Creatinine metabolism in chronic renal failure

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Summary

1. Creatinine metabolism was studied in nine patients with severe chronic renal failure who were nevertheless in a nearly steady state with respect to their creatinine pool. Labelled creatinine was injected intravenously and the specific radioactivity of creatinine in urine was measured during the ensuing 5–7 days.

2. In each patient, the decline in specific radioactivity with time was a single exponential function after 12 h. The volume of distribution of creatinine averaged 49.1 ± 2.8% body weight. The average rate of creatinine production was 148 μmol day⁻¹ kg⁻¹, which is similar to predicted values for normal subjects of the same age, weight and sex. Creatinine metabolism rate/kg body weight, estimated as the difference between production rate/kg body weight, determined radioisotopically, and creatinine appearance rate (excretion plus accumulation), averaged 42 μmol day⁻¹ kg⁻¹.

3. Total creatinine metabolism rate/kg body weight was correlated with serum creatinine. Thus, as serum creatinine rises, an increasing fraction of the produced creatinine was metabolized rather than excreted. This relationship could account for the diminished creatinine excretion commonly seen in patients with chronic renal failure.

4. Extrarenal clearance (metabolism/serum creatinine) of this magnitude (approximately 31% of renal clearance in these patients) would be an undetectably small fraction of normal renal clearance. This could explain the absence of demonstrable creatinine metabolism in normal subjects.

5. Two pathways of metabolism were identified: a recycling of creatinine to creatine and an irreversible degradation of creatinine to products other than creatine.

Key words: chronic renal failure, creatine, creatinine metabolism.

Introduction

The fraction of the creatine pool which is converted into creatinine has been shown to be remarkably constant, presumably because of the non-enzymatic formation of creatinine from creatine (Crim, Calloway & Margen, 1976). Creatinine production should therefore reflect the body creatine pool. Changes in the creatinine pool and hence in creatinine excretion can occur with changes in dietary creatine, intake of arginine or glycine (Bleiler & Schedl, 1962; Crim, Calloway & Margen, 1975; Crim et al., 1976), or with a change in lean body mass (Fitch & Sinton, 1964). Creatinine excretion can also change when the dietary content of cooked meat, containing preformed creatinine, is altered (Camara, Arn, Reimer & Newburgh, 1951).

Decreased creatinine excretion is regularly observed in chronic renal failure, even at serum creatinine concentrations as low as 0.35–0.5 μmol/1 (Goldman, 1954; Effersoe, 1957; Doolan, Alpen & Theil, 1962; Enger & Blegen, 1964).
Although various explanations for this observation have been suggested, the possibility that creatinine metabolism could account for it was suggested by Jones & Burnett (1974). In a study of eight uraemic patients, including three anephric subjects who were accumulating creatinine rapidly, these workers observed the decline of specific radioactivity of plasma creatinine for the first 2–4 days after feeding or injecting labelled creatinine. They concluded that 16–66% of creatinine produced was metabolized or excreted via extrarenal routes. From results of incubation of creatinine with colonic flora, they suggested that conversion of creatinine into creatine and other degradation products by intestinal bacteria might be a major route of creatinine metabolism in renal failure (Jones & Burnett, 1975).

We have recently measured creatinine appearance, defined as the rate of excretion plus accumulation of creatinine, in 27 patients with renal failure of various degrees of severity. The rate of creatinine appearance was lower than expected from estimated rates of creatinine production of subjects of the same age, sex and weight who did not have chronic renal failure. We postulated that a small, constant extrarenal clearance of creatinine could account for the fall in appearance in these patients, since the appearance of creatinine was lower in those patients with a higher serum creatinine concentration (Mitch & Walser, 1978).

To pursue this hypothesis, we have studied the kinetics of labelled creatinine in severely uraemic patients who were in a nearly steady state in respect of creatinine. The production rate of creatinine was estimated from the disappearance curve of injected labelled creatinine. Creatinine metabolism was estimated as the difference between creatinine production and creatinine appearance and the relationship between creatinine metabolism and serum creatinine was examined.

