Neurotoxicology, edited by L. Roizin, H. Shiraki, and N. Grčević. Raven Press, New York © 1977.

Some Observations on the Neurological Effects of Alcohol Intoxication and Withdrawal

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The abuse of alcohol gives rise to a wide variety of neurological disorders. However, the mechanism by which alcohol produces its effect is quite different in each of them. One group of symptoms is due to the toxic effects of alcohol *per se;* another, to the withdrawal of the drug after a period of prolonged inebriation; and still others, to the effects of malnutrition or derangements of liver function. The failure to appreciate these fundamental distinctions among the alcoholic neurological disorders has led to a great deal of confusion and contradictory statements about them in medical writings. In particular, there has been a failure to distinguish clearly between effects of alcohol intoxication and the effects of withdrawal of alcohol following a period of chronic intoxication.

Why delirium tremens and related disorders were ever confused with the effects of alcohol intoxication is difficult to understand. A moment's reflection indicates the basic differences between these syndromes. It is obvious that the symptoms of toxicity, consisting of slurred speech, uninhibited behavior, staggering gait, stupor, and coma are in themselves distinctive and different from the symptom complex of tremor, hallucinations, fits, and delirium. The former group of symptoms is associated with an elevated blood alcohol level, whereas the latter become evident only when the blood alcohol level is reduced. Finally, the toxic symptoms increase in severity as more alcohol is consumed (the drowsy patient becomes stuporous, for example), whereas tremor, hallucinosis, and similar symptoms are suppressed by the administration of alcohol.

The manifestations of acute alcohol intoxication are so commonplace that they hardly require elaboration. These manifestations and the mechanisms by which they are produced do not differ essentially from those of many other sedative-hypnotic drugs and anesthetic agents. For these reasons little more is said of them here, and the remainder of this discussion is concerned with the alcohol withdrawal syndrome.

GENESIS OF DELIRIUM TREMENS AND RELATED SYMPTOMS

It is now generally agreed that the one indispensable factor in the genesis of delirium tremens and related symptoms is the withdrawal of alcohol following a period of chronic intoxication (20). The precise mechanism(s) by which the withdrawal of alcohol produces symptoms is far from clear, however. It is a matter of common observation that the states of chronic intoxication and withdrawal are associated frequently with disturbances of water and electrolyte balance, glucose metabolism, blood gases, liver function,

and so forth, and all of these have been incriminated at one time or another in the genesis of the withdrawal syndrome. Of these many abnormalities, two in particular—hypomagnesemia and respiratory alkalosis—have proved in our experience to be consistently associated with all but the mildest withdrawal symptoms and are probably important in their causation. Our investigations of these factors have been the subject of several articles (18, 20,25,26) to which the reader is referred for a more complete account than can be given here. The following is a brief summary of our observations.

Early in the course of our studies we became aware that patients with "rum fits" were remarkably sensitive to photic stimulation. This sensitivity took the form of coarse clonic movements of the muscles of the face and neck, spreading to involve the trunk and limbs, without loss of consciousness (photomyoclonus), or a major tonic-clonic seizure with loss of consciousness (photoconvulsion). A systematic investigation of large numbers of hospitalized alcoholics disclosed that photomyoclonus or photoconvulsions, or both, could be induced in about half of the patients during the early stages (8 to 60 hr) of alcohol withdrawal, whether or not there had been spontaneous seizures. In contrast, this

