AN END TO KIDNEY FAILURE

Julia Angeles, Investment Manager. Second Quarter 2018

RISK FACTORS

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Kidney glomerulus, the glomerulus consists of a tightly coiled network of capillaries surrounded by podocytes. There about one million glomeruli in each kidney.

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AN END TO KIDNEY FAILURE

Headlines featuring advances in healthcare often focus on innovations in the treatment of well-known conditions such as cancer or Alzheimer's. Despite the lack of media attention, enormous strides are being made in kidney failure or end-stage renal disease (ESRD), in which kidneys cease to function. What would have seemed impossible, even a few years ago, is beginning to look credible.

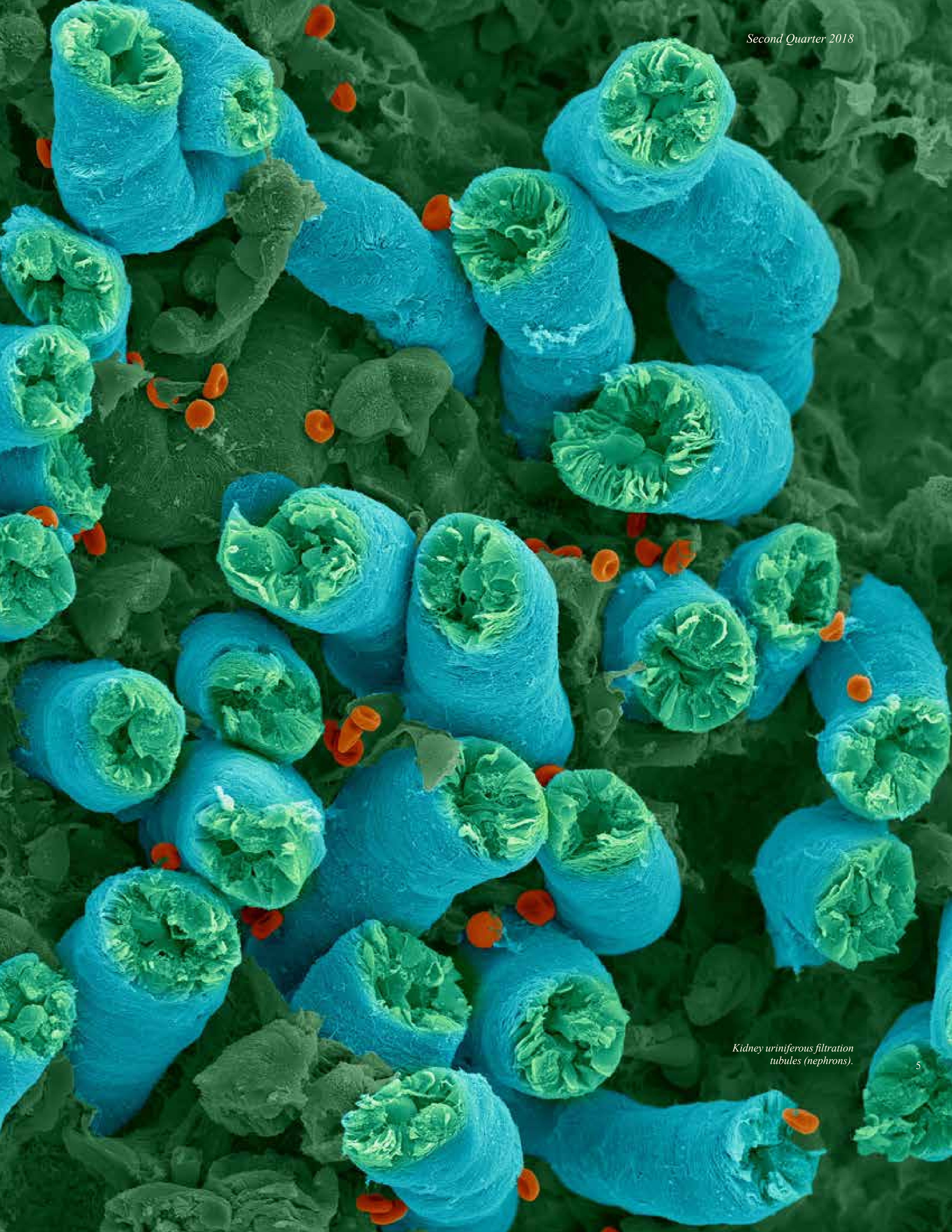
ESRD is a global crisis. A report in *The Lancet* stated that the condition is responsible for one out of every 57 fatal outcomes across the world, while, in the UK, approximately 64,000 people are currently being treated for the condition. These figures are set to rise in line with an ageing population and increases in chronic conditions such as type 2 diabetes and hypertension (abnormally high blood pressure), prime causes of ESRD. Research published in the American Journal of Kidney Diseases and led by RTI International predicted that by 2030, 17% of US adults aged 30 or older will have ESRD.

