo consisted of 2.5% glucose (500 ml/hour).

The study was double blinded. Agents were assigned to patients randomly except when exacerbations consisted solely of optic neuritis. These latter patients were given either mannitol or placebo. However, while this was known to one neurologist (D. S.) responsible for the care and videotaping of the patient, it was not known to the other neurologist (F. D.) assessing the clinical data or to the technician assisting in data recording and responsible for visual function testing. Serum electrolytes were serially monitored during all infusions. Serum osmolality was monitored during mannitol infusions, and serum calcium during the $NaHCO_3$ experiments.

Of the 5 patients who received two agents, 3 received placebo and 2 received mannitol in 1 of the 2 separate trials. Overall, 32 trials were conducted with pharmacologically active agents, and 8 with placebo.

Neurological Testing

Neurological examinations and tests were performed before, immediately after, and at varying intervals after infusion of an agent. Observations were focused mainly on functions constituting the ongoing exacerbation and were continued up to 6 hours after infusion, until any changes reversed to baseline levels or appeared to be stable. Body temperature was recorded at each examination.

The clinical examinations were videotaped. Evaluation of these examinations was performed by a second neurologist (F. D.) who was "blinded" regarding the agent administered, and who had not been involved in the neurological testing procedure. Each patient's complete accumulated video material was analyzed at a single session to facilitate quantification. In most cases, clinical findings were rated on a scale of seven grades, as follows:

Grade	*Function*
0	Normal function.
1	Between normal function and mild deficit. Dysfunction was revealed only upon very thorough testing; it was often fleeting and not noticeable to the patient.
2	Mild deficit. Detectable upon routine testing of a specific function; it only minimally altered the patient's performance in carrying out a given task.
3	Mild to moderate deficit. Readily demonstrable on testing; it mildly but noticeably altered a specific function.
4	Moderate deficit. The specific function could be only partially executed by the patient.
5	Moderate to severe. The patient could initiate only the given task.
6	Severe deficit. The specific neurological function under observation was nearly or completely abolished.

Changes of two or more grades were considered as significant improvement or deterioration. A few signs were evaluated on a scale modified from the above. Tendon stretch reflexes were graded on a scale of 0 to 4, with 2 being normal and 4 representing clonus. Clonus was rated as absent (Grade 0), unsustained (Grade 1), or sustained (Grade 2). Plantar responses were rated as normal plantar flexion (Grade 0), response absent (Grade 1), slight dorsiflexion of the big toe (Grade 2), or full dorsiflexion of the big toe with or without fanning (Grade 3).

Critical flicker fusion frequency (CFF) was tested with a Grass Model HPS-2-B Photo-Stimulator. Testing was done in a darkened room with the light source 0.3 to 3 m from the patient, depending on the severity of baseline visual impairment. The results from 6 trials were averaged. Visual acuity was assessed by determining the minimum separation between two vertical lines that could be resolved by the patient. The two lines were displayed on an oscilloscope and initially superimposed so that only one line was visible. At the beginning of a trial the lines were separated slowly until both lines could be detected by the patient. Acuity was tested monocularly with the results from 6 trials averaged. As in the CFF testing, the visual target was positioned 0.3 to 3 m from the patient, depending on the severity of the baseline visual impairment. Visual field examinations were carried out on a Goldmann Perimeter 940-ST (Haag-Streit AG) using standard techniques for both kinetic and static quantitative perimetry.

