Effect of intravenous sodium bicarbonate, disodium edetate (Na₂EDTA), and hyperventilation on visual and oculomotor signs in multiple sclerosis

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SUMMARY The effects of procedures believed to produce a decrease in serum ionized calcium were tested on visual and oculomotor function in nine multiple sclerosis (MS) patients. Transient improvement in scotomas, nystagmus, and oculomotor paresis occurred with intravenous infusions of NaHCO₃ or Na₂EDTA. Hyperventilation was also tested for its effect on nystagmus and caused marked decreases in frequency. Control experiments with saline infusions did not produce any effect. The probable mechanism and site of action for these effects is discussed. This study demonstrates that certain signs and symptoms in MS can be altered favourably by changes in the internal chemical environment and offers a new approach to the search for a symptomatic therapy in MS.

Multiple sclerosis (MS) is a disease affecting the white matter of the central nervous system. It is characterized pathologically by numerous discrete areas of myelin loss along the course of involved axons. These demyelinated lesions are believed to cause a slowing and block of conduction which in turn is responsible for the clinical signs (Charcot, 1877; Namerow, 1968a; Namerow and Kappl, 1969).

There is reason to believe that this axonal conduction defect is labile and capable of being modified in both a favourable and unfavourable manner. This is suggested by the remarkable fact that small changes in body temperature can markedly alter specific signs in MS (Simons, 1937; Brickner, 1950; Guthrie, 1951; Edmund and Fog, 1955; Nelson, Jeffreys, and McDowell, 1958; Boynton, Garramone, and Buca, 1959; Nelson and McDowell, 1959; Watson, 1959). Heating and cooling cause a transient worsening and improvement respectively. A recent report described an MS patient with optic nerve involvement whose visual acuity decreased from 5/40 to 5/200 after only a 0.25°C temperature rise (Namerow, 1968b). These effects only last as long as the temperature change is maintained. They are not specific for MS, since other neurological diseases are aggravated by hyperthermia. However, they clearly occur with greater frequency and sensitivity in MS (Nelson *et al.*, 1958; Nelson and McDowell, 1959; Namerow, 1968b).

Since an understanding of these temperature effects (especially that of cooling) might reveal a rational basis for a symptomatic treatment in MS, earlier studies were aimed at developing a simple but pertinent conduction model. Studies in a variety of animals—frog (Davis, 1969), lobster (Davis, 1970), guinea-pig (Davis and Jacobson, 1970)—have demonstrated that demyelinated and injured nerves have a heightened sensitivity to reversible thermal block—that is, conduction fails at temperatures within or close to the physiological range. Conversely, it has been shown that cooling restores conduction in injured nerves (Davis, 1970). It has been postulated that these effects are related to critical alterations in the conduction safety factor (Davis, 1970). The safety factor is defined as the ratio of the action current of a nerve fibre to the minimum current necessary to maintain conduction (Tasaki, 1953). This ratio reflects the net effect of many variables involved in the maintenance of axonal conduction. Tasaki found a value of 5 to 7 for the safety factor in amphibian myelinated nerve (Tasaki, 1953). Theoretically, if the safety factor is decreased by axonal injury or disease the conduction mechanisms should become more vulnerable and might fail with a further lowering brought on by adverse alterations in pH, electrolytes, temperature, etc., even though similar changes do not block normal nerve. On the other hand, conditions that increase the safety

factor might improve function in diseased nerve. Heating and cooling might then be thought of as causing a decrease and increase respectively in the safety factor.

This hypothesis offers a reasonable explanation for the temperature effects in MS. It also predicts that pharmacological agents that can increase the safety factor might improve clinical signs in MS. It is well known that calcium ion depletion lowers the threshold for excitation in axons (Misske, 1930; Brink, Bronk, and Larrabee, 1946). Since this would decrease the minimum current needed to maintain conduction, it should increase the safety factor. In support of this, it has been demonstrated that conduction block in injured nerve is reversed by lowering the concentration of calcium ions in the bathing medium (Davis, 1969).

In this paper we report the effect on visual and oculomotor defects in MS of three procedures believed to lower serum ionized calcium. It has been found that infusions of sodium bicarbonate (NaHCO_3) and sodium edetate (Na_2EDTA) as well as hyperventilation improve clinical findings in MS. This study was, in part, previously reported in a brief preliminary communication (Davis, Becker, Michael, and Sorensen, 1970).

