LECTURES 8-9: ARTIFICIAL KIDNEYS

8.1 Introduction

While the kidney is mostly seen just as an organ of excretion, it is more than that. It does remove wastes (urea, ammonia, drugs, toxic substances), but it also removes normal components of the blood that are present in greater-than-normal concentrations. When excess water, sodium ions, calcium ions, potassium ions, and so on are present, the excess quickly passes out in the urine. On the other hand, the kidneys step up their reclamation of these same substances when they are present in the blood in less-than-normal amounts.

Thus, the kidney continuously regulates the chemical composition of the blood within narrow limits. The kidney is one of the major homeostatic devices of the body. The kidney helps to regulate the blood pressure and stimulates the making of red blood cells. The human kidney is also an endocrine gland secreting the hormones erythropoietin and calcitriol, the active form of vitamin D, as well as the enzyme renin.

The basic unit of the kidney is the nephron (see Figure 5.1). It is a long thin tube that is closed at one end, has two twisted regions interspaced with a long hair-pin loop, ends in a long straight portion and is surrounded by capillaries. In each kidney, there are one million nephrons.

Two systems are under development that are expected to improve the renal replacement therapy and may lead to higher survival rates in patients that are waiting for kidney transplantation.

One system uses a pure medical device-based approach. It mimics the excretion and reabsorptions function of the kidney by means of double filtration membranes. One membrane function like a ‘classic’ hemofiltration unit. The second membrane is designed to reabsorb substances from the hemofiltrate, which are lost in the ‘classic’ hemodialysis.

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The selectivity of the membranes can be vastly improved by new production techniques. Smart nanomembranes can be designed to selectively pass molecules, not only based on the size of the molecules, but also on dielectric properties of the molecule.

