CHAPTER 14 - THE RENAL SYSTEM INCLUDING ACUTE OLIGURIC RENAL FAILURE

IMPAIRMENT OF RENAL FUNCTION - OLIGURIA

This chapter is devoted to problem-solving in patients with impairment of renal function. In particular we will emphasize acute renal failure. Mostly, that presents with oliguria (i.e. urine production below 400 mls per day), but some forms of acute renal failure are not associated with oliguria at all, sometimes even polyuria (for example where the brunt of the problem falls on the collecting system whose normal task is to reabsorb water).

PHYSIOLOGY RELEVANT TO MAKING AN ANATOMICAL DIAGNOSIS IN PATIENTS WITH ACUTE RENAL FAILURE/OLIGURIA.

As usual most of the information we obtain clinically about the Anatomical site underlying any condition is based on our Functional diagnosis, because different aspects of renal function are carried out in different anatomical parts of the nephron. We therefore have to begin as usual by outlining the essence of renal function relevant to clinical diagnosis.

A. NORMAL RENAL FUNCTION

The major functions of the kidneys are as follows:

1. The maintenance of a stable body fluid and electrolyte composition, with particular reference to ECF volume, sodium and water control, other electrolytes and acid-base balance.

2. Complementary to the liver in excreting endogenous as well as exogenous materials (foreign drugs, toxins etc.) from the body.

3. A number of endocrine functions including:

   (i) renin release and hence activation of the angiotensin-aldosterone system -important in sodium and blood pressure control.

   (ii) The production of prostaglandins, including liberation of the vasodilator prostacyclin from the glomerular tuft. Non-steroidal anti-inflammatory drugs (NSAIDs) can therefore impair GFR.
(iii) Kallikrein secretion (from the distal tubules and collecting ducts). A vasodilator probably also important in control of renal sodium handling.

(iv) Liberation of vasodilator neutral and acid vasodilator lipids from the medulla.

(v) Erythropoietin, important in stimulation of red cell production.

(vi) Vitamin D (25 OH D) activation (by PTH) to 1,25 OHD3.

B. FUNCTIONS OF THE DIFFERENT ANATOMICAL LEVELS OF THE NEPHRON.

1. Glomerular Function.

The task of the glomerulus is to filter urine, and the structure of its capillaries is such that it will readily filter molecules of less than MW 10,000 but not normally more than MW 50,000 (with a gradient for molecules in between). The epithelial cells of the glomerular loops have a negative charge, which means that anionic substances are less well filtered at any given molecular weight than cationic ones. Just why the kidney should allow ultrafiltration of relatively high molecular weight substances is not clear, because most substances finally secreted or excreted by the kidney are of small molecular weight, and the larger molecules have to be reabsorbed again. Perhaps the answer lies in the flexibility this filtration gives in excreting foreign compounds, toxins and drugs of relatively high molecular weight, including via protein binding.

In most tissues, the balance of Starling's capillary forces are such that the amount of fluid filtered at the arteriolar end is counterbalanced by re-absorption of a similar amount at the venular end. However, the glomerular capillaries end not in venules but in efferent arterioles, which provide a higher resistance, so that there is a net filtration into Bowman's space. The kidney receives approx. 1,300 mls/min. blood flow or one quarter of the cardiac output (well in excess of its metabolic needs) and approx. 20% of the kidney plasma flow is filtered in a single passage. Most of this filtrate is re-absorbed. The GFR is determined by the permeability coefficient (Kf), the forces promoting filtration (largely hydrostatic) and the forces opposing filtration (plasma oncotic pressure, intra-tubular pressure). Kf has the dimensions of mls/min/mm Hg and is proportional to the area and size of the capillaries and the total number of nephrons (approx. 2 million). Normally, there is good autoregulation of renal blood flow (and glomerular filtration). Thus, blood flow is maintained fairly constant over systemic pressures from 80 - 180 mm Hg. Obviously, glomerular vascular resistance must fall as blood pressure falls to achieve this. How this proportionality is maintained is not certain, but it does not seem to be a function of renal innervation or systemic humoral pressor substances. Intra-renal release of humoral substances capable of regulating vascular resistance (e.g. renin/angiotensin) may play a role, as may the intrinsic myogenic response of renal vessels to changes in
pressure. Renal blood flow autoregulation can be overridden in the by excessive sympathetic activity, eg. in severe stress, trauma, blood loss.

Glomerular filtration rate is also maintained, to some extent independent of variations in renal blood flow. Some of this is due to the fact that efferent arteriolar constriction can dominate over afferent constriction in circumstances of falling blood flow (particularly under the influence of angiotensin II). This has the effect of increasing the filtered percentage of any given amount of plasma passing through the glomerulus, i.e. increasing filtration fraction. Second, there is a mechanism called tubuloglomerular feedback whereby decreased tubular flow (to the macula densa region of the early distal tubule) tends to increase glomerular filtration and vice versa. The potential of this mechanism is important.

Glomerular filtration rate can be measured by calculating the clearance of any substance totally filtered by the glomerulus and not reabsorbed lower down in the nephron. This GFR has the dimensions of mls/sec as with any other clearance measurement. Clinically, we use creatinine clearance as an index of GFR, but it is only a rough index compared with, say, inulin clearance. Part of the reason for this is that measured plasma creatinine includes some non-creatinine chromogens. Also, there is a small tubular excretion of creatinine.

In clinical practice, we more frequently use the reciprocal of the plasma level of creatinine as a rough guide to glomerular filtration rate. This has the advantage of not being reliant on the vaguaries of 24-hour urine collections in ward situations, but it makes several assumptions and also has disadvantages. First, unlike creatinine clearance, it depends on the production of creatinine and therefore on total muscle bulk and muscle catabolism (increased in muscle trauma, inflammation; decreased with age). But even apart from this, it has a broad range of normality, and is not linearly related to GFR, rising much less steeply with mild compared with more severe impairment of glomerular function. Thus, GFR can halve without plasma creatinine rising above the normal range (50-100 (micromoles/l)). However, it is helpful as a guide in many situations. More accurate is the formula of Cockroft and Gault; whereby:

\[
\text{Approx. GFR} = \frac{(140 - \text{age}) \times \text{Weight in Kg.}}{50 \times \text{Plasma creatinine (micromoles/l.)}}
\]

Note: (Multiply by 0.85 if female)

Normal GFR = 1.5-2.5 ml/sec
N.B. **Clinical points.** It is important to observe that **GFR has the dimensions of ml/sec.** and not grams or moles/sec. With slowly (i.e. over months or years) deteriorating renal function, the latter remain relatively constant, because creatinine excretion (grams/sec) is the product of a gradually rising plasma creatinine concentration and a gradually falling creatinine clearance (mls/sec) or glomerular filtration rate.

**Practice point:** if creatinine clearance is less than half normal, we can say as a general rule that there must be bilateral impairment of renal function.

About 15% of glomeruli are juxta-medullary in position, send long loops of Henle down into the medulla, and are therefore more important in the renal concentrating mechanism than the more superficial cortical nephrons.

**Glomerular dysfunction**

From this we can see that if the glomerulus is damaged, its function of filtering plasma may be reduced (e.g. by swollen endothelial cells reducing capillary blood flow and narrowing glomerular pores), and in that case there will be retention of sodium, water and other components of the ultrafiltrate.

Its function of holding back protein may also be impaired and correspondingly, proteinuria may develop, particularly for smaller oncotic molecules such as albumin; and if this urinary loss exceeds the liver's capacity to increase albumin production, hypoproteinaemia and oedema may develop (nephrotic syndrome). Note that albumin (MW=70,000) is normally filtered to a small extent by the glomerulus, but reabsorbed in the proximal tubule, so that there is normally less than 150 mg. protein excreted per 24 hour. Smaller molecular weight proteins [Beta-2 microglobulin (MW= 12,000), lysozyme (MW = 14,000), retinol-binding protein (MW=21,000)] are filtered more by the glomerulus and also re-absorbed in the proximal tubule, so these may appear in the urine more than albumin in cases of renal tubular dysfunction. Also, as a guideline, if there are more than 3 grams of proteinuria per day, we can be fairly sure we are dealing with a glomerular lesion. Tubular lesions usually produce urinary protein excretion between 1 and 3 grams per day, and oedema does not occur because albumin losses are small. The full blown nephrotic syndrome with obvious clinical oedema does not usually develop until there is at least 3 and usually 5 grams of urinary loss of plasma proteins (mostly albumin) per day.