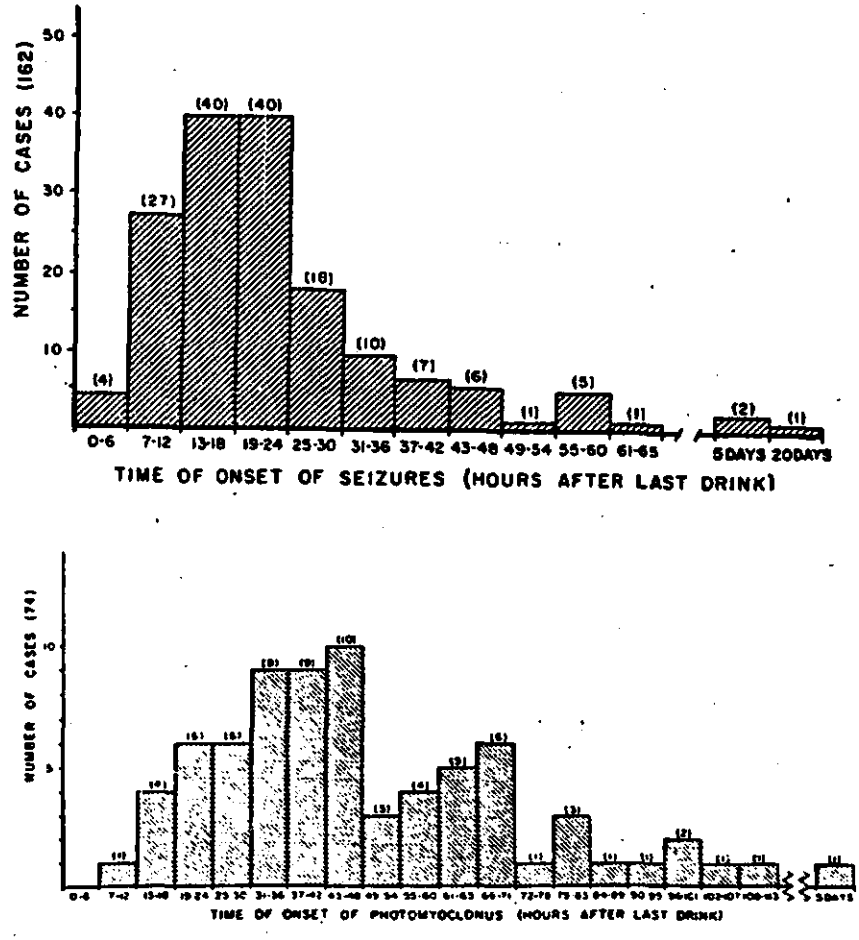


FIG. 1. Relation of the occurrence of spontaneous seizures and of photomyoclonus to cessation of drinking. (From Wolfe and Victor, ref. 25.)

type of photic response could practically never be induced in normal individuals and only rarely in nonalcoholic patients with idiopathic epilepsy (7,18,21).

Photomyoclonic responses in patients with alcohol withdrawal symptoms proved to have much the same temporal relationship to the cessation of drinking as did spontaneous seizures (Fig. 1). The characteristic myoclonic and convulsive responses could often be induced over a period of several hours or even days, and, for long stretches of time (30 to 60 min), stimulation could be repeated at intervals of 5 min without significantly altering the seizure threshold (the number of flashes per second and the duration of the stimulus required to produce myoclonus), provided the patient was allowed to rest for a few minutes between tests. Thus, for the first time, we were provided with an experimental means of assessing: (a) the patients' vulnerability to seizure activity (photic threshold) in the withdrawal period and (b) the effects of administration of a variety of agents on the seizure (photomyoclonus) threshold.

ROLE OF HYPOMAGNESEMIA

Our attention was directed initially to the possible role of magnesium in the genesis of alcohol withdrawal symptoms. We had been impressed, as had others, with the frequent occurrence of hypomagnesemia in the alcohol withdrawal states (2,4,11,13). Our preliminary observations suggested that the administration of magnesium has a salutory effect on tremulousness and vulnerability to photomyoclonus in the early phases of the withdrawal period. These observations prompted a more careful study of these relationships (25). Eighteen alcoholic patients who were free of hepatic or renal disease, diabetes mellitus, hypocalcemia, or malabsorption were subjected to stroboscopic stimulation at the time of their admission to the hospital, and at 8-hr intervals thereafter until the symptoms of alcohol withdrawal had abated. Ten of these patients responded with photomyoclonus; five of the 10 patients who responded in this way also had spontaneous seizures, and three of them went on to develop delirium tremens. Eight patients did not respond to photic stimulation; only one of these had a spontaneous seizure, and none developed delirium tremens. In all 18 patients the serum magnesium levels were significantly lower than in normal control subjects, and the patients with photomyoclonus had lower levels than those who did not respond to photic stimulation (Fig. 2). Furthermore, there was a correlation between the magnesium levels and the photomyoclonus threshold—patients who responded at low frequencies had lower magnesium levels than those who responded at higher frequencies (Fig. 3). Eight of the 10 patients who showed photomyoclonus in the withdrawal period were given magnesium sulfate intravenously in doses of 2 to 6 g (16.7 to 50 mEq). In three patients, administration of 3 g of $MgSO_4$ abolished the response at all fre-

