Nervous System Complications in Uremia

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In patients with end-stage renal disease, nervous system dysfunction remains a major cause of disability. Patients with chronic renal failure who have not yet received dialysis may have symptoms ranging from mild sensorial clouding to delirium and coma. Dialysis itself is associated with at least three distinct disorders of the central nervous system, including the dialysis disequilibrium syndrome, dialysis dementia, and progressive intellectual dysfunction. Peripheral neuropathy is also a major cause of disability in uremic patients. Aluminum probably contributes to the pathogenesis of dialysis dementia. Parathyroid hormone, the levels of which are elevated in patients with renal failure, also may be a uremic neurotoxin. Biochemically, brain calcium levels are elevated in renal failure, possibly because of the action of parathyroid hormone. Studies on synaptosomes have also shown that parathyroid hormone can affect calcium transport in the brain. Intellectual dysfunction, dialysis dementia, uremic neuropathy, and the dialysis disequilibrium syndrome can be diagnosed when the characteristic clinical findings are present and other causes of nervous system dysfunction have been excluded.


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Recent advances in dialytic therapy, renal transplantation, and medical management have greatly improved both the duration and quality of life in patients with end-stage kidney disease. Further, new techniques of both pharmacologic and dietary therapy can decrease the incidence of end-stage renal disease (1, 2). However, in patients with renal failure, nervous system dysfunction remains a major cause of disability, and such patients continue to have neurologic disorders (3-5). Patients with chronic renal failure not yet given dialytic therapy may have symptoms ranging from mild sensorial clouding to delirium and coma (3, 4). Even after the institution of adequate maintenance dialysis therapy, patients may continue to have more subtle kinds of nervous system dysfunction, such as impaired mentation, generalized weakness, sexual dysfunction, and peripheral neuropathy (3-6). The dialytic treatment of end-stage renal disease has itself been associated with at least three distinct disorders of the central nervous system, including the dialysis disequilibrium syndrome, progressive intellectual dysfunction, and dialysis dementia (7-10). The dialysis disequilibrium syndrome occurs in a few patients as a consequence of the initiation of dialysis therapy. Dialysis dementia is a progressive and generally fatal encephalopathy that can affect patients treated with chronic hemodialysis and children with chronic renal failure not treated with dialysis (11, 12). Progressive intellectual dysfunction may also occur in many patients being treated with maintenance dialysis therapy (13). In addition to these central nervous system dysfunction, peripheral neuropathy is also a major cause of disability in uremic persons (5, 14-16).

Besides neurologic disorders specifically related to uremia or dialysis, other neurologic entities occur with increased frequency in patients being treated with chronic dialysis for end-stage renal disease (Table 1) (3, 4). In addition, patients with end-stage kidney disease are also at risk for other neuropathies, structural brain lesions, or metabolic encephalopathies that might affect the general population (4). Therefore, when a patient with end-stage kidney disease has peripheral-nerve dysfunction or an altered mental status, a thorough and complete evaluation is necessary to establish the proper diagnosis.

**Uremic Encephalopathy**

Uremic encephalopathy may occur in patients with either acute or chronic renal failure when the glomerular filtration rate falls below approximately 10% of normal (4). As seen in patients with other organic brain syndromes, these patients have variable disorders of consciousness that can affect psychomotor behavior, thinking, memory, speech, perception, and emotion (4, 5). The severity and rates of progression of symptoms vary directly with the rate at which renal dysfunction develops. In patients with acute renal failure, uremic symptoms are generally severer and progress more rapidly than in patients with chronic renal failure (17-19). In patients with progressive chronic renal failure, the number and severity of symptoms may differ cyclically, with intervals of well-being in an otherwise inexorable downhill course. The symptoms are usually alleviated by dialysis and are generally relieved almost entirely after successful renal transplantation (1, 3, 4).

**Differential Diagnosis**

Uremic encephalopathy should be suspected in patients with renal failure who have clinical signs and
### Early
- Anorexia
- Nausea
- Insomnia
- Restlessness
- Decreased attention span
- Inability to manage ideas
- Decreased sexual interest

### Moderate
- Vomiting
- Sluggishness
- Easy fatigue
- Drowsiness
- Sleep inversion
- Volatile emotions
- Paranoia
- Decreased cognitive function
- Inability to decipher abstractions
- Decreased sexual performance

### Severe
- Itching
- Disorientation
- Confusion
- Bizarre behavior
- Slurring of speech
- Hypothermia
- Myoclonus
- Asterixis
- Convulsions
- Stupor
- Coma

Symptoms consistent with the findings of central nervous system deterioration. However, because the presenting symptoms of uremic encephalopathy may be similar to those of other metabolic encephalopathies (4, 19), some risk for misdiagnosis and mistreatment exist (Figure 1). Another problem with differential diagnosis is that patients with renal failure may also have other intercurrent illnesses that may induce encephalopathy. If a patient with renal insufficiency is taking a drug that has potential central nervous system toxicity and is excreted or metabolized primarily by the kidney, the ensuing central nervous system symptoms may be due either to the drug, which has reached toxic levels at ordinary dose rates, or to uremia (4). In patients with both advanced liver and renal diseases, whether the encephalopathy is due to either hepatic or renal causes or both is often difficult to determine (20). In such patients, blood urea nitrogen and serum creatinine levels do not always adequately reflect the degree of functional renal impairment (21). Thus, many patients with cirrhosis, ascites, and normal blood urea nitrogen and creatinine levels may in fact have a glomerular filtration rate below 30 mL/min (21).

