PART I

Looking at the Disease of Kidney Failure

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What Do Kidneys Do and What Happens When They Fail?

Before we look at what you can do when your kidneys start to fail, it's a good idea to review the basics on how the kidneys work in the body. With this knowledge, you will get a better understanding of why the kidneys are so important in the functioning of your body and the extent of the damage that can occur to your health if things do go wrong.

The two kidneys lie in the abdomen on the muscles of the back, near the waist, and are about 5 inches long. The urine formed from each kidney passes down a long tube called the ureter into the bladder, which can expand to contain and store urine. When urine is passed out of the body, it goes through a tube called the urethra (see Figure 1.1 on the following page).

Each kidney is made up of about 1 million units, called nephrons, which begin with a filter, comprising a tuft of capillaries (the tiniest blood vessels), called the glomerulus. At the glomerulus, liquid is derived from the blood plasma, comprising a solution from which most of the protein

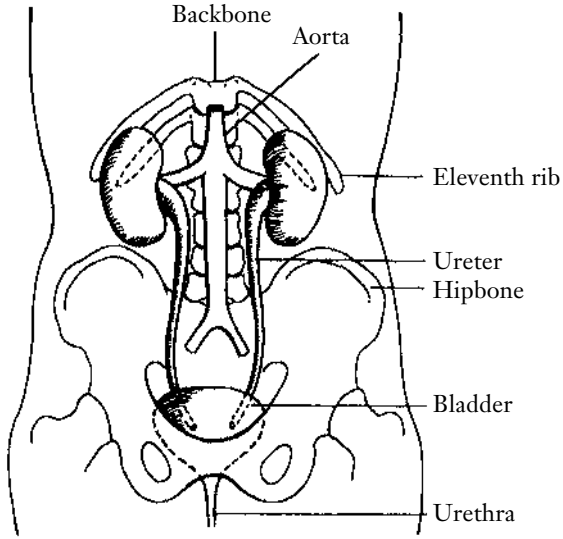

FIGURE 1.1: THE POSITION OF THE KIDNEYS.

From the kidneys, the ureters conduct urine to the bladder, which empties through the urethra. Blood is supplied to the kidneys by two renal arteries from the aorta, the main artery of the body. Reprinted by permission from *Kidney Failure, the Facts*, by Stewart Cameron, Oxford University Press, 1996.

has been filtered out by the glomerular membrane. This solution, called the glomerular filtrate, passes down a long, winding tubule (meaning little tube) and finally into a pouch called the kidney pelvis, which in turn drains into the ureter. During its passage down the tubule, most of the filtrate is reabsorbed, but some constituents are more completely reabsorbed than others; tubular secretion adds other constituents to the fluid. The final urine is small in volume compared to the glomerular filtrate, and differs from it considerably in composition.

By these multiple mechanisms the kidneys achieve their remarkable regulatory capacity. It is very important to recognize that the kidneys' main function is not to excrete wastes; instead, they play a very important role in keeping what is called extracellular fluid constant in its makeup. Extracellular fluid is the medium in which the millions of cells that make up our bodies are bathed. Blood plasma is part of the extracellular fluid, and it circulates throughout the body by the pumping of the heart. The kidneys keep constant the composition of the extracellular fluid, namely its content of salts, acid, nutrients, and many other constituents. The

lungs play a similar role in that they remove carbon dioxide and add oxygen to the blood, so as to keep these two constituents constant.

The principal function of the kidneys is to keep constant the composition of the extracellular fluid, with respect to all other constituents. The kidneys also keep the volume of the extracellular fluid constant. By extraordinarily complex and efficient mechanisms, the kidneys regulate the excretion of water, salt, potassium, calcium, acid, and many other elements, whatever the intake of these substances may be.

Hormones regulate many of the kidney's functions. Hormones are like chemical messengers that are produced in other organs and sent to the kidney via the blood. For example, antidiuretic hormone, a hormone produced in the brain, is secreted in response to the concentration of dissolved solutes in body fluids. A high concentration of dissolved solutes, such as might occur after water loss in a hot environment, stimulates the production of this hormone. The kidney responds to the hormone by making the urine more concentrated and lower in volume, thus conserving water in the body. At the other extreme, a low concentration of dissolved substances, such as might occur after drinking a lot of water, turns off antidiuretic hormone production. As soon as the hormone disappears from the blood (about 30 minutes), the kidneys stop conserving water and do the opposite: The urine becomes very dilute and increases in flow, thus excreting the water load.