Currently, patients are subjected to ongoing dialysis or have to undergo a kidney transplant to stay alive. Dialysis is a procedure that artificially removes waste products and excess fluid from the circulation. The blood is diverted to a dialysis machine, or dialyzer, so that it can be cleaned. Kidney transplantation is recognised as the best available treatment for ESRD in terms of cost, quality of life and prognosis. However, a shortage of donors limits transplantation as a treatment option. Unless you are in the fortunate position of having a family member or friend with a similar tissue type who is willing to make a living donation, those on the waiting list for a kidney transplant can expect, on average, to have a two- to three-year wait to receive a kidney in the UK. This means that finding innovative solutions is more important than ever.

THE SCIENCE

The kidneys are one of the hardest-working organs in the body. The two kidneys, each of which weighs about 160 grams, perform many of the functions required to keep the blood clean and chemically balanced, and between them process around 180 litres of blood per day. Our kidneys help to establish the correct balance of salts and minerals in our blood. They are also responsible for filtering out toxins and secreting several important hormones, including erythropoietin, which promotes the formation of red blood cells. Inside the kidney, the glomeruli, a dense network of capillaries, filters the blood. Tiny tubes coated with a layer of specialised cells (tubules) reabsorb water, salts and minerals into the blood before the remaining waste fluid leaves the body as urine.

It may not affect as many people as cancer and Alzheimer's but, worryingly, the incidence of ESRD is increasing, driven by rises in chronic lifestyle conditions such as diabetes and hypertension. The high blood sugar levels seen in diabetes, the leading cause of ESRD, damages the blood vessels throughout the body over time. Hypertension stretches the blood vessels in the kidneys, scarring and weakening them until they cease to function.



Kidney uriniferous filtration tubules (nephrons).

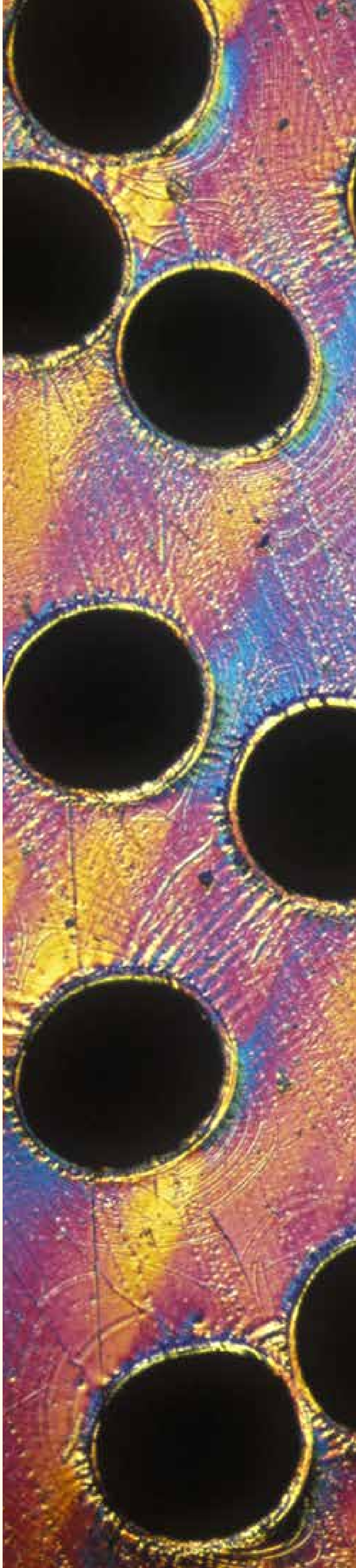
A FLAWED LIFESAVER

Unfortunately, for patients with ESRD, the standard of care remains both poor and expensive. In the developed world, most patients attend a dialysis clinic three times a week to receive three to five hours of treatment per session. Even this is largely unavailable in developing countries. In the UK, home dialysis is available. This uses a smaller machine than those used in hospitals and involves patients learning how to use the equipment themselves.

