Abstract

Background. The increment in glomerular filtration rate (GFR) after a protein load has been taken to reflect the renal reserve capacity; however, this response is preserved in end-stage kidney disease. Tubular secretion of creatinine is increased in relation to the GFR in renal failure, but little is known about the tubular functional response to stimulation despite the fact that tubulointerstitial lesions are always pre-eminent in chronic renal damage. Therefore we decided to compare the urinary creatinine excretion (U\textsubscript{cr}V) and tubular secretion of creatinine (TS\textsubscript{cr}) induced by a test meal in normal individuals and in individuals with reduced nephron mass.

Methods. We studied 12 normal subjects, seven healthy uninephrectomized (kidney donors) and eight patients with chronic renal disease (serum creatinine ranging from 212.2 to 486 μmol/l). They had been on a standard diet for 5 days before the studies. The test meal provided 80 g of animal protein. Three baseline and four stimulated (post-meal) 30-min simultaneous inulin and creatinine clearances were carried out.

Results. We found that normals increased more than twice the U\textsubscript{cr}V (post-meal = 329.5 ± SEM 13.1 nmol/min/kg) and 3.4 times the TS\textsubscript{cr} (114.4 ± 12.7 nmol/min/kg) after the test meal. In contrast, patients were unable to raise their baseline values (P < 0.001), despite a normal increment in GFR. The data in kidney donors fell between normals and patients. Strong correlation existed between the stimulated (but not the baseline) TS\textsubscript{cr} (P = 0.003) and GFR and between U\textsubscript{cr}V post-meal/pre-meal ratio and GFR (P < 0.0001).

Conclusion. The increment in TS\textsubscript{cr} resulting from a protein meal is related to the functioning nephron mass. Evaluation of this increment could have potential clinical relevance.

Key words: creatinine; nephron mass; protein meal; tubular secretion; uninephrectomy

Introduction

Considerable attention has been given to the increment in glomerular filtration rate after an oral protein load [1–5]. This interest is derived, in good measure, from the possibility that a capacity to respond to stimulation implied a functional reserve that could be summoned after specific physiological demands [6–10]. The loss of this functional reserve could then be the earliest manifestation of significant renal damage and reflect the existence of hyperfiltration in the remaining nephrons [11].

At least three lines of evidence are incompatible with these attractive postulates. First, there is a very large variability in the normal response to a protein challenge. In fact, glomerular filtration rate may be unchanged or, at times, decrease in normal individuals after a protein load [2,7–10]. Second, studies in renal transplant donors have demonstrated a normal increment in inulin clearance after a protein meal [12–14], despite a diminished postprandial creatinine clearance [15,16]. Finally, patients with advanced renal failure in whom a putative functional reserve capacity would clearly be exhausted, are capable of raising normally the filtration rate in the remnant nephron population [17–19].

In contrast to the abundance of investigations concerning the stimulation of glomerular filtration rate, there are no studies, to our knowledge, exploring the possibility of stimulating tubular function and defining a tubular reserve function. Since the participation of tubulointerstitial damage in the progression to end-stage renal disease is increasingly evident [20–23], it is attractive to investigate if tubular function can be stimulated in health and if this characteristic is lost in chronic renal failure. Since the tubular secretion of creatinine is stimulated by a meat meal [24–26] we decided to study this physiological response in normals, in uninephrectomized healthy individuals who were kidney donors for transplantation, and in patients with chronic renal failure of moderate degree. Our results show that tubular secretion of creatinine increases...
several fold after a protein meal in normals, but not in patients with renal disease.

**Subjects and methods**

**Normal individuals and patients**

Studies were done in 12 normal (control) subjects, eight patients with chronic renal failure, and seven kidney donors.

The control individuals had a normal physical examination, normal screening haematological (haemoglobin, white cell count, platelets) and biochemical determinations (serum creatinine, fasting blood sugar, uric acid, cholesterol, triglycerides), and normal routine urine analysis. The patients with chronic renal failure were volunteers selected from the outpatient clinic. Their serum creatinine ranged from 212.2 to 486 μmol/l. These patients had the following diagnoses: renal disease associated with essential hypertension (2 patients), bilateral nephrolithiasis (1 patient), membranoproliferative glomerulonephritis (1 patient), focal segmental glomerulosclerosis (1 patient), and uncertain aetiology, grouped as chronic glomerulonephritis (3 patients). The kidney donors were volunteers selected from the transplantation programme of the hospital. They had undergone unilateral nephrectomy 1 month to 12 years prior to the time of study. None of the subjects was receiving medications known to interfere with the renal response to a protein meal, such as non-steroidal antiinflammatory drugs, or medications that block tubular secretion of creatinine, such as trimethoprim–sulphamethoxazole or cimetidine.