METHODS

SUBJECTS Nine MS patients were studied. All had evidence for disseminated lesions and, except for one, a course characterized by exacerbations and remissions. Pertinent data are presented in Table 1. The criteria for patient selection (in addition to a firm diagnosis of MS) was the presence of a visual field scotoma and/or lateral gaze nystagmus.

PROTOCOL Intravenous infusions of NaHCO_3 and Na_2EDTA were tested for effects on scotomas and nystagmus. In addition, the effect of hyperventilation on nystagmus was studied. In those patients who had both

scotomas and nystagmus, only one of these findings was tested in any single experiment and an interval of at least seven days separated each additional experiment. As described below, the selected clinical finding was monitored before, during and after either hyperventilation or an intravenous infusion.

Hyperventilation was performed around 30 to 40 breaths per minute for varying periods as indicated in the Results section. NaHCO_3 infusions consisted of a 5% solution and, except where otherwise noted, were given at 15 to 25 ml./min. Na_2EDTA (1.5 g/1,000 ml. normal saline) was infused in total amounts of 2 to 3 g over 50 to 80 minutes. Blood samples were drawn for calcium and acid-base studies during some experiments.

MEASUREMENTS OF VISUAL SCOTOMAS Subjects participating in the visual field experiments had initial ophthalmological evaluations consisting of visual acuity determination, refraction (both manifest and by retinoscopy), slit lamp examination, and funduscopy examination to rule out ocular disease. Ocular tensions were also tested. Except for the changes frequently seen in MS, as well as minor refractory changes, these tests were not remarkable.

Visual field testing was performed with a Bausch and Lomb Autoplot Tangent Screen under the standard conditions specified in the instrument's operating manual. They were performed by one of the authors (E.S.) who is an ophthalmology resident and experienced with the testing of fields with this apparatus. Targets were selected that gave the most distinct outline of the central field defect for the particular eye being tested.

Refractive errors in these patients were small and in no case did correction improve acuity more than one-half line on a Snellen chart. For this reason, field testing was performed without corrective lenses. In some experiments visual acuity was determined with a Snellen chart after each field determination.

MEASUREMENT OF NYSTAGMUS The subject was seated in front of a perimeter on which were mounted three small lights. One light was mounted in the centre so that upon fixation of it the patient's eyes were in the primary position. The other two lights were placed to the right

TABLE 1
PATIENT DATA

Patient	Sex	Age (yr)	Duration of disease	Exacerbations and remissions	Evidence for dissem. lesions	Most recent exacerbation (months before testing)
R.W.	F	21	7 mth	Yes	Nystagmus and central scotoma	2
E.M.	F	47	5 yr	No (chronic progressive course)	Nystagmus and paracentral scotoma	—
C.N.	M	39	2 yr	Yes	Nystagmus and central scotoma	11
T.A.	M	32	4 yr	Yes	Nystagmus and central scotoma	14
D.R.	F	44	4.5 yr	Yes	Nystagmus and dysphasia	15
M.F.	F	26	15 mth	Yes	Nystagmus and paracentral scotoma	2
P.W.	F	31	2 yr	Yes	Ataxia and paracentral scotoma	12
D.P.	F	37	1.5 yr	Yes	Central scotoma and Hx numbness-tingling, right leg	10
M.S.	F	25	8 mth	Yes	Paraplegia and paracentral scotoma	1

and left of centre at positions that (1) resulted in maximum nystagmus upon their fixation, (2) did not cause subjectively uncomfortable strain, and (3) allowed binocular fixation of targets (in several patients with dysconjugate eye movements testing was performed monocularly by patching one eye). A rigidly fixed head position was maintained by means of a modified dental chair headrest.

Eye movements were recorded electro-oculographically (Shackel, 1960) using gold surface electrodes (Beckman E5G) placed at the canthi of each eye. Two AC-coupled amplifiers (bandpass 0-10,000 Hz, gain of 1,000) were used to increase the signal levels of the corneoretinal potential of each eye.

