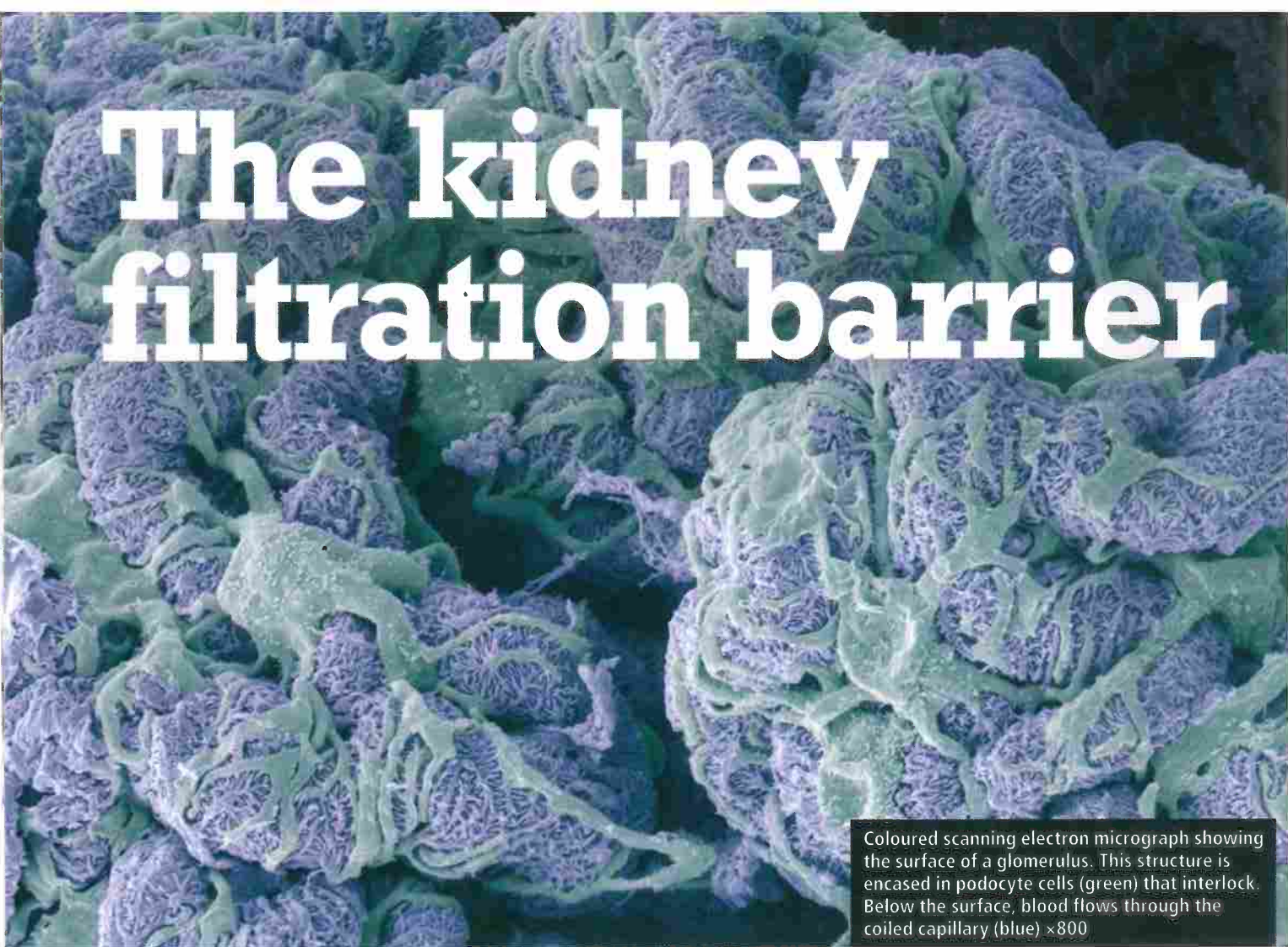


The kidney filtration barrier



Coloured scanning electron micrograph showing the surface of a glomerulus. This structure is encased in podocyte cells (green) that interlock. Below the surface, blood flows through the coiled capillary (blue) $\times 800$

Michael Randles

Our kidneys clean our blood by filtering an incredible 180 dm^3 of fluid every day. Kidney function researcher Mike Randles explains how this is achieved, how it can fail in disease, and treatments that are used to protect or replace kidney function

Healthy kidneys control blood volume and form a barrier which prevents cells and proteins escaping from our blood into our urine, while simultaneously removing toxic products of metabolism from the body by producing urine for excretion. These functions are essential for maintaining our health and wellbeing.