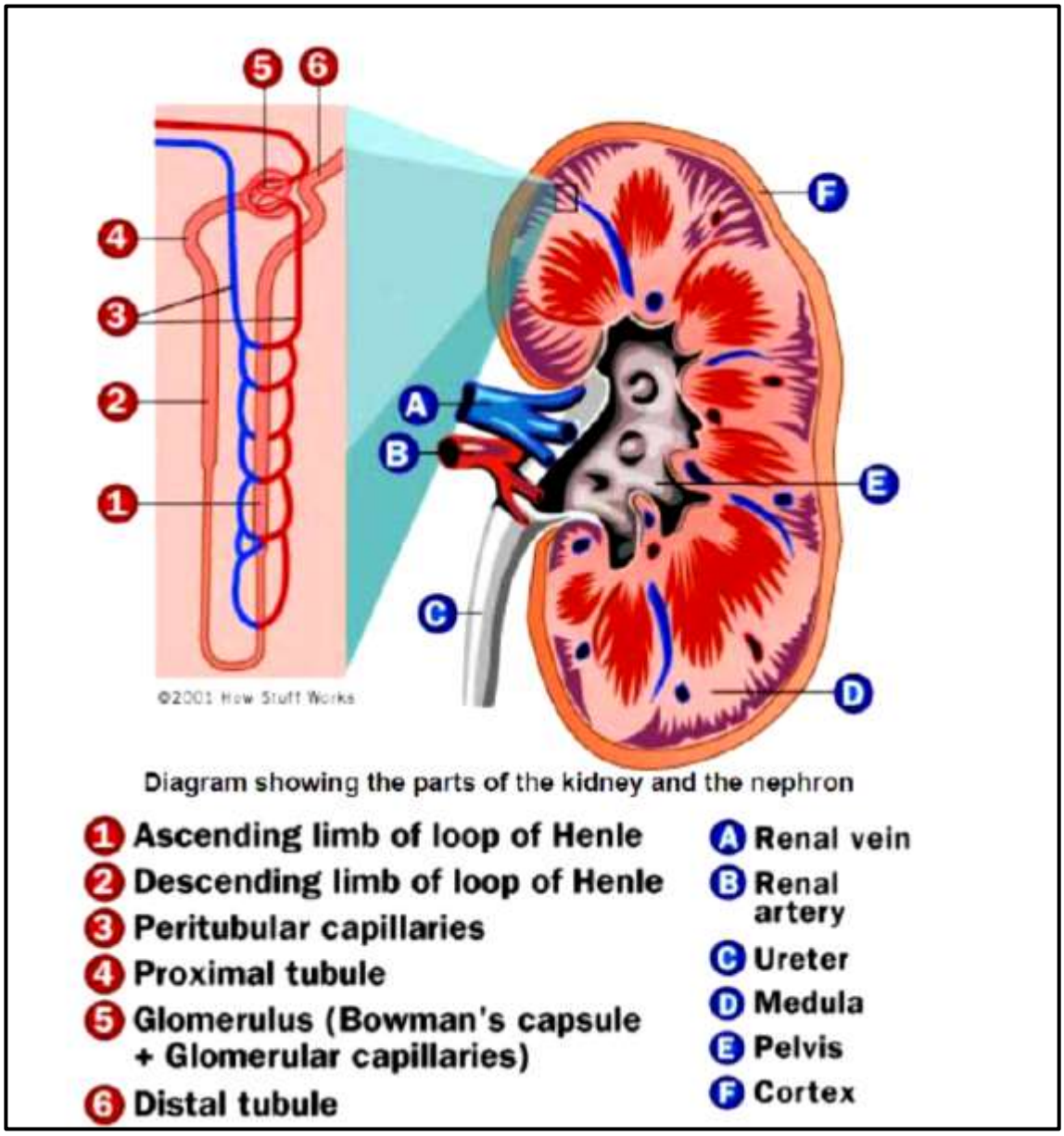

Figure 1: Diagram showing the parts of the kidney and the nephron

A second possibility is formed by the use of living cells or tissues. The cell-based approaches that are currently in development can be divided into the following categories: I) Repair of the kidney by infusion of stem cells, II) Transplantation of fetal kidney tissue,

III) Use of extracorporeal cell-coated devices, IV) Use of in vivo renal cell-coated matrixes. The most promising approach for the near future is likely to be the use of extracorporeal cell-coated devices, since this is the only approach that has entered clinical trials worldwide. This principle is based on a tissue-engineered bioartificial bioreactor that consists of a confluent layer of cultured proximal tubule cells seeded on the luminal side of multiple polysulfone hollow-fibers. This bioreactor is combined with a conventional hemofilter and acts to mimic the process of tubular reabsorption.

In the nephron, approximately 20% of the blood gets filtered under pressure through the walls of the glomerular capillaries and Bowman's capsule. The filtrate is composed of water, ions (e.g. sodium, potassium, chloride), glucose and small proteins (less than 30,000 daltons). The rate of filtration is approximately 125 ml/min or 180 litres each day.

End stage renal disease (ESDR) is treated with different strategies. The best survival outcomes may be expected by live donor renal transplantation. The mortality rate of patients with renal transplants is approximately half that of similar patients remaining on dialysis, despite improvements in dialysis and the morbidity of transplant surgery and immunosuppressive drugs. Transplantation is, however, severely limited by the supply of donor organs; more than three-quarters of transplant candidates die waiting for a kidney.

8.2 State of development

The technology effectively serves as a bridge to transplant. More recently, research is aiming to develop devices which can replace other functions of the kidney besides the clearance of small “chemical waste” molecules from the blood stream. The ultimate aim is to construct an implantable artificial kidney.

8.2.1 Dialysis

The natural kidney provides its homeostatic and clearance function continuously within the body. Current dialysis techniques provide around 10% of the clearance power

of the natural kidney. Hemodialysis (HD) is a technique in which blood is continuously extracted from the patient and directed over a membrane which is in contact with an electrolyte solution known as dialysate.