None of the individuals studied had a history of voiding difficulties and complete bladder emptying after voluntary voiding was confirmed by ultrasound sonography.

Informed consent was obtained from all participants and the experiments were approved by the departmental ad hoc ethical committee.

**Definitions and statistical calculations**

We performed simultaneous serial clearances (UV/P) of creatinine (C\text{cr}) and inulin (C\text{inu}) before (pre-meal) and after (post-meal) the ingestion of a test meat meal. In analysis of the data, clearances were corrected for 1.73 m\text{2} surface area.

The tubular secretion of creatinine (TS\text{cr}) was estimated as the difference between the urinary creatinine excretion (urine creatinine concentration, (U\text{cr})× urine volume, V), and the filtered creatinine (C\text{inu}× serum creatinine concentration (S\text{cr})); TS\text{cr}=(U\text{cr}× V)-(C\text{inu}× S\text{cr}). TS\text{cr} was corrected for kg of body-weight.

The increments induced by the test meal are expressed as the ratio of post-meal/pre-meal determinations. In these analysis, the pre-meal clearance represents the mean of three successive 30-min clearances done before the meal, and the post-meal clearance represents the mean of four successive 30-min determinations after the meal.

Statistical comparisons were done with the help of a commercial statistical package (Instat\textsuperscript{®}) using non-parametric methods: Kruskal–Wallis ANOVA test followed by Dunn’s multiple comparisons test for comparisons between groups, Wilcoxon’s test for paired observations, Friedman test for repeated measures in the same individual, and Spearman’s rank correlation for associations between variables. Two-tailed \(P\) values <0.05 were considered significant.

**Experimental design**

Five days before the test all individuals were prescribed a standard diet containing 2500 calories, 80 g of protein, 87 g of lipids, and 367 g of carbohydrates. Daily sodium intake was adjusted to 100 mmol/day.

The prescribed diet was compared with the listing of the foods consumed during this period and with the calculation of protein intake based on the determination of urea nitrogen and sodium excretion in 24-h urine collected the day prior to the study. Protein intake was estimated from the urea excretion using standard formulae for normal individuals [27] and patients with renal disease [28].

The studies were begun about 9 a.m., after inducing a water diuresis by the oral ingestion of 20 ml of water per kilogram body-weight, followed by half-hourly ingestion of at least an amount equivalent to the urinary volume of the preceding half-hour. Once a steady diuresis was present, usually after about 2 h, veins were cannulated with Teflon catheters in each arm: one side for the inulin infusion and the other side for blood sampling. The loading dose of inulin was 50 mg/kg body-weight, and it was followed by a maintaining infusion calculated to keep plasma levels of inulin at 20 mg/dl for the duration of the test. The maintaining infusion in patients with renal disease was reduced proportionally to the estimated reduction in glomerular filtration rate [29].

After an equilibration period of 1 h, three baseline clearance periods of 30 min each were performed. Then the test meal was given to the subjects who ingested it in 15–25 min. The test meal consisted of 400 g of cooked lean meat, providing 80 g of animal protein, given as two hamburger patties. After the meal was completed, four clearance periods of 30 min each were done. All urinary collections were taken by supervised voluntary voiding and were timed; urine volume was immediately determined and samples were stored. Blood samples were taken at the midpoint of the corresponding urinary collection period.

Inulin determinations in blood and urine were done by conventional methods [30] as reported previously [10]. Creatinine determinations in serum and urine were done by autoanalyser.

The contribution of non-creatinine chromogens in clearance determinations after a protein meal, was tested in four studies (12 pre-meal clearance determinations and 16 post-meal determinations). In these studies, creatinine was determined in urine and serum by autoanalyser as well as by ‘true’ creatinine methods [31,32]. The ratio of ‘true’ C\text{cr}/autoanalyser C\text{cr} was 1.07±SEM 0.034 in the pre-meal clearances (\(n=12\)) and 0.97±SE 0.033 in the post-meal clearances (\(n=16\)).