In patients with normal liver function, protein and amino acids in the gastrointestinal tract are metabolized by bacteria and mucosal enzymes in the colon to form ammonia. The ammonia then enters the liver through the portal circulation, where most of it participates in the urea cycle to form urea (22). Much of the urea so produced is excreted in the urine and the rest enters the colon through hepatenteric recirculation (20). However, in patients with renal failure, because the major route for the elimination of urea is not available, a rapid and sustained increase in blood urea nitrogen levels occur. Because of the elevated blood urea nitrogen level, the amount of urea that enters the colon by recirculation is increased. In uremic patients, the additional urea in the gut is again acted on by bacteria and mucosal enzymes, resulting in further increased ammonia production. This increased production may then lead to an increase in both plasma ammonia concentration and brain uptake of ammonia (23, 24), resulting in an increased risk of patients with both kidney and liver failure for encephalopathy.

Effects of Acute and Chronic Renal Failure on the Central Nervous System

Abnormalities of the mental state are early and sensitive indexes indicating the development of neurologic disorders in patients with acute renal failure. Patients with acute renal failure may initially have signs of toxic psychosis, as well as an abnormal mental status, lassitude, and lethargy, with evidence of disorientation and confusion appearing later. Physical findings may include cranial nerve signs, nystagmus, dysarthria, abnormal gait, and various abnormalities of skeletal muscles, such as weakness, fasciculations, and asymmetrical variation in deep tendon reflexes. As disease progresses, asterixis and hyperreflexia, with unsustained clonus at the ankle, may develop. If uremia is not treated and is allowed to progress, seizures and coma often supervene (3, 4).

Electroencephalograms in patients with acute renal failure are generally grossly abnormal when acute renal failure is first diagnosed (17). In most instances, the percentage of electroencephalographic power less than either 5 Hz or 7 Hz is 20 times greater than the normal value. The abnormal percentages of electroencephalographic frequencies both above 9 Hz and below 5 Hz are not usually improved by dialysis within the first 8 weeks of treatment, although they may return to normal with the recovery of renal function. If renal failure continues, the electroencephalogram may transiently worsen both during and after hemodialysis, and this pattern may continue for up to 6 months after the initiation of dialytic therapy (17, 18, 25-27).

The neurologic manifestations of chronic renal failure are also numerous. Electroencephalographic findings in patients with chronic renal failure are usually not as severe as those reported in patients with acute renal failure. There is generally good correlation between the percentage of electroencephalographic frequencies and power below 7 Hz and the decline of renal function as estimated by the serum creatinine level (5, 26). After the initiation of dialysis therapy, there may be an initial period of clinical stabilization during which time the electroencephalogram continues to deteriorate. However, after approximately 6 months of dialysis therapy, the electroencephalogram
tends to normalize. Normal values may not be reached however, unless the patient receives a kidney transplant (5, 26, 27). In patients with chronic renal failure, certain cognitive functions are also impaired, including attention span, speed of decision making, short-term memory, and mental manipulation of symbols (Figure 1) (28).

Psychological Testing in Chronic Renal Failure

Several psychological tests for patients with chronic renal failure were designed to evaluate the effects of either dialysis, renal transplantation, or parathyroidectomy on central nervous system symptoms in patients with end-stage kidney disease (19, 28, 29). The Trailmaking Test, which is used to assess fine motor ability, is frequently given. When it was administered to patients with renal failure, their performances were generally less than that of normal persons, but their test scores could be improved with practice (29). The Continuous Memory Test, the Choice Reaction Test, and to a lesser degree the Continuous Performance Test have all been shown to correlate with the degree of renal failure (4, 19). Scores on both the Continuous Memory Test and Choice Reaction Test tend to improve after patients have been treated with either dialysis or renal transplantation. Of these tests, the Choice Reaction Time appears to be the most reliable test for showing improvement in patients from therapy (4).

The possible effects of parathyroid hormone on psychological function have also been evaluated in patients receiving maintenance treatment with chronic dialysis. (29). Patients who had parathyroidectomy showed significant improvement in Raven Progressive Matrices percentile scores and visual motor index raw and percentage scores. Cognitive function and nonverbal evaluation in these patients revealed that they had significantly fewer errors on the Trailmaking Test and significantly lower raw and T-score values on the Profile of Mood States Fatigue Scale. Controls who had neck surgery for other reasons showed no change in any of the tests, except for the Trailmaking Test (29).