An additional feature which may arise from glomerular damage is **haematuria,** and of a special type, because during passage through abnormal holes in the damaged glomerulus the red cell membrane can itself become damaged and deformed, so as to produce odd-shaped red cells, particularly well seen on phase-contrast microscopy; red cell "casts" in the shape of renal tubules may also be seen. Another feature of damage to the glomerulus/afferent arteriole is hypertension, and we have to differentiate whether this is due to sodium retention from gross reduction in glomerular filtration rate, or to the release of renin from the afferent arteriole supplying the glomerulus.
2. Proximal Tubular Function

Almost all bicarbonate, and approx. 75% of the sodium, chloride and water are re-absorbed here, isotonically. Despite its isotonic nature, sodium re-absorption requires energy, at least in the second part of its three-step chain of mechanism. (The first step is merely absorption from the lumen down a sodium concentration gradient into the cell, but the second step, which extrudes sodium into the intercellular channels just below the "tight junctions" joining proximal tubular cell luminal aspects, requires energy. Actually, the third step of subsequent diffusion along the tortuous narrow intercellular spaces between the proximal tubules on the way to re-absorption in the peri-tubular capillaries, is passive, but resistance to flow at this level can increase the rate of passive "back-flow" into the tubular lumen, so that proximal tubular reabsorption of (isotonic) sodium chloride is influenced by peri-tubular capillary Starling forces.

95% of the filtered potassium is reabsorbed in the proximal tubule, and much of the calcium (approx 50%), phosphate, and urea as well. Filtered glucose, amino acids, organic acids and small molecular weight proteins are almost entirely re-absorbed in the proximal tubules.

Important: The task of the proximal tubule to not eliminate actual acid (H+) from the body, but to reabsorb bicarbonate. Confusion arises in this respect from two sources. First, the re-absorption of bicarbonate is a complicated step involving the initial secretion of hydrogen ions into the tubule (in exchange for sodium) to combine with bicarbonate and so facilitate its resorption, effectively as CO2. But the effect is not one of net addition of hydrogen ions to the urine. Second, acidosis may arise in cases where there is abnormal proximal tubular function, but this is due to a tubular leak of bicarbonate. The consequence of this is a lowering of plasma bicarbonate which shifts the dissociation of the carbonic acid equation (H2CO3 <---> H+ + HCO3-) to the right, and it is this that increases plasma hydrogen ion concentration.

Other organic molecules including organic acids can be secreted by the proximal tubule, the classic one for clinical measurement of proximal tubular function being para-amino-hippurate (PAH). These substances are secreted by active mechanisms which are saturable and so have a relative tubular maximum. Foreign substances and drugs or their conjugates can also be secreted into the proximal tubular tubule by similar mechanisms.

Thus, proximal tubular dysfunction or disease will produce a loss of sodium, potassium, bicarbonate, calcium, other minerals, as well as water, although to just what extent will depend on how other reabsorption/secretion processes involve these substances further down the nephron, if intact. By and large there are no further such processes for glucose, amino acids, phosphate or organic acid reabsorption, so these tend to appear in the urine in proximal tubular disease. But the tendency for any bicarbonate loss at this level to produce blood acidosis can usually largely be overcome by the more distal nephron, again if intact in function.
As noted above, small molecular weight proteins filtered by the glomerulus are also normally reabsorbed in the proximal tubule e.g. (beta-2 microglobulin, and retinol-binding protein), and measurement of these may be useful in localising a tubular anatomical site of any lesion to the proximal nephron. Hyaline casts are homogeneous cylindrical structures consisting of protein, and usually reflect no more than proteinuria. So-called Tamm Horsfall protein is a glycoprotein of tubular origin (mostly from cells of ascending limb of Henle loop) that may also appear in the urine in renal tubular disease. There, they aggregate with other tubular debris and any filtered protein to form so-called granular casts; hence they are more indicative of tubular damage than hyaline casts.

3. The Loop of Henle

The overall function of the loop of Henle is to generate an osmotic pressure gradient, increasing to a maximum at the tip of the loop in the renal medulla. It does this by a counter-current multiplier/exchanger mechanism which is basically driven by the thick ascending limb of the loop of Henle. There, (sodium) chloride is reabsorbed to bring about an increased sodium chloride concentration in the interstitium, and hence in the descending limb of Henle loop; as this fluid passes down the loop, counter-current exchange takes place through the differential permeabilities of the descending and ascending limb to produce a high osmotic pressure at the medullary tip. This enables re-absorption of water from the adjacent collecting duct in states of dehydration under the influence of the anti-diuretic hormone, ADH, which increases the permeability of the collecting duct to water.

The distal part of the thick limb of the loop of Henle is also responsible for active (sodium) chloride re-absorption. This process is flow-dependent, i.e. the more fluid presented to it, up to a point, the more is re-absorbed. Moreover, much of the sodium chloride is re-absorbed without water, so creating a hypotonic fluid at this level, i.e. "free water" (fluid of lower osmolality than the isotonic ultra-filtrate). In conditions of water load, the production of this hypotonic fluid is paramount in facilitating the excretion of excess water.

Thus, the thick ascending limb of the loop of Henle makes an important contribution to the osmotic forces required for both urinary concentration and dilution. The chloride transport process involved is inhibited specifically by frusemide and other "loop" diuretics acting from within the tubular lumen (having entered there by glomerular filtration).

The loop of Henle re-absorbs about 20-25% of the filtered sodium but less water as discussed (15% approx).

4. Distal Convoluted Tubule

Sodium: The proximal convoluted tubular accounts for about 70% of (isotonic) sodium re-absorption, and the ascending limb of the loop of Henle for a further 20-25%, leaving less than 10% for handling by the distal convoluted tubule. The early part of the DCT reabsorbs NaCl without water, so further diluting the urine, i.e. producing ‘free water’. Most or all of the remaining sodium is re-absorbed in the
latter part of the distal tubule and proximal collecting duct (conjointly referred to as the cortical collecting tubule), largely under the influence of aldosterone, which stimulates the sodium re-absorption - partly directly as isotonic NaCl, but mostly in exchange for potassium (and/or H+). This sodium reabsorption mechanism is stimulated to become extremely important in conditions of bodily ECF volume depletion. Equally, in ECF volume overload, inhibition of aldosterone secretion can to some extent decrease sodium re-absorption; but humoral natriuretic factors are also involved, the best known of which - atrial natriuretic peptides - are those released from the atria when stretched by an increased vascular volume.

The distal convoluted tubule is also the site of formation of ammonium (from glutamine) which is extremely important in the buffering of hydrogen ion for secretion in states of acidosis - particularly chronic ones, because this system is inducible to high activity over time. Not only does ammonium buffer the hydrogen ion, but when secreted into the tubular lumen it is not readily re-absorbed, because it is 'trapped' there as the positively charged ammonium ion. Hydrogen ions added at this level of the distal tubule are also buffered by the conversion of mono-hydrogen phosphate to di-hydrogen phosphate and this, too, is trapped as a highly (negatively) charged ion relatively difficult to re-absorb passively. If NH4+ is not excreted, it is returned to the draining renal vein blood and incorporated into urea by the liver, according to the reaction:

$$2\text{NH}_4^+ + \text{CO}_2 \rightarrow 2\text{H}^+ + \text{urea} + \text{H}_2\text{O}$$

so generating H+ ions (see Ch.15 for detail)

Since potassium is almost completely re-absorbed in the proximal tubule, it follows that it must be actively secreted further down if, as in most diets, there is a high potassium intake; most of this secretion occurs in exchange for sodium in the distal convoluted tubule.

Filtered calcium is also at least 90% re-absorbed by the time it reaches the distal tubule - at least 40% plus of that is re-absorbed in PCT, and 50% plus in loop of Henle thick limb - leaving a maximum of 10% for the distal tubule to handle, percentage re-absorption again depending on diet. (Calcium handling by the kidney and elsewhere is complex, and vitally dependent, as is phosphate metabolism, Vitamin D and parathyroid hormone - see Ch. 18).

5. Collecting Ducts

This is the site of re-absorption of free water in states of dehydration, when the duct is made permeable to water by the action of ADH.

6. The Juxtaglomerular Apparatus (JGA)

This is a complex of several parts of the nephron juxtaposed at one site, including the afferent and efferent arterioles of the glomerulus, a special distal tubular segment near the junction of the loop of
Henle with the distal convoluted tubule called the macula densa, and an intervening region of so-called lacis cells in the interstitium. The JGA has dense adrenergic innervation and prominent lymphatic drainage. Renin is released here from the afferent arteriolar granules either directly by beta-sympathetic nerve stimulation, or by a reduction of local renal arterial pressure (probably via renal afferent arteriolar dilatation during blood flow auto-regulation); there may also be macula densa tubular flow sensing mechanisms which can influence renin release, particularly in less acute states.

