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.

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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 $4\frac{1}{2}$ 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-

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lowed free access to water and food. A second control group of six rats was given 1*M* NaCl (2 ml per 100 g of body weight) intraperitoneally daily for 2 days and then allowed free access to water and food; these rats were killed on day 5. Six normal untreated rats were a third control group.

Vasopressin and 2.5 percent dextrose in water induced a stepwise decrement in serum sodium to 106.3 ± 11.6 m*M* (mean ± standard deviation) at the end of 3 days (normal value, 139.2 ± 2.6). During this phase some animals showed mild lethargy, but most remained clinically normal. After hypertonic saline administration, the rats became less active. By days 5 and 6, they had diminished hind leg extension, ataxic gait, adduction of forepaws, and ruffled fur. Paradoxical hyperactivity and hyperirritability occasionally occurred. Four animals died with seizures or coma on days 5 to 7. One animal seemed normal on day 4 but was found dead the morning of day 5. Four rats remained almost clinically normal throughout the experiment. All animals lost some weight (25.6 ± 17.1 percent) between days 5 and 10. Serum sodium values were 151.8 ± 5.0 m*M* when the animals were killed.

Symmetrical bilateral demyelinative lesions, the principal neuropathological findings in the nine survivors (Fig. 1), were found in the corpus striatum (89 percent), lateral hemispheric white matter (89 percent), deep cerebral cortex (89 percent), hippocampal fimbria (78 percent), anterior commissure (67 percent), thalamus (67 percent), brainstem tegmentum (44 percent), and cerebellum (44 percent). Thalamic and brainstem lesions represented a single continuous longitudinal band of involvement. Lesions were characterized by loss of oligodendrocytes and myelin, prominent vascularity, and infiltration of pleomorphic microglia and foamy macrophages (Fig. 2). Many well-preserved neuronal cell bodies and axons were found in these demyelinative lesions (Figs. 2 and 3). A few rats had cortical petechial hemorrhages. Vascular thrombi were not observed.

In long-term survivors, neuronal loss was found in the thalamic and brainstem tegmental lesions only. In animals that died early, the distribution of lesions was similar, but all of the lesions contained neuronal necrosis. In three of the animals that died early, necrosis of the pyramidal and granule cell layers of the hippocampus also occurred. One rat in this series lived 10 days, was minimally ill, and did not have any lesions.

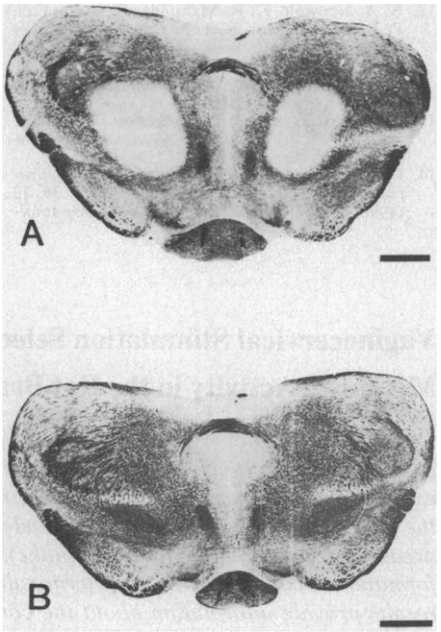

Fig. 1. (A) Cross section of the brainstem-thalamic junction in the rat, with bilateral, symmetrical, round, well-circumscribed zones of pallor indicating the presence of demyelination. Luxol fast blue. Scale bar, 1 mm. (B) Normal control. Luxol fast blue. Scale bar, 1 mm.

No demyelinative lesions were seen in either control animals made hyponatremic for 3 days (100 ± 4.4 m*M* on day 4) and then allowed to self-correct (135.8 ± 3.8 m*M* on day 8) or the controls treated only with hypertonic saline solutions (serum sodium ranged from 156 to 181 m*M* several hours after injection). No abnormalities were found during gross or microscopic examination of the heart, liver, and kidney in experimental or control animals.