Effects of Uremia on the Brain

Biochemical Changes

To ascertain the possible causes of the electroencephalographic abnormalities and the clinical manifestations observed in patients with renal failure, biochemical studies have been done on the brains of both patients and laboratory animals (30-36). In patients with acute renal failure, the brain content of water, potassium, and magnesium is normal, that of sodium and aluminum is slightly elevated (31, 36), and that of calcium is almost twice the normal value (17, 29). Similar results have also been reported in studies on acute renal failure in dogs (30, 31, 37). Studies have also shown that the permeability of the uremic rat brain to certain inert molecules, such as inulin and sucrose, is increased, whereas the permeability to weak acids, such as sulfate, penicillin, and dimethadione, is normal to low (19, 31, 33). In the brain of rats with acute renal failure, creatine phosphate, adenosine triphosphate, and glucose levels are increased, whereas adenosine monophosphate, adenosine diphosphate, and lactate levels are decreased. Thus, the uremic brain appears to use less adenosine triphosphate and to produce less adenosine diphosphate, adenosine monophosphate, and lactate. These changes are also associated with a decrease in both brain metabolic rate and cerebral oxygen consumption (34, 35, 38), and are consistent with a generalized decrease in brain energy use.

In animals with either acute or chronic renal failure, both urea concentration and osmolality are similar in brain, cerebrospinal fluid, and plasma (31, 39). An increase in brain osmolality in acute renal failure due to an increase in the brain urea concentration has been noted (31). However, contrary to observations in patients with acute renal failure and in animals with chronic renal failure, approximately half of the increase in brain osmolality is due to the presence of undetermined solute (idiogenic osmole), and most of the rest is due to an increase in urea concentration (32, 39). Also, in both humans and laboratory animals with renal failure, the pH of cerebrospinal fluid and intracellular pH in the brain are both normal (19, 33, 39). Studies in the brain of both animals and patients with renal failure have generally shown several biochemical changes associated with the uremic state. However, such studies have revealed only limited information about the fundamental mechanisms that might induce the clinical symptoms of uremic encephalopathy.

Subcellular Studies

In several studies, investigators have attempted to evaluate the effects of uremia on the central nervous system by using subcellular analysis. Two early studies showed that the sodium potassium adenosine triphosphate enzyme activity in crude brain preparations was normal to low (34, 40). More recent studies on metabolically active and highly purified brain synaptosomes (vesicles isolated from the presynaptic area in brain) (41) showed that both the sodium potassium adenosine triphosphate pump and several calcium pumps are altered in uremic rats (41, 42). The alterations in the calcium pumps are due largely to parathyroid hormone acting through cyclic adenosine monophosphate-independent pathways (43) and to the uremic environment itself (44). Because the calcium pumps at the nerve terminals mediate neurotransmitter release in the central nervous system, the abnormalities in uremia may affect information processing in the uremic state. Unlike the changes in the calcium and sodium pumps observed in uremia, water and urea permeabilities were not affected either by uremia or by parathyroid hormone (45).

Pathologic Studies

In the brains of patients with chronic renal failure who have died (4, 19, 46), necrosis of the granular layer of
Table 1. Differential Diagnosis of Nervous System Complications of Dialysis

<table>
<thead>
<tr>
<th>Dialysis dementia</th>
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<tbody>
<tr>
<td>Metabolic Encephalopathies</td>
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<tr>
<td>Hypercalcemia</td>
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<tr>
<td>Hypophosphatemia</td>
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<tr>
<td>Wernicke encephalopathy</td>
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<tr>
<td>Hyperosmolality</td>
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<tr>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Drug intoxications</td>
</tr>
<tr>
<td>Trace element intoxications: manganese, mercury, lead, nickel, thallium, boron, vanadium, chromium, tin, cadmium</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
</tbody>
</table>

Hypertensive encephalopathy

Structural lesions

Subdural hematoma
Normal pressure hydroencephalus
Stroke

Dialysis disequilibrium syndrome

Acute trace element intoxication (copper, nickel)
Subdural hematoma
Uremia
Nonketotic hyperosmolar coma
Cerebral embolus secondary to shunt declotting
Acute cerebrovascular accident
Cardiac arrhythmia
Depletion syndrome
Malfunction of fluid proportioning system
Excessive ultrafiltration
Hypoglycemia

the cerebral cortex, small intracerebral hemorrhages, and necrotic foci have been seen. Subdural hemorrhage, once a common finding in uremic patients, now occurs infrequently, and cerebral edema is not generally present in either uremic patients or laboratory animals (29, 31, 32, 37). Pathologic changes in the brains of patients with chronic renal failure who have died generally are nonspecific and may relate to other concomitant underlying disease states (46-48).