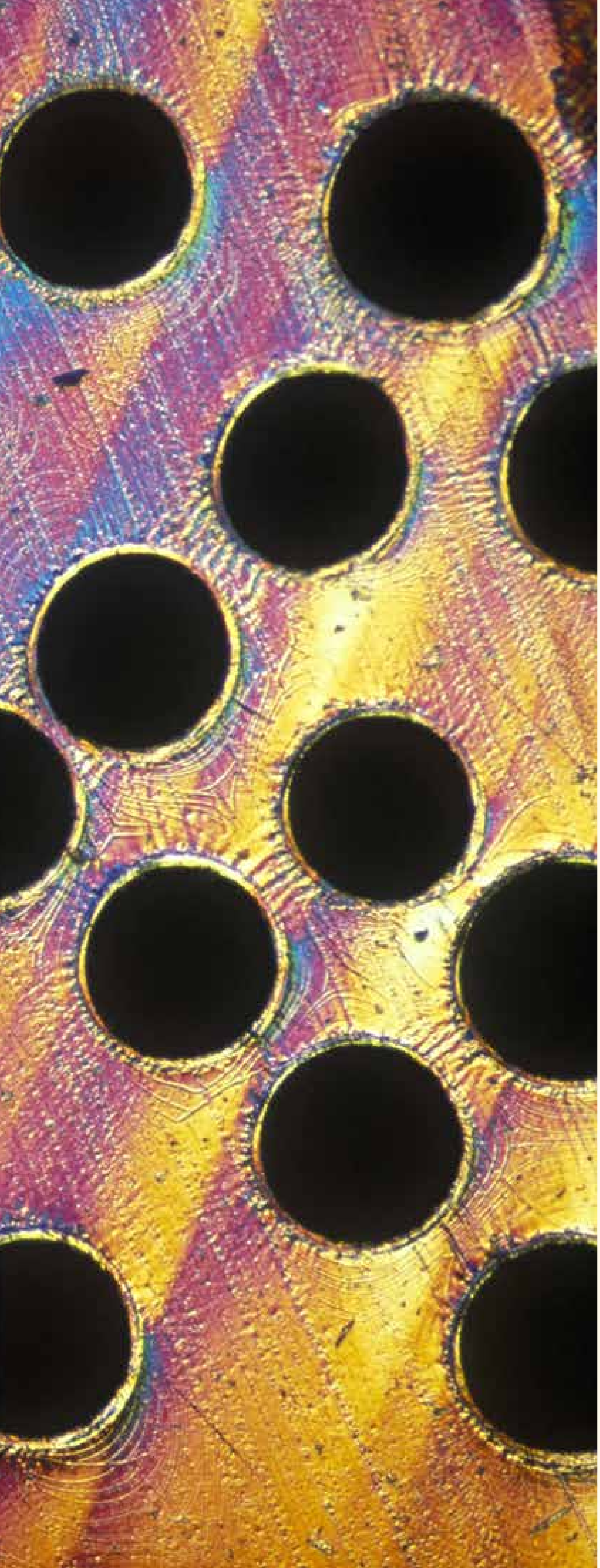
Although dialysis is a life-saving treatment, it can only replicate some of the natural kidney's roles; for example, dialysis cannot produce the hormones that a functioning kidney would, nor balance the acids in the body, which means that patients have to take supplementary medication to restore healthy enzyme and hormone levels. Survival rates are also an issue. According to data from the University of California, San Francisco (UCSF), only 35% of US dialysis patients are still alive after five years. Dialysis has a negative impact on patients' quality of life as their schedules revolve around dialysis treatment, which makes it difficult to pursue a career or have a social life. Dialysis also requires patients to avoid certain foods and limits their consumption of fluids.

Not only are the current treatments for ESRD far from perfect, they also represent a significant cost burden for healthcare systems. In 2009–2010, the NHS was spending £1 out of every £77 of its budget on ESRD. In the US, statistics from the UCSF show that 7% of the total Medicare budget is spent on managing ESRD, while addressing only 1% of the patient population.

Dialysis remains a flawed lifesaver. The smaller and simpler-to-use machines coming on stream suggest home dialysis is the field which perhaps offers the quickest route to improving the quality of life for ERSD sufferers in the short term, but only to a point. It is a marginal improvement, rather than offering a radical solution which replicates the full kidney function or reverses the damage done to the patient's kidney. In a healthcare sector brimming with innovations, the search is on for an alternative.



Hollow cellulose fibers in polyurethane plastics, used in dialysis filter elements.



PREVENTION IS BETTER THAN CURE

For patients and healthcare providers, the most desirable solution to the challenge of ESRD is prevention. Ideally, this would involve all of us making healthy decisions throughout our lifetimes, including overhauling our diets and increasing the amount of exercise we take. This would significantly reduce our chances of developing diseases such as type 2 diabetes, in turn reducing rates of ESRD.

