NEW INSIGHTS AND TREATMENTS OF KIDNEY DISEASE PART 1

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> Best known as the body's filter, the kidney is a complex organ whose failure sets off a legion of debilitating ailments.

As a senior veterinary college student, I was assigned to the intensive care unit and spent one very long afternoon watching an elderly dog on fluids die in uncontrollable seizures because its owners refused to consider euthanasia for this poor animal in total kidney failure. Eleven years later, I euthanized my own dog for the same illness, and both these experiences have given me a special interest in this disease.

Interestingly, pet food manufacturers are also interested in kidney failure (alternatively called renal failure), and the increased availability of low-protein diets, marketed for their reputed benefits to an old dog's kidneys, deserves some scrutiny. In truth, the roles of protein, phosphorus and even vitamin D are hotly debated by veterinary scientists researching kidney failure. Yet many of the marketing claims made today focus primarily on protein levels and actually may reflect the results of experiments done more than a decade ago, often on rats rather than dogs, which now are challenged frequently by newer studies.

One thing scientists and clinicians do agree on, however, is the management of a patient actually ill from kidney failure. This pet must have its phosphorus intake restricted if there is to be any hope of slowing the progressive, inexorable rate of kidney destruction. Additionally, if that pet is nauseous or exhibits vomiting and diarrhea, then protein also must be restricted. In practical terms, most pets in renal failure are fed scientifically formulated diets that reduce both nutrients, and the benefits usually are quickly evident to both the pet's owner and its veterinarian

But what of the aging dog or the dog that shows subtle changes in its urine but not yet any changes in blood values? What diet should be fed to this animal? Can we help such a dog with dietary changes, or do we simply have to wait until the illness actually occurs? And how common is kidney disease in older dogs? Some studies reveal kidney changes in as much as 85 percent of the canine population over 5 years of age, and other studies suggest kidney failure is the second leading cause of disease-related deaths in dogs, behind only cancer and heart disease. Interestingly, some dogs suffer from a form of kidney disease in which they actually lose protein. Could a "senior diet," restricted in protein, therefore be harmful?

Before we can answer such questions, we have to understand the kidney -- no small challenge because this complex organ is much more than an exquisite filter. In addition to cleansing the bloodstream of toxins and keeping the body's salts and minerals in balance, the kidney also is an endocrine organ factory for hormones that variously stimulate red blood cell production by bone marrow (erythropoietin), induce calcium absorption by the intestines (the activated form of vitamin D -- calcitriol) and affect blood pressure throughout the body by retaining sodium (rennin).

While the kidney performs these distinctly different roles, its failure to perform any one of them perpetuates kidney disease. Anemia from failed production of erythropoietin can increase the rate of kidney failure due to low oxygen in the blood. Low amounts of activated vitamin D can hasten failure through calcium and phosphorus imbalances that lead to destructive mineral deposits in the kidney itself. Excessively high or low blood pressure also will damage the kidney. The problems of an animal in kidney failure eventually become far more complex than simply poisoning by body processes due to the key filter failing.

THE NORMAL KIDNEY

The functioning units of the kidney are the nephrons, which number about a million with each able to produce urine. Clinical disease will not develop until roughly two thirds of the nephrons are damaged or destroyed. Such reserve (70 percent of kidney tissue) explains why people and animals can donate an entire kidney and still live a normal life span.

However, the remaining nephrons do change to meet the increased demands placed upon them. They must work harder and become more efficient if the same amount of blood is to be processed. The tiny, twisted capillaries, called the glomeruli or the glomerular tufts, that begin the blood filtration process must expand to allow more blood to flow. Consequently, the glomeruli enlarge as well to receive the plasma like, low-protein filtrate that passes out of the capillaries. The various tubules and ducts that process that filtrate also must increase their efficiency -- whether it is to reabsorb sodium, excrete or absorb water (loops of Henle) or balance potassium and acid exchange (distal convoluted tubules).

Collecting ducts then carry the final product, urine, to the central portion of the kidney and down the ureter to the bladder. Within the kidney, the length of the nephron, including the collecting duct, approximates 2 to 2 ½ inches.

The three hormonal roles of the kidney take place primarily in the glomerulus and proximal tubules where the process of the filtrate transformation and urine production begins. This is logical, since the plasma filtrate at the beginning of the filtering process most closely reflects the conditions in the total body, allowing the hormonal responses of the kidney to correct quickly any imbalances detected.

The first hormonal role occurs when oxygen tension is low. When this happens, erythropoietin is released to stimulate the production of more red blood cells by the bone marrow. In the renal failure patient, injections of erythropoietin are necessary to reverse the anemia, increase oxygenation of the kidney and often extend the life of the patient.