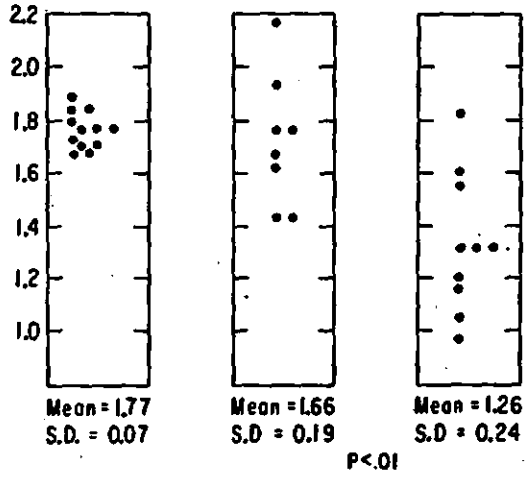


FIG. 2. Serum magnesium (mEq/L) levels in (a) controls (medical students), (b) alcoholics in withdrawal not responding to photic stimulation, and (c) alcoholics responding to photic stimulation. S.D., standard deviation. (From Wolfe and Victor, ref. 25.)

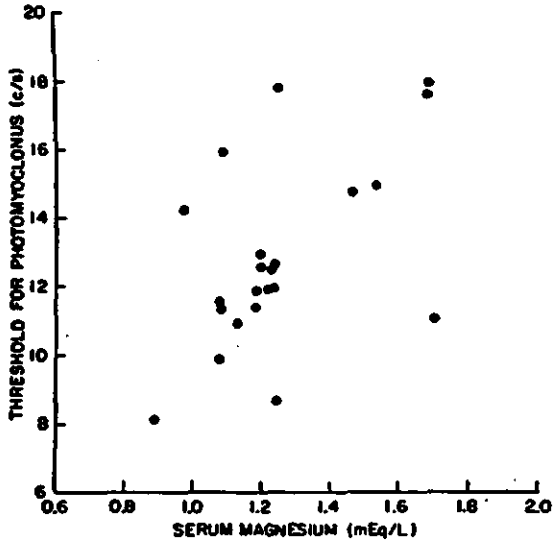


FIG. 3. Relationship between photomyoclonus threshold and serum magnesium levels in the alcohol withdrawal period. (From Wolfe and Victor, ref. 25.)

quencies within minutes after it was given; in the other five patients, all of whom had much lower magnesium levels, there was a significant elevation of the photomyoclonus threshold following the administration of $MgSO_4$.

The close relationship between the photomyoclonus threshold and serum magnesium levels in one of these patients is depicted in Fig. 4. On admission to the hospital, this patient was still intoxicated, at which time he showed no response to photic stimulation. Subsequently, his magnesium level fell and concomitantly a positive response to photic stimulation was elicited. Although the administration of chlordiazepoxide hydrochloride (Librium®) seemed to lessen his tremulousness, it had no significant effect on the photomyoclonus threshold. The intravenous administration of 3 g of $MgSO_4$, however, was accompanied by an elevation of the threshold, and after the second dose of $MgSO_4$ no response to photic stimulation could be obtained.

Thus, the extent to which these patients became hypomagnesemic during alcohol withdrawal correlated closely with a vulnerability to spontaneous seizures and photomyoclonus. The significance of this relationship was supported by the finding that intravenous administration of magnesium sulfate decreased the susceptibility

