Neurodiagnostic Abnormalities in Patients with Acute Renal Failure

EVIDENCE FOR NEUROTOXICITY OF PARATHYROID HORMONE

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ABSTRACT Neurological abnormalities are a major cause of morbidity in patients with renal failure. The pathophysiology of these neurological changes is unclear, and the effects on them of dialysis and return of renal function have not been well studied. Studies were done in 31 patients who had acute renal failure (ARF), all of whom were either treated with dialysis within 5 days or did not survive. Studies on these patients included the electroencephalogram (EEG), motor nerve conduction velocity, and plasma Ca^{++} and parathyroid hormone (PTH) levels. Studies were done at the time ARF was diagnosed, after stabilization on dialysis, during the diuretic phase of ARF, and 3 mo after recovery from ARF. In 16 patients with acute or chronic renal failure who did not survive and in nine patients without renal disease who died, measurements were made in brain of content of Na^+, K^+, Cl^-, Ca^{++}, Mg^{++}, and water.

In patients with ARF for less than 48 h, despite the fact that there were only modest increases in plasma urea and creatinine, there were striking abnormalities in the EEG. The percent EEG power < 5 Hz±SE was 41±8% (normal = 2±1%), whereas the percent of frequencies > 9 Hz was only 22±6% (normal = 62±3%). These changes were unaffected by dialysis, but became normal with return of renal function and remained normal at 3 mo follow-up. The motor nerve conduction velocity was unaffected by either ARF or dialysis. In patients with ARF, the brain Ca^{++} was 46.5±3.2 meq/kg dry wt, almost twice the normal value of 26.9±1.0 meq/kg dry wt ($P < 0.001$). The plasma PTH level was 3.2±0.6 ng/ml (normal < 1.5 ng/ml, $P < 0.01$). The increased brain Ca^{++} was not related to an increased plasma (Ca^{++}) (PO_4^{---}) product ($r^2 = 0.14$, $P > 0.05$). There was a small but significant decrement in brain Na^+ ($P < 0.05$), but brain water, K^+, and Mg^{++} were unaffected by ARF.

Thus, in patients with ARF for less than 48 h, the EEG is grossly abnormal and there are elevated levels of PTH in plasma. The PTH appears to have a direct effect on the brain, resulting in an increased brain Ca^{++} content. The EEG abnormalities are unaffected by dialysis, but they become normal with return of renal function and remain normal after 3 mo follow-up. Thus, PTH may be a major uremic toxin, demonstrating evidence for central nervous system toxicity when there are only minimal abnormalities of other biochemical markers of ARF.

INTRODUCTION

Patients with renal failure may exhibit a number of neurological abnormalities which in recent years have become a major cause of morbidity (1–3). Neurological manifestations are especially marked in patients with acute renal failure, where they are probably best correlated with the rate of development of renal failure rather than any single laboratory value (2).

Assessment of the severity of these neurologic changes in patients with chronic renal failure is often highly subjective. This has led to attempts to quantitate the degree of neurological involvement in chronically uremic patients by using those hospital tests which are commonly available, such as the electroencephalogram (EEG)[1] and measurement of motor nerve conduction velocity (MNCV). Both peripheral neuropathy and an abnormal EEG are present in a

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[1] *Abbreviations used in this paper*: BUN, blood urea nitrogen; EEG, electroencephalogram; MNCV, motor nerve conduction velocity; PTH, parathyroid hormone.

majority of patients with chronic renal failure (1–7). Both the EEG changes and peripheral neuropathy may return toward normal after partial amelioration of uremia by dialysis (8, 9). The causes of these abnormalities are not clear. Many patients with chronic renal failure have concomitant systemic disease states which can also affect the EEG and MNCV, such as diabetes, hypertension, sepsis, peripheral vascular disease, and hepatic insufficiency. Thus, it may be difficult to separate the effects of renal failure, per se, from those of associated medical conditions (2). Therefore, we elected to study patients with acute, rather than chronic, renal failure. Previous studies from this laboratory have suggested that many of the EEG changes found in dogs with acute renal failure are probably secondary, at least in part, to an increased content of Ca^{++} in brain (10) which appears to be mediated through an effect on brain of increased plasma parathyroid hormone (PTH) levels (11). However, neither the applicability of these studies to man nor their potential for reversibility have been established.

