lowering effect of calcitonin need not reflect the ability of the hormone to affect Paget's disease of bone chronically, and thus the only acceptable evidence in support of antibody-mediated relapse during treatment would be obtained by demonstrating a restored response to porcine or human calcitonin in the face of high antibody titres to salmon calcitonin. Such evidence is available for a total of five patients.[11 12]

This work was supported by the Arthritis and Rheumatism Council. We thank Dr C McKerron for allowing us to study patients under his care; Dr J W Bastian, Armour Pharmaceutical Company, Kankakee, Illinois, for supplying synthetic salmon calcitonin for labelling; and Dr F R Singer, UCLA Medical Centre, Los Angeles, for donating guinea-pig anti-salmon calcitonin.

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(*Accepted 12 August 1977*)

Plasma creatinine and urea: creatinine ratio in patients with raised plasma urea

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British Medical Journal, 1977, **2**, 929-932

Summary

We examined the plasma urea and creatinine concentrations and the ratio between them according to diagnosis in 100 unselected and 31 selected adult hospital patients with a plasma urea concentration ⩾ 10 mmol/l (60 mg/100 ml). We also examined plasma urea and creatinine concentrations in 350 unselected consecutive patients, but found no useful relation between the two values.

Congestive heart failure was the most common identifiable cause of a raised plasma urea concentration in the 100 unselected patients (36%). Among these 100 patients the plasma creatinine concentration was a more useful discriminant between prerenal uraemia and intrinsic renal failure than was the urea:creatinine ratio or the plasma urea concentration.

A plasma creatinine concentration > 250 μmol/l (2·8 mg/100 ml) indicated intrinsic renal failure with a 90% probability.

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Introduction

Measurement of the plasma urea concentration is still the usual screening test for renal glomerular failure, but it is generally recognised that the failure must be gross before the plasma urea concentration is clearly raised, and that it may be raised for reasons other than glomerular failure. It has been stated that the causes of a raised plasma urea concentration can be distinguished by measuring the plasma creatinine concentration and calculating the ratio of the two values.[1-4]

Two reasons prompted us to re-examine the diagnostic role of measuring plasma creatinine concentrations and the urea: creatinine ratios. Firstly, the introduction of multichannel analysers has made measurements of plasma creatinine concentrations more generally available, and they are often made when they are not requested. Hence the urea:creatinine ratio is probably being increasingly used as an aid to interpret a raised plasma urea concentration. Furthermore, we were surprised to find that the publications which support the use of the urea: creatinine ratio contain little detailed information, and the conclusions seem to be based more on physiological principles than on a study of the usefulness of the ratio in clinical practice.

As a first step in the re-examination of this problem we studied the relation between plasma urea and plasma creatinine values in 350 consecutive patients in whom the two measurements had been made on the same blood sample. Secondly, we studied the case histories of 100 consecutive patients with a plasma urea concentration ⩾ 10 mmol/l (60 mg/100 ml) who had creatinine measured on the same plasma sample. We also examined the records of an additional 17 consecutive patients with acute intrinsic renal failure and 14 consecutive patients with chronic renal failure to increase the size of the groups with these disorders. We examined the plasma urea and creatinine values and the ratio between them according to the cause of the raised plasma urea concentration. In the larger

groups we also examined the relation between these measurements and mortality during the hospital admission.

Patients and methods

We examined the relation between plasma urea and plasma creatinine concentrations in 350 consecutive unselected patients. One hundred patients with raised plasma urea concentrations were selected from the 1974 file of patient report cards in the department of chemical pathology at St James's University Hospital, Leeds. The cards were examined in alphabetical order of the patients' surnames. Patients were included if they were over 16 and had a plasma urea concentration $\geqslant 10$ mmol/l, and if the same plasma sample had been analysed for creatinine. Patients who were under the long-term care of the renal physician were excluded. We examined the case notes of these patients in detail, and summarised the admission history, the notes on clinical course, and the discharge notes. A further 17 patients with acute renal failure and 14 patients with chronic renal failure were selected from the diagnostic index. This information and the subsequent course (when available) was used to categorise the patients according to the cause of the raised plasma urea concentration. Plasma urea, plasma creatinine, and plasma electrolyte values were recorded for the first sample in which the urea concentration was $\geqslant 10$ mmol/l.

Laboratory investigations—Plasma electrolytes, urea, and creatinine were analysed by standard techniques. In 1974 the laboratory used an SMA 6/60 analyser to measure creatinine simultaneously with urea on samples received during the day whether or not it was specifically requested, but not on those received out of normal working hours.