We have found demyelinative lesions in rats treated with hypertonic saline after a period of hyponatremia. Similar observations have been reported in dogs (*6*). These findings support the view that rapid correction of hyponatremia may lead to CPM in humans. The experimental condition described in this report may thus serve as a model of CPM and provide a method for studying demyelinating mechanisms in general.

Necrosis occurs in severe cases of CPM (*7*) but was a variable finding in the demyelinative lesions in our study. In long-term survivors necrosis was found only in the thalamus and brainstem, whereas in rats that died early (5 to 7 days) it was present at other sites as well. Although we believe that the necrotic lesions represent an end stage of electrolyte damage, we cannot exclude a minor component of anoxia or ischemia, since seizures occurred in animals that died early.

The role of the preceding hyponatremia in this experimental disorder is uncertain. It may be that a period of hyponatremia is required for a sufficient increase in serum sodium to be achieved, or hyponatremia may cause central nervous system injury that predisposes to subsequent development of demyelinative lesions.

How a rapid increase in serum sodium leads to demyelination is not known. Osmotic shifts in the brain lead to complex

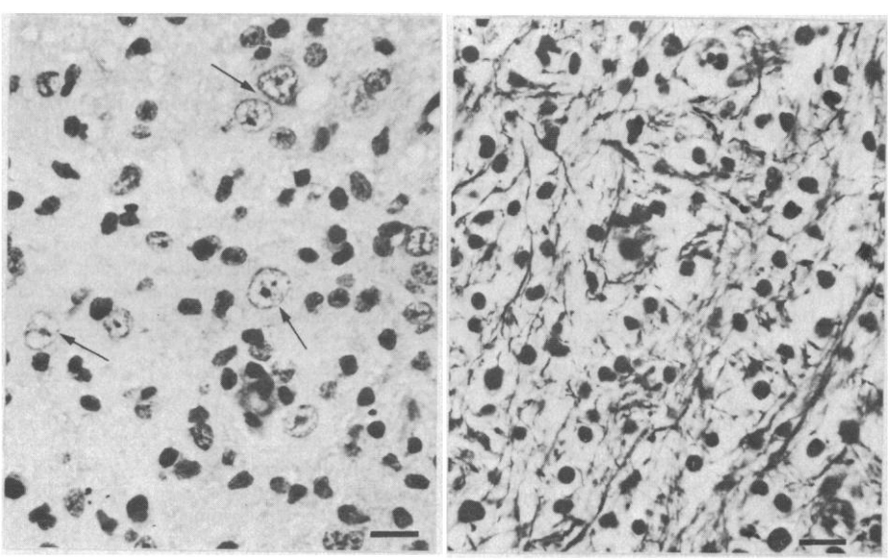

Fig. 2. (left) Photomicrograph of the demyelinative lesion showing hypercellularity resulting from the presence of many pleomorphic microglia (cells with small dark irregular nuclei). Neuronal cell bodies are well preserved (arrows). Hematoxylin and eosin. Scale bar, 20 μm. Fig. 3. (right) Numerous intact axons are illustrated in an area of extensive demyelination. Bodian method. Scale bar, 20 μm.

metabolic events that result in changes in lactate, amino acids, ammonia, and water and alterations in the level of idiogenic osmoles (*8*). These changes may be harmful to oligodendrocytes, the myelin-forming cells of the central nervous system. As suggested by Bass and Sima (*9*), oligodendrocytes in the brainstem are particularly sensitive and may be preferentially involved in osmotic stress.