The purpose of the present study was to evaluate the neurological abnormalities which are present in patients with acute renal failure, to determine their pathophysiology, and to study the effects of both dialysis and recovery of renal function on these abnormalities. Investigation of the pathogenesis of these abnormalities included analysis of brain water and electrolyte content in those patients with acute renal failure who did not survive.

METHODS

Studies were done on a total of 54 patients[2] who were evaluated at the San Francisco Veterans Administration Hospital over an 18-mo interval. These patients were divided into three groups, as follows: (*a*) 31 patients had acute renal failure; (*b*) six patients had chronic renal failure which had been treated with dialysis for at least six months. All of these patients died of causes other than uremia. In the patients with chronic renal failure, measurements were made only of plasma Ca^{++} and phosphate, and of brain content of Ca^{++} and Mg^{++}; (*c*) 17 patients had no evidence of renal disease, parathyroid disease, or cancer, all of which can affect the EEG. These subjects served as controls. Analysis of brain for content of water and electrolytes was carried out on autopsy specimens from a total of 25 patients, of whom 10 had acute renal failure, six had chronic renal failure, and nine control patients died from miscellaneous causes (bacterial pneumonia, sepsis, pulmonary embolus [3], aspiration pneumonia [2], hemorrhagic pancreatitis, acute myocardial infarction). Among the control patients, three had histories of alcoholic cirrhosis, two had severe peripheral vascular disease, one had chronic obstructive pulmonary disease, one had chronic congestive heart failure, and one was admitted with a fracture of the femur.

For the purposes of this study, acute renal failure was defined as a rapid deterioration in renal function as manifested by a mean rise in blood urea nitrogen (BUN) of at least 20 mg/dl per day and(or) of serum creatinine of at least 1 mg/dl per day such that serum creatinine exceeded 4 mg/dl within 3 days of the initial insult. All but 4 of the 31 patients with acute renal failure were oliguric (urine output < 400 ml/day) and the causes were toxic nephropathy (phenacetin [2], meglumine diatrizoate, methicillin, trichloroethylene) in five patients, postoperative (cardiac valve replacement [3], coronary artery bypass graft [3], ruptured abdominal aneurysm [2], perforated peptic ulcer [2], aorta-femoral artery bypass graft [2], nephrectomy [2], large bowel obstruction with perforation [2], leg amputation, craniotomy, and exploratory laparotomy) in 19 patients, and no single obvious etiology in the others. Among the 19 patients with postoperative renal failure, six had shock and five had severe sepsis. All surviving patients were treated with dialysis within 5 days. Patients who had a milder degree of acute renal failure such that dialytic therapy was not required were not included in the study. These patients had a serum creatinine which stabilized at less than 4 mg/dl within 3 days of the onset of acute renal failure. Likewise, patients with known preexisting renal insufficiency, as evidenced by a BUN exceeding 30 mg/dl and(or) serum creatinine in excess of 2 mg/dl, were also excluded from the study. In addition, patients whose acute renal failure was due to either parenchymal renal disease, such as rapidly progressive glomerulonephritis, or to systemic disease states, such as lupus erythematosus, malignant hypertension or polyarteritis, were also excluded.

Studies done on patients who satisfied these criteria included the standard EEG, MNCV, and serum PTH, phosphate (PO_4^{---}), and calcium (Ca^{++}) levels. In those patients who did not survive, measurements were made in brain of the content of Ca^{++}, Mg^{++}, Na^{+}, K^{+}, Cl^{-}, and water. In these patients, death was attributed to concomitant diseases rather than renal failure per se.

EEG recordings were done with a Beckman Accutrace 8-channel electroencephalograph (Beckman Instruments, Inc., Fullerton, Calif.) with subdermal needle electrodes with a time constant of 0.16 s and muscle filter set at 30 Hz. The EEG was analyzed by visual frequency analysis similar to that described by Engel et al. (12) and Laidlaw (13). A 13-s representative segment of the right temporo-occipital lead was selected and measurements of frequency distribution were made (13). All waves in the frequency classes 1-13 Hz were included in the analysis. The number of waves in each frequency class was counted and the percentage of all waves having the same duration was calculated. The average height of all the waves present in each particular frequency class was then measured in millimeters, and the result was multiplied by the percentage of waves present for that frequency class. The resulting number expressed the area (or power) occupied by each frequency of waves for the EEG segment being analyzed. The total EEG segment area was calculated by adding the areas of all frequency classes present. The percentage of the total EEG area occupied by all waves below 5 Hz was then calculated. This gave the percent EEG power less than 5 Hz, which has been shown to be a useful measurement for the quantitative of the presence of abnormal slow waves in patients with metabolic brain disease (7–9). These techniques have previously been described from this laboratory (10).