Each healthy kidney contains around 1 million tiny filters called nephrons (see Figure 1). Nephrons produce urine in three steps: filtration, reabsorption and secretion. The first stage of urine production occurs in the part of the nephron called the glomerulus (see Figure 1). Here, blood is filtered across the walls of glomerular capillaries into sacs called Bowman's capsules, which connect to the collecting — proximal — tubules. This process produces a filtrate that is similar to blood, except that it lacks cells and large molecules, such as proteins. This is because the glomerular capillary wall acts as a barrier to large molecules, but allows water and small molecules to pass through. The glomerular capillary wall is therefore known as the filtration barrier (see Figure 2). The second and third stages of urine production occur in the tubular segments of the nephron, where the

Key words

Kidney
Glomerular filtration
Podocytes
Inherited disease
Basement membrane

fluid produced during filtration is reduced to a manageable urine output of between 1 and 2 dm^3 each day (see *BIOLOGICAL SCIENCES REVIEW*, Vol. 26, No. 1, pp. 37–42).

The rate of glomerular filtration depends on:

- the balance of **hydrostatic pressure** inside the glomerular capillaries compared with that inside the urinary space
- the balance of **oncotic pressure** inside the glomerular capillaries compared with inside Bowman's capsule
- the properties of the filtration barrier itself, namely its permeability and surface area

In humans, the normal rate of glomerular filtration is 125 cm^3 per minute. When this rate decreases to below 15 cm^3 per minute patients are classified as having end stage kidney disease (see Table 1). Urgent intervention is required to keep these patients alive.

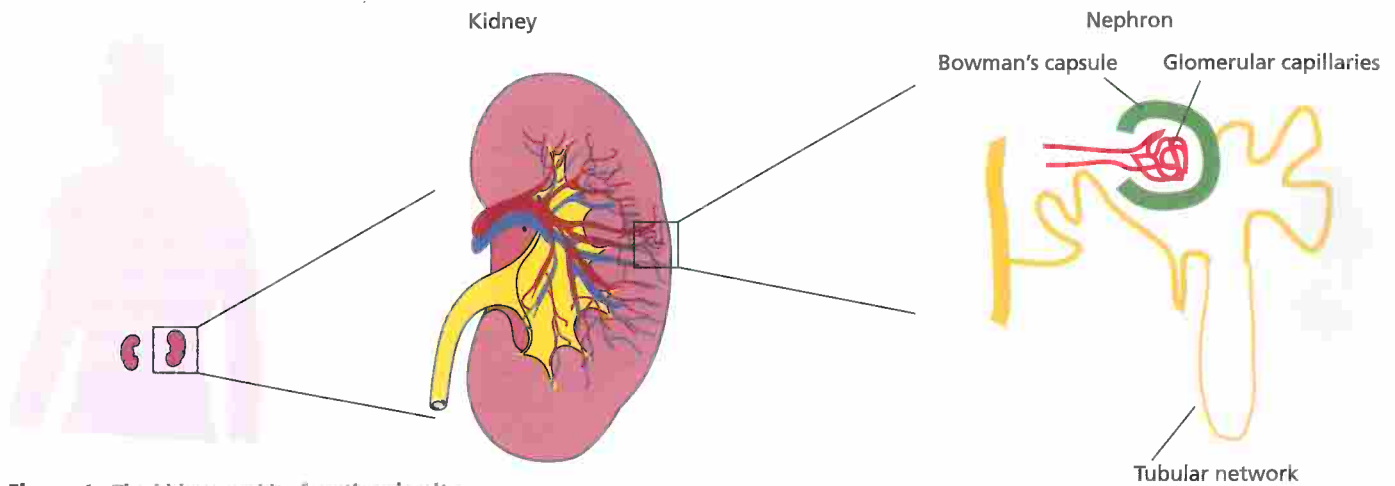


Figure 1 The kidney and its functional units

Kidney disease

Kidney disease can happen suddenly and result in an individual quickly becoming very ill. But in most cases it is a 'silent disease' and individuals may not realise that there is any problem with their kidneys for many years. The most common type of kidney disease is glomerular disease. This is where the filtration barrier becomes abnormally permeable or 'leaky' and large molecules — proteins — escape from the blood into the urine. Measuring the amount of protein in an individual's urine is therefore an easy way to monitor how well their