**Methods**

Ten adults with severe chronic uraemia who were not receiving haemodialysis were studied. The patients gave informed consent for the use of nitrogen-free analogues of essential amino acids, injection of [14C]creatine, and the collection of urine and blood. Patients nos. 4 and 7 were females. The studies were performed under metabolic balance conditions as previously described (Mitch, Lietman & Walser, 1977). All patients had been eating protein-restricted diets for at least 2 months before the study. Two patients were receiving essential amino acid supplements (total nitrogen intake 4-7 g/day) and five were receiving a mixture of keto- or hydroxy-analogues of five essential amino acids and the four remaining essential amino acids as such (total nitrogen intake 3-6 g/day) (Mitch et al., 1977) as supplements to their daily intake of 20–25 g of protein. Two patients were eating protein (6-0 g of nitrogen/day) without supplements. Patient no. 1 was taking one Bactrim tablet daily in an attempt to suppress infection of his remaining kidney, which was drained by a nephrostomy tube placed in the renal pelvis.

[14C]Creatinine (Amersham Corporation, Arlington Heights, Illinois, U.S.A.) was dissolved in sodium chloride solution (0-15 mol/l: saline) and a portion was tested for sterility and pyrogenicity. The remainder was stored at -20°C until use. [14C]Creatinine (12 μCi) was diluted in 30 ml of saline, and exactly 25 ml of the solution was injected intravenously. The remaining 5 ml of solution was stored at -20°C and subsequently used for internal standardization in the counting of radioactivity in that patient’s sample.

It was assumed that urine and plasma specific radioactivities were identical. In patients with a low creatinine clearance, 'excess excretion' of creatinine should be negligible, as it is for urea (Robson, 1964).

At the time of injection of [14C]creatine, the patient emptied his bladder. Subsequent urine was collected by having the patient attempt to empty the bladder every 30 min into a flask containing thymol. This procedure was repeated until at least 75 ml of urine was collected. The duration of these collections varied from 1 to 3.5 h. Collections were repeated once or twice a day for 5–7 days after the injection. The procedure was slightly different for patient no. 1. At the beginning of each timed urine aliquot, the collection bag attached to his nephrostomy tube was replaced by a new bag containing thymol and at least 75 ml of urine was collected. The volume of each aliquot was then measured, the aliquot was stored at 4°C, and the 24 h urine collection was continued.

All urine samples were acidic (pH 5–6). The specific radioactivity of urinary creatinine was determined in each aliquot. Creatinine was isolated as the phosphotungstate salt after its absorption on to Lloyd's reagent (Bloch & Schoenheimer, 1939). The amount of creatinine isolated was measured colorimetrically after its reaction with picric acid and the radioactivity was determined by liquid scintillation counting. The logarithm of the
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Creatinine specific radioactivity of each aliquot was then plotted against the midpoint time for each patient. (The theoretically correct time is not the midpoint time of each collection but rather the logarithmic mean time. However, since the collections were only of about 2 h duration, this refinement was unnecessary.) The first urine sample collected usually reflected incomplete equilibration. The points from 12 h after injection were analysed by log linear regression to give specific radioactivity at the time of the injection. The creatinine pool size on the day of injection was calculated from the initial specific radioactivity of urine creatinine and the μCi of [14C]creatinine injected.

The slope of the linear regression of the logarithm of specific radioactivity on time is the turnover rate of the pool. The product of turnover rate and the initial pool size is the daily creatinine production rate. The confidence limits of production were computed for each patient by using a computer program as previously described (Halperin & Walser, 1957).

The early portion of the disappearance curve was obtained from the radioactivity and creatinine concentration of plasma samples taken 2 and 4 h after [14C]creatinine injection. Plasma creatinine specific radioactivity was not measured more than 4 h after the injection because the plasma radioactivity might contain an increasing proportion of compounds other than creatinine.