The MNCV was measured in the peroneal nerve with a TECA TE-4 Electromyograph system (TECA Corp., White

[2] Raw data on individual patients has been deposited with the National Auxiliary Publications Service (NAPS) as NAPS document No. 03220. This information may be ordered from ASIS/NAPS, Microfiche Publications, P. O. Box 3513, Grand Central Station, New York 10017. Remit in advance $3.00 for microfiche copy, or for photocopy, $5.00 up to 20 pages plus 25¢ for additional pages. Checks should be made payable to Microfiche Publications.

Plains, N. Y.), by methods which have been described (14). For at least 15 min before MNCV measurements were done, the patients were reclining in the study room, which had an ambient temperature of ~22°C.

EEG and MNCV studies were done at four intervals. (*a*) As soon as the diagnosis of acute renal failure had been established: this was usually within 48 h of the insult which caused the renal failure (12 of 16 patients), except in four patients with postoperative acute renal failure who were transferred from other hospitals. In these four patients, EEG and MNCV studies were done 4–7 days after the diagnosis of acute renal failure, and the mean±SE for all 16 patients was 2.8±0.4 days: (*b*) After the patient had been stabilized on dialysis: all patients evaluated at this time had received at least six treatments with dialysis over the 2-wk interval after the diagnosis of acute renal failure, and the day before their next dialysis all had blood urea nitrogen values below 75 mg/dl and serum creatinine of less than 7 mg/dl. (*c*) During the recovery (diuretic) phase of acute renal failure: this was defined as a spontaneous diuresis in excess of 800 ml/day, with a fall in BUN and serum creatinine without dialysis. (*d*) After recovery from acute renal failure: this was at least 3 mo after discharge from the hospital.

Plasma immunoreactive PTH levels were measured at the time of diagnosis of acute renal failure (1½–3 days after the inciting event) at the same time the initial EEG was obtained. PTH was determined by radioimmunoassay[3] utilizing antisera to bovine PTH (15). The upper limit of normal for the assay was 1.5 ng/ml.

In 10 patients who died with acute renal failure, nine patients who died without evidence of renal disease, parathyroid disease, or cancer, and in four patients who died with chronic renal failure, measurements were made of the content of Ca^{++}, Mg^{++}, Na^{+}, K^{+}, Cl^{-}, and water in brain cortical gray matter and subcortical white matter. The brain tissue for analysis was obtained from the anterior frontal lobe of autopsy specimens, consent having been obtained from the next of kin. The analytic methods have been published previously from this laboratory (11, 16, 17). Briefly, after removal of the ependyma, cortical gray matter and subcortical white matter were separated by blunt dissection (17). Triplicate samples (~0.4 g each) were placed in tared conical flasks and weighed to the nearest 0.1 mg. After oven drying (105°C for 48 h) to determine water content, the samples were extracted in 0.75 *N* nitric acid. Electrolytes were measured in the supernate: Ca^{++} and Mg^{++} by atomic absorption spectrophotometry (16), Na^{+} and K^{+} by flame photometry, and Cl^{-} by potentiometric titration (17). In addition, measurements in plasma of Na^{+}, K^{+}, Cl^{-}, phosphate, urea nitrogen, creatinine and glucose, and arterial pH, P_{O_2}, P_{CO_2} and bicarbonate were made at the time acute renal failure was diagnosed and at frequent intervals thereafter.

RESULTS

EEG recordings were done on 16 patients during the course of acute renal failure and after recovery of renal function. The mean±SE age of these patients was 54±5 yr. Because of the substantial mortality, all patients were not studied at each interval. As shown in Fig. 1, the EEGs of all patients were grossly abnormal when the diagnosis of acute renal failure was first established. The percent EEG power < 5 Hz, which is a standard measurement of the percentage of total EEG power devoted to abnormal slow waves, was 41±8%±SE. The comparable value in a normal population (10 subjects) with a similar age distribution (50–60 yr) was 2±1% ($P < 0.001$).