Table 1 Stages of kidney disease

Stage	Glomerular filtration rate/cm ³ min ⁻¹	Presentation
1	>90	Normal kidney function
2	60–89	Mildly reduced kidney function
3a	45–59	Moderately reduced kidney function
3b	30–44	
4	15–29	Severely reduced kidney function
5	<15	End stage kidney disease

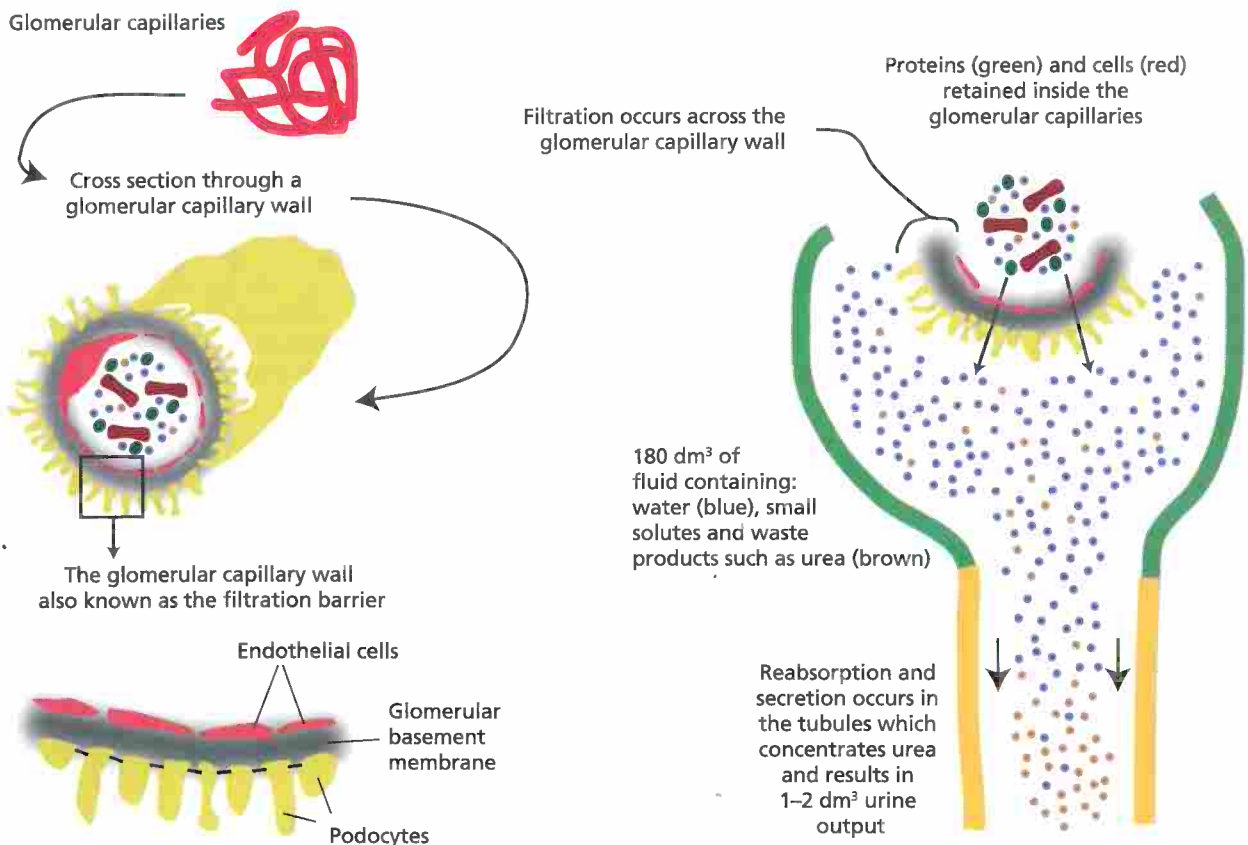


Figure 2 The glomerular filtration barrier



Figure 3 Periorbital oedema

kidneys are working. A lower concentration of protein in the blood as a result of a leaky filtration barrier causes water to move from inside the blood vessels into the surrounding tissue. Affected tissues become swollen — this is called oedema (see Figure 3).