In the developed world, measures to address the scourge of long-term conditions are taking place at a governmental and a personal level. This has seen a rise in sales of wearable exercise devices and people demanding healthier food options; London recently opened its first vegan pub, for example. At the same time, governments and the business world are attempting to change people's behaviour. The UK government has recently brought in a tax on sugary drinks and insurance companies are offering plans that reward healthy choices.

However, changing human behaviours takes time and for people on the transplant list, time is a commodity that is in short supply.

ALL IN THE GENES

Another option is to cure the conditions that cause ESRD in the first place; mainly type 2 diabetes and hypertension. Chronic conditions tend to be complex and driven by multiple factors and type 2 diabetes is no exception. The disease is driven by a mix of behavioural, environmental and genetic factors.

Our understanding of type 2 diabetes has improved over time through painstaking research, but serendipitous discoveries can also act as an important trigger for progress. This was demonstrated when scientists working at Renova Therapeutics discovered that a gene therapy being tested in mice, which the team expected to increase cardiac output and decrease blood pressure, also reduced blood glucose levels. Renova Therapeutics' work into type 2 diabetes is encouraging as it delivers a therapeutic gene that codes for urocortin 2 (a protein involved in regulating aspects of appetite and stress response in mammals) – using a one-off intravenous injection, a common procedure that can be administered in any doctor's office.

As historic challenges associated with gene therapy such as safety have been gradually resolved and new technologies are being developed, gene therapy might be close to becoming a widely-used therapeutic approach across rare and chronic diseases. In this case, removing the threat of type 2 diabetes could have a dramatic effect on rates of ESRD.

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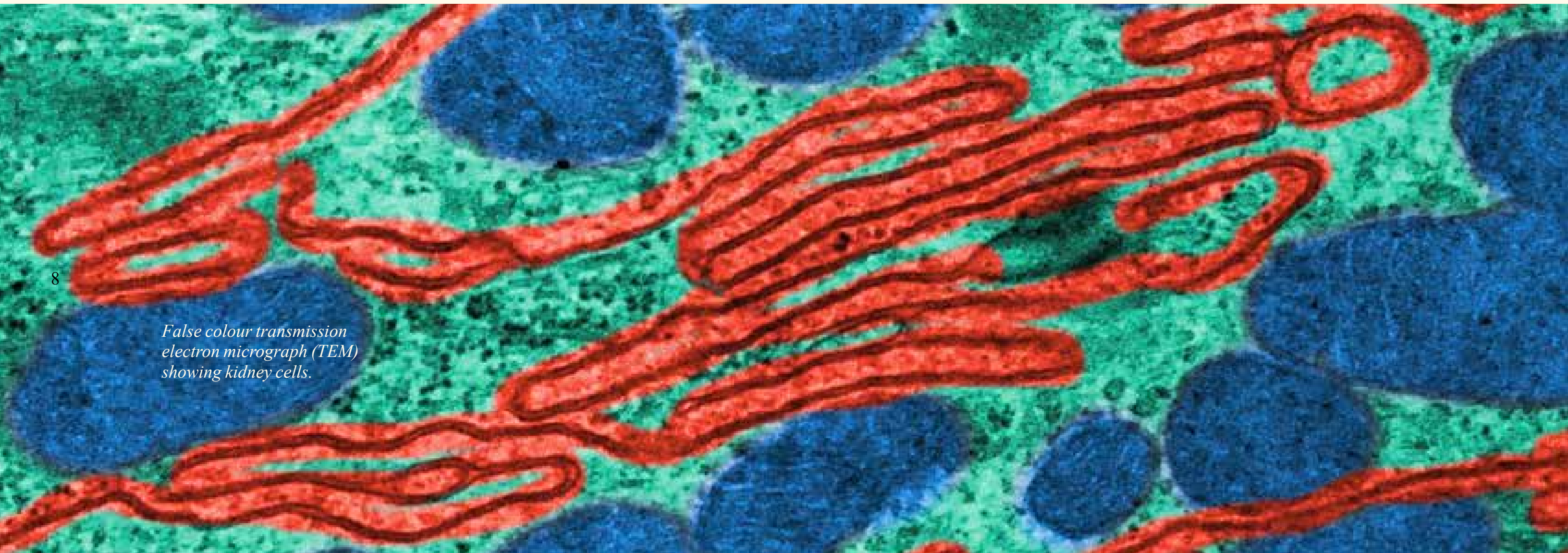


False colour transmission electron micrograph (TEM) showing kidney cells.

