6. UREMIC TOXINS

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INTRODUCTION

Uremic manifestations are unanimously regarded as a consequence of the accumulation of waste products of protein (PR) metabolism ("uremic toxins") that probably exert their toxic effects by inhibiting enzymatic activities [1].

No single metabolite known to accumulate in chronic renal failure (CRF) can be considered the sole cause of uremic manifestations, but many of them (if not all), together with metabolic and hormonal derangements [2, 6], as well as an abnormal electrolyte pattern [7] and altered metabolic and hormonal activities of kidneys, [8, 11] probably contribute to cause uremia. Secondary hyperparathyroidism (HPTH) plays a key role in this context, and parathyroid hormone (PTH) has been referred to as a "uremic toxin" [12, 14]. HPTH is indeed an early complication of CRF, but this is not an adequate basis for considering PTH a "uremic toxin," since the uremic syndrome may appear even in parathyroidectomized patients.

The following survey of "uremic toxins" will be restricted exclusively to the organic waste products of PR metabolism. Their importance is clearly indicated by the fact that the severity of the uremic syndrome is directly related to the degree of retention of PR metabolites. This has been confirmed even recently by the studies on urea accumulation in patients on maintenance hemodialysis (MHD) [15].
UREA

Urea (UR) is the most abundant important PR metabolite and its production increases with a high dietary PR intake as well as in catabolic conditions. It easily diffuses to and from the body fluid compartments and is considered the least toxic PR metabolite.

However, UR given intravenously to normal dogs in doses that raise its serum levels to 600–800 mg/dl causes drowsiness [16]. Nephrectomized dogs on peritoneal dialysis (PD) showed an accelerated uremic syndrome and died within 1 week when UR was added to the dialysate [17]. Uremics on MHD, in whom very high UR levels were obtained by adding it to the dialysate, showed malaise, apathy, drowsiness, and glucose intolerance [18]. These toxic effects have been attributed to the cyanate resulting from oxidation of UR [17]. This is indeed toxic, but only at serum concentrations much higher than those found in uremics [19]. Carbohydrate intolerance was found in normal dogs [20] and in healthy volunteers [21], as well as in patients with mild renal failure submitted to an oral load of UR [2].

Finally, ammonia originating in the oral cavity from bacterial urease activity is certainly responsible for halitosis and probably for stomatitis, and possibly contributes also to the anorexia, nausea, and vomiting of the uremic state.

The opinion that UR is a non toxic metabolite should thus be reconsidered.

CREATININE

Creatinine (CR) originates from the nonenzymatic dehydration of creatine and phosphocreatine in muscle tissue and is excreted, almost exclusively, with urine in amounts directly related to the lean body mass in persons with normal renal function. In CRF patients, the urinary output of CR decreases with the increase in extrarenal clearance occurring in the intestinal fluids due to its bacterial degradation (see Chapter 2) [22–23].

CR is not regarded as an important uremic toxin. Indeed, if injected intravenously to normal persons in doses that raise serum levels up to 100 mg/dl for short periods of time, CR does not cause appreciable disturbances [24].

However, if given by mouth to patients with early renal failure, who are unable to eliminate it rapidly, CR causes impairment of the oral glucose tolerance test [2]. When added in vitro to normal blood samples in amounts that raise the CR concentration to levels that are found in severe CRF, it enhances spontaneous autohemolysis [25] and, when injected intravenously to normal dogs, CR shortens their red-cell survival [26]. Finally, when added to the Krebs-bicarbonate buffer, it inhibits glucose uptake by rat hemidiaphragm in vitro [2].

GUANIDINES

Methylguanidine (MG) is a very strong organic base originating from the non-enzymatic oxidation of CR [27, 28] and perhaps from arginine. MG is retained in renal failure, and its accumulation is aggravated by an increase of its metabolic production [29], due to a high body pool of its main metabolic precursor