Parathyroid Hormone as a Possible Central Nervous System Uremic Toxin

Although many factors may contribute to uremic encephalopathy, most studies have shown no correlation between the degree of encephalopathy and any of the commonly measured blood variables associated with renal dysfunction, such as blood urea nitrogen, creatinine, bicarbonate, or pH (27, 49). However, the role of parathyroid hormone as a possible uremic toxin has been considerably discussed, and substantial evidence suggests that parathyroid hormone may in fact exert adverse effects on the central nervous system in uremia (17, 29, 30, 42, 44, 49, 50).

In uremic dogs, both electroencephalographic and brain calcium abnormalities discussed previously can be prevented by parathyroidectomy (25, 37, 50). Conversely, many of the central nervous system abnormalities observed in uremia, such as electroencephalographic abnormalities, can be reproduced by administering parathyroid hormone to normal animals, while maintaining calcium and phosphate in the normal range. Thus, parathyroid hormone appears to produce some of the central nervous system changes of uremia in normal dogs (25, 40, 51, 52). Similarly, in humans, parathyroid hormone produces central nervous system effects even in the absence of impaired renal function (29). Neuropsychiatric symptoms are among the commonest manifestations of primary hyperparathyroidism (51-54). Patients with primary or secondary hyperparathyroidism have electroencephalographic changes similar to those observed in patients with acute renal failure (29, 30, 55), and one common denominator between these two groups may be the elevated plasma level of parathyroid hormone.

As shown in laboratory animals (25, 30), parathyroidectomy in patients with primary hyperparathyroidism results in improvement in the results from both electroencephalography and psychological testing, suggesting a direct effect of parathyroid hormone on the central nervous system (29). In uremic patients, both the electroencephalographic changes and the abnormalities on psychological testing are also improved by either parathyroidectomy or medical suppression of parathyroid hormone (29, 55). The mechanisms by which parathyroid hormone might impair central nervous system function are not completely understood. However, the increased calcium content in such diverse tissues as skin, cornea, blood vessels, heart, and brain in patients with uremia and secondary hyperparathyroidism suggests that parathyroid hormone may somehow facilitate the entry of calcium into these tissues (49-51). Because calcium is an essential mediator of neurotransmitter release and also plays an important role in much intracellular activity, alteration of brain calcium may possibly disrupt cerebral function by interfering with any of these processes (56, 57). Overall, parathyroid hormone itself may have direct toxic effects on the central nervous system. Similarly, in other systems, parathyroid hormone has been associated with decreased survival of erythrocytes, impaired myocardial contractility, impotence, pruritis, and bone disease (49-51, 58-61).

Neurologic Complications of Uremia Therapy

The Dialysis Disequilibrium Syndrome

In patients with chronic renal failure, several central nervous system disorders may occur from dialytic therapy. For example, the dialysis disequilibrium syndrome can occur in patients being treated with hemodialysis (9). The syndrome may include symptoms such as headache, nausea, emesis, blurring of vision, muscular twitching, disorientation, hypertension, tremors, and seizures (62-64). More recently, the syndrome has been expanded to include milder symptoms, such as muscle cramps, anorexia, restlessness, and dizziness (65, 66). Although it was originally
thought that patients with the syndrome had abnormal electroencephalograms (64), recent studies have suggested that patients in fact have normal electroencephalograms (5, 26, 27). The syndrome has been reported in patients of all ages; however, it occurs most commonly in elderly persons and children (67). The syndrome is generally associated with rapid hemodialysis in patients with acute renal failure but may also occur after routine maintenance hemodialysis in patients with chronic renal failure (63, 68).

The pathogenesis of the syndrome has been extensively studied in animal models of renal failure (31, 33, 69). Previous research suggested that the syndrome was probably due to the reverse urea effect, in which urea was cleared less rapidly from the brain than from the blood, resulting in an osmotic gradient between the blood and brain. This osmotic gradient would then lead to a net movement of water into the brain, resulting in cerebral edema (70). Subsequent studies have shown that during dialysis, urea is cleared from brain at the same rate as it is from blood (31, 69), so there is no blood-to-brain osmotic gradient based on the movement of urea alone. However, rapid hemodialysis in dogs with acute renal failure results in an increase in brain osmolality and cerebral edema. The cerebral edema may be due to a decrease in the intracellular pH of the cerebral cortex from the increased production of organic acids (33). Decreasing the rate and increasing the frequency of dialysis as part of the initial therapy for acute renal failure led to amelioration of both the symptoms and biochemical derangements of the dialysis disequilibrium syndrome (31, 33, 63, 65).