The membrane is designed to allow for diffusive transport of small molecules from the blood to the dialysate while retaining the higher molecular weight compounds such as albumin, coagulation proteins and immunoglobulins in the bloodstream. Dialysis is performed periodically, typically 3 sessions per week, 4-5 hours per session.

The short and infrequent dialysis is associated with an increased risk of under dialysis, fluid overload and hypertension, all factors associated with increased mortality and morbidity. The fluctuations in fluid state make it very difficult to control blood pressure and volume over the weekly cycle. Phosphate control is impossible without strict compliance with a phosphate binding or restriction regime.

Conversely, longer dialysis periods (8-12h) have been shown to maintain blood pressure within the normal range without drugs and to improve survival. Daily dialysis has been shown to normalize blood phosphate without the need for phosphate binders in addition to improved blood pressure control. Longer or more frequent dialysis strategies have not been generally accepted as they are considered to be impractical in the hospital setting. However, if the dialysis is delivered at home (or nursing home), longer and more frequent regimes become practical. At present, home dialysis is available only for a limited number of patients. The technology needs to be developed further to make it really practical and convenient for routine home use for the typical dialysis patient.

Modern dialysis is carried out with dialyses with minimal blood priming required, constant and reproducible performance and minimal dialytic loss of essential constituents such as albumin, despite significantly greater clearance characteristics for small- and medium-sized solutes compared to previously available dialyzers. Further increases in

dialyzer efficiency are increasingly difficult, in large part because of the non-selective nature of current conventional membranes, except on the basis of solute molecular size.

Another problem with HD is the vascular access. The typical blood flow of 400-500 ml/min requires a specialized vascular conduit known as a fistula if made from native vascular tissue, or known as a graft if constructed from synthetic material. Vascular access failure is common; 49% at 18 months for arteriovenous fistulas and 67% for grafts.

Alternatively, dialysis can be effectively performed inside the patient's own abdominal cavity using the peritoneal epithelia as the dialysis membrane; peritoneal dialysis (PD). PD is typically performed at home by the patient themselves, permitting the patient to remain in school, work and enjoy considerable independence, when compared with three-times weekly, in-center dialysis.

Both PD and HD show similar survival benefit in ESRD, with a strong age effect on survival. Teenagers have a 90% 5-year survival on dialysis. This drops to 53% by the age between 40 and 50 and is below 20% by the age of 70. Five-year survival is improved by a factor of four for elderly recipients of a living donor transplant, when compared with patients remaining on dialysis.

8.2.2 Towards the implantable artificial kidney

The research in renal replacement therapy (RRT) must expand from optimizing a chemical purification technique applied to reproducing the function of a complex multicellular organ. The ideal RRT device would mimic the function of natural kidneys – it would be continuously operating, remove solutes with a molecular weight spectrum like natural kidneys, it would be flexible and remove water and solutes based on individual patient needs, it would be wearable or implantable, and it would be biocompatible. In addition, it would be lightweight, low cost, safe and reliable (see Figure 2).

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Dialysis provides clearance of small molecules in blood by diffusive flows across a semipermeable membrane and control of volume status by bulk flow of water and solutes through that membrane. These effects are sufficient to counter the lethal acidosis, volume overload and uremic syndromes which accompany renal failure. The metabolic, endocrine and immune functions of the healthy kidney are not performed by either HD or PD; explaining the low survival of patients who depend on dialysis.

There are two approaches to engineering tubular reabsorption: employing living cells to mimic the function of their native counterparts, or manufacturing a second filtration membrane which permits the passage of salt, water, glucose and sodium bicarbonate, but retards the passage of uremic toxins. The advantage of the former lies in the simplicity of the approach; there is no need to separately implement each of the many transporters on the apical surface of the cell; supply the cell and the cell will supply not only the transporters but in addition, the driving force for reabsorption.