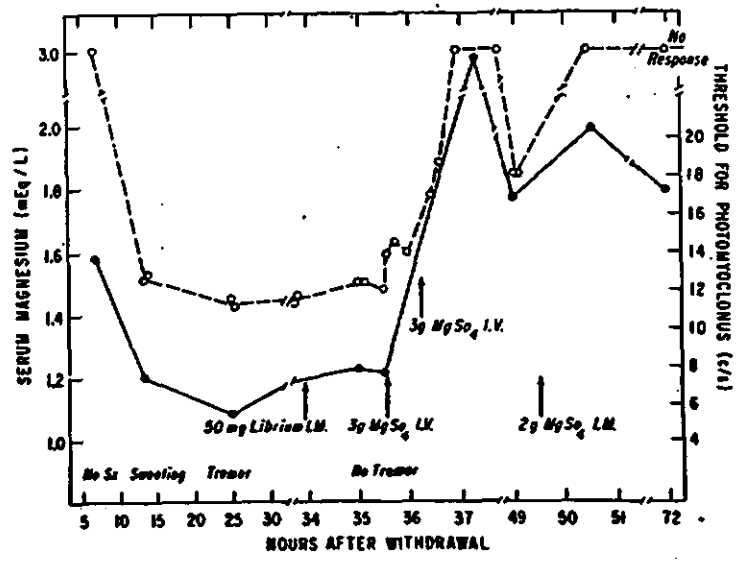


FIG. 4. Relationship of photomyoclonus threshold to serum magnesium level during alcohol withdrawal. ●——●, serum magnesium level; O— —O, photomyoclonus threshold. (From Wolfe and Victor, ref. 25.)

to photomyoclonus. No such correlation could be made between hypomagnesemia and delirium tremens, however. The three patients in this study who developed delirium tremens had very low levels of serum magnesium at the time of admission to the hospital, and in each case the serum magnesium had returned to normal or near-normal levels at the time of onset of the delirium. Others also have noted that delirium tremens may have its onset after the serum magnesium levels have returned to normal (11,22). Thus, whatever the relationship may be of hypomagnesemia to the early symptoms of withdrawal, it probably is not a significant factor in the genesis of delirium tremens.

ROLE OF RESPIRATORY ALKALOSIS

The study cited above (25) disclosed another consistent abnormality in the withdrawal period, namely, the rapid evolution of an alkalotic state. This was in accord with the observations of Sereny et al. (15), who noted a transient rise in the arterial pH of eight alcoholic subjects during the initial 48-hr period of hospitalization. The alkalemia that characterizes the withdrawal state and its relation to hypomagnesemia and photomyoclonus was investigated initially in four volunteer subjects who had been drinking for 60 days before they were withdrawn abruptly (25). The rise in arterial pH values, which could be discerned as early as 8 hr after withdrawal of alcohol, was concomitant with a fall in the serum magnesium level and an increased sensitivity to photic stimulation. These features are illustrated in Figs. 5 and 6. Tremor and hyperreflexia were prominent during the period of hypomagnesemia and alkalosis, and both of these clinical abnormalities abated as the serum magnesium and arterial pH values returned to normal. It is noteworthy that the serum calcium values in these four patients were normal (4.5 to 5.5 mEq/l) throughout the period of intoxication and withdrawal.

The preceding observations prompted a more detailed investigation of the alkalosis that characterizes the alcohol withdrawal state. Nine alcoholics, studied under controlled conditions of drinking and abstinence, were the subjects of this study (24). Following a control period, these patients consumed one to two pints of 100-proof bourbon daily *ad lib*, in addition to an adequate diet, and supplemental vitamins. Four of the patients drank in this way for

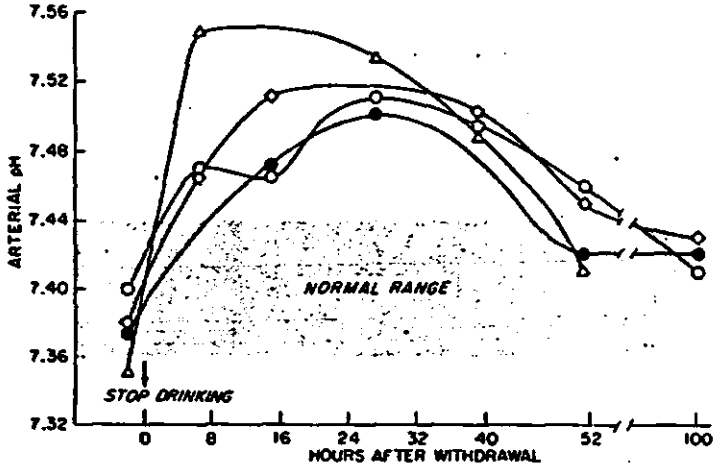


FIG. 5. Arterial pH changes during alcohol withdrawal in four chronic alcoholics, M(●), H(◇), ST(○), and SM(△). (From Wolfe and Victor, ref. 25.)