Analysis of data—We calculated the plasma urea: creatinine ratio and the ratio between the increases of the two variables above the geometric mean values in a healthy population studied in this laboratory (plasma creatinine 88 μmol/l (1·0 mg/100 ml); plasma urea 4·2 mmol/l (25 mg/100 ml)).

Results

Figure 1 shows that in the group of 350 consecutive unselected patients there was no useful relation between plasma urea and plasma creatinine values.

The table shows the various causes of a raised plasma urea concentration in the 100 unselected patients we studied in detail. A further 17 patients with acute renal failure and 14 patients with chronic renal failure were studied.

Figure 2 shows the plasma urea and plasma creatinine concentrations, the ratios between them, and the ratios between their increments in the 131 patients according to the cause of the raised plasma urea concentrations. A plasma urea concentration >30 mmol/l (180 mg/100 ml) was unusual in the absence of renal disease, as was a plasma creatinine concentration >350 μmol/l (4 mg/100 ml).

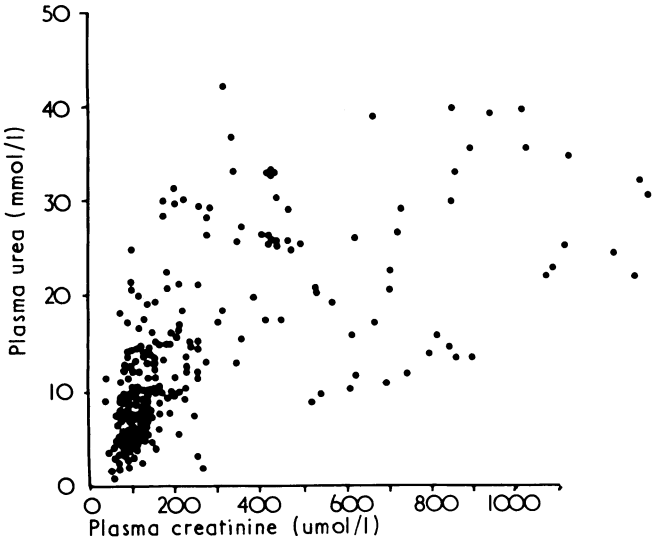

FIG 1—Relation between plasma urea and plasma creatinine concentrations in 350 consecutive patients in whom the two measurements had been made on the same blood sample.

Conversion: SI to traditional units—Plasma urea: 1 mmol/l ≈ 6 mg/100 ml; plasma creatinine: 1 mmol/l ≈ 0·01 mg/100 ml.

Causes of raised plasma urea concentrations in 100 unselected patients with a plasma urea concentration $\geqslant 10$ mmol/l (60 mg/100 ml)

Cause	No of patients
Congestive heart failure	36
Dehydration	12
Post-operation	6
Hypotension	3
Acute renal failure	2
Chronic renal failure	3
Increased urea load	2
Obstructive renal disease	1
Combined causes	9
Unclassified	26
Total	100

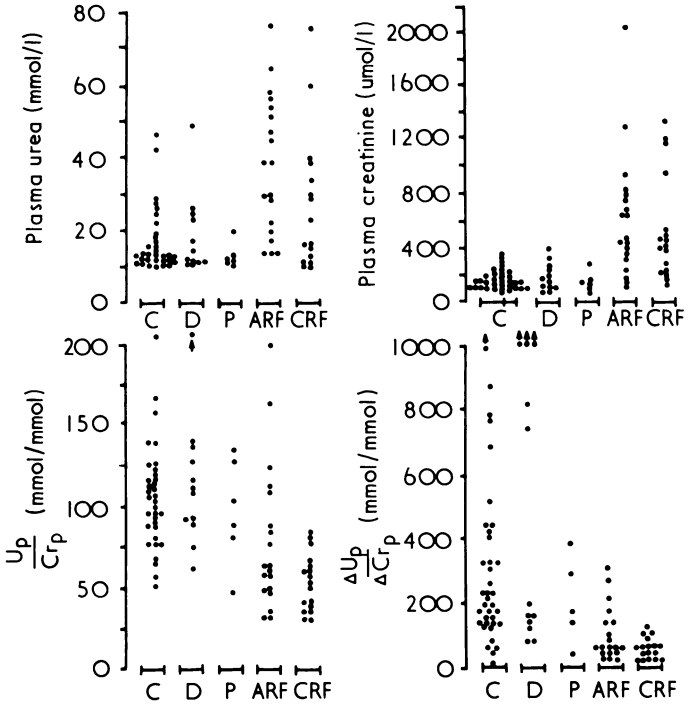

FIG 2—Plasma urea (U_p) and plasma creatinine (Cr_p) concentrations. C = congestive heart failure; D = dehydration; P = post-operation; ARF = acute renal failure; CRF = chronic renal failure. $\triangle U_p$ and $\triangle Cr_p$ are the differences between the patients' U_p and Cr_p respectively and the mean value of U_p and Cr_p in healthy persons. (Four negative values for $\triangle U_p/\triangle Cr_p$ have been omitted; one from C, two from D, and one from P).