The symptoms of the dialysis disequilibrium syndrome are usually self-limited, but recovery may take several days. New approaches to dialysis treatment may have also helped to improve the clinical picture of the syndrome (71), as most cases of seizures, coma, and death were only reported before 1970. Within the last decade, the reported cases have generally been milder, involving nausea, weakness, headache, fatigue, and muscle cramps. The diagnosis of the syndrome must be differentiated from other disorders that may affect the central nervous system in patients treated with dialysis (Table 1) and thus should be one of exclusion (19).

### Table 2. Subgroups of Dialysis Dementia

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Sporadic endemic</td>
<td>No clear relation to aluminum&lt;br&gt;Worldwide distribution&lt;br&gt;No known therapy</td>
</tr>
<tr>
<td>Epidemic</td>
<td>Geographical clusters&lt;br&gt;Often related to aluminum in dialysis water&lt;br&gt;Epidemic usually stops with treatment of water supply&lt;br&gt;Probably related to other trace elements in water (tin, manganese, cobalt, magnesium, iron)</td>
</tr>
<tr>
<td>Childhood</td>
<td>May be due to nonspecific effect of uremia on immature brain&lt;br&gt;No clear association with aluminum</td>
</tr>
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</table>

forms (Table 2): an epidemic form, encephalopathy associated with childhood renal disease, and an endemic form (7, 8, 11, 76, 77). The initial cases of dialysis encephalopathy were all of the endemic form and usually occurred in patients being treated with chronic hemodialysis for more than 2 years (7, 8). The initial symptoms include dysarthria, apraxia, and slurring of speech, with stuttering and hesitancy. The patients may also have personality changes, psychosis, dementia, myoclonus, and seizures. The initial symptoms are usually intermittent and often worsen during dialysis. In most cases, the disease progressed to death within 6 months (36). Recent cases of epidemic dialysis encephalopathy were due to contamination of the dialysate water with trace metals, such as aluminum (72, 75, 78-81).

Early in dialysis encephalopathy the electroencephalogram shows multifocal bursts of high-amplitude delta activity, with spikes and sharp waves, intermixed with runs of more normal background activity (17, 79, 80). These electroencephalographic changes may precede overt clinical symptoms by 6 months. As the disease progresses, the normal background activity of the electroencephalogram may also deteriorate to a predominance of slow frequencies (75). This electroencephalographic pattern, although pathognomonic of dialysis encephalopathy, may also be seen in other metabolic encephalopathies. The diagnosis thus depends on the presence of the typical clinical picture, the characteristic electroencephalographic pattern, and most important, the exclusion of other causes of central nervous system dysfunction (75, 76, 78, 81).

### Role of Aluminum

Aluminum intoxication was probably first implicated in this disorder when studies showed that the aluminum content of brain gray matter in patients with dialysis encephalopathy was markedly elevated as compared with controls (7, 36). The amount of aluminum in the brain was more than three times greater in patients with dialysis encephalopathy than in patients being treated with chronic hemodialysis who did not have dialysis encephalopathy (Figure 2) (7, 36). The
Elevated brain aluminum levels are also present in several other groups of patients who do not have dementia, including patients with acute renal failure, hepatic encephalopathy, or metastatic cancer, or patients more than 60 years old. However, the levels are generally lower than those measured in patients with dialysis encephalopathy (Figure 2) (19, 79, 87, 88). In patients with dialysis encephalopathy, aluminum may affect the development of the epidemic form. However, whether aluminum affects the development of the other types of dialysis encephalopathy (endemic and pediatric), or is only an associated paraphenomenon, remains unresolved.

Other forms of encephalopathy may be related to increased aluminum levels in the brain, including amyotrophic lateral sclerosis, parkinsonism-dementia on Guam (89), and Alzheimer disease (90, 91). Recent evidence suggests that some patients with dialysis encephalopathy have senile plaques and neurofibrillary tangles in their brains similar to those seen in patients with Alzheimer disease (92, 93). In Alzheimer disease, the plaques and neurofibrillary tangles contain aluminum (87, 90, 91), although the exact localization of the aluminum in the brain cells of patients with dialysis encephalopathy is unknown. Many studies on the toxic neurologic effects of aluminum in laboratory animals have been done, although, in most of these studies, the aluminum was given either parenterally or injected directly into the central nervous system (19). When aluminum was given orally to laboratory animals (79, 94, 95), aluminum had no apparent harmful sequelae, although it resulted in increased brain aluminum content (79, 95). In the presence of an abnormal blood-brain barrier, aluminum exerts toxic effects on the central nervous system and is involved in the pathogenesis of several different forms of encephalopathy, including dialysis encephalopathy. A recent study (96) suggested how aluminum may play a role in the central nervous system toxicity associated with dialysis encephalopathy. Tetrahydrobiopterin is needed for the synthesis of several different neurotransmitters in the brain. The enzyme dihydropteridine reductase is necessary to maintain a normal brain concentration of tetrahydrobiopterin. In patients treated with dialysis who had mean plasma aluminum levels elevated to 13 times the control value, the erythrocyte activity of dihydropteridine reductase was reduced in an inverse relation to the plasma aluminum level. The erythrocyte dihydropteridine reductase activity then increased, after the plasma aluminum level was decreased with deferoxamine. A similar situation may exist in the brain as in the erythrocyte, although additional research remains to be done.