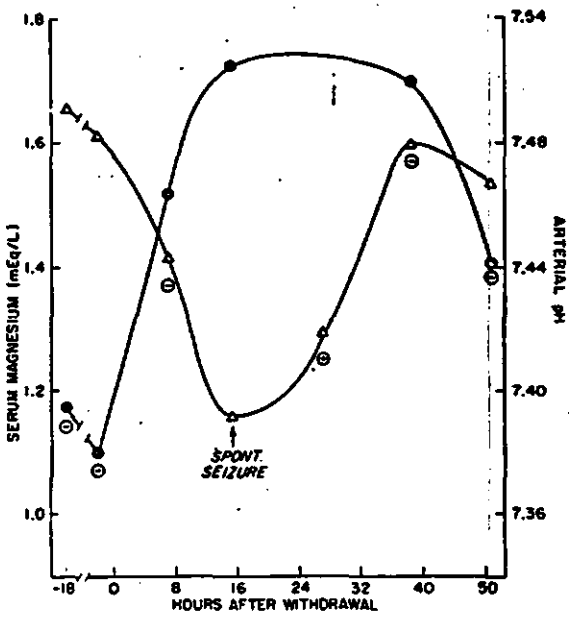


FIG. 6. Relationship between arterial pH, serum magnesium, and photic sensitivity during alcohol withdrawal. ●——●, arterial pH; △——△, serum magnesium; ⊕ photomyoclonus or photoconvulsion response to strobe; ⊖, negative response to strobe. (From Wolfe and Victor, ref. 25.)

60 days; in five patients the drinking period lasted 14 days. Within 8 to 9 hr after the abrupt withdrawal of alcohol there was a significant rise in arterial pH and a concomitant fall in pCO_2, the result of tachypnea and increased depth of respiration (Fig. 7). Furthermore, a correlation could be demonstrated between the severity of the withdrawal symptoms and the magnitude of change of the arterial pH and pCO_2. Only the patients with relatively large changes in pH and pCO_2 (with one exception these were the patients who drank for 60 days) showed spontaneous seizures, photomyoclonus, and severe tremulousness. The fall in serum magnesium levels during the withdrawal period was much greater in the patients who drank for 60 days than in those who drank for 14 days (an average fall of 0.41 mEq/l in the former and 0.10 mEq/l in the latter). Again, serum calcium levels remained in the normal range in all nine patients throughout the study; only two of the nine patients developed acute hypokalemia during the withdrawal period.

The relationships between the clinical and biochemical manifestations of alcohol

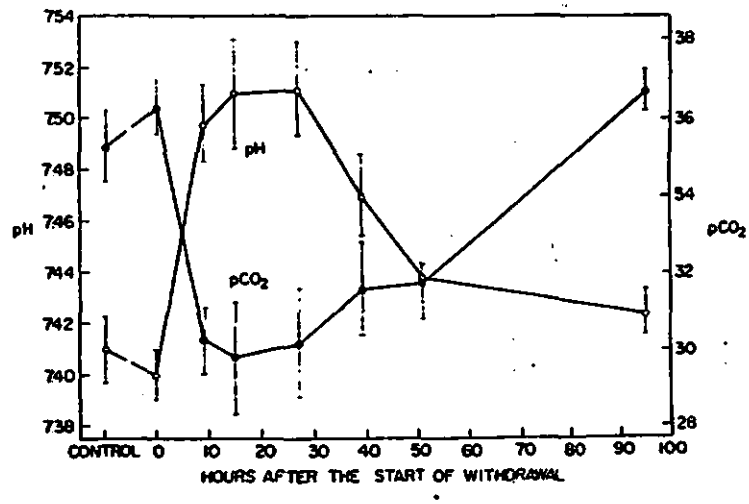


FIG. 7. Arterial pH and pCO_2 during alcohol withdrawal in nine patients. Control values were obtained *prior to* the drinking period. Values at 0 hr were obtained while the patients were still intoxicated, just prior to cessation of drinking. ○——○——○, pH; ●——●——●, pCO_2; ○, mean ±SEM (9 cases). (From Wolfe et al., ref. 24.)