During the study, daily 24 h creatinine excretion (corrected for aliquots removed), and serum creatinine concentration were measured with the aid of an Autoanalyzer. Creatinine appearance rate/kg body weight was then calculated as the algebraic sum of average creatinine excretion rate/kg body weight and the change in creatinine pool size, derived as follows: the creatinine pool size was estimated daily by multiplying the creatinine concentration in serum water by the volume of distribution. The initial volume of distribution was computed as the algebraic sum of average creatinine excretion rate/kg body weight and appearance rate is the rate of creatinine metabolism/kg body weight.

Two of the patients in this series (nos. 3 and 9) and an additional 75-year-old male with a creatinine clearance of 0.13 litre day⁻¹ kg⁻¹ were studied further to determine if creatinine could be converted into creatine. Daily 24 h collections were obtained after injection of [14C]creatinine (10 μCi) and stored at 4°C. Approximately 500 ml aliquots of urine from days 3–6 were acidified to pH 3 with HCl and then placed on a column containing Dowex 50 resin (Na⁺, 100–200 mesh). Five hundred millilitres of sodium citrate buffer (0.2 mol of Na⁺/l, pH 3.4) were then added to the column and the eluate was discarded. Creatine was then eluted with 200 ml of citrate buffer (0.05 mol/l, pH 5) (Picou, Reeds, Jackson & Poulter, 1976). After regeneration of the column, the procedure was repeated, and the final eluate was concentrated by evaporation under reduced pressure. Reaction with picric acid did not yield measurable creatinine. Tests with labelled creatinine showed that more than 98.5% of creatinine was retained on the column, and tests with labelled creatine showed that a similar amount was eluted by this procedure. The creatine present was dehydrated to creatinine by heating at pH 1 (Fitch & Sinton, 1964). The resulting creatinine was isolated as described above and its specific radioactivity determined.

Results

Glomerular filtration rate, estimated as the average of urea and creatinine clearances (Milutinovic, Cutler, Hoover, Meijsen & Scribner, 1975), averaged 0.099 ± 0.014 litre day⁻¹ kg⁻¹ (range 0.031–0.187 litre day⁻¹ kg⁻¹); renal creatinine clearance (Table 1) averaged 0.123 + 0.018 litre day⁻¹ kg⁻¹.

The logarithmic decline in time of urine creatinine specific radioactivity for each patient is shown in Fig. 1. Plasma creatinine specific radioactivity between 2 and 4 h after injection was measured indirectly (see the Methods section) and is also shown. The plasma values lie close to the regression line derived from the measured urine creatinine specific radioactivities. The kinetics of creatinine (or any other metabolite) are multi-compartmental (Shipley & Clark, 1972), but the
## Table 1. Summary of creatinine metabolism in patients with chronic renal failure

Values for weight, serum creatinine and renal clearance, rates of production, renal excretion, accumulation, appearance, metabolism and extrarenal clearance of creatinine are average values. The values in parentheses are the 95% confidence limits of the measurements shown.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Serum concn. (μmol/l)</th>
<th>Renal clearance (litre day(^{-1}) kg(^{-1}))</th>
<th>Volume distribution (l)</th>
<th>Creatinine (μmol day(^{-1}) kg(^{-1}))</th>
<th>Creatinine extrarenal clearance (litre day(^{-1}) kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>68.3</td>
<td>1648</td>
<td>0.039</td>
<td>32-36</td>
<td>132.6 (115.8-148.5)</td>
<td>73 (48.6-68.1)</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>61.6</td>
<td>486</td>
<td>0.239</td>
<td>27-23</td>
<td>137-9 (126.4-150.3)</td>
<td>116.3 (104.3-116.7)</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>61.8</td>
<td>1176</td>
<td>0.100</td>
<td>37-59</td>
<td>192-7 (170-6-215-7)</td>
<td>118 (97.3-111-4)</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>70.2</td>
<td>822</td>
<td>0.122</td>
<td>24-05</td>
<td>111-4 (105-2-118-5)</td>
<td>99.9 (98.1-103-4)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>61.4</td>
<td>990</td>
<td>0.119</td>
<td>32-93</td>
<td>117-6 (106-1-128-2)</td>
<td>117.6 (115-8-144-1)</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>71.2</td>
<td>698</td>
<td>0.167</td>
<td>40-38</td>
<td>142-4 (134-3-153-0)</td>
<td>116.9 (109-6-125-6)</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>58.9</td>
<td>1034</td>
<td>0.128</td>
<td>26-18</td>
<td>161-8 (141-5-184-8)</td>
<td>132-1 (110-5-135-3)</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>81.5</td>
<td>1441</td>
<td>0.077</td>
<td>45-42</td>
<td>181-3 (149-4-209-5)</td>
<td>110.3 (87.5-124-7)</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>61.1</td>
<td>1026</td>
<td>0.121</td>
<td>27-46</td>
<td>153-0 (145-0-159-2)</td>
<td>124 (111-4-129-1)</td>
</tr>
</tbody>
</table>
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absence of a large additional exponential term in
the early disappearance curve of creatinine indicates that the error arising from applying a one-

