The renal system is the most powerful regulator of the body’s internal environment. Healthy kidneys are essential to maintain homeostasis, ensuring stable conditions in which all cells can function optimally. They perform several functions (Montague et al, 2005), including:

- Removal of waste products such as urea, uric acid, creatinine and toxic breakdown products of drugs;
- Regulation of blood volume and pressure;
- Electrolyte (salt) balance;
- Acid-base balance (regulation of blood pH);
- Regulation of the number of erythrocytes (red blood cells);
- Synthesis of vitamin D.

In the absence of disease, the kidneys function optimally into the third decade of life, after which there is a gradual decline in renal function (Figs 1 and 2). Around 15% of people over the age of 70 years have varying degrees of renal disease and dysfunction (Coresh et al, 2007). Factors contributing to the decline in renal function include hypertension, smoking, exposure to lead, obesity and increased inflammatory mediators in the blood (Weinstein and Anderson, 2010).

Anatomical changes

Pre-renal changes
The most important pre-renal (occurring before the kidney) change affecting kidney function is vascular degeneration. In young adults, renal blood flow is estimated to be approximately 600ml/minute; in older people this is often reduced by half (Cukuranovic and Vlajkovic, 2005) primarily due to normal age-related changes in blood vessels (see Part 1 of this series) and is often exacerbated in people with atherosclerosis of the renal artery.

Such blood vessel changes usually lead to ischaemia (reduced oxygenation), particularly in the outer portion of the kidney (renal cortex). Cells gradually die and are replaced with scar tissue, giving the outer surface of aged kidneys a granular or mottled appearance. The arterioles leading to the glomeruli (filtration membranes) show deposition of hyaline (clear cartilage-like material) and collagen below the
Reduced glomerular filtration rate

The glomerular filtration rate (GFR) is a measure of the rate of fluid filtration through the glomerular capillaries into Bowman's capsule. It is expressed in millilitres per minute, and is routinely used to measure the progression of kidney disease (Bit.ly/RASStagesCKD). GFR peaks in the third decade of life, where it may be as high as 140ml/min/1.73m². Blood vessel changes progressively reduce renal blood flow and GFR; in normal ageing, it drops by around 1% of what it was when they were young adults; at 90 years of age it has typically fallen to around 65ml/min/1.73m².

Reduced GFR means reduced clearance of waste products. However, age-related decline in GFR is not observed in all people; indeed many maintain a stable GFR throughout life, which suggests that variables other than age contribute to the decline (Zhou et al, 2008).

Renal changes

Both kidney mass and weight decrease significantly after the age of 50 (Zhou et al, 2008). The kidneys of people in their 20s weigh 250-270g each; in 90-year-olds this has dropped to 180-200g. It has been estimated that, between the ages of 40 and 80, approximately 20% of kidney mass is lost (Choudhury et al, 2016); only 3% of people in their 90s have histologically normal kidney tissue. There is a gradual increase in collagen deposition, leading to progressive kidney fibrosis. In old age, whole nephrons (the functional units in the kidneys) are replaced by fatty material or scar tissue; on average, 70-year-olds have lost 30-50% of their nephrons. Aged nephrons often show a variety of physical defects (Fig 2).

Glomerular abnormalities

The number of damaged glomeruli (glomerulosclerosis) increases, typically leading to progressive capillary collapse. Fewer than 5% of glomeruli show sclerosis in people in their 20s but, by their 80s, this will have risen to around 30% (Weinstein and Anderson, 2010).

Filtration membrane abnormalities

Some nephrons display a progressive thickening and wrinkling of the filtration membrane in the glomerulus and Bowman's capsule, decreasing the renal filtering surface area. The filtration membrane also becomes increasingly permeable, allowing large molecules such as proteins to collect in the filtrate and appear in the urine (proteinuria).

Tubule abnormalities

Some kidney tubules gradually degenerate and are replaced by scar tissue (tubulo-interstitial fibrosis). This seems associated with an increasing number of cells showing features of senescence (Sturmlechner et al, 2017), which reduces the area available for the reabsorption of useful materials such as glucose, amino acids and salts. The distal convoluted tubules often shrink and may develop small pouches (distal diverticula), which can in turn become fluid-filled cysts, increasing the risk of kidney infection and pyelonephritis (Zhou et al, 2008).