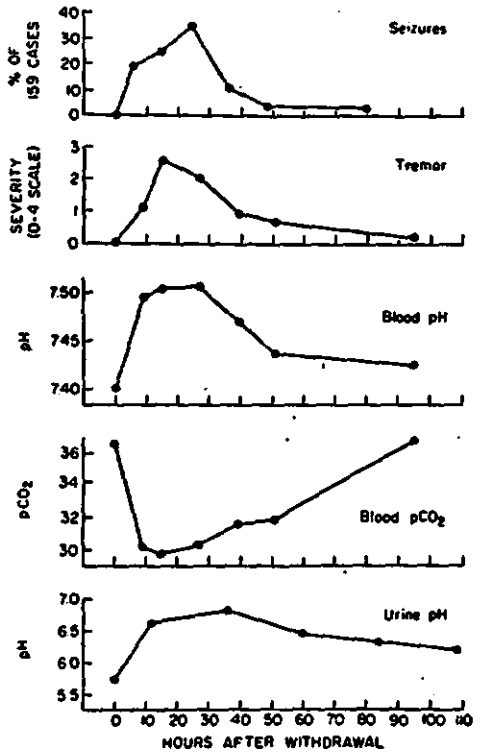
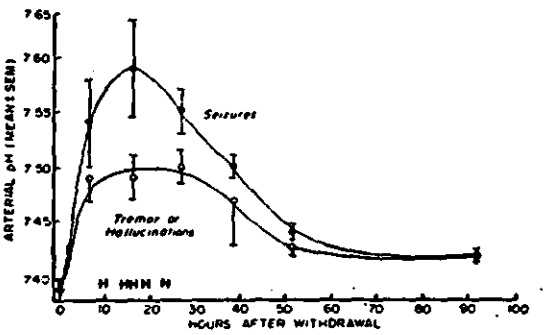


FIG. 8. Correlation between clinical and laboratory findings during withdrawal. (Upper panel represents data from Victor and Brausch, ref. 21); other panels are the mean values of the nine patients in the study of Wolfe et al., ref. 24.)

withdrawal are illustrated in Fig. 8. The upper panel indicates the time of occurrence of spontaneous seizures in relation to the withdrawal of alcohol, based on observations of 159 patients (21). The other data represent the means of values in the nine patients studied by Wolfe et al. (24). The period from 10 to 30 hr following cessation of drinking, during which tremulousness is most severe and most spontaneous seizures occur, coincides with the period of greatest abnormality in arterial pH and pCO_2 and the development of a more alkaline urine.

The foregoing observations, which were made in patients on a metabolic ward during control, drinking, and withdrawal periods, were extended in another study of 31 alcoholics who were admitted from the emergency ward of the Cleveland Metropolitan General Hospital (26). The withdrawal symptoms in this group were much more severe than those of previously-studied patients, allowing us to make observations in nine cases of delirium tremens as well as in 22 patients with the earlier signs of withdrawal (13 patients with tremor and hallucinations and nine patients with seizures).

This study provided confirmatory evidence that the early phase of alcohol withdrawal is consistently associated with respiratory alkalosis and that the severity of the clinical manifestations correlates closely with the magnitude of these biochemical



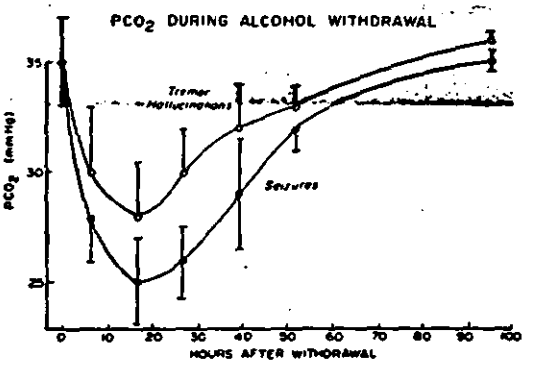


FIG. 9. Arterial pH and pCO_2 values during the withdrawal period in 13 patients with tremor and hallucinations and in nine patients with seizures. (From Wolfe and Victor, ref. 26.)

changes. These features are illustrated in Fig. 9, which shows a maximal degree of respiratory alkalosis between 12 and 21 hr after withdrawal and a concurrence of seizures and hallucinations with the maximal degree of respiratory alkalosis. The reduction in pco_2 and rise in arterial pH was greater in patients with seizures than in those with tremor and hallucinations alone. The respiratory alkalosis had largely corrected itself by 50 hr after withdrawal, at which time the symptoms were minimal. In patients who went on to develop delirium tremens the pH values did not change significantly, but the pco_2 values, which had returned to near normal, again decreased coincident with the onset of delirium tremens (Fig. 10), findings that were interpreted to represent a partially compensated respiratory alkalosis.