We have combined the patients with heart failure and those with dehydration into a group designated as prerenal uraemia (PRU), and compared the results with those of the patients with acute renal failure (ARF). The differences in plasma creatinine concentrations and urea:creatinine ratios between the two groups are small when the plasma urea concentration is slightly raised and greatest in the patients with the highest plasma urea concentrations (fig 3). The mean and range of the urea:creatinine ratio (mmol:mmol) was 103 (51-266) in the prerenal uraemia group, 73 (32-200) in the acute renal failure group, and 53 (30-85) in the chronic renal failure group.

To assess the diagnostic usefulness of these differences in distinguishing prerenal uraemia and acute renal failure, we calculated the probability of acute renal failure according to values of each variable. If a probability of 90% is required before a diagnosis is accepted then the proportion of patients with ARF detected by each variable is much greater for plasma creatinine (75%) than for plasma urea or plasma urea:creatinine concentration ratio (20-30%). This probability of ARF is reached in the present series at a value of plasma creatinine of 250 μmol/l (2·8 mg/100 ml). It must be explained,

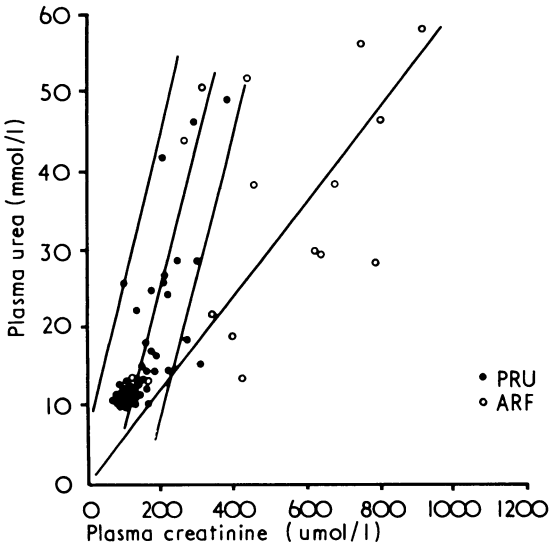

FIG 3—Plasma urea and plasma creatinine concentrations in the first sample in which a raised urea concentration was found in patients with prerenal uraemia (PRU; closed symbols) and patients with acute renal failure (ARF; open symbols).

however, that this value depends on the relative numbers of patients in the two groups, and that the size of the ARF group was increased after the selection of the initial 100 patients. There were too few patients with ARF in the initial group to allow any estimates to be made.

Figure 4 compares the values of the four variables in the patients who died and those who survived in the groups with prerenal uraemia and acute renal failure. Among the patients with prerenal uraemia those who died had higher average plasma urea and plasma creatinine concentrations and urea:creatinine ratios than those who survived. The risk of death therefore increased as the plasma urea concentration increased.

The overall mortality was 58% in the group of patients with heart failure who had plasma urea concentrations ≥10 mmol/l. Mortality increased to 67%, 70%, and 82% in the patients with plasma urea concentrations ≥11·6, 13·6, and 15 mmol/l (70, 82, and 90 mg/100 ml) respectively.