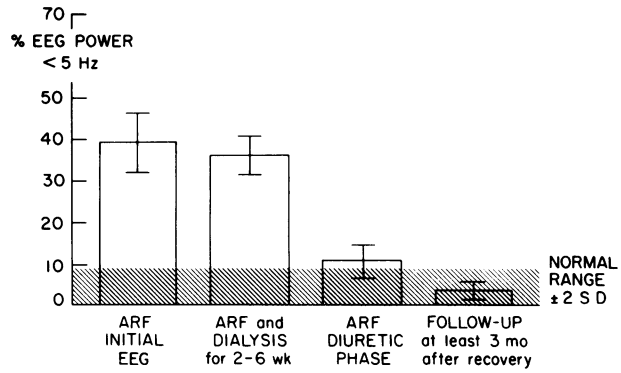

FIGURE 1 Percent EEG power less than 5 Hz in 16 patients with acute renal failure (ARF). The normal range is shown in the cross-hatched area. In patients with ARF, there is a highly significant increase in the percent EEG power below 5 Hz, which is an indicator of the presence of abnormal slow waves. This is not affected by dialysis, but becomes normal with return of renal function.

After treatment with dialysis for 2–6 wk, despite the fact that all patients were well dialyzed by conventional criteria, there was essentially no significant improvement in the EEG (percent EEG power < 5 Hz = 36±5%) (Fig. 1).

Before the last dialysis prior to the diuretic phase of acute renal failure, all patients had BUN less than 70 mg/dl, serum creatinine below 6 mg/dl, and plasma bicarbonate above 18 meq/liter. The serum Ca^{++} and PO_4^{---} were 9±0.3 mg/dl and 4±0.8 mg/dl, respectively. However, when the patients entered the diuretic phase of acute renal failure, within 36 h there was a highly significant ($P < 0.01$) improvement in the EEG (percent power < 5 Hz = 12±4%), so that both the percent EEG power < 5 Hz, and the percent of frequencies > 9 Hz were not different ($P > 0.1$) from normal values (Figs. 1 and 2).

Studies of MNCV were done on 10 patients with acute renal failure. When compared to the values for age-matched controls, there were no significant changes observed during the course of their acute renal failure. When the diagnosis of acute renal failure was first established (2.8±0.4 days), the MNCV was 42±2 m/s, which was not different from that of normal age-matched controls (47±4 m/s). When these patients had been treated with hemodialysis for at least 2 wk, the MNCV was 40±2 m/s, again not different from normal. Neither the MNCV studies done during the diuretic phase of acute renal failure (44±2 m/s), nor those done at least 3 mo after recovery from acute renal failure (40±2 m/s) were different from normal values.

[3] PTH measurements were done by Smith Kline Clinical Laboratory, Inc., Burlingame, Calif.

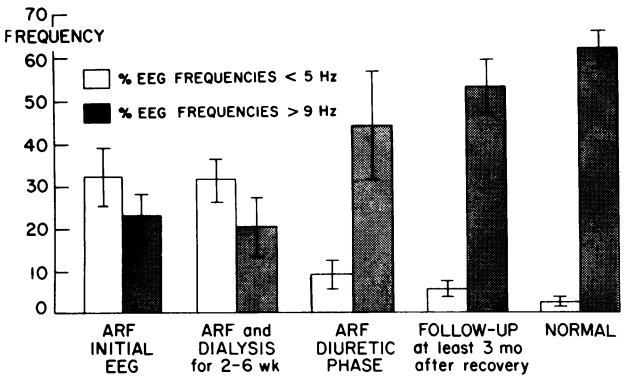

FIGURE 2 Percent of EEG frequencies below 5 Hz, and above 9 Hz. The normal values are on the right. In patients with acute renal failure (ARF), there are significant changes in both those frequencies above 9 Hz and those below 5 Hz. These changes are unaffected by dialysis, but become normal with return of renal function.