Subjects were instructed to maintain fixation on the light that was lit, and told to look 'left' or 'right' as the lights were turned on and off. Thus, an alternating pattern of left lateral, central, and right lateral gaze was elicited with nystagmus appearing during periods of lateral gaze. The duration of fixation at any position varied from 10 to 25 seconds. At the beginning of each experiment a 2 to 3 minute control run was obtained. The procedure to be tested was then begun and nystagmus was monitored periodically throughout the experiment.

Quantitative measurements were obtained by determining the frequency of nystagmus; the use of AC-coupled amplifiers and the usual long-term changes in electrode impedance made it difficult to monitor the amplitude of nystagmus quantitatively in a systematic way.

With the movements of both eyes being monitored independently and with nystagmus often appearing on both left and right lateral gaze, four possible measurements were obtainable. The quality of the records for each eye was rarely equal because of differences of electrode impedance and the noise characteristics of each recording channel, as well as the fact that nystagmus was

sometimes more marked in one eye, usually the abducting eye. Because of this, the particular record with the highest signal-to-noise ratio was selected for quantitative analysis. Thus, in each experiment the nystagmus of one eye in one particular direction of lateral gaze is consistently reported. This was acceptable since the changes in nystagmus on conjugate gaze were qualitatively similar in both eyes with all the experimental procedures.

CHEMICAL DETERMINATIONS Total serum calcium was determined by means of the EDTA titration technique (Bett and Fraser, 1959) and also by the fluorometric method (Jackson, Breen, and Chen, 1962) during the Na_2EDTA infusions. Ultrafiltrable calcium was obtained by the technique of Toribara (Toribara, Terepka, and Dewey, 1957). The ionized calcium was approximated during an Na_2EDTA infusion experiment by determining the calcium in the ultrafiltrate by the EDTA titration method. This value represents the non-EDTA-complexed calcium in the ultrafiltrate, which is mainly in the ionized form, but also includes small amounts of complexed calcium not bound to EDTA.

RESULTS

VISUAL STUDIES Infusions of NaHCO_3 and Na_2EDTA each resulted in marked decreases in the size of visual scotomas. The effect appears gradually within an hour after starting an infusion and slowly reverses within a similar period of time after infusion. Figure 1 shows a typical experiment with NaHCO_3 . Table 2 summarizes the results of six experiments on four MS patients; scotoma size is expressed in area (sq. cm) measured directly from the standard visual field record with a planimeter. Because of the short-

FIG. 1. Scotoma plotted with a 1 mm white target before (upper left), during (upper middle and right), and after (bottom row) intravenous infusion of NaHCO_3 . The scotoma slowly decreases in size during the infusion and then slowly increases, approaching control size after cessation of infusion.

TABLE 2
EFFECT OF NaHCO₃ AND Na₂EDTA INFUSIONS ON SCOTOMA SIZE

Patient	Date	Target (mm)	Eye	Control		Infusion				Post-infusion		
				Area of control scotoma (sq. cm)	Type of infusion	Amt. of infusion at max. response		Area of scotoma at time of max. response (sq. cm)	Percent control (%)	Time of final post-infusion field (min)	Area of scotoma at time of final field (sq. cm)	Percent of control (%)
1. D.P.	30 Jan. '70	1 white	R	55.3	NaHCO ₃	900	534	24.2	43.8	120	40.9	70.0
		3 white	L	56.7	NaHCO ₃	900	534	13.3	23.5	125	37.1	65.4
2. M.F.	6 Feb. '70	1 red	R	18.3	NaHCO ₃ (99°F)	675	400	7.8	42.6	60	17.6	96.2
		1 white	R	4.0	NaHCO ₃ (99°F)	675	400	0.3	7.5	65	4.0	100.0
	25 Feb. '70	1 red	R	17.0	Na ₂ EDTA	1300	2.0 g	4.8	28.2	80	16.8	98.6
		0.5 white	R	5.7	Na ₂ EDTA	1300	2.0 g	1.4	24.6	85	6.6	115.8
3. P.W.	6 Mar. '70	1 white	R	7.2	NaHCO ₃	500	297	1.6	22.3	60	4.8	66.7
	13 Mar. '70	2 white	L	3.1	NaHCO ₃	500	297	0.0	0.0	65	3.3	106.5
		3 red	L	7.9	NaHCO ₃	800	475	1.1	13.9	Patient nauseated and experiment discontinued		
4. M.S.	17 Mar. '70	6 white	R	55.0	NaHCO ₃	800	475	27.2	49.5	60	47.4	85.5