GROWTH FACTOR

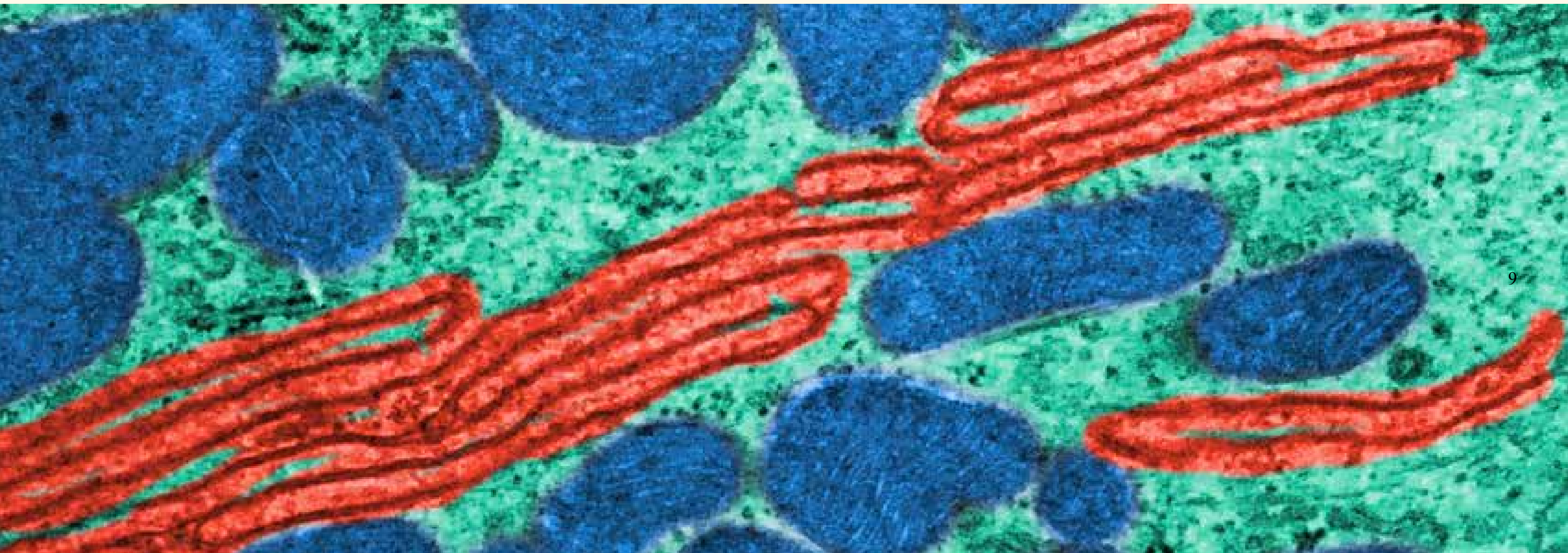
Another solution to the growth of ESRD would be to regenerate the kidneys. This might sound fanciful, and indeed we may still be far away from being able to regenerate a fully functional kidney, but the progress made over the past few years is encouraging.

In 2014, scientists from the Stanford Institute for Stem Cell Biology and Regenerative Medicine in the US and the Sackler School of Medicine in Israel discovered that kidneys regenerate and repair themselves throughout our lifetimes. Not only does this overturn decades of accepted wisdom that dictated that kidneys did not regenerate, researchers also discovered a cellular pathway that facilitates regeneration. In the future, it might be possible to target a certain protein in the pathway and thereby to promote the regenerative capacity of the kidneys.

Thanks to advancements in stem cell research, scientists can transform any cell, for example a skin cell, into a naive cell (stem cell) that can later be triggered and developed into any cell required, in this case a kidney cell. This approach uses what are termed ‘induced pluripotent stem’ (iPS) cells. In research published in the Journal of the American Society of Nephrology, scientists from Kumamoto University in Japan used this technique to engineer kidney tissue in vitro using human-iPS cells, which they then transplanted into a mouse kidney. The researchers found that the mice’s blood vessels readily connected to the human tissue.

Other studies have suggested that a particular type of human kidney cell has the potential to promote kidney injury repair after being injected into the bloodstream intravenously. In work published in the journal Stem Cells Translational Medicine, researchers from the University of Liverpool and the University of Heidelberg in Germany demonstrated that any regeneration involved using this method is likely to be mediated by cell-to-cell communication rather than the injected cells directly interacting with the recipient’s kidney to form new tissue.