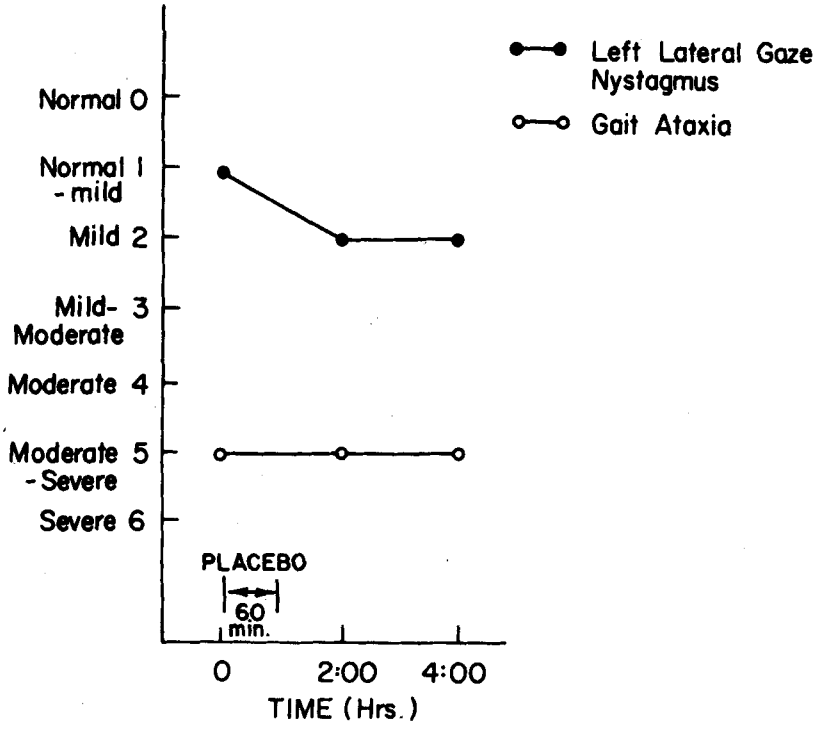
Results

Placebo

Eight patients received placebo (2.5% glucose) infusions (Table 1). Of these, 7 showed no significant clinical change and 1 exhibited an equivocal improvement. For the purposes of subsequent comparison and statistical analysis, we regarded the equivocal change seen in this patient as significant, yielding an efficacy rate of 12.5%. Figure 1 illustrates the results of a typical control experiment.

Mannitol

Five of the 9 patients receiving intravenous mannitol showed definite signs of clinical improvement phase-locked to the drug administration (Table 2). An example of the observed effects of mannitol on CFF frequency and visual acuity in a patient with optic nerve involvement is shown in Figure 2. Before mannitol infusion, the patient's right eye visual acuity was 18 minutes of arc and CFF frequency was 15/second. Af-



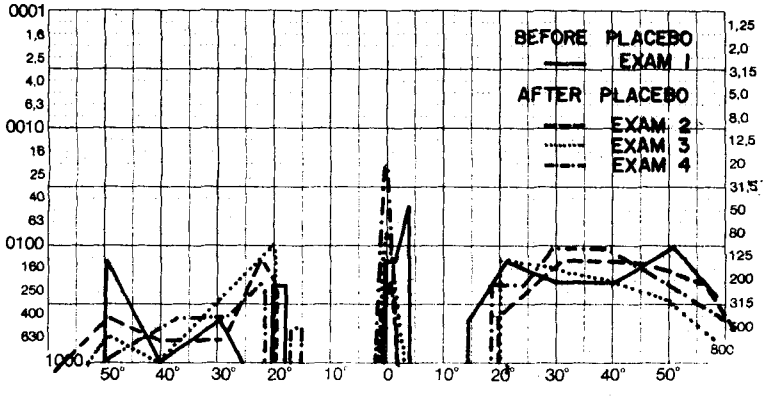


Fig 1. Patient F-26. Absence of significant changes after infusion of placebo (2.5% glucose; 500 ml/60 minutes). The lower portion depicts static-quantitative perimetry of the involved right eye; 0 to 180 degrees meridian. In this and all perimetry data the ordinate represents target brightness in apostilbs; numbers on the abscissa represent the width of the visual field in degrees of arc where 0 degrees is central (macular) vision.

ter the mannitol infusion, there was dramatic improvement in both of these indicators. In addition, there was a striking improvement in the visual field. A normal visual field (static-quantitative perimetry) is shown in Figure 3 for comparison. These effects were accompanied by a rise in serum osmolality. All of the observed changes reversed as the serum osmolality returned toward normal over the ensuing 2 hours.

Similar visual function data were obtained in the

Table 1. Neural Functions and Responses to Intravenous Infusions of 2.5% Glucose

Patient No.	Visual	Oculomotor	Motor (Limbs)
F-30	NT	NT	0
F-26	0	NT	NT
F-31	NT	0	0
F-48	0	NT	+ −
F-29	0	0	0
F-29	0	NT	NT
F-28	− +	0	0
F-44	0	0	0

+ − = questionably improved; − + = questionably worsened; 0 = no change; NT = not systematically tested (not involved in acute exacerbation; see Neurological Testing).

