General - Type 2 RTA is also called proximal RTA because the main problem is greatly impaired reabsorption of bicarbonate in the proximal tubule.

- At normal plasma [HCO₃⁻], more than 15% of the filtered HCO₃ load is excreted in the urine. When acidosis is severe and HCO₃ levels are low (eg <17 mmol/l), the urine may become bicarbonate free.

Features
- Symptoms are precipitated by an increase in plasma [HCO₃⁻]. The defective proximal tubule cannot reabsorb the increased filtered acid load and the distal delivery of bicarbonate is greatly increased. The H⁺ secretion in the distal tubule is now overwhelmed by attempting to reabsorb bicarbonate and the net acid excretion decreases. This results in urinary loss of HCO₃ resulting in systemic acidosis with inappropriately high urine pH.

- The bicarbonate in the filtrate is replaced by an H⁺ excretion which is greater than can be explained by any change in GFR. If glomerular function (ie GFR) is significantly depressed, the retention of fixed acids results in a high anion gap acidosis.

- The increased distal Na⁺ delivery results in hyperaldosteronism with consequent renal K⁺ wasting. The hypokalaemia may be severe in some cases but as hypokalaemia inhibits adrenomedullary secretion, this often limits the severity of the hypokalaemia.

- Hyperkalaemia does not occur and this type of RTA is not associated with renal stones.

- During the NH₄Cl loading test, urine pH will drop below 5.5.

- Note that the acidosis in proximal RTA is usually not as severe as in distal RTA and the plasma [HCO₃⁻] is typically greater than 15 mmol/l.

Causes
- There are many causes but most are associated with multiple proximal tubular defects eg affecting reabsorption of glucose, phosphate and amino acids. Some cases are hereditary.

- Causes include vitamin D deficiency, cystinosis, lead nephropathy, amyloidosis and medullary cystic disease.

Treatment
- Treatment is directed towards the underlying disorder if possible.

- Alkali therapy (NaHCO₃) and supplemental K⁺ is not always necessary. If alkali therapy is required, the dose is usually large (up to 10 mmol/kg/day) because of the increased urine bicarbonate wasting associated with normal plasma levels.

- K⁺ loss is much increased in treated patients and supplementation is required.

- Some patients respond to thiazide diuretics which cause slight volume contraction and this results in increased proximal bicarbonate reabsorption so less bicarbonate is needed.

- This term is no longer used.

- Type 3 RTA is now considered a subtype of Type 1 where there is a proximal bicarbonate leak in addition to a distal acidification defect.

General - A number of different conditions have been associated with this type but most patients have renal failure associated with disorders affecting the renal interstitium and tubules. In contrast to uraemic acidosis, the GFR is greater than 20 ml/min.

- A useful differentiating point is that hyperkalaemia occurs in type 4 RTA but NOT in the other types.

Pathophysiology
- The underlying defect is impairment of cation-exchange in the distal tubule with reduced secretion of both H⁺ and K⁺.

- This is a similar finding to what occurs with aldosterone deficiency and type 4 RTA can occur with Addison's disease or following bilateral adrenalectomy.

- Acidosis is not common with aldosterone deficiency alone but requires some degree of associated renal damage (nephron loss) esp affecting the distal tubule.

- The H⁺ pump in the tubules is not abnormal so patients with this disorder are able to decrease urine pH to < 5.5 in response to the acidosis.

The acidosis occurring in uraemic patients is due to failure of excretion of acid anions (particularly phosphate and sulphate) because of the decreased number of nephrons. There is a major decrease in the number of tubule cells which can produce ammonia and this contributes to uraemic acidosis.

- Serious acidosis does not occur until the GFR has decreased to about 20 ml/min. This corresponds to a creatinine level of about 0.30-0.35 mmol/l.

- The plasma bicarbonate in renal failure with acidosis is typically between 12 & 20 mmol/l. Intracellular buffering and bone buffering are important in limiting the fall in bicarbonate. This bone buffering will cause loss of bone mineral (osteomalacia).

- Most other forms of metabolic acidosis are of relatively short duration as the patient is either treated with resolution of the disorder or the patient dies. Uraemic acidosis is a major exception as these patients survive with significant acidosis for many years. This long duration is the reason why loss of bone mineral is significant in uraemic acidosis but not a feature of other causes of metabolic acidosis.