Impaired renal repair

In young adult kidneys, around 1% of renal cells have the ability to divide and proliferate. This declines with age, reducing the kidneys' ability to repair. The chemical signalling pathways that coordinate cell division and repair in the kidneys also become impaired with age (Bolignano et al, 2014).

Diet and renal ageing

Age-related changes in renal structure and function are thought to occur as a result of both genetic and environmental factors (Bolignano et al, 2014). One factor that appears to play a role is exposure to oxidative stress, which tends to lead to the release of pro-inflammatory mediators. While most oxidative stress is linked to free radicals produced during cellular metabolism, some of it comes from diet. Foods cooked at high temperature (particularly fried or roasted) are high in pro-oxidants; it has been suggested that limiting their intake could reduce oxidative and inflammatory stress on the kidneys (Vlassara et al, 2009).

Gender differences in renal ageing

Although this is still poorly understood, oestrogens such as 17 beta-oestradiol appear to protect the renal system in women from the effects of ageing, while androgens such as testosterone increase the risk of renal dysfunction in men. One hypothesis is that androgens promote fibrosis in the kidney; this may partially explain why chronic kidney disease progresses more quickly in men (Weinstein and Anderson, 2010).

Physiological changes

Older people experience a significant reduction in renal function. Even in the absence of disease, some people over the age of 65 only possess 60% of the renal function of young adults (Razzaque, 2007).
This gradual decline has major health implications, particularly when long-term conditions and circulatory problems are present.

Long-term conditions that lead to fluid overload and oedema – such as heart failure, liver disease and chronic kidney diseases (for example, diabetic and hypertensive nephropathies) – are exacerbated by poorly functioning aged kidneys. Patients with these conditions (commonly managed via diuretics) need their treatment regimens monitored and adjusted to compensate for age-related renal decline. Numerous studies have indicated that obesity, diabetes, high blood pressure, ethnicity and genetics can all contribute to the onset of renal disease in older people (Kazancioglu et al, 2013).

Common age-related physiological changes in renal function are described below.

**Electrolyte imbalance**
Reduced renal blood flow and GFR, together with the gradual loss of nephrons, reduce the kidneys’ ability to keep electrolytes (sodium, potassium, calcium and chloride) within optimal ranges. As these play a major role in maintaining blood pressure and generating nerve impulses, older people may experience hyper- or hypotension and confusion.

Older people are also less efficient at clearing salt, which may be due to reduced GFR (less sodium-laden blood is filtered), tubular degeneration, and reduced sensitivity to hormones such as aldosterone (Musso and Oreopoulos, 2011).

**Reduced acid-base balance**
While the lungs play a role in regulating blood pH, only the kidneys can excrete acidic or basic molecules directly, so they are the ultimate regulators of acid-base balance. With age, they become less efficient at clearing acidic/basic metabolites/ions due to tubule degeneration. This is problematic in older people with diabetes, as acidic molecules such as ketones may accumulate in the blood, leading to life-threatening ketoacidosis.

**Reduced creatinine clearance**
Creatinine is a molecule that is continually generated by skeletal muscles; serum levels usually remain constant because the kidneys clear it from the blood at the same rate as it is produced. By the age of 80, clearance is reduced by around 30% (Choudhury et al, 2016); however, serum creatinine levels remain fairly constant because of the gradual reduction in skeletal muscle mass.

**Polyuria and nocturia**
The progressive loss of nephrons makes the kidneys less efficient at concentrating urine, therefore a greater volume of water is required to excrete toxic waste products. Additionally, the effect of anti-diuretic hormone on the renal tubules is blunted in older people, leading to a larger volume of diluted urine. The result is a gradual increase in urine volume leading to polyuria (frequent urination).

In older patients, it is essential to monitor fluid status for signs of dehydration, and ensure they have free and convenient access to water. Fluids drunk during the evening take longer to be processed, potentially leading to nocturia (nocturnal urination), which is experienced by 80-90% of people aged over 80 years (Kujubu, 2009). Ideally, patients should be reminded to pass urine before going to bed to minimise the problem.