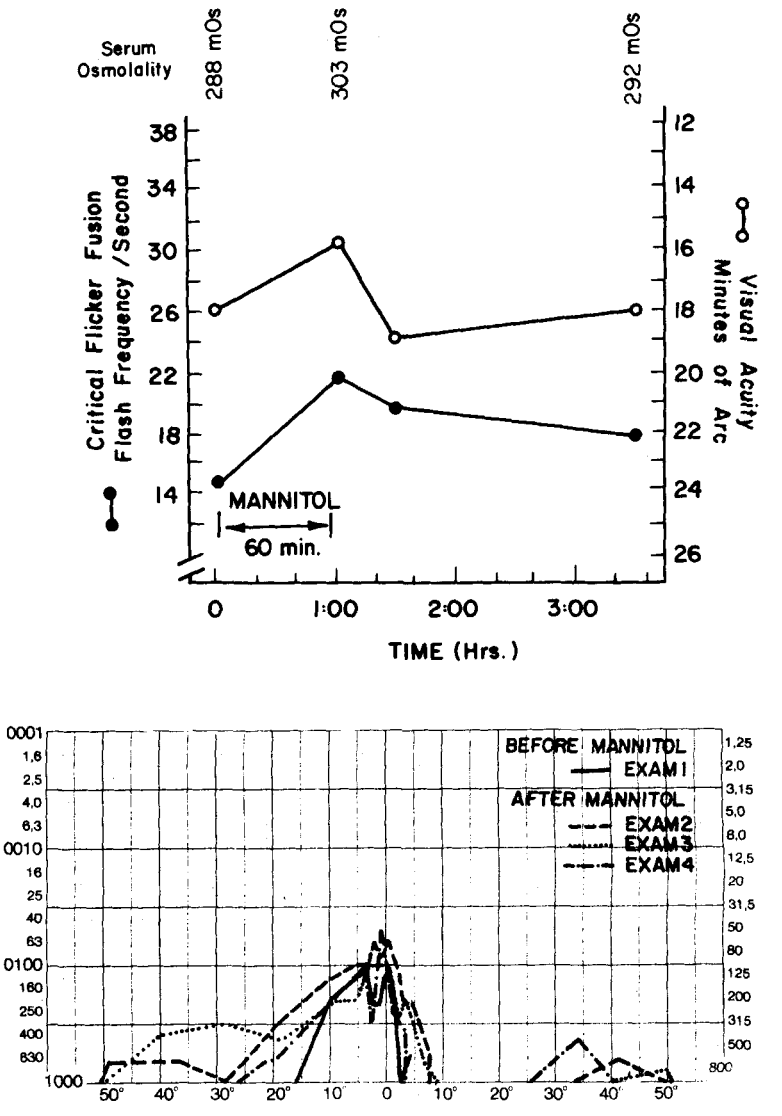


Table 2. Neural Functions and Responses to Intravenous Infusions of 20% Mannitol

Patient No.	Visual	Oculo-motor	Motor (Limbs)	Serum Osmolality
F-39	+	NT	NT	↑
M-38	+	NT	NT	↑
M-43	+	NT	NT	↑
F-19	+	NT	NT	↑
F-34	0	NT	NT	↑
F-39	0	0	0	↑
F-27	+	NT	NT	↑
F-29	NT	0	0	↑
F-27	NT	0	0	↑

+ = improved; 0 = no change; NT = not systematically tested (not involved in acute exacerbation; see Neurological Testing); ↑ = increased.

Fig 2. Patient F-27. Improvement of visual acuity (minutes of arc; average of 6 trials), critical flicker fusion (average of 6 trials), and visual field (static-quantitative perimetry; 0 to 180 degrees meridian) of the right eye during the hyperosmolar state after infusion of 20% mannitol (450 ml/60 minutes) and their reversal toward the pretreatment baseline within 2.5 hours after intravenous infusion. Note the 35-degree nasal extension of the postinfusion field and the appearance of some vision in the temporal field. (Ordinate of lower graph = target brightness in apostilbs.)

other 4 patients whose visual function improved, and all showed a transient elevation of serum osmolality. Two of these patients were concurrently treated with oral prednisolone instead of intramuscular ACTH because their exacerbation was restricted to retrobulbar neuritis (see Methods). The other 4 patients did not exhibit any significant changes in visual function. Com-