Urine flow can range widely depending on a person's intake of fluids: Minimal urine volume, during severe dehydration, may be as little as 250 ml a day (less than a pint), while maximum urine volume, in the absence of this antidiuretic hormone, is many gallons a day. People who can't make this hormone or who don't respond to it, because they have one form or another of a condition called diabetes insipidus (no relation to sugar diabetes), excrete huge volumes of urine and as a result get thirsty. Their fluid intake usually keeps up with their urine output, and they remain only slightly dehydrated most of the time.

The regulation of salt excretion is closely related to the regulation of body water because salt is the dominant dissolved substance in the extracellular fluid. Salt excretion is regulated by hormones that are produced by the adrenal cortex and by the heart. The regulation of salt balance is discussed in Chapter 8.

Another function of the kidneys is the production of important hormones, including:

- Angiotensin, a hormone that raises blood pressure by constricting blood vessels and also stimulates the adrenal cortex to produce yet another hormone, aldosterone, an important regulator of sodium excretion
- Erythropoietin, a hormone that stimulates the bone marrow to produce more red cells whenever their number is reduced; again, this explains why anemia is such a common feature of kidney failure
- Prostaglandins, which help regulate blood pressure, sodium excretion, and other functions.

In addition, the body's production of vitamin D takes place, in part, in the kidneys, which explains why vitamin D deficiency is a prominent feature of kidney failure.

Clearly, the kidney has many functions besides the excretion of wastes. You cannot live without your kidneys because of the important role they play. Complete loss of kidney function causes death within a few weeks. The good news is that we seem to have much more kidney function than we need, because with adequate care a person can survive with as little as 5 percent of normal kidney function. Thus donation of one kidney does not cause any signs of kidney dysfunction in the donor.

What Is Kidney Failure?

Kidney failure means loss of some (but not all) of the filtration capacity of the kidneys, which can be caused by a fall in blood pressure, a blockage of the blood circulation to the kidneys, blockage of urine outflow, or by disease of the kidneys themselves. Many different kinds of kidney disease are recognized, all of which cause loss of filtration capacity, but some of which are rapidly reversible. These reversible types of kidney failure are known as acute kidney failure.

Acute kidney failure can be caused by drugs toxic to the kidneys, by a severe reduction in kidney blood flow (for example, during surgery), and by many other causes. Urine output usually falls drastically, and waste products accumulate in the blood. But amazingly, complete recovery can occur within a few weeks. Patients often need dialysis temporarily.

Chronic kidney failure is generally not reversible, but often (though

not always) gets progressively worse. When about two-thirds of filtration capacity is lost, symptoms of kidney failure begin to appear (see Chapter 3). When seven-eighths or so is lost, survival depends on either starting dialysis or transplanting a new kidney. This is called end-stage renal disease (ESRD).

How Big a Problem Is Kidney Failure?

Over 300,000 patients have end-stage renal disease and are currently on dialysis in the United States, and another 300,000 to 400,000 in other countries. (Hundreds of thousands of others who need dialysis in third world countries don't get it for economic reasons.) By 2010 there probably will be about 650,000 patients with ESRD in the United States, if the same rate of increase continues. Some of this increase represents wider availability; but kidney failure also seems to be getting more common.

These are the only statistics about the prevalence of kidney disease that have any reliability, and they do not measure prevalence of all cases of kidney failure; they measure the prevalence of end-stage kidney disease only, when dialysis is essential to survival. The prevalence of all cases of kidney disease in the United States can be estimated from large surveys of apparently normal samples of the population, in which a main indicator of kidney function, serum creatinine concentration, is measured in thousands of people. By determining what proportion of people in the sample has elevated creatinine levels and multiplying by an appropriate factor, we can estimate the prevalence nationwide.

The disturbing part of this equation is that most people with elevated serum creatinine levels are unaware of the fact. However, it is by no means certain that all of those who have elevated serum creatinine concentrations will go on to manifest chronic renal failure; in some, their serum creatinine level may spontaneously become normal; in others, it may remain slightly elevated but never rise further. For example, according to a recent study of 3,874 patients with elevated serum creatinine concentrations at an urban Veterans Administration center, followed for four years, many do not lose kidney function over time, including more than half of those with only slightly elevated levels and over a third of those with moderately severe kidney failure. It remains to be determined what differentiates those who progress to ESRD from those who do not.

In one large series of patients with chronic renal failure known as the Modification of Diet in Renal Disease Study, 15 percent exhibited no progression after being followed for at least two years. Sylvie Rottey and her colleagues in Belgium followed 83 patients with initial serum creatinine levels of 2 to 5 mg per dl for an average of five years. They found that half didn't progress at all during this interval.

