Our data provide evidence for the involvement of brain areas other than neocortex in chronic alcoholism. The increase in neural transmission time within the auditory brainstem may reflect a direct pathological process of demyelination; this effect has been suspected in alcoholic patients (*23*) and observed in rats fed on alcohol for long periods (*24*). These results could also be caused indirectly by the aberrant fluidizing effects of chronic alcohol intake on cell membranes (*25*), which may result in edema. The use of auditory brainstem potentials may provide critical prognostic information about the progress of brainstem deficits in chronic alcoholics and their potential recovery with prolonged abstinence.

H. BEGLEITER
B. PORJESZ
C. L. CHOU

Department of Psychiatry, State University of New York, Downstate Medical Center, Brooklyn 11203

References and Notes

1. C. Courville, *The Effects of Alcohol on the Nervous System of Man* (San Lucas, Los Angeles, 1955); M. Victor, R. D. Adams, C. H. Collins, *The Wernicke-Korsakoff Syndrome* (Davis, Philadelphia, 1971).
2. J. Haug, *Acta Psychiatr. Scand. Suppl.* **204**, 135 (1968); C. Brewer and L. Perrett, *Br. J. Addict.* **66**, 170 (1971).
3. J. H. Fox, R. G. Ramsey, M. S. Huckman, A. E. Proske, *J. Am. Med. Assoc.* **236**, 365 (1976); M. Myrhed, H. Bergman, S. Borg, T. Hindmarsh, C. M. Idestrom, *Hygiea Acta Soc. Med. Suecanae* **85**, 253 (1976); P. A. Epstein, V. D. Pisani, J. A. Fawcett, *Alcoholism Clin. Exp. Res.* **1**, 61 (1977); M. A. Ron, *Psychol. Med.* **7**, 103 (1977); L. A. Cala, B. Jones, F. L. Mastaglia, B. Wiley, *Aust. N.Z. J. Med.* **8**, 147 (1978); P. L. Carlen, G. Wortzman, R. G. Holgate, D. A. Wilkinson, J. G. Rankin, *Science* **200**, 1076 (1978).
4. O. A Parsons, *Alcoholism Clin. Exp. Res.* **1**, 51 (1977).
5. H. Begleiter and A. Platz, in *The Biology of Alcoholism*, B. Kissin and H. Begleiter, Eds. (Plenum, New York, 1972), pp. 293–338.
6. M. Berglund and D. H. Ingvar, *J. Stud. Alcoholism* **37**, 586 (1976).
7. J. G. Salamy, J. R. Wright, L. A. Faillace, *J. Nerv. Ment. Dis.* **168**, 19 (1980); L. von Knorring, *Neuropsychobiology* **5**, 314 (1976); R. W. Coger, A. M. Dymond, E. A. Serafetinides, I. Lowenstam, D. Pearson, *Biol. Psychiatry* **11**, 435 (1976); A. M. I. Wagman, R. P. Allen, F. Funderburk, D. Upright, *ibid.* **13**, 719 (1978); M. S. Buchsbaum and A. M. Ludwig, in *Biological Effects of Alcohol*, H. Begleiter, Ed. (Plenum, New York, 1980), pp. 561–572; R. B. Hubbard, L. L. Judd, L. Y. Huey, D. F. Kripke, D. S. Janosky, A. S. Lewis, in *ibid.*, pp. 573–578; B. Porjesz, H. Begleiter, R. Garozzo, in *ibid.*, pp. 603–624; A. Pfefferbaum, T. B. Horvath, W. T. Roth, S. T. Clifford, B. S. Kopell, in *ibid.*, pp. 625–640; G. Lelord, E. Aron, H. P. Bidron, B. Garreau, J. Martineau, in *ibid.*, pp. 641–648; L. von Knorring, in *ibid.*, pp. 649–660.
8. B. Porjesz, H. Begleiter, I. Samuelly, *Drug Alcohol Depend.* **6**, 87 (1980); B. Porjesz and H. Begleiter, in *Evoked Brain Potentials and Behavior*, H. Begleiter, Ed. (Plenum, New York, 1979), pp. 277–302.
9. A. Pfefferbaum, T. B. Horvath, W. T. Roth, B. S. Kopell, *Electroencephalogr. Clin. Neurophysiol.* **47**, 637 (1979); B. Porjesz, H. Begleiter, R. Garozzo, in *Biological Effects of Alcohol*, H. Begleiter, Ed. (Plenum, New York, 1980), pp. 603–624.
10. H. Sohmer and M. Feinmesser, *Ann. Otol. Rhinol. Laryngol.* **76**, 427 (1967); D. L. Jewett, *Electroencephalogr. Clin. Neurophysiol.* **28**, 609 (1970); D. L. Jewett and J. S. Williston, *Brain* **94**, 681 (1971).
11. D. L. Jewett in (*10*); A. Lew and H. Sohmer, *Arch. Klin. Exp. Ohren Nasen. Kehlkopfheilk.* **201**, 79 (1972); H. Sohmer, M. Feinmesser, G. Szabo, *Electroencephalogr. Clin. Neurophysiol.* **37**, 663 (1974); J. S. Buchwald and C. M. Huang, *Science* **189**, 382 (1975); J. J. Stockard and U. S. Rossiter, *Neurology* **27**, 316 (1977).
12. A. Starr and L. J. Achor, *Arch. Neurol.* **32**, 161 (1975); A. Starr and A. E. Hamilton, *Electroencephalogr. Clin. Neurophysiol.* **41**, 595 (1976).
13. M. Fabiani *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **47**, 483 (1979).
14. N.-S. Chu, K. C. Squires, A. Starr, *Arch. Neurol.* **35**, 596 (1978).
15. K. C. Squires, N.-S. Chu, A. Starr, *Electroencephalogr. Clin. Neurophysiol.* **45**, 577 (1978).
16. ——, *Science* **201**, 174 (1978).
17. R. L. Spitzer, J. Endicott, E. Robins, *Arch. Gen. Psychiatry* **3**, 773 (1978).
18. J. R. Boston and P. J. Ainslie, *Electroencephalogr. Clin. Neurophysiol.* **48**, 361 (1980).
19. B. J. Winer, *Statistical Principles in Experimental Design* (McGraw-Hill, New York, 1971), p. 526.
20. M. Amadeo and C. Shagass, *Psychophysiology* **10**, 244 (1973).
21. J. J. Stockard, V. S. Rossiter, W. C. Wiedenholt, R. M. Kobayashi, *Arch. Neurol.* **33**, 726 (1976).
22. J. J. Stockard and V. S. Rossiter, *Neurology* **27**, 316 (1977).
23. R. D. Adams, M. Victor, E. Mancall, *Arch. Neurol. Psychiatry* **81**, 136 (1959).
24. E. A. Moscatelli and P. Demediuk, *Biochim. Biophys. Acta* **596**, 331 (1980).
25. J. H. Chin, D. B. Goldstein, L. M. Parsons, *Alcoholism Clin. Exp. Res.* **3**, 47 (1979).
26. We thank the National Institute on Alcohol Abuse and Alcoholism (grant AA 02686) for supporting this work. We thank Dr. Joel Solomon, Sharon Schurtz, and Maureen Meehan for recruiting and screening of patients and Marion Gillespie and Lynda Herskovitz for valuable assistance.