lived effect of hyperventilation and the time necessary for plotting fields, hyperventilation was not studied. Improvement in visual acuity from 20/400 to 20/200 was noted in one patient whose scotoma was centrally located. This experiment is shown in Fig. 2. Note also that, although the scotoma did not return

fully to control size, its configuration has been largely restored. In all other patients scotomas were paracentral in location and baseline visual acuity were either normal or mildly affected (up to 20/400). Significant changes in acuity were not observed in these patients.

FIG. 2. Scotoma plotted with a 3 mm white target before (upper left), during (upper middle and right), and after (bottom row) intravenous infusion of NaHCO₃. Visual acuity improved from control level 20/400 to 20/200 during infusion and gradually returned to 20/400 post infusion.

Scotoma size did not change with normal saline infusions. A typical control experiment is shown in Table 3. Though no change occurs during the saline infusion there is a prompt response on switching to NaHCO_3 which was heated to 99° F (37.2°C)—that is, the temperature of NaHCO_3 at the site of the intravenous hypodermic needle. Thus, the effect is not simply due to a non-specific body cooling caused by the infusion. Also, a decrease in scotoma size did not occur with 10% glucose.

TABLE 3
COMPARISON OF NORMAL SALINE (CONTROL) AND NaHCO_3
ON SCOTOMA SIZE

Infusion	Amount (ml.) (m-equiv)		Time (min)	Area of scotoma (sq. cm)	Percent control (%)
—	—	—	0	17.8	100.0
Normal saline	500	77	25	17.3	97.2
	1000	154	50	18.3	102.8
	675	400	110	7.8	42.6
NaHCO_3 *	—	—	170	17.6	96.2

M.F. 6 Feb. '70. (O.D.) 1 mm red target
*(Heated to 99°F)

The experiment shown in Table 4 and Fig. 3 tests the hypothesis that the NaHCO_3 effect is related to alterations in blood calcium. Two infusions were started in separate arms. NaHCO_3 was infused first and, when the scotoma had shown a clear-cut decrease in size, an infusion of calcium chloride was started in the other arm. Note the return of the scotoma to control size while both NaHCO_3 and calcium chloride infusions are running simultaneously.

In every NaHCO_3 and Na_2EDTA infusion, patients reported paraesthesias. These were most

marked around the mouth and/or distally in the limbs. These usually preceded the changes in scotomas (and nystagmus).

NYSTAGMUS STUDIES The effect of 2 to 3 minutes hyperventilation on nystagmus was tested in six patients. A total of 13 separate experiments were performed (Table 5) and in each case similar alterations were noted. In nine experiments in which eye movements were recorded electro-oculographically there was a 33 to 100% decrease in nystagmus frequency. These effects begin as early as 1 minute after starting hyperventilation and, as seen in Table 5, reach maximum values before 3 minutes; the effect is rapidly reversible. An example of an eye movement recording with hyperventilation is shown in Fig. 4. Figure 5 (top) shows the typical time course of the nystagmus change from onset to recovery.

Since a lowering of body temperature improves nystagmus in MS, the question was raised whether the decrease in nystagmus frequency with hyperventilation might be due entirely to a cooling effect related to the rapid exchange of the cooler room air. That this was not the case was established by the following experiment.

The patient (R.W.) breathed air that had been either heated or cooled by passing it through a heat exchanger; the temperature of the inspired air was monitored with a thermistor probe and a Yellow-springs Instrument thermometer. It was discovered that lowering the air temperature, during quiet breathing (not hyperventilation) produced a decrease in the frequency of nystagmus. A decrease in nystagmus frequency occurred from 3.0 beats/sec with air at 80°F (26.7°C) to 2.3 beats/sec with air at 75°F (23.9°C) (23% decrease). On a second trial lowering the temperature from 78.8°F (26°C) to 71.5°F (22°C) lowered the frequency from 2.8 beats/sec to 1.9 beats/sec (32% decrease). In another experiment seven days later, it was observed that heating air