Urea determinations were by autoanalyser and urinary sodium by flame photometry.

**Results**

Table 1 presents the data in controls, patients and kidney donors obtained prior to the studies. The three groups were comparable in age and in protein and sodium intake. The baseline serum creatinine levels (mean±SEM) were higher in the patient group (274.9±25.28 μmol/l) than in donors (91.1±9.00 μmol/l) and normals (84.0±2.68 μmol/l).

Table 2 summarizes the data obtained before and after the protein meal and, in the lower part, the
changes in $C_{\text{in}}$, $C_{\text{cr}}$, $U_{\text{cr}}, V$, and $TS_{\text{cr}}$ produced by the test meal expressed as Pre/Post ratios. Significant differences between the groups existed in pre-meal and post-meal clearances of inulin and creatinine. Creatinine excretion and tubular secretion of creatinine were not significantly different in the pre-meal studies in normals, donors, and patients; however, after the test meal the patients with chronic renal disease had lower urinary creatinine excretion ($P < 0.001$) and tubular secretion of creatinine ($P < 0.001$) than control individuals. The urinary excretion and tubular secretion of creatinine in donors was lower than in normals and higher than in patients with renal disease, but these differences did not reach statistical significance.

The post-meal/pre-meal ratio of $C_{\text{in}}$ is similar in normals and donors, while patients showed a larger increment in glomerular filtration than normals (post-meal $C_{\text{in}}$/pre-meal $C_{\text{in}} = 1.35 \pm 0.09; P < 0.01$ vs control group). In contrast, the increment of $C_{\text{cr}}$ following a protein meal is smaller in the patient group (post-meal $C_{\text{cr}}$/pre-meal $C_{\text{cr}} = 1.05 \pm 0.03; P < 0.01$ vs controls). $U_{\text{cr}}, V$ increases 2.2 times in normals and in uninephrectomized individuals and only 1.3 times in patients ($P < 0.001$). There is a substantial variability in the calculated $TS_{\text{cr}}$; nevertheless it increases 3.4 times in normals and 2.7 times in kidney donors, but not in renal patients, after a protein meal ($P < 0.05$). These findings are essentially similar if the $TS_{\text{cr}}$ is expressed in terms relative to the glomerular filtration rate (Table 2).

Urinary volume (ml/min) in the Pre-meal studies (controls $= 9.0 \pm 0.65$; patients $= 7.2 \pm 0.46$; donors $= 8.1 \pm 0.87$) and in the Post-meal studies (controls $= 8.6 \pm 1.10$; patients $= 6.5 \pm 0.39$; donors $= 6.9 \pm 0.54$) were not significantly different. Urinary Na excretion ($\mu$mol/min) before the meal was similar in controls (195 $\pm 16.6$), patients (182 $\pm 19.5$), and donors (189 $\pm 25.2$); after the test meal the urinary Na increased significantly ($P < 0.01$) in controls (248 $\pm 18.1$). The postprandial increment in patients (206 $\pm 19.5$) and in donors (224 $\pm 12.8$) did not reach statistical significance ($P > 0.05$). The fractional Na excretion (%) also increased after the meal in controls (Pre $= 1.40 \pm 0.03$; Post $= 1.59 \pm 0.06$, $P < 0.05$), while