18 August 1980; revised 18 November 1980

Dialysis in Schizophrenia: A Double-Blind Evaluation

Abstract. *Eight chronic schizophrenia patients completed a research program consisting of ten weekly sessions of active hemodialysis and ten weekly sessions of sham dialysis in a double-blind design. Previous reports of therapeutic efficacy were not substantiated. None of the patients improved during active dialysis; four patients worsened.*

Feer *et al.* (*1*) reported in 1960 that three out of five schizophrenic patients improved after only one or two hemodialyses. No further attempts were made known until 1977, when Wagemaker and Cade (*2*) reported dramatic improvement in five physically healthy schizophrenic patients treated with weekly dialyses for up to 16 weeks. Since that report there has been intense interest in this area of clinical investigation as evidenced by reports of both positive (*3*) and negative (*4, 5*) clinical psychiatric findings, technical reports about dialysis (*6*), and biochemical papers exploring possible mechanisms of action of dialysis in relation to endorphins (*5, 7*). In a recent literature review (*8*) it was noted that of 92 physically healthy schizophrenics who had been dialyzed 42 showed marked or some improvement. However, these reports do not all include information about the diagnostic criteria of schizophrenia employed, duration of illness, method of behavioral evaluation, and type and quality of improvement, or precise description of dialysis equipment. Our double-blind study of weekly hemodialysis of schizophrenic patients was undertaken to investigate the therapeutic claims made for this procedure. Since we finished our study two other double-blind studies have been published to date (*9*): Linkowski *et al.* observed improvement in six of seven patients on real dialysis and in three of five on sham dialysis, and Diaz-Buxo *et al.* observed no effect in four patients.