C. CONTROL OF DIFFERENT PHYSIOLOGICAL VARIABLES BY THE KIDNEY

1. SODIUM AND WATER

Glomerular Processes. The kidney is in some ways a peculiar organ. First, renal blood flow is much higher than required for its active metabolic processes. Moreover, this high level of blood flow is closely auto-regulated over wide levels of blood pressure - it is as if the kidney has 'decided' that a high blood flow is important per se. It may be that this partly relates to the maintenance of glomerular filtration and tubular nephron flow in different circumstances. Even so, the glomerulus has the potential to adjust the amount of glomerular filtrate quite independent of blood flow, by altering efferent versus afferent arteriolar constriction (e.g. if renal blood flow does, despite auto-regulation, tend to fall, GFR can be maintained by increasing filtration fraction through differential efferent arteriolar constriction and afferent arteriolar dilatation).

Another way glomerular filtration is buffered against any extreme change is via so-called 'tubulo-glomerular feedback.' Increases in chloride concentration of fluid presenting to the macula densa region leads to a reduction in GFR to that nephron. This is dependent on renin release from the nearby afferent arteriole of the JGA. However, whilst helping to buffer GFR against severe change, this does represent a paradox in relation to renin's involvement in sodium control, and this will be considered further below.

Tubular Na+ reabsorption. Further down the line, namely in the renal tubules, much of the filtered sodium, water etc. is automatically re-absorbed, but although in one sense buffering against rapid increases in GFR leading to fluid and electrolyte loss in the urine, this 'glomerulo-tubular balance' can also be seen as a mechanism maintaining a fairly steady state of fluid and electrolyte delivery to the distal tubule, because the contrary also holds, viz. if GFR falls, proximal nephron sodium chloride re-absorption falls as well.

The mechanism of glomerulo-tubular balance is not fully understood. It is partly automatic and passive and that can be seen where GFR is increased by efferent arteriolar constriction (e.g. via angiotensin II). This increases glomerular filtration fraction, and has the consequence of removing more ultra-filtrate from the blood flowing through the glomerulus, hence increasing oncotic pressure in the downstream capillary network around the proximal tubules, This, in turn, enhances the third
step in the chain of proximal tubular sodium re-absorption - it increases the rate of uptake of fluid into the peri-tubular capillaries, and therefore the rate of diffusion of isotonic sodium chloride along the narrow tortuous channels between the proximal tubular cells, so limiting fluid 'back-leak' into the proximal tubular lumen. Reduction in peri-tubular capillary hydrostatic pressure brought about by efferent arteriolar constriction also contributes to the Starling forces promoting such diffusion. Contra-wise, decreasing efferent arteriolar constriction at any given blood flow will decrease filtration fraction and therefore GFR, but this will be countered by reduction in the passive third step of isotonic sodium chloride re-absorption in the proximal tubule through shifting the balance of Starling's forces in the peri-tubular capillaries towards lesser re-absorption from the interstitium.

Thus, the kidney appears to have built-in automatic, often passive, buffering systems to ensure that no matter how the overall body fluid and electrolyte composition may change, there will be little change in blood flow, GFR or the amount of tubular fluid delivered to the distal nephron. Superficially, you may think that this is all very sensible, and if you only look at one side of each equation, it can often appear to be. Thus, maintaining blood flow to the metabolically active tubules is very important to their viability in any state of generalised drop in blood pressure. Also, glomerulo-tubular balance is important in preventing huge losses of water and electrolytes from the kidney in the face of high any unusual increase in GFR. However, such a mechanism would appear adversely placed to increase the amount of sodium and water eliminated from the kidney in states of volume overload, and to reduce it in states of ECF volume depletion (where glomerulo-tubular balance means that associated falls in GFR from severe ECF volume depletion will, per se, result in a lesser proximal nephron isotonic sodium re-absorption, and therefore sodium loss).

**Diuretics, Sodium and Water**

**Frusemide** is one of the most potent diuretics, and acts by inhibiting chloride re-absorption along the whole length of the thick ascending limb of the loop of Henle.

**Osmotic diuretics** are nonreabsorbable solutes such as mannitol. The proximal tubule cannot maintain a significant osmotic gradient across it, because of its high water permeability. Consequently, a solute filtered at the glomerulus, yet not re-absorbed in the proximal tubule, will retard the re-absorption of fluid. Sodium re-absorption along the tubule will therefore have to occur against an increasing concentration gradient and so will be limited. In this way, more sodium and chloride will be delivered to the ascending limb of Henle's loop, but at lower concentration. There, similar factors will also determine that chloride will not be well re-absorbed in the thick part of the ascending limb, thereby reducing the build-up of medullary osmotic gradients (which determine water reabsorption from the collecting ducts) as well as impeding renal sodium chloride re-absorption overall. Such patients are therefore at risk of both sodium and water loss (the latter partly in an obligatory way due to the presence of the osmotically active mannitol). Osmotic diuresis mechanisms are dealt with more fully in Chapter 16.
Thiazide diuretics are of particular interest. They act more on the distal convoluted tubule, and in so doing affect the formation of "free water" much more than counter-current exchange/multiplication. Hence, patients tend to be at risk of water overload. This is particularly true in occasional individuals where the thiazide diuretic also sensitises the ADH receptors of the collecting duct, so stimulating water re-absorption (inappropriately) to give total body water excess; (chlorpropamide, carbamazepine and some other drugs can do much the same thing - see also Ch 16).

Late Distal Collecting Tubule Diuretics

These diuretics cause urinary sodium loss (mostly in exchange for potassium and/or hydrogen ions) in the late distal tubule and proximal collecting duct. The best-known are the aldosterone antagonists such as spironolactone, but the newer agents amiloride and triamterine do much the same thing independent of aldosterone.

2. ACID BASE BALANCE

An extremely important function of the kidney to be taken up in more detail later in Chapter 15. Suffice it to say here that the overall function of the kidney is to excrete non-volatile acids. In terms of our making an Anatomical diagnosis, we should appreciate that many aspects of the nephron contribute to acid base balance, so we cannot expect the mere measurement of plasma pH to help us localise any lesion anatomically within the kidney. A reduction of glomerular filtration rate causes a reduction in the amount of acid excreted by the kidney through reducing the filtration of non-volatile organic acids and phosphate. The proximal convoluted tubule is responsible for bicarbonate re-absorption and the distal convoluted tubule for hydrogen ion secretion. All of these aspects are crucial to the maintenance of normal bodily pH. Nonetheless, further dissection of any acid-base disturbance and the company it keeps, is often useful in localising the site of the nephron involved in any renal problem.

Proximal tubular lesions are characterised by acidosis due to bicarbonate wasting, with corresponding reduction in plasma bicarbonate and therefore dissociation of carbonic acid to increase plasma hydrogen ion concentration (Henderson-Hasselbalch equation), so lowering plasma pH. In this situation, sodium bicarbonate may appear in the urine, but acidosis is not usually severe because it can be compensated for in large part by the distal tubular secretion of the accumulated hydrogen ions (using ammonium and other ions such as phosphate to buffer them). To maintain electrical neutrality, any proximal tubular bicarbonate lost has, of course, to be accompanied by some cation, usually sodium, and this eventually causes ECF volume depletion with secondary stimulation of the renin-angiotensin-aldosterone system. Aldosterone (acting in the distal tubule) helps minimise sodium loss, but does so at the expense of potassium exchange, so proximal tubular lesions are often associated with some hypokalaemia.
Proximal tubular damage may also be associated with the appearance of glucose, amino acids and other organic acids, as well as small molecular weight proteins (e.g. retinol-binding protein, (beta2 microglobulin).

In distal tubular lesions, hydrogen ions cannot be formed as NH4+, so that severe acidosis can result. The standard test is to give an ammonium chloride load by mouth and measure urinary pH after five hours, by which time the pH should have fallen below 5.3 if distal tubular function is normal. In distal tubular lesions there may also be abnormalities in plasma calcium and potassium.

3. POTASSIUM

This is filtered by the glomerulus but almost entirely (95%) reabsorbed in the proximal convoluted tubule, so that any dietary excess must be excreted in the distal tubule (distal part of the DCT and proximal collecting duct). This occurs largely in exchange for sodium under the influence of aldosterone.