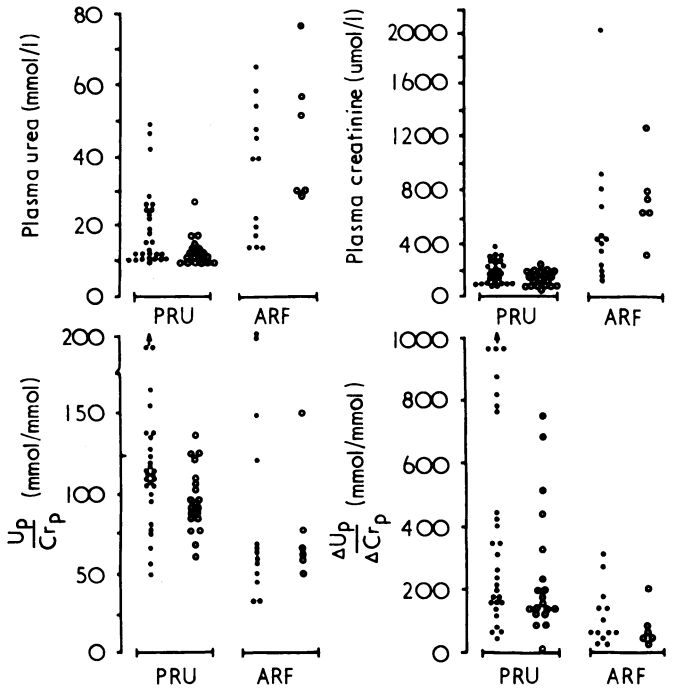

FIG 4—The U_p, Cr_p, U_p/Cr_p and $\triangle U_p/\triangle Cr_p$ (see legend to fig 2) in patients with prerenal uraemia (PRU) and acute renal failure (ARF) who survived (closed symbols) or died (open symbols).

Discussion

The three general causes of a raised plasma urea concentration are decreased glomerular filtration rate, an increased load of urea for excretion (from the diet or tissue metabolism), and an increased tubular reabsorption of urea. The plasma creatinine concentration is increased, however, only when glomerular filtration is low. We found no useful relation between plasma concentrations of urea and creatinine in this hospital population as a whole, and the one measurement cannot therefore be regarded as a general substitute for the other.

When the plasma urea concentration is greatly raised, measurement of the plasma creatinine concentration will certainly distinguish glomerular failure from the other causes of a raised plasma urea concentration, particularly prerenal uraemia. This is the basis of the theoretical argument for the usefulness of the two measurements in clinical practice, and the suggestion that the two groups may be distinguished using the plasma urea:creatinine concentration ratio.[1-4] In the present study, however, we were less able to discriminate between the groups with the use of the urea:creatinine ratio than with plasma creatinine measurement. This is a surprising conclusion, but one which emphasises that the acceptance of the urea:creatinine ratio is based on theoretical considerations rather than on a clear-cut demonstration of its practical usefulness. The lack of discrimination when using the urea:creatinine ratio arises because a wide range of values is possible for the ratio in either group when the plasma concentrations of urea and creatinine are near normal. When the plasma urea concentration is high, the urea:creatinine ratio is different in the two groups, but then so is the plasma creatinine concentration. If a patient with a raised urea concentration has a plasma creatinine concentration >250 μmol/l (2·8 mg/100 ml) he probably has intrinsic renal failure.

We were surprised to find that heart failure was the most common cause of a raised plasma urea concentration in a general hospital, although this feature is known to be common in patients with heart failure (39%,[5] 48%[6]). Nevertheless, in many patients the value was just above the "upper limit of normal." For example, 29 (39%) of the 71 patients studied by Thayer,[5] had a raised plasma urea concentration (>6·7 mmol/l (40 mg/100 ml)), but only 9 (13%) had a value greater than 10 mmol/l, and only 4 (6%) had a value greater than 13·6 mmol/l. Although a value as high as 33 mmol/l (200 mg/100 ml) has been reported in a patient with heart failure,[7] it has been suggested that this is quite exceptional, and that the presence of renal failure should be considered at values of 20-30 mmol/l (120-180 mg/100 ml).[8] Our results show that a plasma urea concentration >27-30 mmol/l (162-180 mg/100 ml) is unusual in patients with heart failure. Most earlier authors attributed the increased plasma urea values of heart failure to the fall in glomerular filtration rate,[9 10 11] and this view is still held by some.[3]

We could find only one study of plasma creatinine values in patients with heart failure. Thayer[5] reported that 39% of patients with heart failure had a raised plasma urea concentration, but only 8% had a raised plasma creatinine concentration, and the highest value was 235 μmol/l (2·7 mg/100 ml). Of our patients with heart failure 36 had a plasma urea concentration ≥10 mmol/l, and only 12 had a plasma creatinine concentration >130 μmol/l (1·5 mg/100 ml). These results suggest that a fall in glomerular filtration rate is not always the major cause of the increased plasma urea values of heart failure. Increased protein breakdown with an increased load of urea for excretion as a cause of the raised plasma urea values of heart failure was at first dismissed,[9] but was later demonstrated.[6 7] Nevertheless, its contribution to the rise of plasma urea concentrations has not been defined.

The relation we observed in heart failure between the plasma urea concentration and subsequent mortality confirms the finding of Domenent and Evans.[7] The relation between plasma creatinine and subsequent mortality in patients with heart failure has not been studied before. In our series no patient with heart failure survived if the plasma creatinine concentration was > 220 μmol/l (2·5 mg/100 ml).