The patients in our study were five women and three men admitted to the Clinical Center at the National Institutes of Health and diagnosed schizophrenic

Table 1. Means and standard errors of psychiatrists' ratings of their patients' symptoms during the 2 weeks prior to the dialysis sessions, the last 2 weeks of sham dialysis sessions, the last 2 weeks of active dialysis sessions, and the 2 weeks immediately following the last dialysis session. Ranges for the ratings were: global psychosis and depression, 1 to 15; total Brief Psychiatric Rating Scale, 24 to 168; thought disorder cluster, 3 to 21; individual items, 1 to 7. N.S., not significant.

Symptom	Period				*F*	*P*
	Before dialysis	Sham dialysis	Active dialysis	After dialysis		
Global psychosis	8.0 ± .6	9.1 ± .8	8.9 ± .5	9.1 ± 1.0	1.2	N.S.
Global depression	5.2 ± .9	5.5 ± 1.2	5.3 ± 1.0	5.1 ± .8	.08	N.S.
Total BPRS	63.2 ± 4.3	67.7 ± 5.1	65.4 ± 4.2	66.9 ± 5.2	.6	N.S.
Thought disorder cluster	11.4 ± 1.4	11.8 ± 1.5	11.6 ± 1.3	11.4 ± 1.5	.1	N.S.
Hallucinatory behavior	3.4 ± .7	3.4 ± .8	3.3 ± .7	3.3 ± .7	.3	N.S.
Unusual thought content	4.4 ± .6	4.4 ± .5	4.3 ± .5	4.2 ± .6	.1	N.S.
Conceptual disorganization	3.7 ± .6	4.1 ± .6	4.0 ± .5	3.9 ± .6	.6	N.S.
Suspiciousness	4.4 ± .7	4.5 ± .7	4.4 ± .8	3.9 ± .8	1.4	N.S.

0036-8075/81/0306-1066$00.50/0

by their psychiatrists using 1978 research diagnostic criteria (*10*). Their age was 30 ± 2.6 years, and they had been ill for 10 ± 2.3 years. All gave written informed consent to participation in the study, and in most cases a family member also gave informed consent. Antipsychotic and other medications were discontinued 4 to 6 weeks prior to the start of the hemodialysis series, which consisted of ten consecutive real dialyses and ten sham dialyses, each lasting 5 hours (*11*). The double-blind was maintained by use of an opaque dialyzer. The raters had no access to vital signs or clinical biochemical data that could have revealed whether the patient was receiving active or sham dialysis. A coil dialyzer with an 18-μm cuprophane membrane (surface area 0.8 m^2) was used for active dialyses; in the sham dialyzer tubing replaced the membrane. Questionnaires answered by the patients after each session showed that they were not able to detect with consistency whether they had received active or sham dialysis.

Each patient's psychiatrist evaluated him or her weekly, double-blind, using the Brief Psychiatric Rating Scale (BPRS) (*12*) and the Bunney-Hamburg Global Assessment (GA) (*13*). The nursing staff assessed the patients daily using the GA scale. Paired *t*-tests (two-tailed) were done to determine whether there were statistically significant differences in the ratings for the group between the 2 weeks prior to active dialysis and the last 2 weeks of active dialysis, which is the time of hypothesized maximum effect. Analysis of variance for repeated measures (ANOVA) was done on the ratings for the following time periods: (i) the 2 weeks before the dialysis sessions were begun; (ii) the last 2 weeks of sham dialysis; (iii) the last 2 weeks of active dialysis; and (iv) the 2 weeks immediately following the final dialysis session. The psychiatrists' and nurses' ratings correlated highly (*14*).

In the psychiatrists' ratings of the whole patient group there was no statistically significant difference between the 2 weeks prior to active dialysis and the last 2 weeks of active dialysis (7.8 ± .64 versus 8.9 ± .47, $t = 2.19$, P = N.S.). The ratings by the nurses concur. ANOVA revealed no significant difference in global psychosis ratings by the psychiatrists for the periods measured (Table 1). In individual ratings, no patient showed a decrease during the last 2 weeks of active dialysis compared to the 2 weeks prior to active dialysis. No patient received a rating in the nonpsychotic range during active dialysis (Fig. 1). The ratings by psychiatrists on the BPRS support these findings. No significant difference was found between the total BPRS score of the group before active dialysis and at the end of active dialysis (Table 1). ANOVA of all four time periods also showed no difference in the total BPRS scores. Furthermore, most patients did not change in psychotic behavior as measured by the BPRS thought-disorder cluster (*15*), which consists of conceptual disorganization, hallucinatory behavior, and unusual thought content (Table 1).