TABLE 4
REVERSAL OF NaHCO_3 INDUCED IMPROVEMENT IN VISUAL FIELDS BY SIMULTANEOUS INFUSION OF CaCl_2

Time (min)	0	5	10	15	20	25	30	35	40	45
I NaHCO_3 (5%) infusion										
Infusion (ml.)			200		400	500		600	750	
NaHCO_3 (m-equiv)			119		238	298		377	446	
Serum CO_2 (m-equiv/l)	26.2					41.2				36.9
II CaCl_2 infusion										
Infusion (ml.)							50	100	200	
Calcium (g)							0.6	1.2	2.4	
Serum calcium (mg/100 ml.)						8.5				12.5
III Visual fields (scotoma area in sq. cm)										
1 mm red target	20.2		10.0		8.0		14.2		20.7	
0.5 mm white target	6.6		3.1		1.6		3.6		5.8

FIG. 3. Scotoma plotted with a 1 mm red target. Control (upper left); during NaHCO_3 infusion (upper middle and right); after switching to simultaneous infusions of NaHCO_3 and CaCl_2 (bottom row). The decrease in scotoma size seen with NaHCO_3 is inhibited by CaCl_2 .

from 84°F (28.9°C) to 100.8°F (38.2°C) (still without hyperventilation) increased nystagmus frequency from 1.8 beats/sec to 2.7 beats/sec (an increase of 50%). Thus, changing the temperature of inspired air during normal respiration does change the nystagmus frequency in the direction to be expected. However, with a nystagmus frequency of 2.7 beats/sec, while breathing air at 100.8°F (38.2°C) (not hyperventilation) the subject was instructed to hyperventilate, and within 3 minutes the nystagmus disappeared. Thus, although increased inspired air

temperature increased the control level of nystagmus, hyperventilation still caused a cessation of nystagmus. Under these conditions (air temperature greater than body temperature) hyperventilation is not at all likely to produce a cooling effect. NaHCO_3 and Na_3EDTA infusions were given to three patients, all of whom showed marked decreases in nystagmus frequency. The results of five experiments are given in Table 6. The time course of the frequency change in two typical experiments is seen in Fig. 5 (centre and bottom). No effects were

TABLE 5
EFFECT OF HYPERVENTILATION ON NYSTAGMUS FREQUENCY

Subject	Date	Nystagmus frequency (control)(beats/sec)	Minimum nystagmus freq. during HV (beats/sec)	Percent control(%)	Time to minimum frequency (min)(sec)	Recovery time (min)(sec)
R.W.	8 Aug.	2.66	1.33	50.0	0:25	2:00
	22 Aug.	2.83	1.75	61.7	2:15	1:00
		3.16	1.75	55.0	1:37	1:15
	29 Aug.	3.57	1.41	39.5	2:30	1:30
	10 Oct.	3.00	1.33	39.0	2:45	5:00
	24 Oct.	2.25	1.33	59.0	2:00	2:00
E.M.	15 Aug.	2.33	0.00	0.00	1:00	2:00
	3 Oct.	2.21	1.50	67.9	3:00	2:30
C.N.	28 Nov.	1.88	0.60	32.0	2:45	1:45
	5 Dec.	2.58	0.90	34.8	1:00	3:00
T.A.	1 Aug.	Phenomenon observed clinically				
D.R.	1 Aug.					
	12 Sept.					
M.F.	14 Nov.

FIG. 4. Electro-oculogram of lateral gaze nystagmus before, during, and after hyperventilation. A prompt decrease in nystagmus frequency occurs during hyperventilation and rapidly reverses after hyperventilation.

seen with control saline infusions. In addition, solutions of NaHCO_3 heated to 99°F were still effective, thus eliminating a non-specific body cooling as the cause of the decrease in nystagmus

DIPLOPIA STUDY In the only patient experiencing diplopia (M.F.) dramatic improvement occurred with a NaHCO_3 infusion. Mild weakness of right eye adduction was clinically evident upon left lateral gaze and the patient experienced diplopia with the false image appropriately displaced laterally. During the NaHCO_3 infusion the two images