Finally, it should be emphasized that apart from the changes in serum magnesium, arterial pH, and pco_2, no consistent biochemical abnormalities were found associated with symptoms of withdrawal. Measurements of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum proteins, etc., were normal and values of serum sodium, chloride, calcium, potassium, and glucose, estimated repeatedly during the withdrawal period, disclosed only a few instances of hypoglycemia and slight depression of the serum potassium in eight of the 31 patients. In these respects, the findings were much the same as in our previous studies, which disclosed no consistent biochemical abnormalities during the period of chronic intoxication as well as during the withdrawal period.

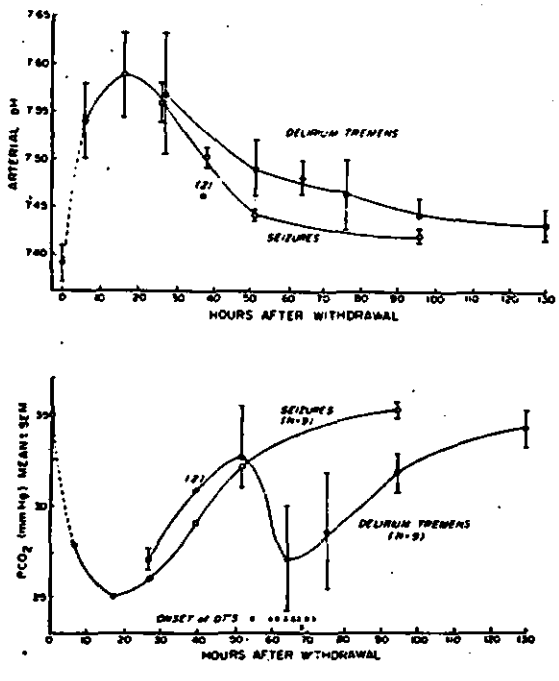


FIG. 10. Comparison of pH and pCO_2 values in patients with alcohol withdrawal seizures and those with delirium tremens. (From Wolfe and Victor, ref. 26.)

COMMENT

It may be concluded from the foregoing observations that the initial phase of the alcohol withdrawal period (approximately 48 hr after the cessation of drinking) is consistently associated with two abnormalities: (a) acute transient hypomagnesemia and (b) respiratory alkalosis, which is most likely the result of hyperventilation. Furthermore, the severity of the withdrawal symptoms bears a close relationship to the magnitude of change of these biochemical abnormalities. It has been our observation that the administration of magnesium raises the seizure threshold in the initial phase of the withdrawal period and that it may allay other abstinence symptoms as well. Preliminary observations suggest that correction of respiratory alkalosis also may have a salutory effect on withdrawal symptoms, but more data are required to be certain of this effect.

In addition to the experimental evidence presented above, there is considerable indirect evidence to suggest that hypomagnesemia and respiratory alkalosis are *important* in the causation of withdrawal symptoms. Manifestations of both central

and peripheral nervous system irritability have been described repeatedly in states of magnesium deficiency. In several animal species, a deficiency of magnesium has been associated with the occurrence of convulsive seizures, and a lowering of serum magnesium in cattle appears to be responsible for muscular tremor and twitching, apprehensive behavior, and violent convulsions (9,10). In man, magnesium deficiency states may be associated with tremor, twitching, convulsions, carpal-pedal spasms, and occasionally with visual and auditory hallucinations, and some of these phenomena can be reversed by the administration of magnesium (5,17). It should be emphasized that this therapeutic effect cannot be attributed simply to the sedative or anesthetic actions of magnesium (16).

It is well known that hyperventilation frequently precipitates seizures in patients with epilepsy and causes a decrease in the frequency of brain waves in normal individuals. It is also well known that respiratory alkalosis caused by hyperventilation may be accompanied by tremors and carpal-pedal spasms. A striking example of the effects of hyperventilation is seen in patients with chronic lung disease who have high arterial pCO_2 and normal or slightly decreased pH. When these patients are mechanically hyperventilated, the pCO_2 decreases and arterial pH increases, and if such treatment is prolonged or excessive, the patients may develop disorientation, hallucinations, tremor, hyperreflexia, generalized muscular irritability, seizures, and hyperpyrexia (1,3,8,14). These symptoms have been quickly relieved by simply allowing pCO_2 to increase (14). In some circumstances, alkalosis *per se* appears to be responsible for a state of heightened neuromuscular irritability; for example, an increased incidence of audiogenic seizures occurs in rats pretreated with sodium bicarbonate (12).