compartment model is negligible. The linearity of
the relationship for each patient indicates that the
injected $^{14}$C-creatine had mixed uniformly with
the creatinine pool and that creatinine was being
formed and eliminated at equal and constant rates.
The slope and intercept of the linear regression line
for each patient were calculated and production
rates and volume of distribution estimated. Table 2
shows measured and derived data from a repre-
sentative experiment (patient no. 6).

The rate of accumulation of creatinine varied
from $-14.6$ to $11.5\ \mu mol\ day^{-1}\ kg^{-1}$. In only one
patient (patient no. 3) was there a statistically
significant change of the creatinine pool. In this
patient, renal function improved progressively for
unknown reasons; hence creatinine accumulation
was a negative quantity. The absolute value of
accumulation averaged $1.4 \pm 0.3\%$ of the
creatine pool, calculated as the product of serum
creatinine and the volume of distribution of
creatinine. Thus these patients were virtually in a
steady state with respect to their creatinine pool.

The volume of distribution of creatinine in these
patients averaged $49.1 \pm 2.8\%$ of body weight.
Patient no. 4 had a creatinine space of $34\%$ of body
weight which may be related in part to her obesity.
Urea space measurements in obese patients with
chronic renal failure are also occasionally lower
than expected (Walser, 1974).

The creatinine production rates and their 95%
confidence limits are shown in Table 1. The limits
were calculated from the variance of both the slope

TABLE 2. Original and derived data in a representative experiment
Regression of log, specific radioactivity on time: slope, $-0.387 \pm 0.018$; intercept,
$0.3800\ nCi/\mu mol$. Volume of distribution: $40.38$ litres; $(10000\ nCi\ dose/\text{intercept})/
(\text{serum creatinine}/0.95)$. Creatinine production: $10.17\ mmol/day$; $(10000\ nCi\ dose)/\text{(slope)}/(\text{intercept})$. Regression creatinine pool on time: slope, $+0.062 \pm 0.177$
mmol/day; the rate of accumulation. Creatinine appearance rate: $8.39\ mmol/day$; the
average excretion rate and accumulation rate. Creatinine degradation: $1.79\ mmol/day$;
the difference between creatinine production and appearance rates.

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Weight (kg)</th>
<th>Creatinine Serum concn./0.95 (μmol/l)</th>
<th>Urine creatinine specific radioactivity (nCi/μmol)</th>
<th>Urine creatinine excretion (mmol)</th>
<th>Creatinine pool (mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>72.20</td>
<td>0.652</td>
<td>8.939</td>
<td>0.2933</td>
<td>26.50</td>
</tr>
<tr>
<td>0.76</td>
<td>71.40</td>
<td>0.698</td>
<td>8.515</td>
<td>0.2011</td>
<td>27.62</td>
</tr>
<tr>
<td>1.04</td>
<td>70.60</td>
<td>0.726</td>
<td>8.090</td>
<td>0.1902</td>
<td>28.16</td>
</tr>
<tr>
<td>1.74</td>
<td>71.05</td>
<td>0.698</td>
<td>6.454</td>
<td>0.0849</td>
<td>26.19</td>
</tr>
<tr>
<td>3.05</td>
<td>70.90</td>
<td>0.670</td>
<td>0.0731</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.05</td>
<td>71.10</td>
<td>0.707</td>
<td>9.629</td>
<td>0.0663</td>
<td>27.78</td>
</tr>
</tbody>
</table>
and the intercept of the regression line by a method which takes into account the strong negative correlation between estimates of these variables (Halperin & Walser, 1975). No apparent differences were detectable in calculated values for creatinine production rates/kg body weight between patients ingesting essential amino acids, the analogue supplements or a low protein diet.