Therefore, as a general rule, proximal tubule defects tend to cause hypokalaemia (see also 2. above), and distal tubular defects hyperkalaemia. Such defects may either be structural or functional. In Addison's disease there is an absence of circulating aldosterone, and hence potassium cannot be excreted in exchange for sodium in the distal tubule, so that hyperkalaemia results. A similar situation may arise in conditions causing atrophy of the afferent arteriolar renin-containing cells (hypo-renemic hypoaldosteronism); also, of course, with the angiotensin converting enzyme inhibitors and angiotensin receptor blockers; NSAIDs, too, may inhibit renin release and cause hyperkalaemia by a similar mechanism.

4. UREA

Urea moves passively out of the proximal tubules, but except for the inner medullary portion of the collecting duct, the rest of the tubular epithelium is essentially impermeable to urea. Because of this, urea becomes increasingly concentrated in the more distal nephron. However, just as with H2O, the medullary collecting ducts become permeable to urea under the influence of ADH. The important consequence clinically is that urea clearance falls with falling urine flow rates, as seen in states of dehydration and/or ECF volume depletion. This is reflected as a much greater rise in plasma urea than plasma creatinine (a marker of GFR) in those situations. As we shall see, this can be helpful in the diagnosis of what we call acute pre-renal failure.

The usual rate of rise of urea in acute renal failure is approx. 5 mmol/l/day. However, this is increased in states of increased protein catabolism/breakdown (infection, burns, trauma, muscle injuries, high protein diet), and reduced with low protein intake etc. Important to bear in mind where there is a disproportion of blood urea rise versus creatinine, especially before labelling your patient "acute pre-renal failure".
5. CONTROL OF BLOOD PRESSURE

The kidney exercises an important role in blood pressure control, especially via the renin-angiotensin system.

**Practice point.** From all the above, it almost seems that the kidney not only makes sure that it samples a high and fairly constant amount of plasma ultra-filtrate at the glomerulus, but that a fairly constant amount of this, in turn, passes through the more proximal nephron to the macula densa and beyond. This leads one to the general view that, despite significant reabsorption of fluid and electrolytes in the proximal nephron, it is the distal nephron which is mainly responsible for varying the amount of substances finally excreted in the urine. Moreover, to do that requires the presentation of a reasonably constant sample volume to it. Looked at in this way, all the glomerulo-tubular balance and tubulo-glomerular feedback mechanisms now make sense in presenting the distal nephron with an amount sample of ultra-filtrate that can then be varied either up or down as conditions require. Further, we know that the distal nephron is the site of fine regulation of sodium, water, potassium, calcium handling etc., so whole nephron function does seem to fit together in a rational way when viewed overall.

**CLINICAL DIAGNOSIS OF (ACUTE) OLIGURIC RENAL FAILURE**

**A. ANATOMICAL DIAGNOSIS**

Fist, we must as usual define the Anatomical site of the lesion. This first comes to the BROAD question of whether the problem is PRE-RENAL (low ECF or circulating blood volume) compromising renal flow and producing secondary impairment of renal function; RENAL; or POST-RENAL (obstructive) renal failure.

1. **Pre-renal failure**

   a). **Pre-renal oliguria**

   This is when there is acute reduction in the plasma volume to below a critical level. It may either be brought on by blood loss, or loss of sodium chloride and water reducing overall ECF volume. Less commonly, severe acute protein loss may produce expansion of the interstitial fluid at the expense of a fall in circulating plasma volume.

   Distinguish ECF volume depletion (salt and water loss) from dehydration (water depletion only). These terms are sometimes used loosely and interchangeably, but our use of them well be strictly as indicated. Rarely does water depletion per se result in pre-renal failure, because loss of water is distributed right across all body fluid compartments, and so bodily cellular functions are affected long before renal blood flow is reduced. Also, if kidney function remains normal, urine volume will fall -
though not to below 400 mls per day, because of the obligatory loss of water needed for the kidney to carry out its task of ridding the body of osmotically-active waste products.

The kidney is particularly vulnerable to any acute severe drop in circulating blood volume because, in that situation, in order to maintain blood pressure (in the interests of brain perfusion) the sympathetic nervous system is activated and readily shuts down skin, splanchnic as well as renal blood flow. Indeed, if there is associated fear/anxiety (e.g. car accidents), renal blood flow may fall dramatically even without a detectable alteration in systemic arterial pressure. (You may think this odd, because renal blood flow is normally closely auto-regulated independently of pressure, but with acute blood loss or other sympathetic discharge, such as that related to fear, fright, anxiety etc. this can readily be over-ridden). This reduction in renal blood flow results, of course, in functional renal impairment, because of a reduction in GFR and tubular function.

Hence in assessing any acute renal failure, make sure you look to see whether there is an adequate circulating blood volume. Arterial blood pressure is a relatively poor index of this, because reflex baroreceptor mechanisms ensure that blood pressure is reasonably maintained. Pulse rate and volume are a better guide, but not as good as the indicators at the capillary and venous level, because of baroreceptor control of heart rate and blood pressure.

The **jugular venous pulse** can be very useful in determining the state of "fullness" of the vascular compartment. This is particularly so in sub-acute and chronic ECF volume depletion where you should examine the central venous pressure (JVP) carefully. If the patient has a much reduced vascular volume, JVP may be almost zero; if you cannot detect it with the patient at 45 degrees, lie him/her flat, and if you are still not able to see it, obliterate the external jugular vein above the clavicle with your finger and watch the rate of rise of the venous pressure - it will be very slow indeed in states of ECF volume loss. The other way of detecting extra-cellular fluid volume loss is to look for evidence of intestinal fluid volume depletion, such as wrinkling of the skin and poor skin tissue turgor. There may also be dryness of the tongue, but this is also seen with dehydration, i.e. pure water loss.

**Acute Blood loss.** Despite its value in sub-acute to chronic ECF volume depletion, the JVP is sometimes misleading in states of acute blood loss. This is probably because this situation is associated with severe sympathetic discharge, which not only constricts the arterioles, but the venules as well, so driving blood from the normal peripheral capacitance vessels more centrally to the larger veins, and tending to maintain jugular venous pressure. This can make matters difficult in treatment as well as diagnosis, because the JVP, too, then becomes a poor indicator not only of when the patient has a low blood volume, but of when he has had sufficient blood replacement.

The **best indicator of the state of the peripheral circulation in acute blood loss**, particularly that associated with anxiety, fright, etc. as in motor vehicle accidents (i.e. where there may be severe sympathetic discharge) is the **state of perfusion of of the tissues**, and this is best examined clinically by determining the **warmth and colour of the hands and feet**. Their perfusion tends to run parallel to
that of the kidney and splanchnic beds. Indeed, many medical directors of acute trauma units do a regular round of "uncovered toes" to determine when the patient has had sufficient transfusion.

The history as usual, will be all-important in diagnosis of pre-renal failure, particularly a history of trauma and/or blood loss.

*Examination* looking now for both the signs of acute blood loss (which are sometimes hidden as in a bleed from the GI tract) and of more chronic ECF depletion (tissue turgor etc).

*Examination of the urine* will be very helpful in diagnosing pre-renal impairment of renal function. The urine should be very low in volume (but not less than the obligatory 400 mls per day) with of maximum specific gravity of 1.030 (osmolality 1200mosm/l). In the compensated state, there will be very little sodium in the urine (<10 mmol/day) but urinary urea will be highly concentrated.

*Investigations* of value in pre-renal failure are plasma urea versus creatinine. Classically, as described above, urea will be elevated above normal much more than creatinine, because plasma creatinine mostly depends on glomerular filtration, whereas urea clearance falls off markedly as urine flow rate becomes reduced in any hypovolaemic state.

b). Renal Failure Secondary to Pre-Renal Failure

Prolonged severe reduction in circulating blood volume results in functional failure going on to renal damage from ischaemia. From the pathological standpoint, the tubules are most sensitive to ischaemic damage, and the classical syndrome complicating severe uncorrected blood loss is *acute tubular necrosis*. We might expect that this would cause polyuria with loss of electrolytes, potassium, amino acids etc. (because the normal task of the tubules is to re-absorb these substances). And sometimes this is the case (polyuric acute renal failure). But oliguria is characteristic, at least initially. In part, this is due to an associated impairment of glomerular blood flow and filtration particularly in the early phase, when the condition is often referred to as *acute ischaemic vasomotor nephropathy*. But it takes more than reduced glomerular filtration to produce the profound oliguria and deterioration of renal function usually seen in this condition. In this respect there are many theories, but the simplest is that the tubules become blocked by both ischaemic tubular cell swelling and by desquamated material from necrotic cells; and when this blockage is combined with a leakiness of more proximal areas of the tubule, it gives rise to a back - diffusion of fluid into the interstitium, so it is not hard to see how oliguria could result.