### Table 2. Tubular secretion of creatinine after a protein meal

<table>
<thead>
<tr>
<th></th>
<th>Controls $(n=12)$</th>
<th>Patients $(n=8)$</th>
<th>Donors $(n=7)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-meal studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{in}}$ (ml/min)</td>
<td>98.2 ± 288</td>
<td>28.3 ± 3.69*</td>
<td>77.4 ± 4.25</td>
</tr>
<tr>
<td>$C_{\text{cr}}$ (ml/min)</td>
<td>121.3 ± 343</td>
<td>363.4 ± 4.06*</td>
<td>98.4 ± 7.76*</td>
</tr>
<tr>
<td>$S_{\text{cr}}$ (μmol/l)</td>
<td>84.01 ± 2.68</td>
<td>274.9 ± 25.28*</td>
<td>91.1 ± 9.00</td>
</tr>
<tr>
<td>$U_{\text{cr}}, V$ (nmol/kg/min)</td>
<td>149.8 ± 5.31</td>
<td>136.1 ± 7.87</td>
<td>127.8 ± 8.66</td>
</tr>
<tr>
<td>$TS_{\text{cr}}$ (nmol/kg/min)</td>
<td>29.9 ± 6.30</td>
<td>30.7 ± 6.23</td>
<td>21.9 ± 9.23</td>
</tr>
<tr>
<td>Post-meal studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{in}}$ (ml/min)</td>
<td>106.5 ± 4.01</td>
<td>37.3 ± 4.55*</td>
<td>87.1 ± 6.02*</td>
</tr>
<tr>
<td>$C_{\text{cr}}$ (ml/min)</td>
<td>163.7 ± 6.20</td>
<td>37.5 ± 4.28*</td>
<td>119.0 ± 7.70*</td>
</tr>
<tr>
<td>$S_{\text{cr}}$ (μmol/l)</td>
<td>139.7 ± 5.83</td>
<td>342.1 ± 24.11*</td>
<td>151.2 ± 11.79</td>
</tr>
<tr>
<td>$U_{\text{cr}}, V$ (nmol/kg/min)</td>
<td>329.5 ± 13.13</td>
<td>171.6 ± 8.46*</td>
<td>279.4 ± 23.90</td>
</tr>
<tr>
<td>$TS_{\text{cr}}$ (nmol/kg/min)</td>
<td>114.4 ± 12.65</td>
<td>5.53 ± 19.66*</td>
<td>76.6 ± 13.34</td>
</tr>
<tr>
<td>Post/pre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{in}}$</td>
<td>1.09 ± 0.05</td>
<td>1.35 ± 0.09b</td>
<td>1.13 ± 0.06</td>
</tr>
<tr>
<td>$C_{\text{cr}}$</td>
<td>1.36 ± 0.06</td>
<td>1.05 ± 0.03b</td>
<td>1.24 ± 0.08</td>
</tr>
<tr>
<td>$U_{\text{cr}}, V$</td>
<td>2.23 ± 0.10</td>
<td>1.28 ± 0.07*</td>
<td>2.19 ± 0.12</td>
</tr>
<tr>
<td>$TS_{\text{cr}}$</td>
<td>3.40 ± 1.79</td>
<td>1.23 ± 1.66*</td>
<td>2.73 ± 1.06</td>
</tr>
<tr>
<td>$S_{\text{cr}}/C_{\text{in}}$</td>
<td>3.44 ± 1.79</td>
<td>−0.93 ± 1.40*</td>
<td>2.44 ± 0.96</td>
</tr>
</tbody>
</table>

Data are mean/SEM. $C_{\text{in}}$ (inulin clearance) and $C_{\text{cr}}$ (creatinine clearance) corrected for 1.73 m$^2$. $U_{\text{cr}}, V$, urine creatinine excretion; $TS_{\text{cr}}$, tubular secretion of creatinine; $S_{\text{cr}}/C_{\text{in}}$, per unit of glomerular filtration rate. Pre-meal data represent, in each subject, the mean of three consecutive 30-min periods before the test meat meal. The Post-meal data represent the mean of four consecutive 30-min periods after the test meal. *P < 0.001; bP < 0.01; P < 0.05 vs control.
the changes observed in the donors (Pre = 1.69 ± 0.05; Post = 1.79 ± 0.03) and in the patients (Pre 4.48 ± 0.15; Post 3.92 ± 0.18) were not statistically significant (P > 0.05).

The urinary excretion of urea (µmol/min) before the meal was similar in controls (310 ± 20), patients (281 ± 38) and donors (291 ± 34). After the meal the urinary urea excretion increased in controls (431 ± 25, P < 0.01 vs Pre-meal) and to a lesser degree in donors (413 ± 36, P = 0.07 vs Pre-meal) but it was reduced in the patients (312 ± 33, P < 0.01 vs controls).

The serial determinations of C_{in} and C_{cr} before and after the test meal in normal subjects and in patients are shown in Figure 1. In order to simplify the figure, the data of the donors, which falls between normals and patients, are not presented. Several aspects are demonstrated in the figure: first, pre-meal C_{cr} are higher than C_{in} in normals and in renal patients. Second, the increment of glomerular filtration rate (C_{n}) observed after the protein meal in normals and in patients, in relation to their respective baseline C_{in} is comparable. Third, a steep rise in C_{cr} is observed after the protein meal in normal individuals, but not in patients with renal failure. In fact the observed pre-meal differences between C_{cr} and C_{in} are practically absent in the post-meal studies in the patients.