The creatinine appearance rate/kg body weight was 75 ± 4% of production rate and varied from 44 to 100% (Table 1). The 95% confidence limits for the rates of appearance are also shown in Table 1. They were calculated from the error of the average daily creatinine excretion and the error of the rate of accumulation of creatinine, by using the variances of these two quantities. Subtraction of the rate of appearance from the daily production rate of creatinine gives the daily rate of creatinine metabolism. The value of the rate of metabolism for each patient is shown in Table 1 as well as the confidence limits for metabolism. (The upper confidence limit of metabolism was calculated as the upper confidence limit of production minus the lower confidence limit of appearance; the lower confidence limit of metabolism was calculated as the lower confidence limit of production minus the upper confidence limit of appearance. The resulting limits doubtless have a statistical reliability exceeding 95%; the exact reliability is indeterminate.)

Rates of creatinine metabolism varied from 0 to 76 μmol day⁻¹ kg⁻¹, and averaged 25-6% of daily production rates. Patient no. 5 had a calculated creatinine metabolism of −11.5 μmol day⁻¹ kg⁻¹, but because this has no physiological meaning, his rate of metabolism is shown as zero. The reason for this finding is unknown, but may be related to the estimation of metabolism for several measured variables. As expected, the confidence limits of metabolism for patient no. 5 include zero, and as shown in Table 1, the confidence limits for metabolism of patient no. 4 are close to zero but the limits for patients with high rates of creatinine metabolism are not close to zero. This is consistent with our conclusion that creatinine was metabolized by these patients.

Metabolism was positively correlated with production (Fig. 2; y = 0.68x + 119.54, r = 0.78, P < 0.02). This correlation strongly suggests that some portion of metabolized creatinine was contributing to creatinine production. If this inference is correct, then from the slope of the regression line relating production to metabolism it can be estimated that, on the average, 68% of metabolized creatinine was recycled to creatinine, possibly first by forming creatine. To obtain further evidence for this pathway, creatine was isolated from the urine of three patients after an injection of [¹⁴C]creatine. On days 3 and 4, creatine specific radioactivity was 0.043–0.079 nCi/μmol in patients nos. 3 and 10, and on day 6 it was 0.067 nCi/μmol in patient no. 9. Creatine excretion in these patients, estimated as the increment in urine creatinine content after the sample was heated in acid (Fitch & Sinton, 1964), averaged 610, 345 and 566 μmol/day for patients nos. 3, 9 and 10 respectively.

In another experiment, 10 μCi of [¹⁴C]creatine was added to the 24 h urine collection of a patient with renal insufficiency of the same degree as the patients studied. After the urine had been standing 6 weeks at 4°C, no label could be detected in
creatinine, indicating that conversion of creatinine into creatine does not occur spontaneously under these conditions.

Total creatinine metabolism/kg body weight was positively correlated with serum creatinine concentration (Fig. 3; \( r = 0.69, P < 0.05 \)). Thus the quantity of creatinine metabolized increases as serum creatinine rises. Extrarenal clearance (metabolism divided by serum creatinine) averaged 0.038 ± 0.008 litre day\(^{-1}\) kg\(^{-1}\). There was no correlation between renal and extrarenal creatinine clearances or between extrarenal creatinine clearance and creatinine appearance.