Deionization of the water used to prepare the dialysate is now done as a preventive measure to reduce aluminum concentration in dialysate fluid (75, 78, 82). However, deionization not only removes aluminum but also cadmium, mercury, lead, manganese, copper, nickel, thallium, boron, and tin (7, 97, 98). Among these other potentially neurotoxic elements, there are few reported measurements of the brain content of cadmium, mercury, nickel, thallium, or boron.
In one study, eight patients with encephalopathy had increased manganese levels in cortical white matter, along with elevated levels of aluminum in gray matter (77). Thus, not only aluminum, but several other trace elements may play a role in the pathogenesis of dialysis encephalopathy.

Despite these unresolved questions, most outbreaks of epidemic dialysis encephalopathy have been associated with high levels of aluminum in the dialysate (75-78). Thus, therapy has been directed toward removing aluminum both from the dialysate and from the patients. Lowering the dialysate aluminum levels to below 20 μg/L by deionization and reverse osmosis appears to largely prevent the onset of the disease in patients in whom dialysis is being started (75-78). In patients with overt disease, eliminating the source of aluminum has only rarely resulted in improvement (78, 79, 82, 99). Diazepam or clonazepam appears to be useful in controlling seizure activity associated with the disease; however, these agents usually become ineffective later on and do not alter the usually fatal outcome (80, 81). An improvement in symptoms has been reported in patients treated with desferoxamine (100). However, some studies suggest that desferoxamine without diazepam may lead to a worsening of symptoms (99), and desferoxamine administration has been associated with neurotoxicity in other situations (101). Removing aluminum from the dialysate water largely prevents the occurrence of dialysis encephalopathy (epidemic form). Removing aluminum from patients with dialysis encephalopathy does not modify established endemic or epidemic disease. Treating sporadic cases, in which the cause of the encephalopathy is unclear, is more difficult. In these cases, dialysis encephalopathy should be differentiated from other metabolic encephalopathies and structural neurologic lesions in the brain (Table 1) (19, 81, 102).

Many other possible causes for dialysis encephalopathy have been proposed, including normal pressure hydrocephalus (103), slow virus infection of the central nervous system (104), and regional alterations in cerebral blood flow (105, 106). In one series, six patients with dialysis encephalopathy had abnormal cerebrospinal fluid dynamics and mild dilatation of the cerebral ventricles (103). However, other studies have suggested that many patients with end-stage renal disease without dialysis encephalopathy may also have ventricular dilatation with cerebral atrophy (105, 107). Slow virus infection of the nervous system may also be a possible cause of dialysis encephalopathy. The clinical manifestations of dialysis encephalopathy resemble those of slow virus infections, such as Creutzfeldt-Jakob disease (108). New advances in research on prions have suggested that this infectious protein may play an important role in the pathogenesis of certain degenerative diseases of the central nervous system (109). Although the prion protein has not been studied in patients with dialysis encephalopathy, future investigation may provide some insight into the pathogenesis of this disorder. However, the cause of endemic dialysis encephalopathy remains unclear.

Finally, dialysis encephalopathy has also been reported in several children who were neither dialyzed nor exposed to aluminum compounds. Therefore, the cause of encephalopathy in such children cannot be attributed to aluminum alone and may represent developmental neurologic defects resulting from exposure of the growing brain to a uremic environment (11, 12, 80).

Intellectual Impairment
Another frequently recognized complication in many patients with chronic renal failure being treated with dialysis is intellectual impairment (10, 13, 110). However, the syndrome is not as well defined as dialysis encephalopathy; no anatomic lesion can be correlated with intellectual deterioration, and no associated neurologic abnormalities occur. The methods for assessing intellectual function include the full Wechsler Adult Intelligence Scale, the Walton-Black Modified Word Learning Test, and the Block Design Learning Test. Although some studies have suggested that the overall intellectual level in patients with chronic renal failure does not differ significantly from that in normal persons (111), most studies have suggested that the full-scale intelligence quotient as measured by the Wechsler Adult Intelligence Scale in patients treated with dialysis is below that of the general population. Impairment of intellectual level as measured by the Wechsler deterioration quotient has also been noted. The data on verbal learning obtained with the Walton-Black Modified Word Learning Test and performance learning obtained with the Block Design Learning Test did not indicate any gross learning abnormality. The results of psychological testing show that chronic renal failure is often associated with organic-like loss of intellectual function, particularly information processing capacities, but the cause is unclear (10, 13, 110-112).