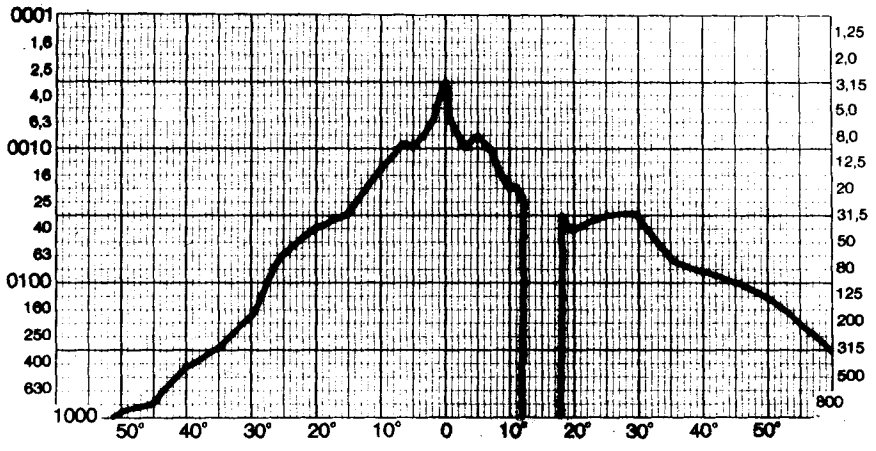


Fig 3. Normal visual field (left eye) by static-quantitative perimetry; 0 to 180 degrees meridian. Data obtained from a normal male subject by the same procedures as used to evaluate patients with multiple sclerosis. (Ordinate = target brightness in apostilbs.)

pared with placebo results, a positive outcome for mannitol in 5 of 9 patients is significant at the 95% confidence level ($\chi^2 = 3.44$).

Sodium Bicarbonate

Five of the 8 patients given intravenous $NaHCO_3$ improved, and 3 remained unchanged (Table 3). Compared to placebo, this is also significant at the 95% confidence level ($\chi^2 = 4.27$). All 8 patients showed a transient increase in the serum sodium level and partial pressure of carbon dioxide and a reduction in the serum calcium concentration. Figure 4 illustrates the result of a typical experiment. Note that the transient clinical improvements are again phase-locked to the $NaHCO_3$ infusion.

ACTH

Four of the 8 patients given 70 U of ACTH intravenously over 1 hour showed acute transient improvement (Table 4). These acute improvements suggest an extraadrenal ACTH action. This is also supported by data indicating that maximal adrenal cortical secretion is obtained in adults with a total dose of only 25 U infused over 8 hours [5], and our patients were also receiving a background dose of 40 U of ACTH intramuscularly twice daily. Compared with placebo, this result was significant at a marginal 90% confidence level ($\chi^2 = 2.62$). No consistent serum electrolyte changes accompanied the clinical changes. Figure 5 illustrates the clinical changes in CFF frequency and static-quantitative perimetry after an ACTH infusion.

Table 3. Neural Functions and Responses to Intravenous Infusions of 7.5% $NaHCO_3$

Patient No.	Visual	Oculo-motor	Motor (Limbs)	Serum Calcium
M-33	0	NT	+	↓
F-40	NT	NT	0	↓
F-29	+	+	+	↓
M-27	NT	+	+	↓
F-29	+	+	+	↓
M-33	0	NT	+	↓
F-27	0	NT	0	↓
F-25	NT	0	NT	↓

+ = improved; 0 = no change; NT = not systematically tested (not involved in acute exacerbation; see Neurological Testing); ↓ = decreased.

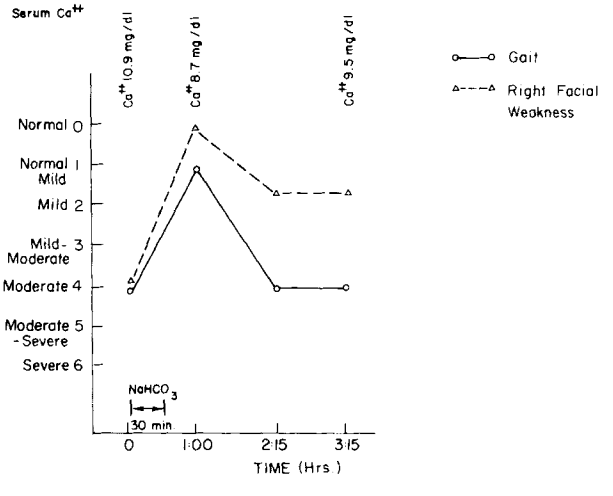


Fig 4. Patient F-29. Brief improvement phase-locked with infusion of 7.5% $NaHCO_3$ (450 ml/30 minutes) and resulting transient hypocalcemia.