One can usually get some idea from the history of whether or not acute tubular necrosis is likely by the severity of blood loss and the time which has elapsed before it is fully restored. Also, quite early on, urine osmolality tends to approximate that of plasma regardless of the state of water balance, due to the early derangement of countercurrent mechanisms. As the condition progresses, urinary sodium tends to increase and become greater than 40 mmol/litre (contrast pre-renal oliguria above) - even in the face of a low plasma sodium. There may also be small molecular weight proteinuria such as
beta-2 microglobulin and retinol-binding proteins from tubular failure to reabsorb filtered protein. Tubular casts of protein may result, although their diagnostic value is not high. Another useful test is to give IV frusemide, which may cause a diuresis in the early stages of this condition. But do this only after adequate restoration of blood volume, and after taking urine for diagnostic analysis.

2. Renal Causes of renal failure

Diagnosing the Anatomical site along the nephron of any renal impairment can be done from our knowledge of the physiology of the different nephron segments. Hypertension, oedema, proteinuria of more than 2 grams per day in the urine, with red cell casts and odd-shaped red cells (damaged from passage through distorted glomerular capillaries), all point to a glomerular lesion. Also, pure glomerular types of acute renal failure are not usually associated with a urine sodium concentration of less than 20 mmol/l (contrast pre-renal failure), or more than 40 mmol/l (contrast "acute tubular necrosis" above).

On the other hand, a small amount of protein in the urine such as Tamm Horsfall protein, beta 2 microglobulin, retinol-binding protein together with "granular" casts (protein debris gelled in Tamm Horsfall protein) would indicate a tubular lesion.

More specifically, the additional presence of glucose and amino acids in the urine would suggest a proximal tubular lesion. A high sodium and low potassium in the urine would suggest a distal tubular lesion affecting the normal action of aldosterone.

Other distinctions between proximal and distal collecting duct lesions, particularly in relation to acidosis, have already been discussed.

Loop of Henle lesions occur in a number of conditions, and the prototype is the action of various diuretics, particularly frusemide, discussed above.

A lesion in the distal collecting duct would be suggested by a very dilute urine in the face of dehydration (inference with ADH effect). This defect can be either structural or functional. For example, hypokalaemia induces impaired functioning of the collecting duct receptors to ADH, and in 'nephrogenic diabetes insipidus,' ADH receptors are effectively lacking; on the other hand, non-responsiveness to ADH may also result from structural collecting duct dysfunction secondary to chronic lower urinary tract obstruction.

3. Post-renal (Obstructive) Renal failure

This is usually produced by urinary tract obstruction at or below the level of the prostate i.e. at a single site, but occasionally by bilateral ureteric obstruction (from stones) or by unilateral ureteric obstruction in those with a single kidney.
**Practice Point.** Whereas the pre-renal failure produces oliguria, obstructive renal failure usually produces complete anuria, or at most a urine output of 200 mls per day. In any patient with renal impairment, exclude both pre-renal and post-renal failure before assuming the kidney itself to be at fault. Examine the abdomen carefully for bladder distension, because that is the hallmark of obstruction below the level of the bladder. Also do a rectal examination (prostate), and examine the urethra including the urethral meatus; ensure that the prepuce retracts normally, because its meatus may also stenose, block, and cause urinary obstruction, especially in infants. Examine the urine microscopically: Red cells in cases associated with damage to the endothelim, white cells and organisms in infection. Also examine for urinary crystals, particularly calcium phosphate (in bilateral ureteric calcium stone obstruction) and urate (uric acid stones are radiolucent).

Even if there is no clinical evidence of bladder obstruction, still exclude bilateral obstruction at the level of the ureters or above (or unilateral ureteric obstruction in patients with a solitary kidney). The most useful investigation in this respect are examination by abdominal ultrasound and/or CT scanning; if there is obstruction then there will be dilatation of the collection system above the obstructed point(s). And calculi may also be identified to help aetiological diagnosis.

An important principle in diagnosis of acute renal failure is to **exclude any remediable cause** and in this respect pre-renal and post-renal failure are paramount.

**HIERARCHIC APPROACH TO ANATOMICAL DIAGNOSIS OF RENAL DYSFUNCTION**

First, make sure that the patient does not have any **evidence of hypovolaemia** and/or interstitial volume depletion. Next look for evidence of urinary outflow tract obstruction clinically (enlarged bladder, prostate, urethral or meatal stricture etc.). Exclude obstruction by further investigation if necessary.

Any **pain** is important in diagnosing the anatomical site of the lesion. Thus, bilateral "colicky" loin pains radiating to both groins or the testes would strongly suggest the presence of **bilateral obstruction of the ureters**. The kidney itself does not give rise to a great deal of pain, but there may be a dull ache, e.g. in patients with acute renal failure due to bilateral renal artery embolism causing infarction (rare, but important). Look for localising signs including urinary signs i.e. red cells, granular casts, red cell casts, red cell morphology, tubular cell casts, white cells, protein, glucose, sodium concentration, urine Na/K ratio, and urine/plasma osmolality ratio.

**General Functional Effects** also help to localise the site of the problem in acute renal dysfunction. For example, hypertension probably signifies a glomerular lesion (from fluid retention or renin release or both). Oedema may also arise from a glomerular protein loss as indicated by proteinuria of at least 3 grams per day and hypoalbuminaemia of less than 30 grams/l (NR 35-50). Note from this that there are really two sorts of acute impairment of glomerular function, one with the emphasis on reduction of
GFR and oedema (without significant hypoproteinaemia), together with blood pressure elevation and relative oliguria; and the other ('nephrotic syndrome') where the essential defect is leaky capillaries in the glomerulus with resultant proteinuria, hypoproteinaemia and oedema, usually without oliguria or hypertension. In the early phases of the nephrotic syndrome, the proteinuria can be relatively selective for smaller molecules (e.g. more albumin than globulin in the urine).

Tubular abnormalities may give rise to electrolyte disturbances, such as low ionised calcium (with twitching, Chvostek's sign, Trousseau's sign) potassium retention (causing cardiac irregularities and even cardiac arrest); acidosis (increased ventilation); confusion (accumulation of urea and other toxic products), glycosuria, phosphaturia and aminoacid-uria (proximal tubular lesions).

**B. CLINICAL PATHOLOGY DIAGNOSIS**

In the history, this is given to you by the usual indicators i.e. mode of onset, time-intensity relationships etc. In this respect a sudden onset as usual means obstruction of hollow tubes, but in the renal system this can either be an obstruction to the vascular supply of the kidney or to the urinary collecting system. The difference between these two can be dissected by the fact that ureteric obstruction causes severe colicky pain.

Examination: examine the urinary tract including the bladder. Also examine both loins and try to palpate the kidneys, not only their size but any evidence of tenderness which might signify inflammation. In addition, the renal system is one where we do have excretions (urine) available for examination and this may help Pathological diagnosis greatly - polymorphs and organisms from bacterial inflammation, and red cells from capillary damage with ulceration, trauma, infarction etc. Urinary eosinophils suggest an allergic condition, such as occurs in the idiosyncratic "interstitial nephritis" reaction to some drugs, e.g. the NASIDs, gentamicin, amoxycillin, sulphonamides. Urinary cell cytology is important in diagnosing of malignancy within the renal/urinary system.

**C. FUNCTIONAL DIAGNOSIS IN ACUTE OLIGURIC RENAL FAILURE**

Because the kidney is a somewhat inaccessible organ, we are to a large extent reliant on our Functional diagnosis for the assessment of the Anatomical site of the lesion, so we will already have this diagnosis in hand in most cases. However, the degree of dysfunction is also important in its own right, particularly in terms of treatment (e.g. signs of potassium intoxication such as cardiac irregularities must be treated immediately as it is a potential cause of sudden death in acute renal failure).
D. AETIOLOGICAL DIAGNOSIS

Examples.

Sore throat preceding post-streptocccocal acute renal failure.

Atrial fibrillation in the context of renal artery embolism.

Analgesic/NSAD abuse, and

Diabetes with urinary infection in the context of renal medullary necrosis.

Vesico-ureteric reflux predisposing to chronic renal infection.