To determine possible causes of the observed EEG abnormalities, studies of brain Na^+, K^+, Cl^-, Mg^{++}, Ca^{++}, and water content were done in 10 of the patients who died with acute renal failure. In these 10 patients, the time±SE from onset of renal failure to death was 9.4±3.1 days. As shown in Table I and Fig. 5, there was a highly significant increase in brain content of calcium (Ca^{++}) when compared to nine age-matched control patients who died without renal failure, parathyroid disease, or cancer. In brain gray matter, Ca^{++} content±SE in patients with acute renal failure was 46.5±3.2 meq/kg dry wt (normals = 27.0±1.0 meq/kg dry wt, $P < 0.001$). Brain magnesium (Mg^{++}) content was not different from normal values in either white or gray matter (Fig. 3). As shown in Table I, Na^+ content of brain gray matter was significantly less in patients with acute renal failure than in the control group ($P < 0.05$). There were also significant decrements in brain white matter content of Na^+ ($P < 0.05$) and Cl^- ($P < 0.01$) when compared to normal values (Table I). Neither K^+ nor water content were different in acute renal failure patients versus age-matched controls (Table I).

TABLE I
Effects of Acute Renal Failure (ARF) on Brain Electrolyte Content in Man

			H_2O	Na^+	K^+	Cl^-	Ca^{++}	Mg^{++}
			g/hg wet wt		*meq/kg dry wt*			
Gray matter								
Mean	Normal	(9)	85.84	691	312	598	26.9	62.7
±SE			0.57	36	16	64	1.0	2.2
Mean	ARF	(10)	85.39	555*	315	444	46.5‡	64.4
±SE			0.56	41	17	38	3.2	2.4
White matter								
Mean	Normal	(9)	71.34	225	163	198	10.1	30.3
±SE			0.84	16	10	18	1.4	2.6
Mean	ARF	(10)	71.04	171*	161	133§	13.8	27.6
±SE			0.56	14	12	13	1.0	2.7

* $P < 0.05$ vs. control.
‡ $P < 0.001$ vs. control.
§ $P < 0.01$ vs control.
( ) = No. of patients.

Possible reasons for the striking elevations in brain Ca^{++} were then investigated, including measurements of serum PTH activity. 12 patients with acute renal failure had serum PTH determinations done when the diagnosis of acute renal determinations was first established. There was a significant increase in serum PTH in the acute renal failure patients to 3.2±0.6 ng/ml (normal < 1.5 ng/ml, $P < 0.01$), as shown in Fig. 4. Serum Ca^{++} in these same patients (±SD) was 7.6±1.0 mg/dl, which is significantly less than normal (9.6±0.6 mg/dl, $P < 0.01$), and serum PO_4^{---} was 5.6±1.0 mg/dl (normal = 3.8±0.4 mg/dl, $P < 0.01$).

Because elevations in serum (Ca^{++}) (PO_4^{---}) product may produce calcifications in many soft tissues, studies were undertaken to determine any possible relationship of the serum (Ca^{++}) (PO_4^{---}) product to brain Ca^{++} content in our patients. Measurements of brain Ca^{++} were compared to plasma (Ca^{++}) (PO_4^{---}) product in nine patients who had died of various causes (other than cancer) and who had normal renal and parathyroid function, in six patients with chronic renal failure who had died of various causes, and in nine patients who had died during the course of acute renal

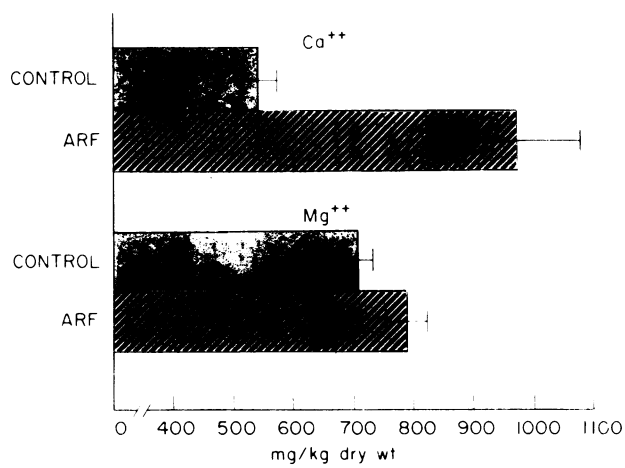

FIGURE 3 The brain (cortical gray matter) Ca^{++} and Mg^{++} content in 9 normal subjects and 10 patients with acute renal failure (ARF). There is a highly significant increase of brain Ca^{++} in patients with ARF ($P < 0.001$), but brain Mg^{++} is unaffected. (Ca^{++} = 20.04 mg/meq and Mg^{++} = 12.16 mg/meq.)