Cell-to-cell communication involves one cell producing a signal that induces changes in the behaviour of another cell. It is an approach that could yet develop into a viable treatment for ESRD. For example, a Japanese company, SanBio, is performing advanced clinical trials into a treatment for traumatic brain injury that is based on the same principle.

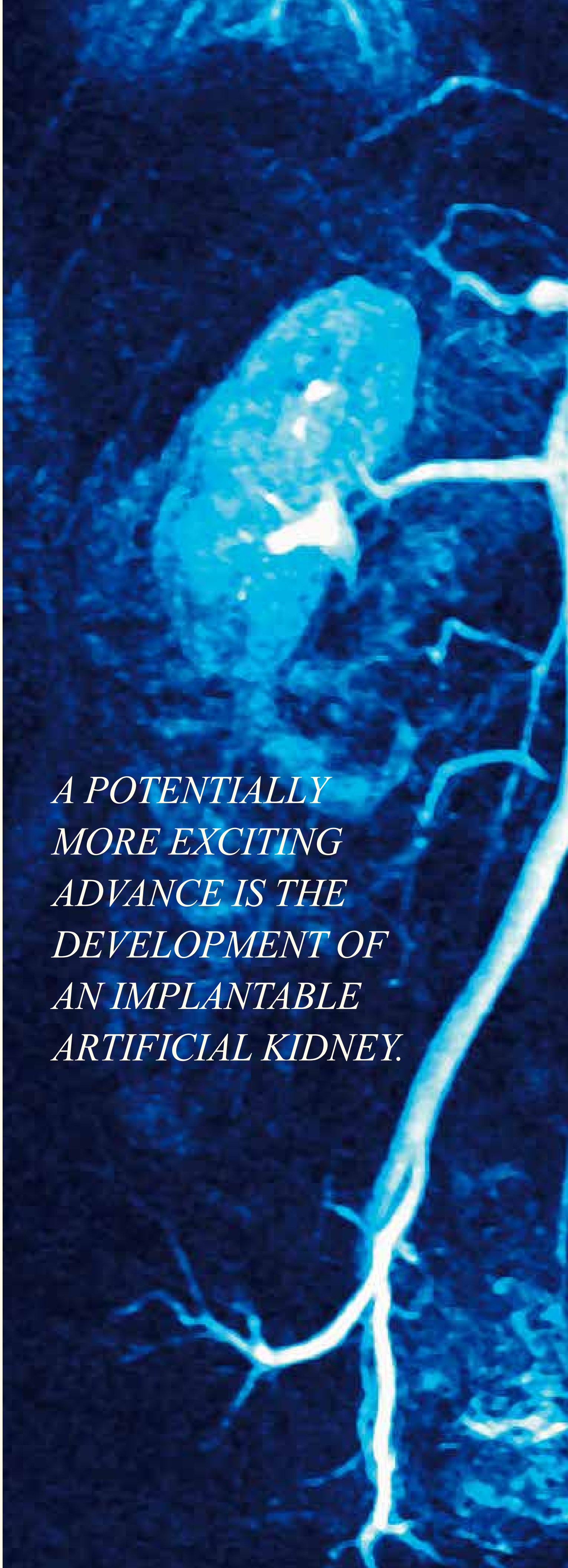


ARTIFICIAL INTELLIGENCE

Another solution might be to replicate the kidney's functions as closely as possible without compromising the patients' quality of life. It is known that prolonged dialysis is associated with substantially improved outcomes and there are two interventions that can provide continuous dialysis – wearable and implantable.

The development of a wearable artificial kidney represents significant progress (a Dutch company, Nanodialysis has made great strides in this area). A potentially more exciting advance is the development of an implantable artificial kidney. In the US, researchers from the UCSF, Vanderbilt University and the University of Michigan have developed an implantable kidney that is designed to closely replicate the functions of a biological kidney, for example, continuous filtration and blood volume control. The device is designed to be connected to the patient's blood supply and bladder and implanted near their own kidneys.

The technology was developed by combining innovations in the semiconductor industry (semiconductors are key components in electrical circuitry) with cell biology. One of the components of the implantable kidney is a silicon nanofilter that removes toxins, salts and water from the circulation using only the force of the body's own blood pressure. A 'bioreactor' contains human kidney cells that reabsorb salts and water from the filtrate to control blood volume. Any waste that is not reabsorbed flows to a tube attached to the bladder and is removed as waste in the urine (just like a 'normal' kidney). Encouragingly, after spending two decades on this project, the researchers are ready to test it in humans and expect clinical approval by 2020.



A POTENTIALLY MORE EXCITING ADVANCE IS THE DEVELOPMENT OF AN IMPLANTABLE ARTIFICIAL KIDNEY.