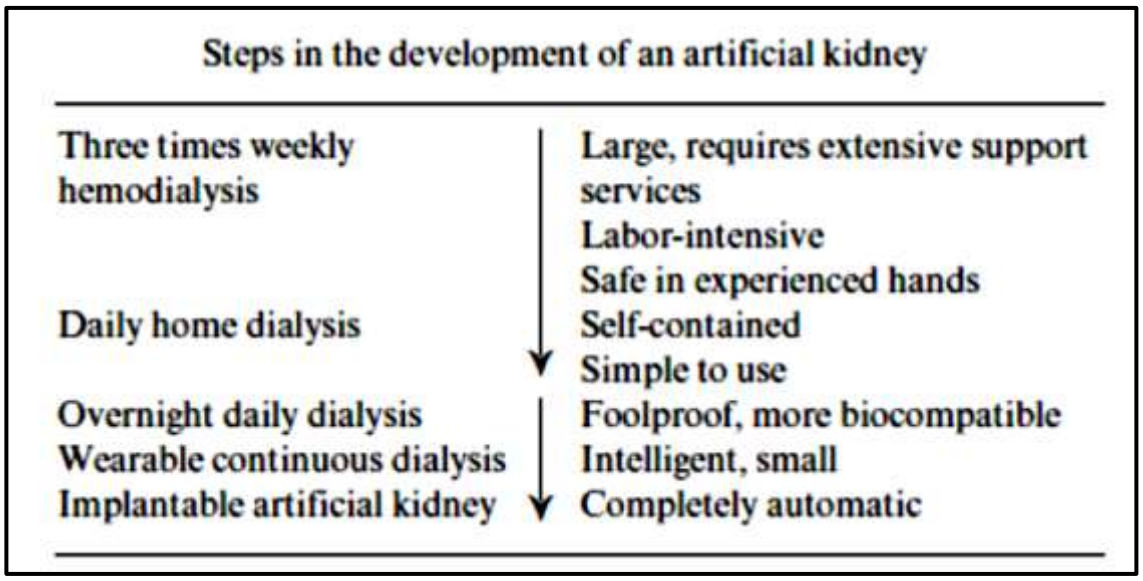

Figure 2: Flow scheme showing steps in the development of an artificial kidney.

8.3 Cell/tissue-based approach for function recovery

Long-term chronic renal replacement therapy with hemodialysis and peritoneal dialysis provides mostly intermittent filtration function and continues to have

unacceptably high mortality and morbidity rates. This is mainly caused by the fact that these approaches lack the potential to fully mimic the main metabolic functions of the kidney, such as

i) removal of toxic waste products,
ii) regulation of electrolyte balance,
iii) removal of excess water,
iv) calcium and phosphate metabolism,

8.3.1 State of development

The current decade has witnessed the development of several cell-based approaches for kidney treatment, which can roughly be divided into the following categories:

I) Repair of the kidney by infusion of stem cells
II) Transplantation of fetal kidney tissue
III) Use of extracorporeal cell-coated devices
IV) Use of in vivo renal cell-coated matrices

A novel and very promising approach to renal replacement therapy relies on combining ultrafiltration by a conventional hemofilter with tubular reabsorption by a bioreactor of cultured kidney cells. A tissue-engineered bioartificial bioreactor has been built by Dr. Humes and has entered clinical trials in the USA. The bioreactor, known as the renal assist device (RAD), consists of a confluent layer of cultured proximal tubule cells seeded on the lumen side of multiple polysulfide hollow-fibers (see Figure 4).