Four individual symptoms of psychosis measured by the BPRS—conceptual disorganization, unusual thought content, hallucinatory behavior, and suspiciousness—were not significantly different during the last 2 weeks of active dialysis from the 2 weeks before active dialysis. There were no significant differences between these four items when examined with ANOVA. No individual patient became asymptomatic on any of these four items during active dialysis. Linkowski *et al.* (*9*) noted significant improvement in affective symptoms following active dialysis. We were unable to replicate this improvement in depression in our patients (Table 1).

In our study, unlike studies previously reported, each patient underwent both sham and active dialysis and so served as his or her own control. Factors such as a changed environment and increased attention were therefore the same for sham and active dialysis. Furthermore, patients were under similar observation and had been admitted to the unit at least 2 months prior to the beginning of the dialysis.

To date, the particulars of the dialysis technology in many studies have not been published. There is some possibility that the disparity of results may be related to differences in dialyzers or in frequency of dialysis. We dialyzed patients at the same frequency as reported by Wagemaker and Cade in their first report (*2*) and used similar equipment. They noted that women were more responsive than men, but in our study three of the five female patients and one of the three male patients deteriorated.

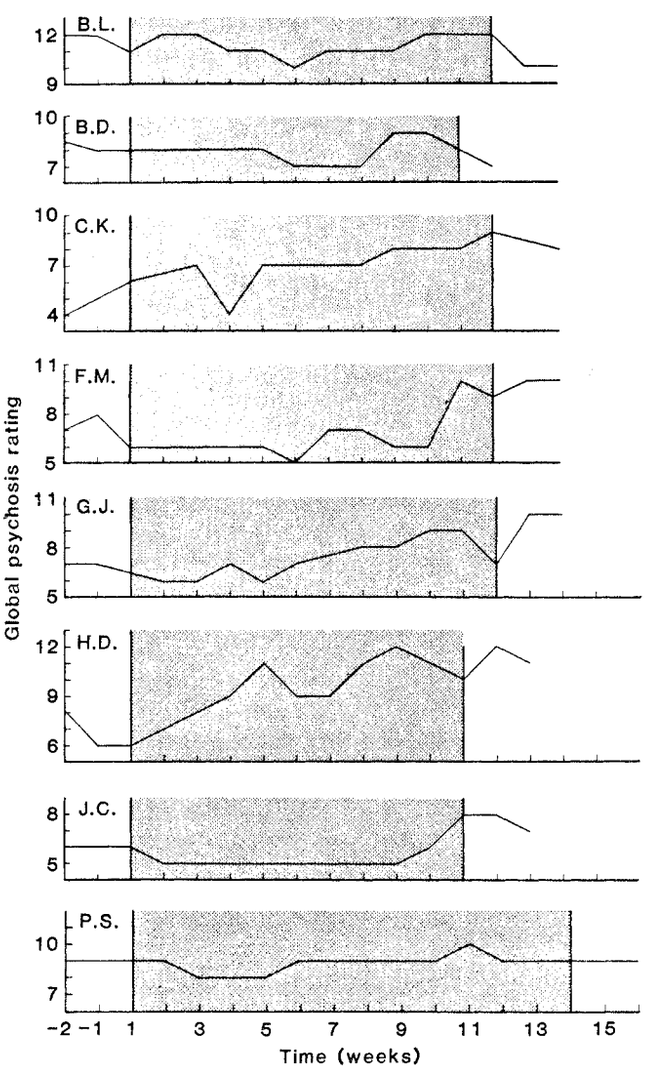

Fig. 1. Double-blind ratings of global psychosis of each patient by his or her psychiatrist for the 2 weeks prior to active dialysis, during the active dialysis (shaded area), and the 2 weeks following active dialysis. In four cases the ten active dialyses took place over 11 weeks because of technical difficulties such as infiltration of the fistula or because of a refusal by the patient. Patient P.S. received 12 dialyses in 14 weeks because she refused sessions at weeks 6 and 7. Four patients (B.L., B.D., G.J., P.S.) remained unchanged by the end of active dialysis, and four (C.K., F.M., H.D., J.C.) were more psychotic.