Table 4. Neural Functions and Responses to Intravenous Infusions of 70 U of ACTH

Patient No.	Visual	Oculomotor	Motor (Limbs)
M-35	NT	0	0
F-19	+	NT	NT
F-34	0	0	NT
F-39	+	NT	NT
F-27	NT	+	+
F-29	0	+	+
F-29	0	0	0
F-27	0	0	0

+ = improved; 0 = no change; NT = not systematically tested (not involved in acute exacerbation; see Neurological Testing).

Sodium Chloride

Three of 7 patients given NaCl infusions showed possible mild improvements (Table 5). The results were not significantly different from those in the placebo group. Two patients remained unchanged and 2 had a transient adverse reaction characterized by skin flushing, lassitude, tremulousness, and emotional lability (crying). This reaction lasted 3 to 4 hours. Six of 7 patients exhibited transient elevations of serum sodium after infusion.

"Standard" ACTH Therapy

In addition to these short-term observations, the study yielded some uncontrolled and unblinded data concerning the effects at the end of a standard 10-day treatment of 40 U ACTH given intramuscularly twice daily. Fourteen of the 34 patients in this study were followed for 10 days using the same quantitative neurological assessment described in the Methods section. Thirteen of the 14 (93%) demonstrated significant improvement. Nine of these (69%) had also improved earlier with short-term infusions of mannitol (2 patients), $NaHCO_3$ (3), and ACTH (4). Qualitatively, the changes were in the same categories for both the agents and the intramuscular ACTH, except

Fig 5. Patient F-19. Intravenous adrenocorticotropic hormone (ACTH) (70 U/60 minutes) induced transient improvement of right eye critical flicker fusion (average of 6 trials) and visual field (static-quantitative perimetry; 0 to 180 degrees meridian). Note the nasal extension of the postinfusion field, the appearance of vision in the temporal field, and their reversibility. (Ordinate of lower graph = target brightness in apostilbs.)