Idiosyncratic immuno-mediated reactions to drugs in interstitial nephritis.

Angiotensin converting enzyme inhibitors precipitating acute (pre-) renal failure in patients with bilateral renal artery stenosis or unilateral stenosis in a solitary kidney. Be particularly watchful where combined ACEI and ARB blockers of the renin-angiotensin system are being used together, as in hypertension treatment

Drugs such as gentamicin causing glomerular/proximal tubular damage.

Hypercalcaemia, hyperuricaemia predisposing to stone formation.

CHRONIC RENAL FAILURE

We will deal with this more when we discuss electrolyte disturbances. Much of what we find is predictable. There tends to be a reduced glomerular filtration rate and therefore fluid and water retention in glomerular failure. Glomerular/afferent arteriolar involvement also usually leads to persistent hypertension. This hypertension may aggravate glomerular and other renal damage and worsen the renal failure. Potassium tends to accumulate in chronic renal failure. A more subtle defect is in calcium metabolism, because the kidneys are the site of (tubular) conversion of the relatively inactive 25 OH vitamin D to its biologically active 1,25-OHD3 form. If the tubules are diseased, therefore, we have the equivalent of a lack of vitamin D, and this tends to reduce intestinal calcium absorption, lower plasma calcium and cause osteomalacia. The lowered plasma calcium, in turn, usually stimulates the parathyroid glands to release PTH in an attempt at compensation. This helps elevate serum calcium, but it provokes calcium reabsorption from bone, with a resultant complicated picture of what we call 'renal osteodystrophy,' which is at least in part a combination of osteomalacia
(Vit. D lack) and secondary hyperparathyroidism. Renal osteodystrophy may also include osteosclerosis i.e. areas of increased bone density, the cause of which is uncertain, but may be partly due to the relative normalisation of calcium (through the secondary hyperparathyroidism) in the presence of a high phosphate (from the renal failure) thus increasing the calcium X phosphate product, and predisposing to calcification.

'Tertiary hyperparathyroidism.' If secondary hyperparathyroidism is prolonged, it may eventually lead to autonomous activity of the parathyroid glands, and even adenoma tumour formation, in which case the plasma calcium now becomes uncontrolled and may even rise to levels above normal. This is a particularly dangerous situation as hypercalcaemia can itself have severe effects on the kidney, both structural and functional, such as loss of concentrating ability, afferent arteriolar constriction (hypertension), reduced GRF, and defects in acidification. Because of all these factors it is important to limit any tendency for both calcium and phosphate to rise in chronic renal failure. Phosphate binders are available for this purpose. On the other hand, early in the hypocalcaemic phase of chronic renal disease it may help to give small doses of calcium and/or 1,25-OH3 vitamin D so as to inhibit the development of secondary or tertiary hyperparathyroidism. This does no harm if plasma calcium is watched carefully. If the patient is seen at the stage of autonomous or 'tertiary' hyperparathyroidism with hypercalcaemia, the parathyroid glands may have to be removed. In practice, the management of hypercalcaemia is extremely difficult, because normalizing calcium too much may cause what is referred to as 'adynamic bone syndrome.' This can lead to osteoporosis and fractures, so it is now thought best to keep plasma calcium a little low and PTH on the high side.

In chronic renal failure other effects can develop including anaemia (from a lack of erythropoietin), susceptibility to infection (from neutrophil leucocyte impairment); bruising (from defects in platelet function); pigmentation (from MSH fragment accumulation); itch (partly from retained urea); peripheral neuropathy (cause uncertain, but probably involves 'middle molecules' that are normally filtered by the glomerulus but not by artificial renal dialysis membranes). Nausea and vomiting are prominent gastric symptoms, and severe weakness can arise, from both general debilitation and electrolyte disturbances.

MCQs & PROBLEM SOLVING

A. Mechanisms in Disease

A patient is sent to you with a diagnosis of acute (3 day) unilateral right renal artery embolism with secondary renal infarction and moderate haematuria. The embolus is believed to have cleared 24 hour ago. Which of the following would be recognised features:

1. The production of less than 500 mls of urine per day.
2. Acute right-sided colicky right upper abdominal quadrant pain radiating to the back.

3. Red cell casts in the urine.

4. Abnormal red cells in the urine on phase-contrast microscopy.

5. A urine sodium of <10 mmol/l.

6. A fixed specific gravity in the urine of 1.010 (urine osmolality 300 m.mol./l.).

7. Urine protein loss selectively affecting immunoglobulins more than albumin.

8. Hypoproteinaemia.


11. Low plasma pH.

12. Abrupt onset of the condition.

13. Oedema.


15. Atrial fibrillation would be an important consideration from the aetiological standpoint.

**Answers** at end of chapter.

**B. Problem-Solving MCQ.**

Now to a really complex problem. If you have followed the method of building up a diagnosis as recommended, and especially in reaching many interim conclusions along the way, then you will be ready for this. But be warned, it is not for the faint-hearted!

A 53 year old (1) male butcher (2) is admitted to hospital in "shock" after two severe haematemeses two hours apart, and on arrival in hospital has a further haematemesis of approx. 500 ml. (3). Prior to the episode he had been relatively well except for a recent bout of his old "indigestion" (4), from which he has suffered for a number of years, in bouts averaging up to three weeks, interspersed with periods of freedom usually of some months (5). On questioning, this indigestion has taken the form of
a "burning" epigastric pain occurring one to two hours after meals, occasionally waking him at night, and usually relieved within ten minutes or so by antacids (6). During the last three weeks the pain has occurred more regularly and has been more severe, particularly at night (7).

In between bouts of epigastric pain he has been well, without any disturbance of micturition, bowels, appetite, and no weight loss or fever (8). No history of shortness of breath, ankle swelling, headache, or visual disturbance, but he does admit to "bad nerves" and he was particularly upset recently by the death of his brother (9). He normally drinks '4-5 beers/day' for some years, but more in the past month (10). He is a cigarette smoker of 25 per day average, again more recently (11). No family history of any specific organic disease, but there has been some domestic conflict with his eldest son over the last 6-12 months (12). No relevant past history. Medications: antacids only (13). Note: the details of this history were obtained only after initial resuscitation (14).

Examination reveals a somewhat obese confused man, with extremely pale, cold, white extremities, undetectable radial or foot pulses, but a brachial pulse of 130/min with poor volume and a "thready" character (15). Temp. 36 deg. C (16). Blood pressure 80/50 mm Hg (lying). JVP not visible even with patient lying flat (17). No cardiomegaly, two heart sounds, no murmurs, no added sounds. Chest clear. Abdomen somewhat obese, but no splenomegaly or hepatomegaly detectable (18). No renal masses or loin tenderness. Some epigastric tenderness (19). No bladder palpable (20). PR: normal prostate (21), black, tarry, offensive liquid stool on glove (22). CNS: drowsy and somewhat confused (23). Skin: hair distribution normal, no palmar erythema, clubbing or spider naevi, no jaundice, no parotid swellings, no unusual bruising (24). Endocrine: no gynaecomastia or testicular atrophy (25). Urine examination (catheter specimen): volume 50 mls (26), urine osmolality 450 m.mol./l. (27), urinary sodium 8 m.mol./l. (28). Microscopy NAD (29).

On admission to E.D., transfusion was begun immediately, and 1.5 litres of blood were given intravenously over the next hour (30). At that stage blood pressure had risen to 110/60 mm Hg, pulse had fallen to 108/min, and the JVP had risen to 2 cm (31). Nonetheless his hands and feet remained cold and white (32) and the urinary output through the catheter had only been 10 mls over the hour (33). He appeared restless. At this stage it was felt that time should be allowed for the circulation to "re-adjust", so he was merely observed for the next three hours (34). At the end of that time his haemoglobin was 70 grams/l, BP 120/65, JVP 2 cms, no basal lung crepitations, pulse rate 96/min (35). However there was only a 15 mls urinary output over the two hours and his hands and feet remained cold (36).