The timing of discontinuation of neuroleptics may explain some of the differences noted in response to hemodialysis. Marder *et al.* (*16*) reported that 8 of 22 psychotic schizophrenic patients temporarily showed a significant improvement following withdrawal of antipsychotic agents. It is possible that the improvement noted in some studies in which neuroleptics were discontinued the day before the first dialysis or during the ongoing dialysis treatment may be explained by the drug withdrawal. The patients in our study had been off neuroleptics for 4 to 6 weeks and had a well-established, stable base line of symptom ratings. Other explanations for differences may be spontaneous remission, placebo effect, or denial of symptoms.

In conclusion, although the possibility of a small subgroup responsive to dialysis remains, our data indicate that hemodialysis should not be considered to be a treatment for schizophrenia at this time.

S. C. SCHULZ
D. P. VAN KAMMEN*
Biological Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland 20205
J. E. BALOW
Arthritis and Rheumatism Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Maryland 20205
M. W. FLYE
Department of Surgery, University of Texas Medical Branch, Galveston 77550
W. E. BUNNEY, JR.
Biological Psychiatry Branch, National Institute of Mental Health

References and Notes

1. H. Feer *et al.*, *Compr. Psychiatry* **1**, 338 (1960).
2. H. Wagemaker and R. Cade, *Am. J. Psychiatry* **134**, 684 (1977).
3. H. Wagemaker and R. Cade, *South. Med. J.* **71**, 1463 (1978); *Psychopharmacol. Bull.* **15**, 13 (1979); J. B. Drori, R. Weinstein, T. Weis, *ibid.*, p. 17; G. Splendiani *et al.*, *Proc. Eur. Dial. Transplant Assoc.* **16**, 90 (1979); R. Hambroukx and L. Bellengier, *ibid.*, p. 40; N. M. James and M. T. W. Hearn, *Am. J. Psychiatry* **137**, 488 (1980); N. Nedopil, D. Dieterle, N. Matussek, H. Hippius, H. J. Gurland, G. Hillebrand, *Nervenarzt* **51**, 123 (1980).
4. H. M. Emrich *et al.*, *Am. J. Psychiatry* **136**, 1095 (1979); S. Sidorowicz *et al.*, *Acta Psychiatr. Scand.* **61**, 223 (1980).
5. V. Höllt, G. Hilderbrand, B. Schmidt, J. H. Gurland, *Pharmako-psychiatr./Neuro-Psychopharmakol.* **12**, 399 (1979)
6. W. J. Kolff, *Artif. Organs* **2**, 277 (1978); P. Kroll, F. K. Port, K. R. Silk, *J. Nerv. Ment. Dis.* **166**, 291 (1978); S. M. Cohen, S. C. Scheiber, H. Yamamura, *ibid.* **167**, 475 (1979).
7. R. M. Palmour, F. R. Ervin, H. Wagemaker, R. Cade, in *Endorphins in Mental Health Research*, E. Usdin, W. E. Bunney, Jr., N. S. Kline, Eds. (Macmillan, London, 1979), p. 581; *Abstr. Soc. Neurosci.* **7**, 320 (1977); F. E. Bloom, in *Cell Receptor Disorders*, T. Melnechuk, Ed. (Western Behavioral Sciences Institute, La Jolla, 1978), p. 134; M. Ross, P. A. Berger, A. Goldstein, *Science* **205**, 1163 (1979); R. V. Lewis, L. D. Gerber, S. Stein, R. L. Stephen, B. D. Grosser, S. F. Velick, S. Udenfriend, *Arch. Gen. Psychiatry* **36**, 237 (1979).
8. D. L. Fogelson, S. R. Marder, T. Van Putten, *Am. J. Psychiatry* **137**, 605 (1980).
9. P. Linkowski, J. L. Vanherweghem, C. Jadot, J. Mendlewicz, *Lancet* **1979-II**, 1381 (1979); J. L. Vanherweghem, P. Linkowski, C. Jadot, J. Mendlewicz, *Proc. Eur. Dial. Transplant Assoc.* **16**, 148 (1979); J. A. Diaz-Buxo, J. A. Caudle, J. T. Chandler, C. D. Farmer, W. D. Holbrook, *Am. J. Psychiatry* **137**, 1220 (1980).
10. R. L. Spitzer, J. E. Endicott, E. Robins, *Research Diagnostic Criteria for a Selected Group of Functional Disorders* (New York Biometrics Research, New York State Psychiatric Institute, New York, 1977).
11. Blood access was created surgically by formation of an arteriovenous fistula in the nondominant arm. Additional technical methodology was as follows: (i) an Extracorporeal or Travenol machine was used with a recirculating single pass design; (ii) blood flow rate was 200 ml/min and dialysis flow rate was 300 ml/min; (iii) dialysate was Renal Systems Formula RS-101, which in addition to electrolytes included acetate 36.6 mEq/liter and glucose 205 mg/ml.
12. J. E. Overall, L. E. Hollister, P. Pichot, *Arch. Gen. Psychiatry* **16**, 146 (1967).
13. W. E. Bunney, Jr., and D. A. Hamburg, *ibid.* **9**, 280 (1963).
14. Pearsonian correlation coefficients of the psychiatrists' and nurses' ratings were psychosis, $r = 0.74$, $P < .0001$; depression, $r = 0.64$, $P < .001$; and mania, $r = 0.69$, $P < .0001$.
15. J. E. Overall, in *ECDEU Assessment Manual for Psychopharmacology*, W. Guy, Ed. (Department of Health, Education, and Welfare, Washington, D.C., 1976).
16. S. R. Marder, D. P. van Kammen, J. P. Docherty, J. Rayner, W. E. Bunney, Jr., *Arch. Gen. Psychiatry* **36**, 1080 (1979).
17. The authors thank the patients and nursing staff of the 4-East Clinical Research Unit under S. Beal, head nurse, for their enthusiastic participation; E. Haller, D. Miller, M. Smith, B. Frost, and W. Jennings for technical assistance with the dialysis procedures; D. Stokes of Extracorporeal Medical Specialties, Inc., for providing the dialysis machine; J. Colison for assistance in data analysis; and E. Churgin and D. Drake for editorial and typing assistance.
* Address reprint requests to D.P.v.K.