TABLE 6
EFFECT OF NaHCO_3 AND Na_2EDTA INFUSIONS ON NYSTAGMUS FREQUENCY

Subject	Date	Nystagmus frequency (control) (beats/sec)	Minimal nystagmus frequency during infusion:		Percent control (%)
			Bicarbonate (beats/sec)	Na_2EDTA (beats/sec)	
R.W.	5 Sept.	3.59	1.00		28
	29 Aug.	2.67		1.17	45
C.N.	28 Nov.	1.84	1.05		57
	5 Dec.	2.50		1.10	44
E.M.	3 Oct.	2.59	1.83		71

FIG. 5. Timecourse of decrease in nystagmus frequency with hyperventilation (top), NaHCO_3 infusion (middle), and Na_2EDTA infusion (bottom).

gradually came together and then fused into a single image; at the time of fusion the adduction weakness was no longer clinically discernible. Shortly after stopping the infusion the adduction weakness again became evident and diplopia returned. On re-starting the NaHCO_3 infusion the same effects were again observed.

CHEMICAL STUDIES Table 7 summarizes the changes in blood chemistry measured during some of the experimental procedures. Hyperventilation in one patient produced a respiratory alkalosis with an arterial pH of 7.67. NaHCO_3 produced the expected metabolic alkalosis with CO_2 values rising as high as 43 m-equiv/l. During the NaHCO_3 infusions decreases in total calcium were small varying from 0.3-1.3 mg/100 ml. and lesser decreases occurred in ultrafiltrable calcium (0.2-0.8 mg/100 ml.) The Na_2EDTA infusion produced a 2.1 mg/100 ml.

TABLE 7
BLOOD CHEMISTRY DATA

I. Hyperventilation

	Arterial blood			
	pH	pCO ₂ (mm)	Negative base excess (m-equiv/l.)	Total serum calcium (mg/100 ml.)
E.M. (18 July '69)				
Control	7.40	39.0	2.2	8.0
Hyperventilation (3 min)	7.67	19.0	5.0	8.2
				5.25 5.00

II. NaHCO₃ infusions

	Total serum calcium (mg/100 ml.)	Ultrafiltrable calcium (mg/100 ml.)	CO ₂ (m-equiv/l.)
A. E.M. (15 Aug. '69)			
Control	8.4	6.1	26.5
NaHCO ₃ (356 m-equiv)	8.1	5.3	43.0
B. R.W. (5 Sept. '69)			
Control	8.1	6.2	23.6
NaHCO ₃ (356 m-equiv)	6.8	5.75	36.1
C. E.M. (3 Oct. '69)			
Control	8.2	6.0	25.1
NaHCO ₃ (356 m-equiv)	7.5	5.5	42.1
D. D.P. (6 Mar. '70)			
Control	8.9	5.9	24.3
NaHCO ₃ (356 m-equiv)	8.4	5.7	39.3

III. Na₂EDTA infusion

	Total serum calcium (mg/100 ml.)		Ultrafiltrable calcium (mg/100 ml.) (EDTA titration)
	Flame photometry method	EDTA titration method	
M.F. (25 Feb. '70)			
Control	8.9	8.8	6.35
Na ₂ EDTA	6.8	—	3.2*

*The ultrafiltrable calcium value obtained by EDTA titration method during the Na₂EDTA infusion can be used as an estimate of the ionized calcium, since it measures the calcium not complexed with EDTA in the ultrafiltrate.

lowering of total serum calcium along with a 3.1 mg/100 ml. decrease of serum ionized calcium (estimated by EDTA titration of ultrafiltrate).

DISCUSSION

This study demonstrates that visual scotomas, nystagmus, and oculomotor paresis in multiple sclerosis can be improved by hyperventilation and/or infusions of NaHCO₃ and Na₂EDTA. Since these effects do not occur with normal saline infusions given at room temperature and since solutions of NaHCO₃ heated to 99°F are effective, the phenom-

enon cannot be due to a non-specific body cooling caused by the infusion. In the case of hyperventilation a cooling effect has also been ruled out, since the change in nystagmus occurs even when the inspired air is heated to 100.8°F (38.2°C). It is therefore concluded that the effect is due to a more specific alteration in the internal environment. Before discussing this particular aspect further, the probable site of action of this alteration will be considered.