If left untreated, glomerular disease leads to damage to the cells in the glomerulus and irreversible scarring. This scarring reduces the surface area available for filtration (see Figure 4a and b). As a consequence, the rate of glomerular filtration decreases, the blood is cleaned less efficiently and metabolic waste products, such as creatinine and urea, build up in the

bloodstream. Eventually, the function of the kidney must be replaced artificially through dialysis, or by transplanting a donated kidney into the patient (see *BIOLOGICAL SCIENCES REVIEW*, Vol. 26, No. 1, pp. 37–42). But what causes the glomerular filtration barrier to break down?

Many things damage the glomerular filtration barrier, including high blood pressure, viral infections, autoimmune diseases and diabetes. This makes diagnosing and treating glomerular disease extremely complex. However, the discovery of gene mutations that cause glomerular disease has greatly improved our understanding of how the filtration barrier works. This enhanced understanding is beginning to pave the way for better treatments for patients. Remarkably, many of these genes are expressed in just one cell type — the podocyte.

Inherited kidney disease

Podocytes are found in one of the three specialised layers that make up the glomerular filtration barrier (see Figure 4c). Two of the layers are made of

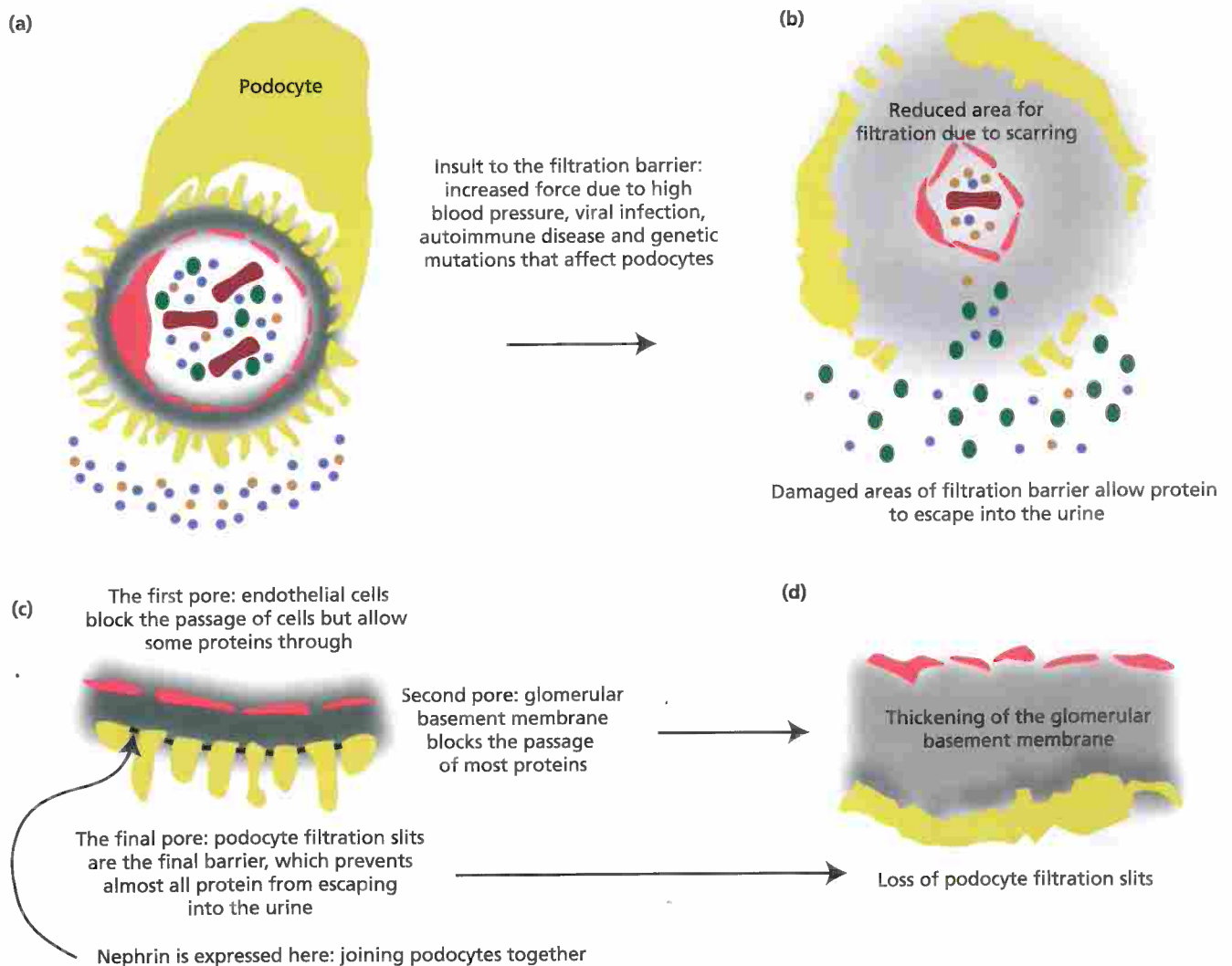


Figure 4 The glomerular filtration barrier **(a)** and **(c)** normal and **(b)** and **(d)** during disease

cells — endothelial cells on the 'blood side' and podocytes on the 'urine side'. Sandwiched between these two layers is a network of proteins called the glomerular basement membrane. There are many theories to explain how the glomerular capillary acts as a filter and barrier. The most well accepted is that the three layers act as a series of 'pores', which become progressively smaller (see Figure 4c). Studies of genetic diseases have supported the idea that the podocyte layer is the most important.

Podocytes took centre stage in glomerular biology in 1998 when a protein called nephrin was discovered. The gene that codes nephrin is faulty in a severe form of kidney disease which has a high incidence in Finland. This disease affects infants who have inherited two faulty copies of the nephrin gene. They leak massive amounts of protein into the urine. The infants therefore require infusions of albumin to replace the large amount of protein lost from the circulation. Ultimately, these infants will have both kidneys removed and dialysis or transplantation to replace their kidney function. Nephrin is only expressed by podocytes and detailed studies of nephrin have shown why this protein is so important.