**Reduced clearance of toxic metabolites**
Special care must be taken with drugs that are excreted/eliminated in the urine. Dosages of water-soluble drugs – such as certain antibiotics, amphetamines and digitals – may need adjustment according to renal function to avoid toxic accumulation. Indeed, overestimation of the GFR can lead to unexpected drug toxicity in older patients (Zhou et al, 2008). However, other organs and tissues, particularly the liver, play a role in drug metabolism and clearance, so their ageing also increases the risk of drug toxicity.

**Reduced insulin clearance**
The kidneys remove around 50% of secreted insulin from the peripheral blood. Although reduced GFR along with degeneration and loss of nephrons significantly diminish older people’s ability to clear it, response to insulin is gradually blunted with age, which offsets the reduced clearance (Zhou et al, 2008).

**Changes in erythropoietin and vitamin D biosynthesis**
The cells that form the tubules of the nephron, along with the peritubular cells, produce erythropoietin (EPO) and play a role in vitamin D biosynthesis. Tubular degeneration often leads to reductions in EPO, which can lead, in turn, to reduced erythrocyte production and anaemia. However, some studies have demonstrated increases in EPO secretion – these may be driven by age-related resistance to the effects of this hormone (Bolignano et al, 2014).

Reduced vitamin D biosynthesis impairs the absorption of calcium and phosphate in the gut, which can contribute to osteoporosis (Zhou et al, 2008).

**Post-renal changes**
With age, the bladder gradually loses its elasticity due to an increase in collagen fibres in its wall. Loss in elasticity and...
fibrosis of the bladder can contribute to incomplete emptying during micturition (urination), particularly in men with prostate enlargement. There is conflicting evidence as to whether bladder volume changes with age; recent research suggests it rarely changes (Pfisterer et al, 2006).

Ageing and urinary incontinence
The urinary sphincter often weakens with age and this may lead to urinary incontinence – a problem often compounded by age-related changes in the nervous system. However, urinary incontinence is not a normal consequence of ageing, as many individuals never experience it, even in extreme old age.

Research indicates that around 11.6% of people aged 65-80 years experience incontinence; this rises to around 35% in those over 85, and to 69% in over-85s living in nursing homes. Women seem to be at greater risk of incontinence than men (26.6-35.0% compared with 12.6-24.0% in those aged 85 years or older); this may be due to weakened pelvic floor muscles as a result of childbirth.

Incontinence can have a major negative impact on psychological wellbeing and quality of life (Ranson and Saffrey, 2015).

Ageing of the urethra and prostate
Reports on age-related changes to the female urethra are contradictory; some indicate that the urethra shrinks and its walls become thinner and atrophied (Jai-paul, 2017), while others report no evidence of change in its length (Pfisterer et al, 2006). Age-related changes in vaginal pH can encourage abnormal microbial growth, increasing the risk of urinary tract infections.

Most middle-aged and older men experience a benign enlargement of the prostate gland (prostatic hyperplasia) (Fig 3); this results in a gradual compression of the urethra, making micturition more difficult. The onset of prostate cancer is also caused by an increase in prostate size and causes a similar compression of the urethra and reduction in strength of the urethral stream. Tests such as prostate-specific antigen, together with physical examination of the prostate, are often necessary to differentiate between malignancy and age-related prostatic hyperplasia.

Conclusion
Although it appears that little can be done to slow age-related changes to the renal system, research indicates that a high-protein diet can normalise GFR in some older people (Musso and Oreopoulos, 2011), potentially improving kidney function. Renal function must be assessed before making any dietary changes, as pre-existing renal disease can preclude high protein intake. In recent years a number of studies have demonstrated the anti-aging effects of calorie-restricted diets. Long-term caloric restriction appears to be effective at reducing the effects of renal ageing, with vascular damage, glomerulosclerosis and tubular fibrosis all reduced in animal models (McKiernan et al, 2007).

Although age-related decline in renal function is inevitable, the kidneys have a built-in redundancy – the renal reserve – and, in the absence of disease, will function adequately throughout life. NT

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