**Interim Conclusions?**

After consultation with a physician, he was given immediate further transfusion of blood together with an intravenous infusion of dopamine (a renal vasodilator dosage) (37) which resulted in improvement of the colour and temperature of his extremities back to normal and a rise of BP to 140/90 mm Hg; JVP 5 cms, pulse 84/min; a few fine late inspiratory basal lung crepitations (38). However, urinary output remained at less than 20 mls/hour (39).
A program of 'watchful expectancy' was adopted and the patient had no further episodes of haematemesis. His haemoglobin 24 hours later was 120 g/l and blood pressure, pulse, JVP, and chest auscultation were all normal; good peripheral perfusion with warm hands and feet (40). Nonetheless, urine output remained less than 15 mls/hour (41) and microscopy revealed a great deal of debris with some dead cells and granular casts (42); no red cells, but some hyaline casts (43). Urine biochemistry: a trace of glycosuria (44), an osmolality of 300 m.mol/l. (45), urine sodium 80 mmol/l (46), and abnormally high amounts of amino-acids (47), beta 2 microglobulin and retinol-binding protein (48). Plasma creatinine at this stage was elevated to twice normal (49) and blood urea to 4 times normal (50). Plasma sodium 130 mmol/l (51), chloride 95 mmol/l (52) potassium 7.8 mmol/l (53). Plasma osmolality 270 m.mol/l. (54). Blood pH 7.32, bicarbonate 20 mmol/l, arterial pCO2 30 mm Hg (55). Subsequent urine culture revealed no growth (56).

Solve the problem in the usual way and then answer the following.

Which of the following is/are correct?

1. On presentation this man probably had pre-renal oliguria due to renal shut-down associated with blood loss.

2. The only odd feature in the initial diagnosis was the urinary sodium, which one would have expected to be higher.

3. This man's long-term outcome would have been better had more time been taken to obtain the detailed history before rushing in to immediate blood transfusion.

4. By the end of the first hour, all the signs indicated that blood volume had been restored to normal.

5. The use of dopamine as a renal vasodilator was counter-productive because it merely allowed over-transfusion to increase venous back-pressure on the kidney, so reducing its effective renal blood flow still further.

6. Had dopamine and further transfusion been given earlier, this patient may have restored his urinary output and renal function to normal.

7. The haematemesis was probably due to oesophageal varices secondary to cirrhosis of the liver.

8. The most recent investigations indicate that this man has now developed bilateral renal infarction.

9. There is now evidence of renal tubular dysfunction.

10. He now has evidence of a metabolic alkalosis.
11. There is current evidence of a reduction in glomerular filtration rate.

12. He still appears to have an element of pre-renal impairment.

13. Ultrasound would be likely to show bilateral dilatation of the pelvi-calyceal/ureteric systems.

14. The most urgent electrolyte problem needing treatment is the low plasma sodium.

15. At this stage the diuretic frusemide would characteristically be expected to result in a brisk diuresis and natriuresis.

16. The "anion gap" is normal.
## Problem Solution - 1

### Ch. 14. Renal Problem-solving.

|--------|-------|------|------|

**Interim Conclusion** 1.

**Upper G.I. tract**

- Hyperacute onset.
- Bleeding — ? approx 2 litres blood.
- **?? Why**!

**Further History.**

4. Recent acute episode, severe (?).

- Ulcer.

5. Background Chronic relapsing (3/52) & remitting (3/12) course. i.e. Non-progressive, (= prob. not Cancer)


4. Long-term "Indigestion" =

6. 'Burning epig. pain, 1-2 hrs. after meals, sometimes at night. Relieved by ‘antacids’

**Interim Conclusion** 2.

**Duodenum**

- Chronic remitting & relapsing process.
- ? Recurrent ulcer.
- Recent severe episode

Upper abdo. pain, relieved by antacids.

7. More severely recently. (Also haematemesis, consistent with ulcer.)

8./9. Direct questioning. No specific symptoms, apart from ? "Bad nerves", & recently more stressed due to death of brother.

10. Chronic mod. EtOH intake, more in past month.

11. Cigs. 25/day, more for 1/12.

12. More Stress past 6-12, espec. recently.

13. Rx antacids

**Footnote.**

Obs. 4. is presented partly as background history and as such could be allocated entirely to the Why? column. But where any background history leading up to a current illness is so similar to, and so obviously relevant to, the present complaint, it is best to discuss it first as part of the presenting problem.

In any event, the Why? column is best reserved for information relating to the underlying cause of the present condition.

In respect of initial column allocation of information, a good ‘rule of thumb’ is:

If in doubt, place the information first in the How? column. It can always be transferred later.

A case in point is with obs. 6. Where the phrase ? peptic ulcer, ? duod, is placed initially in the How? Column, and then transferred to the Where? and What? columns later in this same part of the table.
Ch. 14. Renal Problem-solving (contd.).

**Examination Findings.**

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<tr>
<td>16. Temp 36°C = sl, low — in view of 15., could this be related to reduced skeletal muscle blood flow, with consequent inability to maintain normal body temp. through shivering?</td>
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<td>16. Certainly No evi. of generalised inflammation.</td>
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<td>17. BP, 80/50 = V. low BP. JVP, also V. low</td>
<td>V. low circulating blood volume.</td>
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<td>presumably — 2° to blood loss — see 3. above.</td>
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<tr>
<td>Thus bleeding upper GI vances unlikely as a cause of blood loss.</td>
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<td>19. Some epig. tenderness ? due to acute peptic ulcer</td>
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<td>20. No bladder palpable = No lower urinary tract obstrn.</td>
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<td>21. PR. No prostatic enlargement.</td>
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<td>22. ? Ulcerative process Upper GI blood loss — see also 3. above.</td>
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<td>22. Melaena. presum. 2° to</td>
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<tr>
<td>Upper GI, tract. — see also 3., above.</td>
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<tr>
<td>23. CNS. — sl. confusion not likely 2° to liver dysfn. ? 2° to reduced cerebral perfusion.</td>
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<tr>
<td>24. Hair distrbn. normal. No palmar erythema, clubbing, or spider naevi. No jaundice or bruising.</td>
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<td>25. No gynaecomastia or testicular atrophy</td>
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<td>24. ± 25. = — No evi. of liver dysfunction.</td>
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<tr>
<td>? no evi. of 2° effect of</td>
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<tr>
<td>24. No parotid swelling = EtOH on parotids.</td>
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<tr>
<td>→ ? Functional change.</td>
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<tr>
<td>Urine micro — NAD. =</td>
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</table>
| ↔ No evi. of pathological renal process.
PROBLEM SOLUTION-3

Interim Conclusion 3.

|---------|--------------------|-------------------------------|--------------------------------|

Subsequent course in hospital.

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<td></td>
<td>30. 1.5 l. blood transfusion over 1 hr.</td>
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<td></td>
<td>31. BP. (lying), pulse rate improved, and JVP. back to normal but,</td>
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<td></td>
<td>32. peripheral skin circ. still ↓</td>
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<td>33. Prob. renal circ. as well. (↓ urine output prob. 2 to ↓ RBF/GFR.)</td>
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<td>34. Not good Rx — peripheral circ. ↓ indicates need for more blood.</td>
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<td>35. 3 hrs. later — Hb. ↓ — from grad. haemodilution, → signs of ↓ central blood vol., but</td>
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<td>36. Still evid. of ↓ skin &amp; renal circ.</td>
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<tr>
<td></td>
<td>37. Further blood transfusion + renal vasodilator (dopamine).</td>
<td></td>
<td>?? Why — RBF should, like skin blood flow, now be normal, other things being equal.</td>
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<tr>
<td></td>
<td>38. ↓ central &amp; skin circ. rel. N., ↓ JVP, ↑, &amp; basal lung creps. = perhaps even sl. overt-transfused but</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>39. Urinary output still ↓</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>40. 1 day later. — Central &amp; skin circ. now normal, but</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>41. Urine output still v. low. =&gt;</td>
<td></td>
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</tbody>
</table>

Interim Conclusion 4.

| Renal | Continuing problem, though no evident path. process. | Slow, but eventual good return of both (1st.) central & (2nd.) skin circulation. | Renal haemodynamics — or at least renal function — still impaired. | ??Why! |