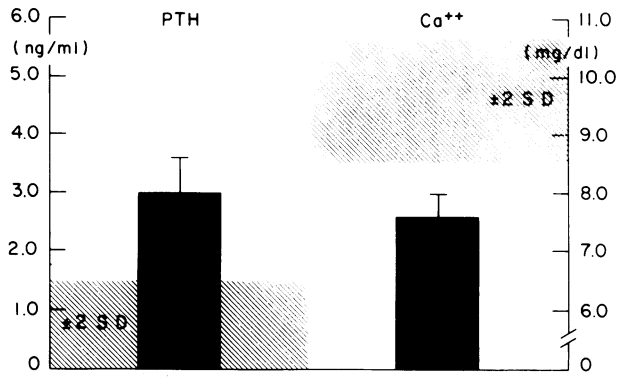

FIGURE 4 Plasma levels of parathyroid hormone (PTH) and Ca^{++} in patients with acute renal failure (ARF). PTH levels are more than twice the upper limit of normal ($P < 0.01$) and plasma Ca^{++} is significantly less than normal ($P < 0.01$). The shaded areas show normal ranges for Ca^{++} and PTH.

failure. In each case, the highest serum (Ca^{++}) (PO_4^{---}) product during the hospitalization before death was noted and the results are shown in Fig. 5. There was no significant correlation between brain Ca^{++} content and plasma (Ca^{++}) (PO_4^{---}) product in these 24 patients ($r^2 = 0.14$, $P > 0.05$).

DISCUSSION

These studies show that in patients with acute renal failure, there are marked abnormalities in the EEG at a time when there are only minimal changes in those blood chemistries which are commonly used as clinical markers of renal function (serum urea and creatinine). Associated with the EEG abnormalities are substantial elevations in plasma PTH levels accompanied by significant increases in brain content of Ca^{++}. The initially abnormal EEG findings are not altered by hemodialysis, but approach normal values during the diuretic phase of acute renal failure, and are completely normal 3 mo after return of renal function. Acute renal failure, in contrast, did not have a significant effect on MNCV.

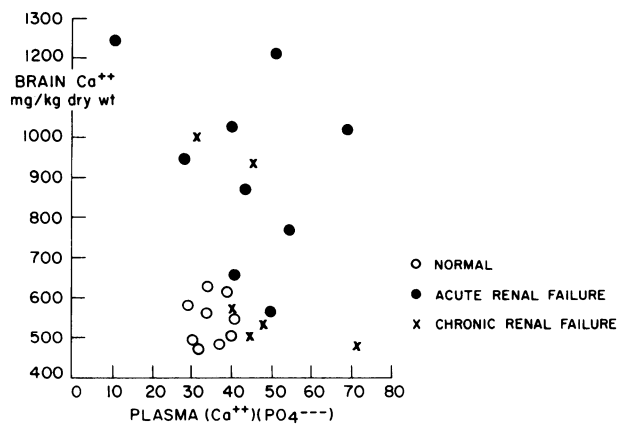

FIGURE 5 The relationship between brain Ca^{++} content and plasma (Ca^{++}) (PO_4^{---}) product in 24 patients. There is no significant correlation ($r = 0.37$; P = NS).

The exact causes of the EEG changes in these patients with acute renal failure are not clear. Previous studies have shown that in patients with either acute or chronic renal failure, similar EEG changes can not be related to any number of abnormalities in commonly measured blood chemistries (2, 8). The EEG abnormalities may in some manner be related either to the acute elevation of plasma PTH (Fig. 4) or to concomitant increases in brain Ca^{++} content (Fig. 3). Previous studies in both patients (18, 19) and laboratory animals (20) with acute renal failure have revealed elevated levels of PTH, but not this soon after the diagnosis. Data from the present study show evidence of elevated PTH levels in patients less than 48 h after the onset of acute renal failure (Fig. 4).