Podocytes have a unique shape — they have a large body and many 'arms' that send out long 'fingers'. They wrap around the glomerular capillaries and their 'fingers' join with those of neighbouring podocytes to form structures called filtration slits (see Figure 4c). Filtration slits are vital for normal glomerular filtration, because the loss of these slits is the most common change seen in glomerular disease, regardless of its cause (see Figure 4d). Nephrin acts like a bridge between adjacent podocytes, keeping filtration slits the correct size and allowing signals about the external environment to be passed between neighbouring podocytes.

Since the discovery of nephrin, another 45 genes have been shown to be required for the formation and maintenance of podocyte filtration slits. If any one of these genes is faulty, the glomerular filter cannot function properly, causing glomerular disease.

The podocyte and its filtration slits are important for the glomerular capillary wall to act as a barrier to proteins. This is why many researchers are seeking ways to strengthen podocyte filtration slits and protect the filtration barrier. However, there are diseases that affect the other layers of the filtration barrier, and these too can lead to glomerular disease where protein escapes into the urine.

The glomerular basement membrane in Alport syndrome

In 1927 Cecil Alport described an inherited kidney disease that affects teenagers, causing them to have blood and protein in their urine. Sixty-three years

Terms explained



Biopsies Samples of tissue taken from the body for analysis.

Glucocorticoid steroids Hormones released from the adrenal gland.

Hydrostatic pressure Pressure exerted by fluid in a confined space.

Immunosuppression Reduces the activation or efficacy of the immune system.

Oncotic pressure A form of pressure exerted by proteins in a blood vessel.

Osmotic Diffusion of water through a partially permeable membrane.

Peritoneum The membrane that forms the lining of the abdominal cavity.