23 June 1980; revised 19 December 1980

Rapid Correction of Hyponatremia Causes Demyelination: Relation to Central Pontine Myelinolysis

Abstract. *The human demyelinative disorder central pontine myelinolysis may be an iatrogenic disease caused by a rapid rise in serum sodium, usually when hyponatremia is corrected. Rats treated with hypertonic saline after 3 days of vasopressin-induced hyponatremia had demyelinative lesions in the corpus striatum, lateral hemispheric white matter, cerebral cortex, hippocampal fimbria, anterior commissure, thalamus, brainstem tegmentum, and cerebellum. Thus, rapid correction of hyponatremia can lead to demyelinative lesions and may be the cause of central pontine myelinolysis in man.*

Central pontine myelinolysis (CPM) is a human demyelinative disorder of unknown etiology occurring in a setting of chronic illness, alcoholism, and electrolyte derangements (*1*). The pons is principally affected, but in severe cases, demyelinative lesions have been found in the corpus striatum, in the thalamus, and at the junction of the gray and white matter in the cerebrum and the cerebellum (*2*).

Twelve patients with CPM, later confirmed at autopsy, were hyponatremic (serum sodium 130 m*M* or less) before CPM developed; before the onset of neurological symptoms, each patient had had a rapid increase in serum sodium (20 to 30 m*M* in 3 days), which was sustained for an additional 3 to 5 days (*3*). We proposed that CPM may be an iatrogenic disorder caused by a rapid rise in serum sodium, usually as a result of correction of hyponatremia. We now report that demyelinative lesions in the rat are produced by the attempt to correct hyponatremia rapidly.

Experiments were performed on 14 male Sprague-Dawley rats, aged 3 to 4½ months and weighing 325 to 400 g. Hyponatremia was induced by the subcutaneous injection of 1 unit of vasopressin tannate (Parke, Davis) per 100 g of body weight and an intraperitoneal injection of 2.5 percent dextrose in water equal to 5 percent of body weight (*4*). Vasopressin and 2.5 percent dextrose in water were given twice daily (9 a.m. and 4 p.m.) on days 1 and 3 and once on day 2. During this phase, water and food were restricted. On days 4 and 5, animals received 1*M* hypertonic saline (2 ml per 100 g of body weight) as a single intraperitoneal injection (*5*). On day 6, animals were given free access to the laboratory diet and water. Serum sodium values were obtained by anesthetizing the animals lightly with ether and removing about 0.75 ml of blood from the tail up to three times over the 3-day hyponatremic phase.

Animals that survived the experiment were killed by overexposure to ether on days 8 to 10, at which time blood for sodium determination was obtained by cardiac puncture. Brains were fixed in 10 percent Formalin and processed routinely for light microscopy. Paraffin sections were stained with hematoxylin-eosin, Luxol fast blue for myelin, and by the Bodian method for axons.

Control animals were six rats made hyponatremic for 3 days, as the experimental rats had been treated, and then al-

0036-8075/81/0306-1068$00.50/0