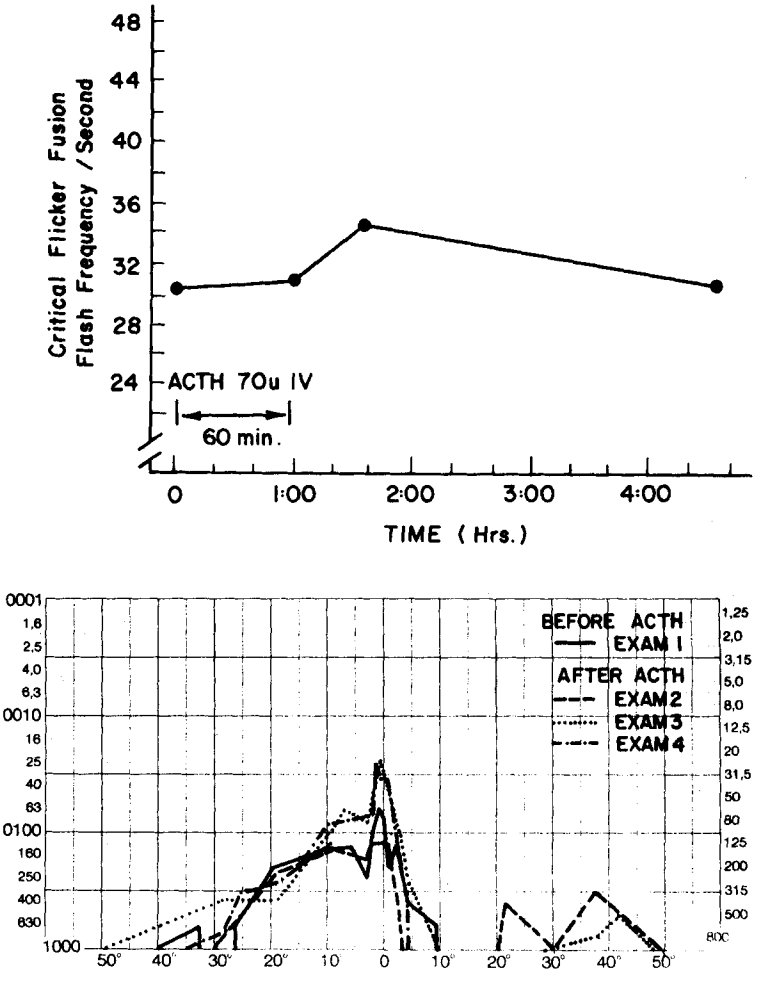


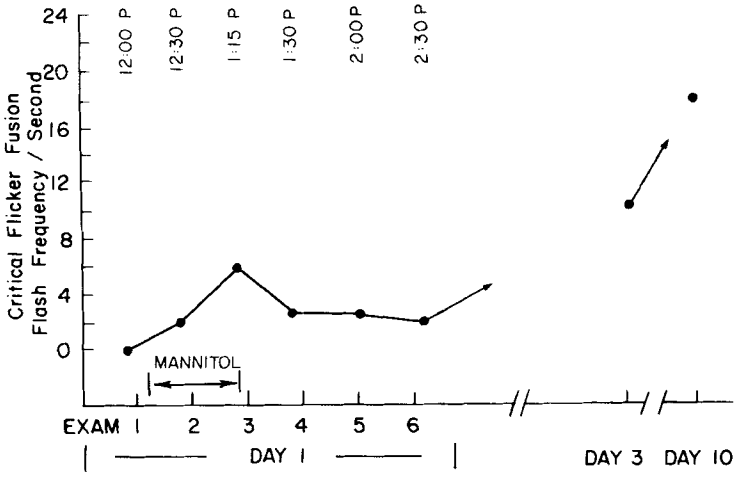
Table 5. Neural Functions and Responses to Intravenous Infusions of 5% NaCl

Patient No.	Visual	Oculo-motor	Motor (Limbs)	Sodium
F-29	0	−	−	↑
F-48	0	NT	−	↑
F-30	0	+	+	0
F-42	+	+	+	↑
M-28	+	+	+	↑
M-44	0	0	0	↑
F-42	0	0	0	↑

+ = improved; − = worsened; 0 = no change; NT = not systematically tested (not involved in acute exacerbation; see Neurological Testing); ↑ = increased.

that additional improvements appeared in some patients later in the course of the standard (10-day intramuscular ACTH) treatment. Aside from the latter, no significant differences were observed between the immediate effects of the agents and the slower effects of the standard treatment. Of the 4 patients who improved after the standard 10-day ACTH treatment but who did not change with the short-term infusions, 2 received placebo, 1 intravenous ACTH, and 1 $NaHCO_3$. The 1 patient who did not improve after 10 days of ACTH therapy also did not respond to the short-term infusion of ACTH early in the course of treatment. Figure 6 illustrates the long-term improvement in CFF frequency observed during a 10-day course of ACTH, and also shows the acute response to intravenous mannitol given at the beginning of ACTH therapy. Note that the CFF frequency response before treatment in this patient was not measurable because of the severity of visual impairment.

Fig 6. Improvement of critical flicker fusion (average of 6 trials) of the right eye during and after intravenous infusion of mannitol (20%; 450 ml/60 minutes) with resulting hyperosmolality (300 mOsm at 12:30 PM; 305 mOsm at 1:15 PM), and its reversal toward the pretreatment baseline within 90 minutes postinfusion. Note the inability to discern light flickers before the infusion. Values obtained for Days 3 and 10 reflect subsequent improvement during the continuing 10-day adrenocorticotropic hormone treatment (40 U intramuscularly twice a day).



Discussion

The results indicate that both mannitol and $NaHCO_3$ induce a transient phase-locked improvement in signs in exacerbating MS at the 95% confidence level, with short-term intravenous ACTH possibly having a similar beneficial effect at the 90% confidence level. These agents mimic some of the known effects of ACTH, which may be important in the therapeutic action of this agent in MS.

Mannitol is a potent hyperosmolar antiedema agent. When used in patients with cerebral edema and increased intracranial pressure resulting from brain neoplasms, significant improvements in signs and symptoms can occur within a few hours. Similar changes can be seen with glucocorticoids. In both instances the effect can be attributed to the shared antiedema action of these agents. The mannitol-induced improvement reported here supports the concept that a glucocorticoid, antiedema action is an important component of ACTH therapy in MS. It also suggests that edema may have an important role in the production of signs and symptoms in MS.