**Discussion**

Daily creatinine excretion (\(\mu\)mol/kg) of normal individuals varies considerably (Camera et al., 1951; Kampmann, Siersbæk-Nielsen, Kristensen & Hansen, 1971; Cockcroft & Gault, 1976). However, the average daily excretion, determined from three consecutive daily collections, has recently been shown to be a remarkably precise measure of lean body mass, estimated from whole-body \(40\)\(^K\) (\(S_p/y = 0.05\), where \(y = \) lean body mass) (Forbes & Bruining, 1978). The fact that 90% of body creatine is contained in muscle and that a constant percentage of this pool is converted into creatinine each day by a non-enzymatic mechanism presumably accounts for this relationship. Although Forbes & Bruining (1978) have shown that creatine excretion/kg lean body mass is not influenced by age or sex, creatinine excretion/kg body weight is affected by both (Kampmann et al., 1971; Cockcroft & Gault, 1976). These findings in subjects without chronic renal failure may reflect a loss of lean body mass/kg body weight as age increases, and the fact that lean body mass is a larger percentage of body weight in males than in females.

In addition to lean body mass, creatinine excretion is also influenced by diet. Normal subjects fed with creatine have an expanded creatine pool and increased creatinine excretion (Crim et al., 1976). Similarly, normal subjects placed on a creatine-free diet have a gradual fall in creatinine excretion to values about 70% of those obtained on a normal diet (Bleiler & Schedl, 1962). These changes occur in spite of maintenance of nitrogen balance, suggesting that a change in body creatine content rather than lean body mass has occurred (Bleiler & Schedl, 1962; Crim et al., 1975). Because 1.7% of creatine is converted into creatinine daily, the half-time of approach to a new steady state of creatinine excretion is 0.693/0.017, or 41 days. A more rapid change in creatinine excretion can be observed when the dietary content of cooked meat changes. This occurs because cooking converts preformed creatine into creatinine (Camara et al., 1951). Thus a change in creatinine excretion may not reflect a change in lean body mass if the amount of cooked meat eaten is not constant. In the present study, the diet did not change and could not have contained more than 0.8–2.4 mmol of creatinine, from the data of Camara et al. (1951).

Patients with chronic renal failure are known to have reduced creatinine excretion (Goldman, 1954; Effersøe, 1957; Doolan et al., 1962; Enger & Blegen, 1964; Jones & Burnett, 1974; Mitch & Walser, 1978). We found that, in the most severely affected patients, creatinine appearance may fall to as little as one-third of the value predicted for subjects of the same age, sex and weight who do not have chronic renal failure (Mitch & Walser, 1978). We suggested that this difference could be due to the presence of a small but relatively constant extrarenal creatinine clearance. An alternative explanation is that patients with chronic renal failure are wasted, and that their lean body mass is a smaller fraction of body weight. In a study of 77 patients with chronic renal failure, Coles (1972) found that the ratio of lean body mass to body weight was the same as that of normal subjects. In the present study, measured production rates of creatinine averaged 105 ± 6% of production rates predicted for that of normal subjects of the same age, sex and weight, formulae for production derived by Mitch & Walser (1978) from data of Cockcroft & Gault (1976) being used. This supports the findings of Coles (1972).

Subtraction of the estimated quantity of metabolized creatinine contributing to creatinine production, 0.68 times the rate of metabolism, from the measured production rate/kg body weight, gives an estimate of the average quantity of creatinine synthesis derived from creatine synthesized de novo. This quantity averaged 89% of production estimated from age, sex and weight (Mitch & Walser, 1978). The difference may be related to diminished creatinine and creatine intake rather than altered lean body mass, since these patients had been receiving a low protein diet for months.

An alternative interpretation of the correlation shown in Fig. 2 is that production of creatinine de novo varies between patients and, by virtue of its effect on serum creatinine, is a major determinant.
of metabolism. However, the results show no correlation \( (r = 0.27) \) between production and serum creatinine. Hence, this interpretation seems less likely. Nevertheless, we cannot dismiss this possibility in view of the correlation between metabolism and serum creatinine concentration (Fig. 3).