This work was supported by a grant from the West Riding Medical Research Trust.

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(*Accepted 12 August 1977*)

SHORT REPORTS

Glucose reabsorption from ileal loops

Since 1950 the use of an isolated loop of small bowel for urinary drainage after total cystectomy has been the treatment of choice.[1] Eiseman and Bricker[2] studied electrolyte reabsorption from the loop, finding that urea and chloride were reabsorbed, but that hyperchloraemic acidosis did not occur. The fact that reabsorption of glucose may occur in diabetics and can be of clinical significance does not seem to have been appreciated. I present two cases which demonstrate these points.

Case reports

Case 1—A 60-year-old man was found on glucose tolerance test to have mild diabetes with a normal renal threshold. He underwent total cystectomy for carcinoma, the ureters being transplanted into an ileal loop. He was first seen three weeks after operation, when he was drowsy and dehydrated. Because of diuresis, of 500-1000 ml daily, he had been in negative fluid balance, and this had persisted for seven days. His blood glucose had never been higher than 19·4 mmol/l (349·5 mg/100 ml) in this period, and the average concentration was 16 mmol/l (288·3 mg/100 ml) (seven readings). Although his renal threshold was constantly exceeded, glucose never appeared in his urine. He was treated with chlorpropamide, 250 mg daily for four days; his blood glucose concentration fell to below his renal threshold and the diuresis ceased.

Case 2—A 65-year-old man with mutiple transitional cell carcinomata had a total cystectomy. Both ureters and his right kidney were also removed. Postoperatively he had a left nephrostomy and an ileal loop conduit from the left renal pelvis. He was a mild maturity onset diabetic with a normal renal threshold. Two days after operation he was passing urine from the nephrosotomy and via the ileal loop. He was given an intravenous infusion of 50 g of dextrose and 10-ml samples of urine were taken simultaneously from the nephrostomy and via the loop on two occasions at ½-hourly intervals. The urinary glucose concentrations were as follows:

	Nephrostomy	*Loop*
Urinary glucose (mmol/l)	6·9 (0·12 g/100 ml)	0
	5·6 (0·10 g/100 ml)	0

There was thus total reabsorption of glucose from the loop.

Discussion

Case 2 shows that glucose reabsorption can occur from an ileal loop. The inappropriate diuresis in case 1 was probably an osmotic diuresis due to a raised blood glucose. Under normal circumstances the excreted glucose would have been lost in the urine but owing to reabsorption from the loop this did not occur. The patient was diabetic and impaired glucose metabolism led to a vicious circle of glucose excretion and reabsorption with consequent continuous osmotic diuresis. This problem should be anticipated in diabetics undergoing this surgical procedure and is particularly apt to arise in mild diabetics where the relatively low blood sugar concentration may be misleading. The use of dextrose infusions in the postoperative period will make its occurrence more likely. Di Matteo *et al*[3] have shown in dogs that metaplasia of the mucosa of the loop will occur with time, and it may be that reabsorption of glucose is, therefore, temporary.

Two main conclusions may be drawn. Firstly, reliable control of diabetes after formation of an ileal loop is not possible from the results of urine analysis alone, at least in the postoperative period. Secondly, a persistent osmotic diuresis may occur if the blood sugar is allowed to remain above the renal threshold.

I thank Mr Grant Williams for permission to report on patients under his care.

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(*Accepted 24 May 1977*)

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Trial of polyunsaturated fatty acids in non-relapsing multiple sclerosis

The possibility of a relationship between multiple sclerosis (MS) and the consumption of polyunsaturated fatty acids, suggested by a number of dietary[1] and biochemical[2] studies, led to the setting up of a controlled trial of linoleic acid in this disease.[3] The two-year trial showed that relapses were significantly less severe and tended to be less frequent in the treated group. These findings encouraged us to undertake a larger trial and we now report the result of the first part of a double-blind study in which 268 patients participated. The clinical pattern of MS varies, but two major groups are distinguishable: those with acutely relapsing and remitting illness and those with chronic progressive disease. Since a response to dietary supplementation might differ in the two groups, the trial was stratified. The patients with chronic progressive disease were recruited more rapidly than the others and this group therefore completed the two-year period of the trial first. The present report concerns only patients in the chronic progressive group.

Patients, methods, and results

A total of 152 patients with chronic progressive MS were admitted to the trial and were randomly allocated to one of four treatment groups: *Group A* received eight capsules daily of Naudicelle oil (Bio-Oils Research Limited).