Vasoconstrictor Substance that causes contraction of the muscular wall of blood vessels and subsequent narrowing of the blood vessels.

later, individuals with this disease were found to be homozygous for a mutation in the gene *COL4A5*. Mutations in another two related genes — *COL4A4* and *COL4A3* — have since been shown to cause similar diseases, collectively known as Alport syndrome.

In addition to kidney disease, Alport syndrome results in hearing loss and eye abnormalities. To understand why this happens we must first understand the proteins for which genes *COL4A3*, *COL4A4* and *COL4A5* code. All three genes are required to produce type IV collagen, which forms networks in structures in the body called basement membranes. These are found in the eye, ear and glomeruli. Within the kidney, these three genes are expressed by only one cell type — the podocyte.

Kidney **biopsies** from Alport patients show that the glomerular basement membrane becomes increasingly abnormal over time (see Figure 5). This is because the glomerular basement membrane is weakened when type IV collagen is faulty, making it more susceptible to damage by the constant force of glomerular filtration. It is not only podocyte filtration slits that are required for the barrier properties of the glomerular capillary wall — the glomerular basement membrane is also important.

Treatment of glomerular disease

Glucocorticoid steroids and **immunosuppression** are effective treatments for many glomerular diseases, especially those with immune causes. This is because these drugs reduce inflammation and scarring, both of which damage the glomerular filtration barrier. However, for reasons that are poorly understood, these drugs are ineffective for treatment of glomerular diseases caused by faulty genes.

Another common cause of glomerular damage is high blood pressure. This increases the forces to which the filtration barrier is exposed, which progressively damages both the cells and the glomerular basement membrane. To protect the filtration barrier in patients with high blood pressure, drugs that interrupt the renin–angiotensin–aldosterone system are used. This system induces the release of a potent **vasoconstrictor**, which causes blood vessels to become narrower and blood pressure to increase. Interruption of this system with drugs lowers blood pressure, which also reduces the force to which the glomerular filtration barrier is exposed. In patients with Alport syndrome these drugs reduce the strain on the filtration barrier, which preserves the structure of the faulty glomerular basement membrane and prolongs life expectancy.

For many patients with kidney disease, dialysis eventually becomes a necessity. This treatment replaces the blood filtration role of the kidney. There are two types of dialysis — haemodialysis and peritoneal dialysis.

In haemodialysis, blood is taken from the patient via a needle, filtered by a machine and the cleaned blood is returned to the patient. This process takes several hours, three times each week.