### Ch. 14. Renal Problem-solving (contd.)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>?Renal tubules</td>
<td>(Ischaemic)</td>
<td>Necrosis.</td>
<td>Prolonged ↓ in renal blood flow. (Renal Ischaemia)</td>
</tr>
<tr>
<td>Prox. tub. &amp; Henle loop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal tubule</td>
<td></td>
<td></td>
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</tbody>
</table>

| 44 | ? Trace glucose in urine - ? prox. tubular dysfunction. |
| 45 | ? Urine osmolality approximates plasma (see also 54, below). |
| 47 | 2 to prox. tub. dysfunction |
| 48 | Amino-aciduria |
| 49 | High urinary Na + |
| 50 | Poor prox. tubular funct. |
| 51 | Plasma creatinine ↓ x 2. |
| 52 | ? 2 to muscle breakdown or, |
| 53 | ? 2 to ↓ GFR. |
| 54 | Blood urea ↑ x 4. |
| 55 | Odd in this context - see discussion. |
| 56 | Plasma Na + sl. low. = |
| 57 | [Thick asc. Henle /early DCT f. n. (Site of formation of ‘free water’).] |
| 58 | Plasma Cl- rel. lower than Na +. |
| 59 | Plasma K + dangerously high!!! |
| 60 | ? 2 to ↓ distal tubular function. |
| 62 | Blood pH 7.32 = acidaemia. |
| 63 | Art. pCO2 low, thus not resp. acidosis. |
| 64 | Art. bicarb. also low, therefore |
| 65 | Metabolic acidaemia. |
| 66 | ? also part 2+ to pl.K + |
| ? 2+ to distal tub. dysfunction. |
| Anion gap = | [Pl. Na+ (130) + K+(8)] minus [Pl. Cl- (95) + HCO3-(20)] |
| = 23. (N = 12-20) |
| Thus, anion gap ↑ |
| ? Nature of extra ion |
| ? lactate (2+ to recent ‘shock’). |
| ? phos. etc., 2+ to ↓ GFR./altered renal tub. fn. |
| But, can at least say, |
| Metabolic acidaemia not merely 2+ to hyperkalaemia |

56. Urine culture — NAD. = No evid. of infection as the cause of renal dysfunction.
**PROBLEM SOLUTION-5**

Ch. 14. Renal Problem-solving (contd.).

**Conclusions.**

Because we have taken such care to draw interim conclusions as we have gone along, this now largely becomes a matter of putting these together.

<table>
<thead>
<tr>
<th>Anatomic Diagnosis</th>
<th>Pathological Diagnosis</th>
<th>Functional Diagnosis</th>
<th>Aetiol. Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Gl. Tract, probably Duodenum</td>
<td>Recurrent ulcer.</td>
<td>Peptic ulcer</td>
<td></td>
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<tr>
<td>b). Recent severe episode</td>
<td></td>
<td></td>
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<tr>
<td>3. Further Complic.</td>
<td>Prolonged ↓ in RBF.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a). Glom.-erulus.</td>
<td>Ischaem. cell swelling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b). Renal tubules.</td>
<td>(i) Ischaem. cell damage</td>
<td>↓ in GFR, to approx. 1/2 (creatt × 2) &amp;</td>
<td></td>
</tr>
<tr>
<td><strong>(ii) Ischaemic cell necrosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of integrity of tubular cell lining</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Probable DCT/collecting duct luminal blockage by necrotic cell debris.</td>
<td></td>
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</tr>
<tr>
<td><strong>41. Oliguria.</strong></td>
<td>Leakage of tubular fluid above block back into interstitium.</td>
<td></td>
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</tbody>
</table>

**Oliguria otherwise difficult to explain — would normally expect polyuria in cases of failure of normal renal tubular function. — see also Discussion.**
A. PROGNOSIS.

Recovery from the now-present ‘acute tubular necrosis/acute vasomotor nephropathy’ is possible, but the lesson to be learned from this case is that, to be adequate, blood replacement must not only immediately correct the central circulation but the peripheral circulation as well, and this includes the circulation to the kidney — which is particularly sensitive to the effects of decreased blood flow, especially the tubules.

Obs 50: urea elevated more than creatinine. This would normally suggest some ongoing decrease in ECF volume, but not likely in this case with such good peripheral circulation. More likely that urea has accumulated from blood breakdown in the gut.

B. INVESTIGATIONS.

1. Functional diagnosis - fairly clear
2. Pathological diagnosis. — Further analysis of the urine would help determine the extent of glomerular damage (eg. odd-shaped cells on phase-contrast microscopy; red cell casts). This might also help better delineate the Anatomical Diagnosis.
3. Anatomical diagnosis. — see above.
4. Aetiological diagnosis.— No real need to look beyond the recent increase in stress and cigarette smoking, but always ask the patient what he/she thinks brought the condition on.

C. TREATMENT.

1. Functional.
   a). Deal immediately with very high plasma K⁺ to prevent cardiac arrest!! Give calcium gluconate (to counter the effects of ↑ pl. K⁺ on cardiac muscle), and insulin plus glucose (to reduce plasma K⁺ levels per se.) in the short term; and K⁺ uptake resins per rectum (eg. resonium A) for more long-term plasma K⁺ control.
   b). Correction of acidemia. Caution. First wait and see what happens after potassium falls. pH is not very low anyway, and may correct itself when plasma K⁺ returns to normal (ask yourself why).
   c). Plasma sodium is not really very low at present, but since urinary output is low, it is important to restrict daily oral water intake to balance water output (= urine output plus insensitive water losses). In this respect, the patient must be on a fluid balance chart and, just as importantly, must be weighed daily.

2. Pathological.
   Too late now to do much but wait and see, but glomerular damage may well heal and tubules regenerate given time. Meanwhile, it is important to maintain the patient in a normal state of fluid and electrolyte balance (see Functional treatment above).

3. Anatomical.
   Again, no specific treatment except time.

4. Aetiological.
   a). Observe stools for any further occult bleeding, daily check on haemoglobin for the same reason.
   Further transfusion as necessary.
   b). H₂ antagonists are rational treatment, although there is no good evidence that they hasten healing of acute bleeding peptic ulceration; the more potent H⁺pump (H⁺,K⁺ -ATPase) inhibitors (e.g., omeprazole) be better. Deal with the underlying stress problem so as hopefully to prevent ulcer recurrence. And once the stress has been dealt with, cigarette smoking may be easier to stop or at least curtail. If stress and/or cigarette reduction long term not possible, then give long-term H₂ antagonists to keep the ulcer healed.
   c). If in doubt, gastroscopy to view lesion and quarterise and bleeding point.
   d). Surgery is necessary in some cases.
MCQ ANSWERS

1. Mechanisms in Disease.
   2, 3, & 4 correct.

2. Clinical Problem solving case.
   1, 6, 9, 11 correct. All others false

INTERIM COMMENTS: BIOCHEMISTRY IN DIAGNOSIS

The foregoing chapters have by no means covered all of the broad spectrum of clinical diagnosis. Nor are they meant to, because this would require a manuscript the size of a textbook! But I hope and believe that they will have given you sufficient information and grasp of the general principles involved for you to now go about clinical problem solving in all of the other areas, including for example anaemia, cough, gastro-intestinal haemorrhage, abdominal pain, headache etc. After you have obtained all of the clinical information in each of your patients, always try to use our broad method to reach a diagnosis, and make sure that this includes statements about the anatomy, clinical pathology, and functional consequences (including sequelae and complications) of the condition, as well as the underlying aetiological cause. Again, if as is bound to happen in particular cases, you recognize some condition in an individual patient, make sure of two things;

1. That each syllable of your "of-the-rack" diagnosis does fit your individual patient, and

2. That it includes an appropriate diagnosis in all four of our diagnostic categories. Text book diagnoses can only ever describe the average patient or the broad spectrum of disease e.g. "duodenal ulcer", "myocardial infarction". But each of your patients is an individual, and because of that you can go much further, not only in the functional and aetiological diagnoses, but in the pathological one as well (e.g. chronic duodenal ulcer, or more commonly, acute relapsing duodenal ulcer; acute myocardial infarction; or, in other patients, acute myocardial infarction preceded by crescendo angina).

The rest is up to you. Only with practise and more practise will you eventually become proficient in making such complete diagnoses in individual patients in this way. But it is worthwhile, and not just in the 'typical' case (which in reality are not all that common), but particularly in cases of which you, or perhaps anyone else, has not previously seen the like. After all, if we do not have broad principles of making clinical diagnoses, how are we ever to recognise any new syndrome or any importantly new variant of some previously well-recognised disease entity.

Clinical diagnosis is the essence of diagnostic problem-solving, because this is where you frame your broad impression of the patient's problem. A sound clinical impression will not only make for good
rational further investigation by special tests, but keep these to a minimum, because you will only need to investigate in any of the areas of the four clinical diagnostic categories where there is uncertainty.

BIOCHEMICAL DIAGNOSIS IN DISEASE

Most of what we have discussed so far has been related to physiology and other aspects of basic medical sciences aimed at helping you make a clinical diagnosis. Whilst it has been true that we have often also gone into the realms of investigation, the problem-solving exercises set have been mostly clinical. But in the chapters that follow we have to consider some areas where biochemistry is essential to diagnosis.