The Diagnosis of Kidney Failure

How many people actually know they have chronic renal failure and have been properly diagnosed in order to receive treatment? Unfortunately, the answer to this question is not known even approximately. In a study reported at the American Society of Nephrology meeting in 2000, 889 U.S. relatives of dialysis patients were screened. The *majority* had signs of kidney disease, but most of these people were "unaware of their renal risk status." If we compare this statistic to people with diabetes, 70 percent of diabetics were aware that they had diabetes, while only 10 percent of subjects with evidence of chronic renal disease were aware of having it. Perhaps most alarming was the observation that the patients' physicians, when sent the results of the survey, often failed to change any aspect of their treatment. (We'll discuss this more in the next chapter.)

A survey of 1,436 adults in Venezuela revealed six individuals with persistently elevated creatinine levels, without apparent cause for acute renal failure. Only one of these six was aware of having chronic kidney disease. This was a surprisingly low frequency.

In a survey of 23,121 healthy Japanese schoolchildren, only 200 had signs of kidney disease, generally undiagnosed previously, emphasizing the relative infrequency of kidney disease in children.

In a large survey of apparently healthy adults in the United States, when the results were multiplied by the U.S. population, 800,000 adults nationwide were estimated to have serum creatinine levels above 2 mg per dl, and 10.9 million to have levels above normal (1.5 mg per dl).

Unfortunately, no surveys have determined how many of those surveyed were aware of having a high creatinine level. Defining prevalence in terms of measures whose results are not known to the subjects may be useful for fund-raising purposes, but it is not useful for these individuals' medical care.

A striking difference between true prevalence and diagnosed disease was shown in diabetic kidney disease by a report from Atlanta. In 1994 the authors reviewed hospital charts of 260 people with diabetes aged 64 to 75. Only 63 percent of the sample had their urine analyzed during their admission. Of these, 31 percent had urine protein of 1+ or greater, indicating advanced kidney disease. Twenty-five percent of the people with diabetes had elevated serum creatinine, but abnormal kidney function was noted in the discharge summaries of only 8 percent. "None [!] of these patients' medical records indicated that they had received dietary instructions about protein restriction, education about avoiding unnecessary use of NSAID's [nonsteroidal anti-inflammatory drugs, see Chapter 19], or education about diabetic renal disease." (These are some of the treatments we'll be discussing later in the book). Angiotensin-converting enzyme-inhibitors (ACEIs) or angiotensin-receptor blockers were no more likely to be used in those with abnormal renal function than in those without, despite the fact that these drugs are now widely recommended for patients with kidney disease (see Chapter 9). Thus most of these patients and their physicians apparently were unaware of the presence of renal disease and so did nothing about it.

A similar study of diabetic Medicare beneficiaries was reported from Seattle. Of 785 diabetics, 38 percent had urinary protein of 1+ or greater. But only 26 percent of patients known to have diabetic kidney disease and without contraindications to ACEIs were treated with ACEIs at discharge.

A recent report by Italian nephrologists documents similar findings. They reviewed the charts of 288 diabetics seen at a clinic in 1997. Although blood glucose was recorded in 99 percent, serum creatinine was recorded in only half and urine protein was seldom checked.

According to a recent summary, "30 percent to 40 percent of ESRD patients enter ESRD treatment only after an emergency-room visit triggered by undiagnosed renal failure." The authors conclude that "the pre-ESRD population is remarkably poorly followed."

In a recent review, the records of 155,076 patients who started dialysis between 1995 and 1997 were examined. Sixty percent of them had subnormal serum albumin concentrations, indicating malnutrition, and 51 percent had severe anemia. Only a small minority were treated by erythropoietin hormone injections, despite this drug being indicated for renal anemia (see Chapter 11). Heart disease was also prevalent and undertreated. The authors concluded that their data revealed

"an alarmingly poor quality of pre-ESRD care among patients beginning dialysis in United States." Clearly this circumstance accounts in part for the high morbidity and mortality of ESRD patients in the United States. The authors were unable to explain the reasons for their findings.

One factor may be the official government attitude toward predialysis care, which is well illustrated by a recent pamphlet for the general public entitled "Kidney Failure: Choosing a Treatment That's Right for You" released by the National Institute of Diabetes and Digestive and Kidney Diseases. The pamphlet describes dialysis and transplantation but makes no mention of predialysis care. However, the National Institutes of Health has started a program with the express purpose of education in predialysis care.

It is clear that early renal insufficiency is still widely ignored in the United States.