Another potential mechanism for demyelination may be related to vasogenic edema secondary to osmotic opening of the blood-brain barrier. Whether a result of endothelial cell shrinkage (*10*), enhanced transvesicular transport (*11*), or some other mechanism, edema is seen after osmotic stress (*10, 12*) as well as in CPM (*13*). Edema may cause demyelination (*14*). If this mechanism is correct, it might explain the localization of the lesions in our experimental animals as well as in human CPM. Demyelination would be expected to be maximal in areas where gray matter with its rich vascular supply (source of edema fluid) is interwoven with white matter (where the bulk of the myelin is contained). Such an admixture is characteristic of the human pons; in the rat, this pattern is prominent in the striatum, thalamus, and upper brainstem, where the lesions were found. Demyelinative lesions were not found in the pons in the rat, which has far more white than gray matter.

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Vaginocervical Stimulation Selectively Increases Metabolic Activity in the Rat Brain

Abstract. *Vaginocervical stimulation affects progesterone secretion, sperm transport, sexual receptivity, locomotion, and perception of pain in female rats. In this experiment, vaginocervical stimulation produced statistically significant increases in the metabolic uptake of carbon-14-labeled 2-deoxy-D-glucose in the following brain areas (ordered by magnitude of uptake): medial preoptic, mesencephalic reticular formation, bed nucleus of stria terminalis, dorsal raphe, and globus pallidus. The results provide information about the concurrent processing of sensory stimulation by several neural areas and indicate that the medial preoptic area is a receiving area for copulatory stimulation.*

Stimulation of the female rat's vaginal cervix by the male during coitus (or copulomimetic stimulation) has several behavioral and physiological consequences: it potentiates the lordotic posture of the female (*1*), initiates the neuroendocrine reflex necessary for subsequent pregnancy (*2*), releases luteinizing hormone (*3*), facilitates transport of sperm from the vagina into the uterus (*4*), and inhibits somatic reflexes, locomotion, and pain (*5*).

It is known that the pelvic nerves, which innervate the cervix and portions of the vagina, are the parts of the peripheral nervous system that mediate several of these effects (*6*). However, the central nervous system mediators are not as well known, even though the classical techniques of recording, lesion, and stimulation have all been applied to this problem. For example, electrophysiological recordings show altered firing rates in response to copulomimetic stimulation in brain areas extending from the nucleus reticularis gigantocellularis caudally to the medial preoptic area rostrally. These responsive areas include parts of the hypothalamus, the median eminence, the amygdala, the hippocampus, the midbrain, and the lateral septum (*7, 8*). Lesions of the reticular formation, the dorsal raphe, the lateral vestibular nucleus, the habenula, the hypothalamus, the preoptic area, the lateral septum, the corpus striatum, or the cerebral cortex affect lordosis behavior (*9*). Electrical or electrochemical stimulation of several hypothalamic areas can initiate the progestational state (*10*).

We used the ^{14}C-labeled 2-deoxy-D-glucose (2-DG) method of autoradiogra-

Table 1. Relative concentration of ^{14}C in selected brain areas. The data were derived from optical density measurements of 2-deoxy-D-[^{14}C]glucose autoradiographs. Each value is the ratio of the ^{14}C concentration in each gray matter structure to the ^{14}C concentration in the average white matter for that animal. For each structure, the increase of relative ^{14}C concentration in the stimulated females is expressed as a percent of the control value.

Structure	Relative concentration of ^{14}C		Percent increase over control value
	Vaginal stimulation	No stimulation	
Medial preoptic area	1.89 ± 0.18	1.38 ± 0.21	37.0*
Reticular formation	2.05 ± 0.26	1.67 ± 0.19	22.8†
Nucleus of the stria terminalis	1.98 ± 0.16	1.62 ± 0.15	22.2†
Locus coeruleus	1.89 ± 0.51	1.55 ± 0.29	21.9
Lateral preoptic area	2.17 ± 0.24	1.79 ± 0.29	21.2
Anterior hypothalamus	1.60 ± 0.08	1.32 ± 0.18	21.2
Dorsal raphe	2.24 ± 0.17	1.85 ± 0.21	21.1†
Habenula	2.89 ± 0.23	2.40 ± 0.37	20.4

*$P < .014$ by Mann-Whitney U test (one-tailed). †$P < .029$ by Mann-Whitney U test (one-tailed).

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