Figure 2 shows the relationship between C_{in} and C_{cr} in the pre-meal and post-meal studies in all the individuals. The left side of the Figure demonstrates how controls, patients, and uninephrectomized individuals show pre-meal C_{cr} values relatively similar with respect to their position above the line of identity. On the right side of the Figure, the post-meal C_{cr} determinations in normal individuals separates sharply from the line of identity, while the kidney donors’ data essentially remain unchanged from the pre-meal determinations, and in the patients the post-meal determinations are closer to the line of identity.

The serial determinations of TS_{cr} in patients, kidney donors, and control individuals are shown in Figure 3. Significant increments in TS_{cr} (P < 0.01), were found, in relation to the mean pre-meal value, in control individuals 30, 60, 90 and 120 min after the meal. Kidney donors have a less important increase (P < 0.05) in TS_{cr} after the meal. In contrast, no significant differences were found between the post-meal and pre-meal TS_{cr} in patients with renal disease.

There was no correlation between TS_{cr} and C_{in} in baseline studies, but there was a significant (r = 0.455, P = 0.017) in the post-meal values. The increase in urinary creatinine excretion induced by a protein meal (post-meal U_{cr}V) is highly correlated (r = 0.796, P < 0.0001) with the baseline glomerular filtration, as shown in Figure 4. Less significant correlation exists between the increment in TS_{cr} (post-meal TS_{cr}/pre-meal TS_{cr}) and the glomerular filtration rate (r = 0.459, P = 0.016).

**Discussion**

The increment in renal blood flow and glomerular filtration rate that follows a protein meal has been known for more than 60 years [33], but in 1983, Bosch et al. [6] tested this physiological response and defined the renal functional reserve as the difference between the post-meal (test) and the baseline glomerular filtration rate. This interest (reviewed in [2] and [5]) was in part generated because the observed pre-meal filtration rates were found after a protein challenge. More importantly, additional confusion is added by the use of creatinine clearance in studies of renal reserve capacity. It should be emphasized that creatinine clearance, while simple and convenient, is not an accurate marker of glomerular filtration rate [35,36] particularly after a protein meal. Creatinine is secreted by the renal tubule and is produced by the creatinase in the urine, with the result that the so-called reserve capacity is too variable to be of practical use; in fact, a fall in filtration rate is sometimes found after a protein challenge. More importantly, the remnant nephron population in patients with chronic renal failure responds with a normal increment in renal blood flow and glomerular filtration rate after a protein challenge [17–19].

Additional confusion is added by the use of creatinine clearance in studies of renal reserve capacity. It should be emphasized that creatinine clearance, while simple and convenient, is not an accurate marker of glomerular filtration rate [35,36] particularly after a protein meal. Creatinine is secreted by the renal tubule and this tubular secretion is increased substantially after a mealt [24–26]. It is therefore not surprising that protein-induced increments in C_{in} are 20–30% smaller than the increments in C_{cr} [1,12,15,16,37–39]. Many of these discrepancies, we reasoned, could be due to the fact that it was the capacity to increase the TS_{cr} after a protein meal, rather than the capacity to increase glomerular filtration rate, that is the physiological response capable of discriminating between normal and diseased kidneys. To test this possibility we analysed three baseline and four stimulated (post-meal) clearance periods which included 120 min after the test meal. We decided to examine mean data from
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**Fig. 2.** Relationship between the clearances of inulin \( (C_{in}) \) and creatinine \( (C_{cr}) \) in the baseline (pre-meal) and stimulated (post-meal) studies in normals (closed circles), kidney donors (open triangles) and patients with renal disease (open squares). After the test meat meal (right panel), the \( C_{cr} \) separates sharply from the line of identity in normals, while in patients the \( C_{cr} \) tends to joint with it.

In fact we found, as shown in Figures 1 and 2, that the increment in post-meal \( C_{cr} \) is absent in patients with chronic renal damage. In particular, Figure 2 demonstrates how the \( C_{cr} \) separates sharply from \( C_{in} \) in post-meal determinations of normals, while patients' data are situated at the line of identity and the data of kidney donors are situated between the normals and the patients.