HOME FROM HOME

Perhaps the least favourable solution are technologies that aim to tackle the inefficiencies in current treatments for ESRD without introducing a genuine paradigm shift.

The benefits of home dialysis are widely recognised, including improved clinical outcomes, quality of life and cost effectiveness. Despite this, uptake remains very low. This is because the current home-based technology is not patient-friendly and requires double the time spent on the machine to achieve similar outcomes to clinic-based dialysis.

However, one company, Quanta, offers a dialysis technology that is easing the shift towards home dialysis. Quanta's dialysis machines offer several benefits compared to existing clinic-based dialysis equipment, while delivering a similar performance. The company's machines are less than a quarter of the size and weight of a standard machine, simple to use and feature a cartridge-based system that reduces the necessary cleaning. Quanta's product has been approved in Europe and the company expects to generate revenue within the next two years.

INVESTING IN THE LONG TERM

ESRD is both a complicated and debilitating condition, with an equally complex set of solutions. While the innovations discussed here offer a glimpse of an improved future for patients, too many people are still having to endure the misery of waiting for a donor organ that may never arrive.

This is why it is vital to continue pushing the parameters of scientific knowledge in the hope of identifying novel and transformational solutions. The challenge for investors is to identify which technology will benefit patients the most in the long term and invest their time and capital in supporting those companies to execute on that promise. Although early stage, the innovations taking place illustrate that preventative and curative solutions, as opposed to managing ESRD through dialysis, are becoming increasingly realistic treatment options. They also demonstrate the benefits of scientists' perseverance and wider disciplinary collaboration.

WHAT DO MY KIDNEYS DO FOR ME?

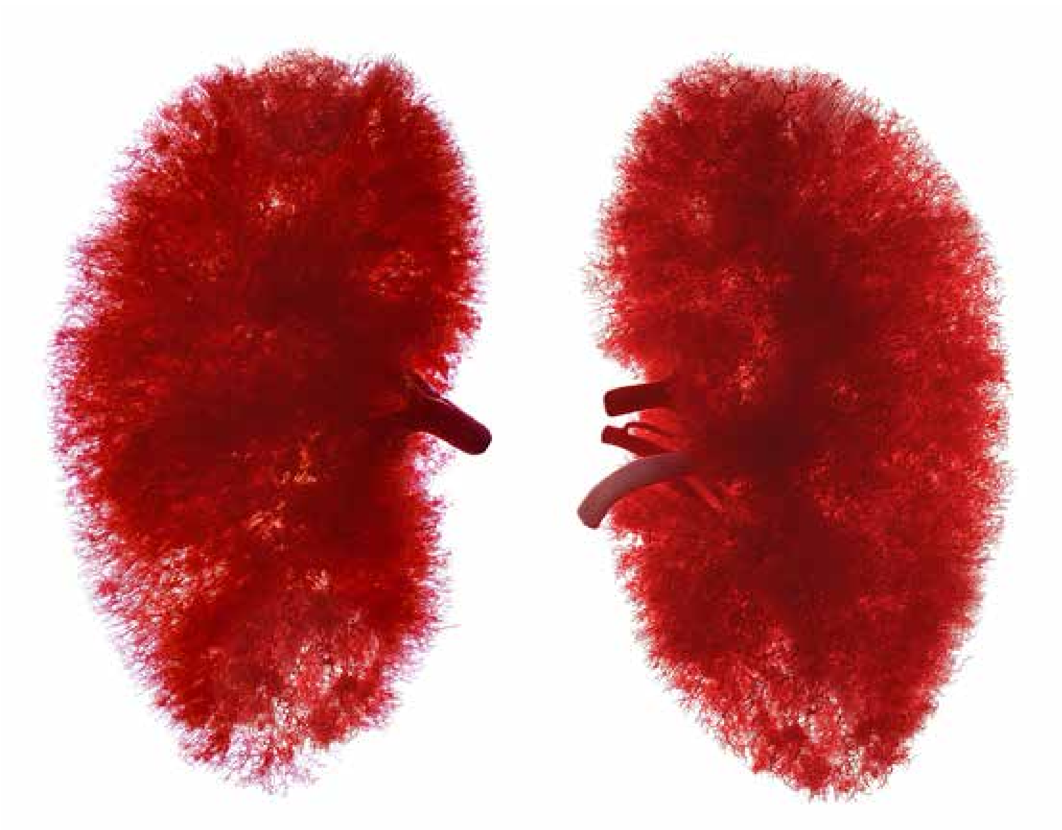
The kidneys have a number of vital roles in the body, including:

BLOOD FILTRATION

Each day the kidneys filter approximately 180 litres of fluid.