In experimental animals, the EEG abnormalities induced by injections of parathyroid extract are similar to those associated with acute renal failure (10, 21). In previously parathyroidectomized dogs with acute renal failure, the EEG is essentially normal (10). There are several recent studies which relate brain Ca^{++} content to PTH and EEG changes. After 3 days of either acute renal failure or PTH injection in dogs, brain Ca^{++} is elevated and the EEG is abnormal (10, 21). After cessation of the PTH injections for 5 days, both brain Ca^{++} and the EEG have returned to normal (21). This situation may be analogous to normalization of the EEG with recovery of renal function in patients with acute renal failure (Figs. 1 and 2). In chronic states of PTH excess, the situation is different. In patients with hyperparathyroidism, brain Ca^{++} is elevated (22); the EEG is abnormal (22, 23) and improves toward normal after parathyroidectomy, but not for several months (22). In these patients, then, the EEG is abnormal although PTH levels are in the normal range (22). It is a reasonable assumption that brain Ca^{++} might return toward normal more rapidly in patients whose acute renal failure (and acute hyperparathyroidism) is relieved than in patients with long standing hyperparathyroidism. Thus, the EEG changes may actually correlate best with changes in brain Ca^{++} content.

Our patients (Figs. 1 and 2) had normal EEGs during the diuretic phase of acute renal failure. The most likely explanation is that with amelioration of the uremia, brain Ca^{++} rapidly returned toward normal. Parathyroid hormone levels were not evaluated during the diuretic phase of the acute renal failure in the present study. However, both renal excretion and renal metabolism are major routes for disposal of PTH (24, 25). It is possible that with the onset of the diuretic

phase of acute renal failure, plasma PTH levels might rapidly return toward normal.

There are very few measurements of brain electrolytes in man, which is due in part to the difficulties in obtaining suitable tissue samples. Also, human brain samples will usually be obtained at least 24 h post mortem. Our values for normal human brain are very similar to those reported by other investigators for H_2O, Na^+, K^+, and Cl^- (26), and Ca^{++} and Mg^{++} (26–28).

Several additional lines of evidence suggest that the EEG abnormalities in patients with acute renal failure may be related to elevations of brain Ca^{++} content. (*a*) Studies in animals have shown that hemodialysis results in a fall of brain Ca^{++} content (11). (*b*) In the present study, brain Ca^{++} content in patients treated for at least 6 mo with hemodialysis (32.2±1.6 meq/kg dry wt) was significantly less ($P < 0.025$) than that in patients with acute renal failure 46.5±3.2 meq/kg dry wt). (*c*) The EEGs in patients with chronic renal failure treated with dialysis tend to approach a normal pattern (6–9), whereas those in patients with acute renal failure are grossly abnormal (8) (Figs. 1 and 2).

Factors other than hyperparathyroidism and acute renal failure which might contribute to the observed EEG abnormalities include coexisting hypoxia, hyponatremia, hypoglycemia, and advanced liver disease (29). However, EEGs on patients who had such contributing factors were not included in this study. Furthermore, previous studies in animals (10) have shown that neither changes in systemic acid base balance nor plasma electrolytes could account for the EEG changes observed in acute renal failure. Cerebral edema may also produce EEG abnormalities. However, brain water was normal both in our patients (Table I) as well as in others with acute renal failure (30).

Changes in brain electrolytes other than Ca^{++} might also affect the EEG. In the patients with acute renal failure, brain content of K^+, Mg^{++}, and water were similar to normal values (Table I). Brain content of Na^+ was significantly less than normal (Table I). This also has been observed in dogs with acute renal failure (17). However, similar EEG changes are observed in hyperparathyroid but nonazotemic dogs, in whom brain Na^+ is normal (10). The significance of the depressed brain Na^+ in uremic subjects is not known at this time.

A normal EEG depends on the integrity of both cerebral cortex and deeper brain structures, and most metabolic abnormalities which depress sensorium will also affect the EEG in a parallel manner (29, 31). Other causes of coma do not generally produce diffuse slowing of the EEG, so that such findings usually indicate a severe cerebral metabolic disturbance.