Uremic Neuropathy
Two broad categories of peripheral neuropathy have been described in terms of the pattern of neuronal involvement (113, 114). One category involves processes that result in a bilaterally symmetrical disturbance of nerve function that can be designated as polyneuropathies (axonopathies). Polyneuropathy is usually associated with toxic substances, metabolic disorders (uremia, diabetes, deficiency states), and certain immune reactions that act diffusely on the peripheral nervous system. The other category involves isolated lesions of peripheral nerves or multiple isolated lesions of peripheral nerves that are designated as mononeuropathies. In severe symmetrical polyneuropathies, a generalized loss of peripheral nerve function may occur, and the impairment is usually maximal distally. This condition is characterized by a mixed motor and sensory polyneuropathy, with a distal distribution that often results in weakness and wasting in the arms and legs (115). Distal sensory changes of "glove and stocking" distribution may also occur (116). The motor nerve conduction velocity is frequently used to as-
sens peripheral neuropathy (113, 114). However, the test is somewhat unreliable in uremic persons, because the procedure itself has a normal daily variation of up to 20% (115). Thus, motor nerve conduction velocity has very limited use in detecting moderate impairment of peripheral nerve function (117). Sensory nerve conduction velocity probably is more sensitive than motor nerve conduction velocity, but has not been widely used (115, 118). Although peripheral neuropathy in patients with renal failure has been long recognized, it was not fully appreciated until chronic dialysis therapy began to be used in the early 1960s (3, 116).

Neuropathy of some degree is probably present in about 65% of patients with end-stage renal disease who are being treated with dialysis (3, 14). When the glomerular filtration rate is greater than about 10% of normal, peripheral neuropathy is uncommon (3, 5, 115). Many asymptomatic patients with chronic renal failure have autonomic neuropathy on physical examination, such as impotence and postural hypotension (16, 118, 119). Moreover, abnormal nerve conduction may be present when symptoms or findings are absent on physical examination (118).

Uremic neuropathy is a distal, symmetrical, mixed polyneuropathy that belongs to a group known as dying-back polyneuropathies, or central-peripheral axonopathies (120). Possible causes of such central-peripheral axonopathies include many types of toxic compounds (120). Uremic neuropathy is also associated with a secondary demyelinating process of the spinal cord, particularly involving the posterior columns, as well as other portions of the central nervous system (113). Motor and sensory modalities are both generally affected, and lower extremities are more severely involved than are the upper extremities (3, 5, 115, 116, 118, 121, 122). Clinically, uremic neuropathy cannot be easily distinguished from the neuropathies associated with certain other metabolic disorders, such as diabetes mellitus, chronic alcoholism, and various deficiency states. The occurrence of uremic neuropathy is not related to the type of the underlying kidney disease. However, certain diseases that can lead to renal failure may simultaneously affect peripheral nerve function in a manner separate from the manifestations of uremia. Such diseases include amyloidosis, multiple myeloma, systemic lupus erythematosus, polyarteritis nodosa, diabetes mellitus, and hepatic failure (116).

Biochemistry

The general features of metabolic neuropathy apparently are similar to specific descriptions of uremic neuropathy (115, 116). The cellular basis for such axonopathies, however, remains unclear. Several chemically unrelated neurotoxic compounds and metabolic abnormalities can cause strikingly similar patterns of distal, symmetrical polyneuropathy in humans and animals (114). Neurotoxic compounds may deplete energy supplies in the axon by inhibiting nerve fiber enzymes required for the maintenance of energy synthesis. Resupply of these enzymes from the neuronal soma may fail to meet the increased demand for enzyme replacement in the axon, causing the concentration of enzymes to decrease in distal regions. This decrease may then lead to a local blockade of energy-dependent axonal transport, which could produce pathologic changes in nerves (121), culminating in distal fiber degeneration (114, 120).

Symptoms

The restless-leg syndrome is a common early manifestation of chronic renal failure (3, 116). Clinically, patients have sensations in their lower extremities, such as crawling, pricking, and pruritus. The sensations are generally worse distally and are usually more prominent in the evening. The burning-foot syndrome, which occurs in less than 10% of patients with chronic renal failure, actually consists of swelling sensations and tenderness of the distal lower extremities (3, 115, 116). The physical signs of peripheral nerve dysfunction often begin with loss of deep tendon reflexes, particularly in the knee and ankle. There is also impaired vibratory sensation and loss of sensation in the lower leg in the form of "stocking glove" anesthesia. The sensory modalities that are lost include pain, light touch, vibration, and pressure (3, 5, 115, 116).