URINE

The kidneys remove 1–1.5 litres of urine daily.



HOMEOSTASIS

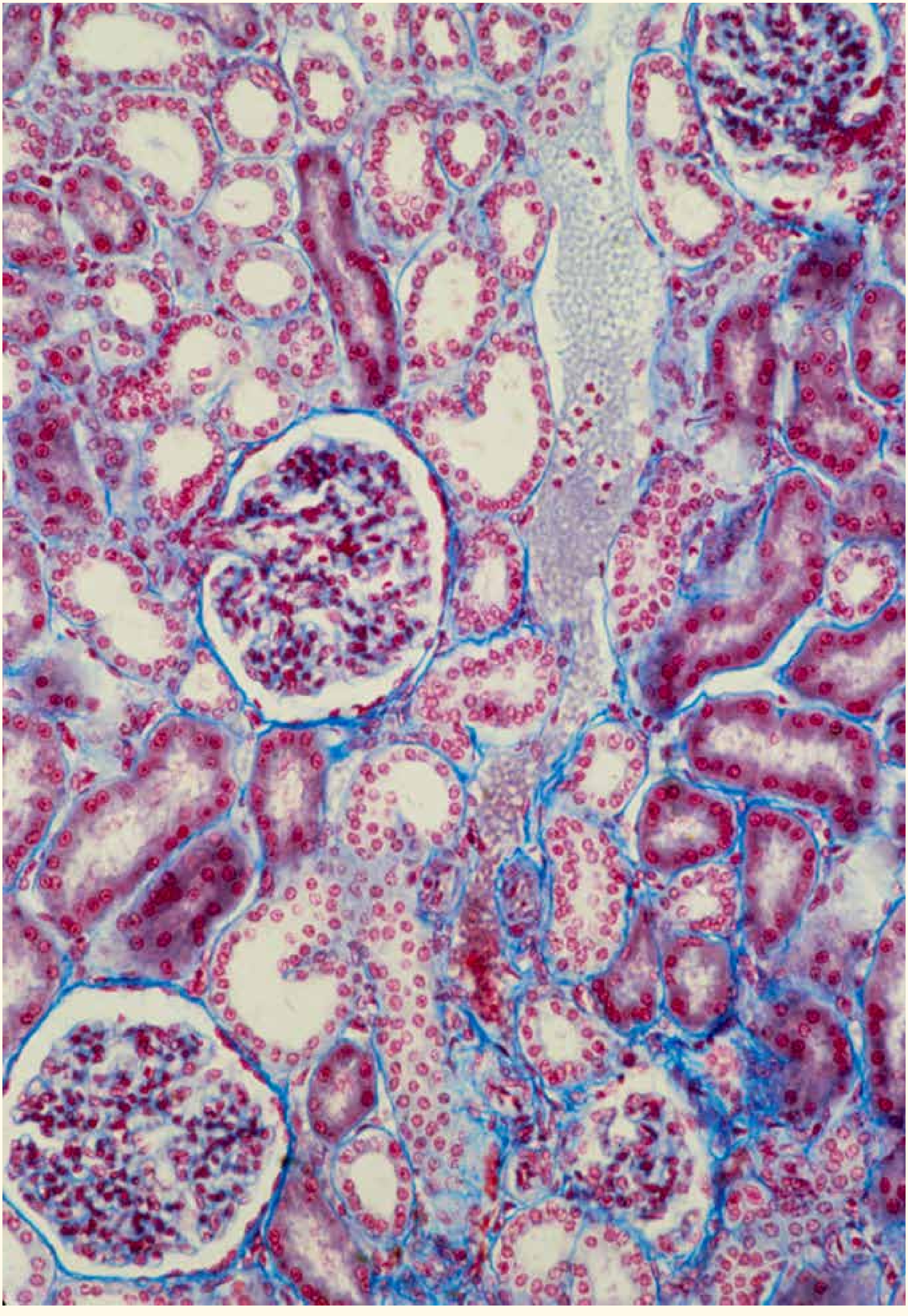
The kidneys maintain the body's balance of essential electrolytes (such as sodium and potassium), and water.

WASTE MANAGEMENT

The kidneys filter out many waste products from the blood, including urea and creatinine.

HORMONE REPLACEMENT

The kidneys secrete a range of hormones vital to physiological functioning, including renin, which regulates blood pressure, and Erythropoietin, which is involved in the production of red blood cells.



Light micrograph of normal human kidney

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