The exact cause of the elevated levels of PTH in our patients with acute renal failure is not fully elucidated. It has previously been suggested that either phosphate retention (32), a primary resistance to the skeletal action of PTH (18), or a deficiency of one of the active metabolites of vitamin D (33) might be contributing factors. Any of these conditions could lead to a fall in plasma Ca^{++} concentration, resulting in an increase in plasma PTH levels. There is also some recent data which suggests that impaired renal degradation of PTH plays a role in the elevated plasma PTH levels seen in patients with renal failure (24). All of the aforementioned conditions were probably present in our patients, and the experimental design does not permit further elucidation of the cause of the elevated PTH levels.

The exact mode of action of PTH on brain tissue is not known. Other studies suggest that an elevation in the plasma (Ca^{++}) (PO_4^{---}) product can lead to soft tissue calcification (34). Such a sequence is highly unlikely in the present study for several reasons: (*a*) There was no correlation ($r^2 = 0.14$, $P > 0.05$) between the brain Ca^{++} content vs. the plasma (Ca^{++}) (PO_4^{---}) product in nine normal subjects and 15 patients with renal failure (Fig. 5); (*b*) Most of our patients were hypocalcemic (Fig. 4); (*c*) The mean (Ca^{++}) (PO_4^{---}) product in our patients with renal failure (Ca^{++} = 7.6 mg/dl; PO_4^{---} = 5.6 mg/dl) did not exceed normal values. In addition to the brain, PTH has been shown to enhance entry of Ca^{++} into several tissues, including myocardium (35), aorta (36), cornea (37), lung (11, 38), and renal cortex (11, 39).

PTH appears to have an effect on the permeability of several cell membranes to Ca^{++} (40), and this action may play a role in the increased tissue Ca^{++} content observed in hyperparathyroid states. There are at least two channels whereby Ca^{++} can enter cells (41). In one of these, depolarization of the cell membrane can occur as a consequence of interaction of PTH with a receptor site, leading to activation of membrane-bound adenyl cyclase. This would lead to a resultant increase of intracellular cyclic AMP with possible inhibition of phosphodiesterase (41). There are in brain several Ca^{++} binding phosphoproteins, adenyl cyclose, and a phosphodiesterase (42). The resultant membrane depolarization will lead to an increase in permeability of the potential-dependent Ca^{++} channel, with a subsequent rise in intracellular Ca^{++} content (41).

The normal intracellular free Ca^{++} concentration in brain as well as other neural tissues is probably less than 10 μmol/liter (41, 43). There are a large number of Ca^{++} mediated processes in neural cells (neurotransmitter activity, substrate transport, protein synthesis) (41) and alterations of intracellular Ca^{++} content could interfere with any of these processes, which might in part account for the observed EEG changes.

The MNCV in our patients was not affected by acute renal failure (Fig. 4). In one study of motor nerve func-

tion in a patient with acute renal failure, MNCV was normal (5) with minimal elevation in the threshold of excitability, although there was evidence of segmental damage to the Schwann cell-myelin sheath. Thus, MNCV may be too crude a functional test to evaluate minimal changes in peripheral nerve function (1, 3). However, our data suggests that neither a specific "uremic toxin" nor the presence of a uremic environment (44) is enough to cause acute measurable alterations in MNCV (45). It appears, rather, that progressive anatomical nerve damage (segmental demyelination, decrease in axis cylinder diameter, axonal degeneration) is largely responsible for uremic peripheral neuropathy (4, 46). Because such changes usually take several months to occur, it is perhaps not surprising that our acute renal failure patients had no impairment in MNCV.

In general, it appears that in patients with acute renal failure for less than 48 h there are elevated plasma PTH levels. Accompanying the high PTH levels are an increased brain Ca^{++} content and an abnormal EEG. The EEG is unaffected by dialysis but returns to normal with return of renal function (Figs. 1 and 2). It is unlikely that an elevated brain Ca^{++} is the only biochemical abnormality in the brain which contributes to an abnormal EEG in patients with renal failure. Many other neurochemical alterations have been described in the brain of animals with acute renal failure (1, 3). It is probable that other mechanisms also contribute to the EEG abnormalities observed in patients with acute renal failure, but demonstration of such factors is at present lacking. Thus, PTH may be a major uremic toxin, showing evidence of possible central nervous system toxicity when there are only minimal abnormalities of other biochemical markers of acute renal failure.

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