Uremic Toxins as Causes of Neuropathy

Several potential uremic toxins might lead to the uremic neuropathy (122-126). Although any or all of these agents may play a role in the development of uremic neuropathy, the actual evidence that any of them are bona fide neurotoxins is scant (122). For example, middle molecules, compounds with molecular weights of 500 to 2500 Da, may be neurotoxins. The theory of the toxic effect of middle molecules is based on early observations in a few patients, and these initial impressions have not been confirmed by other studies (122, 126). Maneuvers that might be expected to increase the removal of middle molecules have had little demonstrable beneficial effect on peripheral nerve function (116, 118, 127).

The identification of several other potential uremic toxins has been based on their elevated concentrations in plasma and their correlation with depression of motor nerve conduction velocity (53, 122). However, these studies have not taken into account that depressed motor nerve conduction velocity can be cyclical, with abnormally low values one day and higher values the next (117) and that a daily variation in motor nerve conduction velocity occurs, which approaches 20% (117, 118, 122). Other issues not addressed in these studies are the findings that depressed motor nerve conduction velocity in laboratory animals associated with high plasma levels of potential uremic neurotoxins has generally not been confirmed in humans with renal failure (17, 18, 118), and that the best correlation of impaired motor nerve conduction velocity is with the serum creatinine level (118, 122), which suggests a nonspecific effect of uremia on nerve function. Possible uremic toxins include urea, creati-
nine, parathyroid hormone, myoinositol, transketolase, guanidine derivatives, and middle molecules (115, 116, 118, 122-125). Although an impairment in motor nerve conduction velocity can be related to levels in blood of these substances, the best correlation was obtained between reduced motor nerve conduction velocity and a reduction in the glomerular filtration rate (115). Of the several potential uremic neurotoxins, parathyroid hormone has probably received the most attention (49). Suggestions that parathyroid hormone may be a uremic neurotoxin are based on a possible correlation between plasma parathyroid hormone levels and motor nerve conduction velocity in patients with chronic renal failure (49, 51, 122), and on a possible effect of parathyroid hormone on motor nerve conduction velocity in dogs (39, 49-51). However, in patients with hyperparathyroidism without uremia, parathyroid hormone has no consistent observable effect on peripheral nerve function (51, 122). When dialysis therapy is begun, motor nerve conduction velocity either stabilizes or improves (5, 116), even though most of these patients have elevated plasma parathyroid hormone levels (60, 61). In dogs with renal failure for 2 days to 6 months, motor nerve conduction velocity was not significantly altered (39). Presently, no single uremic toxin has been shown to affect peripheral nerve function. Most of the evidence suggests that uremic neuropathy may be related to anatomical nerve damage and also to the cumulative effects of multiple toxic agents, and usually takes months to years to develop (116, 118-121).

Effects of Dialysis and Transplantation

In most patients with end-stage renal disease and neuropathy, the neuropathy will either stabilize or improve with regular dialysis therapy (116). In patients whose neuropathy is mild, dialysis may result in apparent recovery. When patients have severe neuropathy before dialysis therapy is begun, recovery may be only partial, even after several years of dialysis. In some patients, an initial worsening of motor nerve conduction velocity may occur over a several-month period, followed by gradual improvement (116, 118, 122). The most important variable that determines the effects of dialysis on nerve function seems to be the condition of the patient before dialysis therapy. When dialysis therapy is started, with a glomerular filtration rate in excess of about 10 mL/min, clinical neuropathy and associated disability are rare, and further progression of neuropathy usually does not occur (5, 116, 118).

The effects of successful renal transplantation on uremic neuropathy are more consistent than are those of dialysis. Usually, a progressive improvement in peripheral nerve function occurs for 6 months to a year after renal transplantation. The clinical remission appears to have a biphasic course, with an early phase of rapid (1 to 3 months) remission, followed by a slow, gradual improvement (128). Nerve deafness secondary to uremia is also largely reversible by renal transplantation, usually within 2 years (15, 16). Some improvement in both impotence and autonomic neuropathy also occurs (15, 53, 119).

Autonomic and Cranial Nerve Dysfunction

Uremic neuropathy is not limited to impairment of motor nerve function. Autonomic dysfunction is common and is usually associated with postural hypotension, impaired sweating, abnormal Valsalva maneuver, and alternation in gastric motility (116, 119). Dialysis-related hypotension is often associated with autonomic insufficiency (119). The autonomic nervous system function can be evaluated by means of the hand-grip dynamometer, which measures the maximum voluntary contraction; the heart rate response after a Valsalva maneuver (usually at an expiratory pressure of 40 mm Hg for 12 seconds), which is used to determine the Valsalva ratio; and the vascular response to norepinephrine infusion. These techniques have been described previously (119).

Cranial nerves are also often affected in uremic patients and the nerve involvement is most often manifested as transient nystagmus, miosis, heterophoria, and facial asymmetry (15). Involvement of the eighth nerve affecting both auditory and vestibular divisions is most commonly seen. In such cases, deafness due to uremia should be distinguished from that associated with various hereditary interstitial nephropathies and ototoxic drugs (15).

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