The symptoms associated with alkalosis are thought to be due to the direct effect of increased pH on nerve and muscle, or possibly the result of decreased CO_2 tension. They are probably not due to the effects of lowered ionizable calcium, which is invoked frequently as a cause of the so-called tetany that accompanies alkalosis; Walser (23) has pointed out that the changes in ionizable calcium that accompany alterations in blood pH are probably too small to cause these effects.

Studies by Wollman et al. (27) have shown that hyperventilation in normal men, sufficient to lower pCO_2 and produce alkalosis, causes a decrease in cerebral blood flow of as much as 40%. When alkalosis is induced by sodium bicarbonate, however, an increase rather than a decrease in cerebral blood flow occurs, so that cerebral vasoconstriction appears to be caused by lowered CO_2 tension rather than by alkalosis *per se*. Thus, a low pCO_2 may cause cerebral hypoxia, thereby potentiating the direct effect of alkalosis on neural excitability and accounting for many of the symptoms seen during alcohol withdrawal.

It is therefore postulated that the compounded effects of hypomagnesemia and alkalosis, each of which is known to be associated with hyperexcitability of the nervous system, are sufficient to produce photomyoclonus and spontaneous seizures and perhaps other symptoms that characterize the early phase of alcohol withdrawal. The precise relationship between hypomagnesemia and alkalosis is not understood. Possibly, the latter may be responsible for the former by causing a shift of magnesium into bone and other intracellular sites, just as alkalemia causes a shift of potassium from extracellular to intracellular compartments. What it is that induces the respiratory alkalosis in the first place is a matter of speculation. The effect of chronic alcohol intoxication on the neuronal elements in the brainstem that control respirations is to cause a decrease in ventilatory response to carbon dioxide (6). Possibly,

removal of the depressant effect of alcohol is followed by a "rebound" phenomenon, resulting in an increased sensitivity of the "respiratory center" to carbon dioxide, and, in turn, hyperventilation.

CONCLUDING REMARKS

The studies reported here have led us to recognize two phases of the withdrawal syndrome—an early or minor phase and a late or major one (delirium tremens). This concept is both of theoretical and practical importance, and the failure to distinguish between these two aspects of the withdrawal syndrome is largely responsible for the confusion in the literature pertaining to the diagnosis and treatment of alcohol withdrawal.

By far the largest number of patients who experience alcohol withdrawal symptoms show only *the minor syndrome*, i.e., varying degrees of tremor, general muscular weakness, insomnia, and anorexia, and less often, of hallucinations and seizures ("rum fits"), having their onset as early as 6 to 8 hr after withdrawal, reaching a peak of severity between 10 and 30 hr, and abating largely by 40 to 50 hr. As has been pointed out, these symptoms correlate closely with vulnerability to photic stimulation, a fall in serum magnesium, and a rise in arterial pH and a drop in pCO_2, the result of respiratory alkalosis. These symptoms are almost invariably benign and respond readily to a variety of sedative-hypnotic drugs.

A *small* proportion of patients experience *the major syndrome* or *delirium tremens*, which has its onset between 60 and 80 hr after withdrawal and is characterized by profound confusion, increased psychomotor activity (restlessness, tremor, jactitations, vivid hallucinations), and overactivity of the autonomic nervous system (fever, tachycardia, severe diaphoresis). Spontaneous seizures, if they occur, always precede the onset of delirium tremens, and once delirium tremens becomes established the patient is no longer vulnerable either to spontaneous seizures or to photic stimulation. Hypomagnesemia does not seem to be significant in the pathogenesis of delirium tremens, and the relationship to respiratory alkalosis is variable. Delirium tremens is potentially a lethal disease, and its duration and outcome are influenced very little by the administration of sedative-hypnotic drugs; the crucial elements of treatment are the control of dehydration and electrolyte imbalance and the management of hyperthermia and shock, should these complications become manifest.

ACKNOWLEDGMENT

Some of the work reported here was supported by a grant from NINCDS, National Institutes of Health.

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