The importance of an antiedema action of ACTH was suggested by Miller and co-workers in 1961 [7] when rapid improvement was often observed in acute retrobulbar neuritis treated with ACTH. They concluded that this may ". . . be related to the special conditions associated with this lesion, in which the tension of inflammatory edema in a nerve closely invested by its bony canal is dramatically manifested as acute failure of visual acuity." This is also supported by the data of Rawson and associates [8] who were impressed with the rapidity of visual improvement in ACTH-treated acute retrobulbar neuritis. They also reported

that a very rapid relief of ocular pain occurred within a few hours of the initiation of ACTH treatment.

In some instances of optic neuritis, severe altitudinal visual field defects and even total blindness can occur. These might possibly be in part accounted for by a secondary ischemia resulting from edema. Such defects can be irreversible, and contrast with the often more reversible and smaller scotomas seen in MS. It is possible that early treatment with mannitol, in conjunction with glucocorticoids, might be of value in preventing dysfunction and damage secondary to edema. Although further studies are necessary to test this hypothesis, we believe that patients with unusually severe florid optic neuritis for whom there is a concern about permanent damage should be considered for early treatment with mannitol infusion along with glucocorticoids. Dosages that are currently recommended for cerebral edema would appear to be appropriate.

The improvement seen with $NaHCO_3$ confirms the results of an earlier unblinded report [3]. It is believed that the $NaHCO_3$ effect is due to the induced alkalosis and accompanying decrease in serum ionized calcium, which increases the conduction safety factor. Since mineralocorticoids can also induce alkalosis, they would be expected to produce some transient improvement in MS. The lack of any clinical improvement with NaCl infusion supports the view that alkalosis, rather than hypernatremia, is the basis for the effect of $NaHCO_3$.

Arnason [2] has postulated that ACTH might, in part, improve MS as a result of an unknown extraadrenal effect, perhaps even by a direct action on neural tissue. Many peptides have specific neurotransmitter and/or neuromodulatory roles, and fragments of ACTH devoid of hormonal activity have important effects on complex brain function underlying behavior and learning [6]. Since maximal adrenocortical stimulation is obtained in adults with a total dose of only 25 USP units infused over 8 hours [5], it is likely that the baseline dose of ACTH given to our patients (40 U intramuscularly twice a day) produced maximal adrenal stimulation. In that event the massive amount of additional ACTH given intravenously (70 U over 1 hour) is likely to have produced its effect extraadrenally. Although a definitive statement is not possible without study of the adrenocortical response to our protocol, the acute changes do support an extraadrenal action of ACTH in MS.

All of the acute effects we observed could be accounted for by alterations in impulse conduction, either by means of a direct action on the excitable membrane or, in the case of mannitol, indirectly through a decrease in tissue edema. The resulting clinical changes would be expected to be short-lived after cessation of drug administration, and would also be most pronounced at times of heightened physiological lability of the diseased axons. Lability is extraordinarily marked during an exacerbation and gradually lessens on remission [4]. This hypothesis could account for the very rapid improvement sometimes seen soon after initiating ACTH treatment, as well as for the rapid partial rebound sometimes observed after treatment ceases. In addition, a putative extraadrenal ACTH effect could help explain observations that suggest a superiority of ACTH over corticosteroids in treating MS [1].

Of the patients who were followed quantitatively throughout the 10-day ACTH treatment, improvement occurred in an extraordinarily high percentage (93%). This must be assumed to include a substantial placebo effect, as these observations were unblinded and not controlled. As noted earlier, however, 69% of the improved patients reacted favorably to short-term infusions of mannitol, $NaHCO_3$, and ACTH; coincidentally, this group of patients cooperated better in our follow-up period. Thus, it is possible that we had inadvertently selected a group of patients with a high probability for responding to a 10-day course of ACTH treatment. The only patient observed not to have improved after 10 days of ACTH did not change with short-term infusion of ACTH either. It thus appears that patients sensitive to short-term infusions of mannitol, $NaHCO_3$, and ACTH were also responders to 10-day ACTH therapy. If this relationship could be confirmed, such short-term infusions might be a useful screening method for selecting patients likely to respond to ACTH therapy.

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