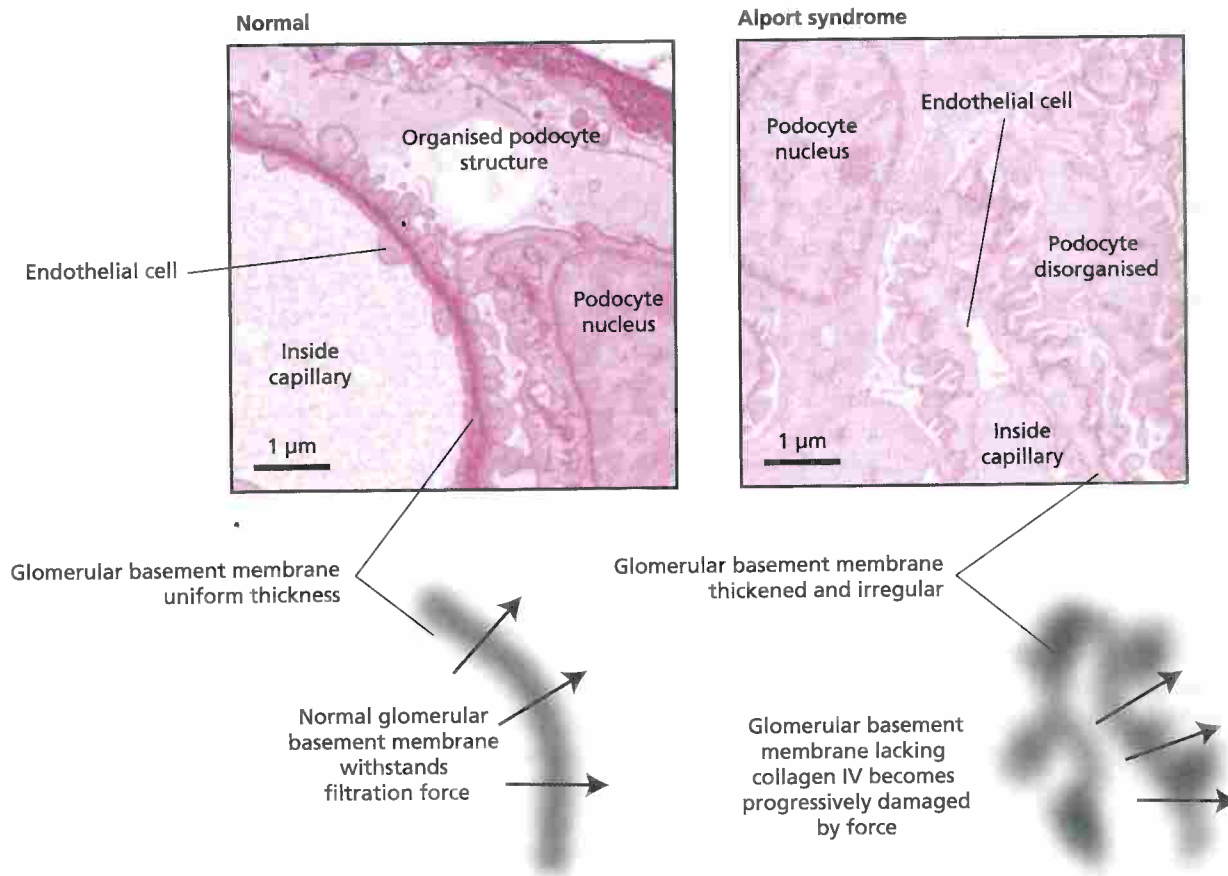


Figure 5 Transmission electron micrographs of the glomerular filtration barrier

Peritoneal dialysis pumps dialysis fluid, which contains ions and glucose similar to that of normal blood plasma, into the area surrounding the **peritoneum**. Waste products and excess fluid move from the blood vessels in the peritoneum into the dialysis fluid by diffusion. The dialysis fluid is then drained from the cavity. This process is quicker than haemodialysis, taking only 30–40 minutes, but it must be performed several times daily or overnight. One benefit of peritoneal dialysis is that it can be done at home, but some patients develop scarring of the peritoneum.

Both forms of dialysis replace only a small fraction — about 1% — of kidney function. This is because glomerular filtration normally happens 24 hours a day rather than for short defined periods. Furthermore, our kidneys do more than filter. They secrete enzymes and hormones required for blood pressure control, red blood cell production and bone and mineral metabolism. This means that dialysis is only a temporary measure and transplantation is ultimately required. After successful transplantation there is a risk that the patient will reject the kidney because their immune system is likely to recognise the donated kidney as 'non-self'. This is why life-long immunosuppression therapy is required for transplant patients. As there is a shortage of available kidney donors it is imperative for scientists to find new therapies to protect or restore the glomerular filtration barrier.

Further reading

For further information about kidney disease and current research:
www.kidneyresearchuk.org

For more detail about Alport syndrome:
www.alportuk.org and www.alportstudy.com

Dr Michael Randles studied biochemistry at the University of Bristol and then moved to The University of Manchester to study for a PhD. He currently works in the Wellcome Trust Centre for Cell-Matrix Research at The University of Manchester where he investigates disease mechanisms in Alport syndrome

Key points

- The kidneys contain around 1 000 000 filters, called glomeruli, which constantly remove waste products from our blood by filtering it to produce urine.
- Damage to glomeruli is the most common cause of kidney failure worldwide and this damage is accelerated by a number of factors such as diabetes and autoimmune and genetic diseases.
- Our understanding of how glomeruli filter and become damaged in disease has been enhanced by studying rare genetic diseases that affect the kidney.
- The discovery of mutations in nephrin and collagen IV genes revealed the podocyte as a key component of the glomerular filter.
- Treatments for glomerular disease include steroids and immunosuppression, or drugs that lower blood pressure.
- Lowering blood pressure is beneficial because it reduces strain on glomeruli, thereby protecting them from mechanical damage.