While the changes in nystagmus could be due to an effect on the central and/or peripheral nervous system (brain, cranial nerve, neuromuscular junction, muscle) the improvement in the scotomas is most likely due to an effect on the central nervous system since the neural components of vision are all central structures. Since refractive changes might be important these were looked for but none was found.

A scotoma is classified as a negative sign, in that it reflects a diminution or absence of function. In MS it is caused by a demyelinating lesion(s) in the optic nerve which results in an impairment of axonal conduction. The marked decrease in the size of scotomas seen with NaHCO₃ and Na₂EDTA infusions suggests that an improvement of conduction has occurred in these diseased axons. That is, the scotoma changes would appear to be due to an effect within the central nervous system probably occurring at the region of the demyelinated lesion and resulting in an improvement of axonal conduction. Although a similar mechanism might be operating for the changes seen in nystagmus, it is important to keep in mind that, unlike scotomas, its pathophysiological basis is unknown and thus any hypothesis must be considered with caution.

The improvement in clinical findings in MS with hyperventilation, NaHCO₃ and Na₂EDTA is probably due, at least in part, to a lowering of serum ionized calcium, which increases axonal excitability and in turn produces an increase in the conduction safety factor. There is evidence for a formidable blood-CSF barrier to calcium in normals (Soffer and Toribara, 1961; Schain, 1964), multiple sclerosis patients (Merritt and Bauer, 1931), and patients with disorders of calcium metabolism (Hebert, 1933). However, it is conceivable that there is a localized breakdown of the blood-brain barrier to calcium at the site of MS plaques which might not produce a marked change in CSF calcium. This is supported by the finding of Broman (Broman, 1944) that increased uptake of trypan blue occurs in MS plaques. Thus, a low serum ionized calcium might alter brain calcium in MS where it counts most—that is, at the site of the demyelinating lesion. This idea of a breakdown in the blood-brain barrier for calcium is also sup-

ported by our experimental observation that the decrease in scotoma size with an infusion of NaHCO_3 is reversed by a simultaneous infusion of calcium chloride. Though this is probably due to the correction of the induced hypocalcaemia, another possibility is that a transient hypercalcaemic state induced by the CaCl_2 infusion caused a depression of nerve excitability.

It is well known that hyperventilation (Fanconi and Rose, 1958), NaHCO_3 (Moore, 1970) and Na_2EDTA (Soffer and Toribara, 1961) have in common the ability to lower serum ionized calcium. The first two are believed to lower serum ionized calcium due to the resulting alkalosis which favours serum protein binding of calcium. The pH effect is related to competition of calcium and hydrogen ions for negative sites on the protein. In the case of Na_2EDTA , ionized calcium is decreased by the formation of Ca-EDTA complex. In addition to changes in calcium, other factors may be important. Lorente de Nó has shown that CO_2 has an important stabilizing effect on nerve which is independent of pH and that lowering of CO_2 increases excitability (Lorente de Nó, 1947). Since CO_2 readily passes the blood-brain barrier the central decrease in pCO_2 with hyperventilation might add to the enhancement of the safety factor. In the case of Na_2EDTA the possibility that it can pass the blood-brain barrier in MS patients must also be considered; available evidence suggests that it does not pass the blood-CSF barrier in normal man (Soffer and Toribara, 1961). The pH itself may also have a direct effect on conduction. Lorente de Nó found no significant changes over wide ranges in excised frog nerve (Lorente de Nó, 1947), but in the squid giant axon increases in the internal or external pH tend to enhance excitability (Tasaki, Singer, and Takenaka, 1964). Another factor, especially with the sodium bicarbonate infusion, may be an increase in serum sodium concentration which might increase the amplitude of the action potential (Hodgkin and Katz, 1949). All of these changes could enhance the conduction safety factor.

Although the preceding theoretical considerations may require modifications when more data are available, the phenomena described in this paper indicate that clinical signs in MS can be improved by chemical means. The implication seems clear that a search for effective drugs is warranted. Based on the proposed mechanisms, a reasonable approach would be to screen carefully drugs which might enhance the conduction safety factor. Theoretically some of the veratrum alkaloids which prolong the action potential duration and produce a decreased threshold for stimulation might be effective (Goodman and Gilman, 1965). These studies are in progress.

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