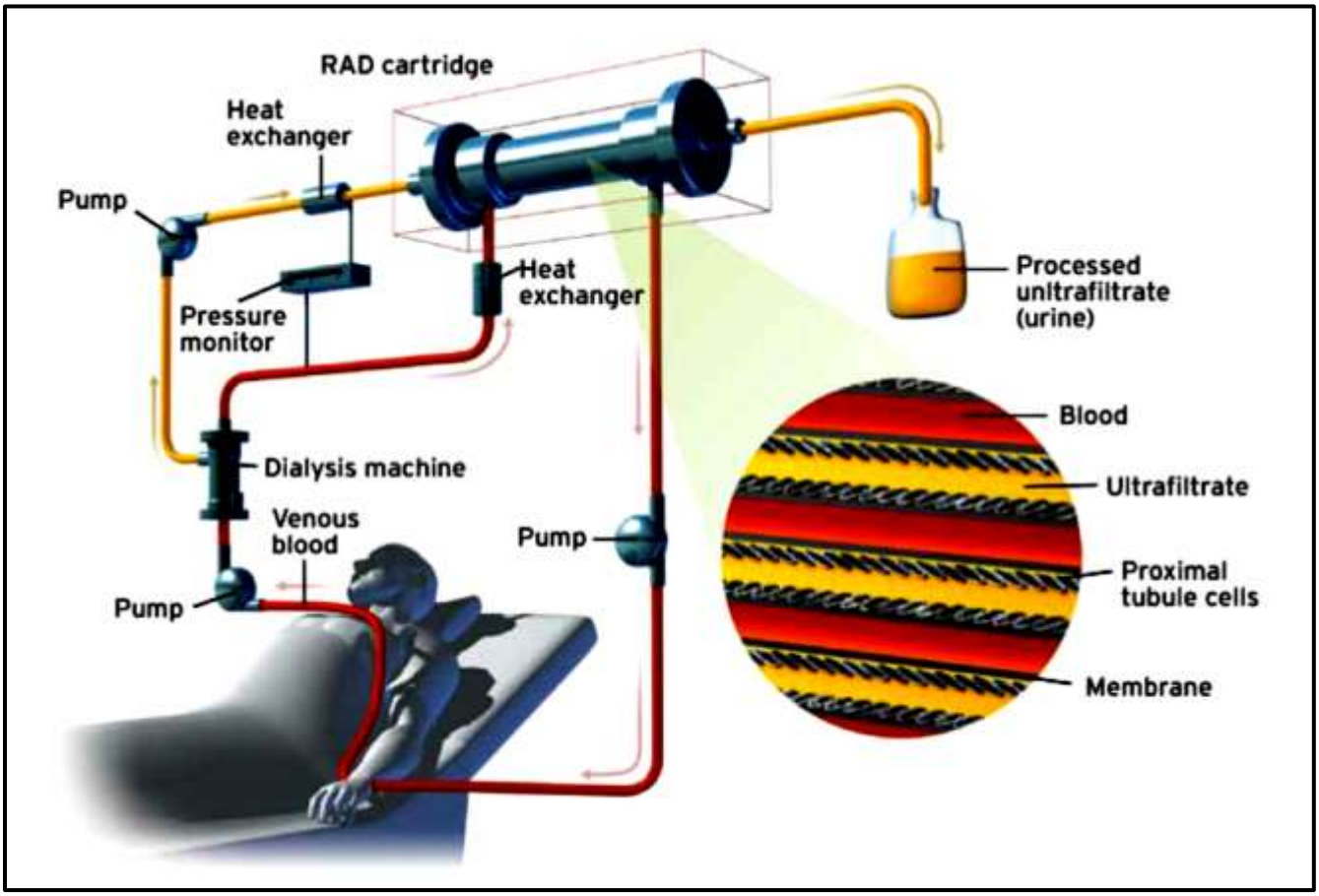

Figure 4: The renal assist device (RAD), under development at RenaMed Biologics

According to the manufacturer, these cells:

1) recover essential non-waste blood products from the passing filtrate and returns them to the circulation,
2) produce vitamins or vitamin precursors and release them into the circulation,
3) produce several soluble molecules critical for volume control and blood pressure regulation,
4) are the gatekeepers for residual toxic compounds in the filtrate,
5) sense infectious and inflammatory components and communicate with the body's host defense system.

Large animal studies have been completed with the use of this extracorporeal circuit. The RADs maintained viability and functionality in the extracorporeal circuit.