While the tubular secretion capacity for drugs such as ampicillin and cephalaxin is reduced in renal failure [41,42], the \( T_{cr} \) is known to be maintained in patients with advanced renal disease, as confirmed in the pre-meal studies (Table 2); in fact the contribution of tubular secretion of creatinine is more important in renal failure, relative to the correspondingly depressed GFR. This is the reason why the \( C_{cr} \) overestimates the GFR more significantly as the renal function deteriorates. \( C_{cr}/C_{in} \) ratios reported in the literature in patients with moderate degrees of renal failure vary from 1.57 [36] and 1.70 [35] to 1.29 [43] and 1.04 [44]. Our patients had pre-meal \( C_{cr}/C_{in} \) mean ratio of 1.28, only slightly higher than the 1.24 ratio found in the normals.

While these results are within the range published in the literature, the \( C_{cr}/C_{in} \) ratios in the patients are lower than those found in patients with comparable renal insufficiency in the more recent studies [35,36]. The reasons for this discrepancy are not clear, but baseline determinations in our patients were probably influenced by the standard diet given for 5 days before the test. In this diet, the renal patients received a large protein load in relation to their baseline GFR. Since
the TS<sub>cr</sub> shows a tendency to fall in the renal patients 30–60 min after the protein meal (Figure 3), it is conceivable that the pretest diet of 80 g protein per day could induce a reduction in baseline TS<sub>cr</sub> (and consequently, a lower C<sub>cr</sub>/C<sub>in</sub> ratio) in the renal patients.

The data in Figure 2 and the serial studies shown in Figure 1 raise the interesting possibility that the mean of 3–4 C<sub>cr</sub> determinations after a protein meal could be an acceptable substitute of C<sub>cr</sub> determinations in patients with GFR below 50 ml/min.

Serial studies of TS<sub>cr</sub> before and after the test meal (Figure 3) demonstrate how baseline TS<sub>cr</sub> is essentially similar in normals, patients, and kidney donors, but 30 min after the meal, TS<sub>cr</sub> increases in normals and remains unchanged or falls in the patients (Figure 3). In fact the ability to raise the TS<sub>cr</sub> after the test meal appears to be directly related to the glomerular filtration rate since there is a significant correlation between GFR and TS<sub>cr</sub> in the post-meal studies (P = 0.017).

Normal individuals with two functioning kidneys increase the TS<sub>cr</sub> 3.4 times after the meal, while the uninephrectomized normals (kidney donors) were only able to raise their TS<sub>cr</sub> 2.7 times. This finding is in contrast with the preserved haemodynamic response of denervated transplanted kidneys insensitive to stimulation by the sympathetic nervous system [45]. Renal patients with roughly 70% reduction in renal function (GFR 28.3 ± 3.69 ml/min, Table 2) showed no change or a reduction in TS<sub>cr</sub> after the test meal. These findings raise the possibility that baseline TS<sub>cr</sub> in these patients, while similar in absolute terms to that in normals, is however at its maximum capacity (Tm<sub>cr</sub>). In these circumstances, TS<sub>cr</sub> cannot be raised further and may even be depressed by a creatinine load. Depression of Tm at high levels of filtered load have been found for PAH and diodrast in normals [46] and is attributed to a combination of passive diffusion and exhaustion of some component in the metabolic system involved in tubular transport [46]. Similar conditions may be present in our patients with reduced functioning renal mass; these patients received with the test meal a creatinine load 3.6 times larger per unit of GFR than the load received by the normal individuals.

Finally, the increment in urinary creatinine induced by a protein meal (post-meal U<sub>cr</sub>V/pre-meal U<sub>cr</sub>V) is impressively correlated with the filtration rate of the kidney (P < 0.0001, Figure 4).

In summary, our studies show that the stimulation of the tubular secretion of creatinine after a protein test meal clearly discriminates between normals and patients with moderate and severe renal failure. The data obtained in subjects encompassing a wide range of kidney function (normals, kidney donors, and patients with chronic renal failure) would suggest that the capacity to increase the tubular secretion of creatinine after a meat meal is directly related to the functioning renal tissue. Under the conditions of our study, the urine creatinine raises to levels of 300–350 nmol/min/kg (95% confidence interval) during the 2 h after a meat meal, which represents a 2.2-fold increment over baseline values. Further studies are necessary to define the natural history of the loss of this tubular reserve capacity in the progression of renal damage and the potential clinical relevance of its evaluation in course of renal disease.

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