The present study shows that extrarenal clearance becomes increasingly important in total creatinine clearance as renal clearance declines. The average extrarenal clearance measured in the present study, 0.038 ± 0.008 litre day\(^{-1}\) kg\(^{-1}\), is quite close to the average value (0.041 ± 0.005 litre day\(^{-1}\) kg\(^{-1}\)), which we have previously predicted would be necessary to account for the observed reduction in creatinine appearance in chronic renal failure. Hence, an estimate of lean body mass in uraemic patients can be obtained by adding 0.038 litre day\(^{-1}\) kg\(^{-1}\) to measured renal clearance in the same units, and multiplying this sum by serum creatinine concentration. Creatinine production of patients with chronic renal failure estimated in this way, when compared with that of normal subjects with the same age, sex and weight (Cockcroft & Gault, 1976; Mitch & Walser, 1978), provides an index of lean body mass.

Jones & Burnett (1974) presented evidence for creatinine metabolism in eight patients with chronic renal failure, including three patients who were being dialysed. They fed or injected \(^{14}\)C-creatine and measured changes in the specific radioactivity of plasma creatinine, concluding that 16–66% of creatinine produced was metabolized. This conclusion is in agreement with our results, but a more complete comparison cannot be made for the following reasons. In four of their patients, they used only four specific radioactivity measurements over time periods as short as 40 h to calculate production rates. Only four of their semi-logarithmic plots of creatinine specific radioactivity against time are presented. In three patients who were rapidly accumulating creatinine, production was calculated with the assumptions that rates of production and clearance were constant, but no data were presented to support these assumptions. The rate of accumulation as a percentage of the pool was as high as 72%/day in these three patients. In the remaining patients, accumulation was calculated without taking into account changes in body weight, making it difficult to estimate the stability of the creatinine pool. In the present study, all nine semi-logarithmic plots were linear (Fig. 1) and accumulation varied from 0.5 to 2.7% of the pool/day.

Studies in man (Waterlow, 1977) and animals (Bloch & Schoenheimer, 1939) have indicated that administered creatinine can be recovered quantitatively. However, because normal renal creatinine clearance is about 2.7 litres day\(^{-1}\) kg\(^{-1}\), an extrarenal clearance of approximately 0.04 litre day\(^{-1}\) kg\(^{-1}\) would be undetectable. In fact, some creatinine metabolism must occur in normal subjects, because oral administration of creatinine results in increased excretion of methylguanidine (Gonella, Barsotti, Lupetti & Giovanetti, 1975).

The creatine specific radioactivity of patients nos. 3, 9 and 10 was of a similar magnitude as that of creatinine in patients nos. 1–9 and higher than expected, considering the large size of the creatine pool. As pointed out by Picou et al. (1976), 90% of creatine exists in muscle and the remaining 10% seems to be in another pool with more rapid turnover. Thus creatine derived from creatinine must have mixed first with the smaller pool; excretion from this pool would account for the higher than expected specific radioactivity. Indeed, creatine has been found in the serum of uraemic patients (Lazdins & Dawson, 1978). Our results provide strong evidence that creatinine was directly converted into creatine rather than first being metabolized to other substrates, which would have greatly diluted the \(^{14}\)C, yielding a low specific radioactivity.

The site of creatinine metabolism has not been identified in the present study, but Jones & Burnett (1975) have shown that anaerobic incubation of creatinine with gut flora results in production of creatine, sarcosine, hydantoin, methylamine and unidentified molecules. Gonella, Barsotti, Lupetti, Giovanetti, Campa & Falcone (1976) found similar results when gut flora and creatinine were incubated aerobically. In a previous study (Mitch et al., 1977) we administered oral neomycin and kanamycin to seven patients with severe chronic renal failure and were unable to demonstrate a change in creatinine appearance despite the fact that flora hydrolysing urea were suppressed. Gonella et al. (1976) administered oral para-momycin to uraemic subjects and were also unable to demonstrate a change in creatinine excretion. Although these results suggest that creatinine metabolism may not occur in the gut, a more likely explanation is that the organisms metabolizing creatinine were not suppressed by these antibiotics.

The volume of distribution of creatinine obtained (49.1 ± 2.8% of body weight) agrees with that obtained by other investigators. Jones & Burnett (1974) found that this volume averaged 48.3 ±
that, in estimating creatinine accumulation from serial measurements of serum creatinine, one-half of body weight is an appropriate estimate for the creatinine space. The importance of this observation is 3.0%.

References