The second hormonal function of the kidney also involves blood flow. If blood pressure drops and flow to the glomerulus falls, as occurs in shock after an automobile accident, then glomerular cells release the hormone renin, which can increase blood pressure, consequently restoring blood flow to the kidney. Blood pressure is increased in several ways, but chiefly through salt retention by the kidney itself. In the failing kidney, blood pressure also decreases, so renin is released. The resulting hypertension initially increases blood flow through the weakening kidney, but ultimately this high blood pressure destroys the fine glomerular capillaries. Terminally, all the excess sodium in the body can lead to edema (an abnormal accumulation of fluid resulting in swelling) and heart failure, further complicating a severe condition.

The final hormonal system involving the kidney is thought by some researchers to be the most important to the renal failure patient. If calcium levels in the blood are too low, stores of vitamin D will be

converted to its active form and released as a hormone into the body to increase calcium absorption by the intestines.   The importance of calcium to the body, and its role in kidney health and disease, cannot be explained without discussing phosphorus at the same time.   These two minerals are the primary components of bone, and bonelike deposits will form in normal tissue if either mineral is too highly concentrated in the bloodstream. This happens passively simply because calcium will precipitate as a phosphate salt if enough ionized calcium and ionized phosphate are in proximity to each other. To avoid this and maintain a safe and constant ratio between the two minerals, the body exercises several hormonal controls in the kidney, the thyroid and the parathyroid gland.

Additionally, calcium is essential to heart and muscle function, as are sodium and potassium, because these minerals are exchanged back and forth across muscle cell membranes to effect contraction. Severe Imbalances of any of these minerals create weakness and abnormal heart rhythms. The normal kidney/parathyroid gland hormonal feedback systems work to conserve calcium and prevent bonelike deposits in soft tissue. Since calcium and phosphorus come into the blood stream from both the diet and from bone, the kidney and the parathyroid glands exert their effects chiefly on the intestines, the skeleton, and on the major route of mineral excretion – the urine produced by the nephron tubules.

The activated form of vitamin D produced in the kidney is considered a hormone because it exerts its action on a distant location.   Chiefly, it increases calcium concentrations by increasing absorption from the intestines.   Parathormone, produced by the parathyroid gland in the neck, also is sensitive to the blood's calcium concentration. When calcium levels are low, parathormone encourages mobilization of calcium from bone. Since phosphorus is liberated from the bone at the same time, parathormone increases the excretion of phosphorus from the kidneys to keep the ratio between the two minerals constant.

In the early stages of kidney disease, these hormonal feedback systems work well, but by the time the kidneys have only 15 percent to 25 percent of their remaining nephrons still functioning, these control methods actually can contribute to disease. Health decline and death are very rapid from that point.   Due to lack of activated vitamin D combined with excessive parathormone levels, calcium phosphate salts actually precipitate in the kidney itself, hastening its destruction through mineralization.   Blood pressure becomes dangerously high due to excessive release of rennin -- the kidneys' attempt to increase blood flow faster and harder through fewer and fewer nephrons.   This eventually destroys the delicate, remaining glomeruli and associated capillaries.   Finally, erythropoietin cannot be produced, and the resulting anemia further decreases the blood supply to the kidney. An anemic renal failure patient often is considered terminal ("end stage") because erythropoietin production is one of the last things to fail.

DISEASES AFFECTING THE KIDNEY

Given the complexity of the kidney it is not surprising that many breeds report kidney disease in young dogs due to gross malformations, subtle abnormalities in development or premature atrophy of nephrons. Kidney disease can occur sporadically in any young dog, but distinct syndromes have been defined for the Cocker Spaniel, Norwegian Elkhounds, Lhasa Apso, Shih Tzu, Basenji, Samoyed, Doberman Pinscher, Cairn Terrier, Standard Poodle, Pembroke Welsh Corgi, Soft-coated Wheaten Terrier and Bull Terrier. In some, the genetics have been defined precisely, while in others a higher–than-expected breed incidence of kidney disease is all that has been reported to date.   Tiny puppies may be presented for stunted growth, poor appetite, vomiting, diarrhea, inability to be house-trained and drinking excessive amounts of water. Alternatively, dogs as old as 5 years of age may begin to show these signs of illness.   Since the nephron is such a complicated piece of plumbing, any single part of it can fail to develop properly and lead to disease in a young dog.

A few well-described cases illustrate this. The Samoyed type of congenital kidney disease is an abnormal multiplication of cells in the glomerulus, eventually choking this structure. It is inherited as a dominant, sex-linked trait, killing males before 15 months of age while carrier females may live a normal life span despite abnormal urine and blood tests.

In contrast, Cairn Terrier pups usually are recognized as stunted and unhealthy well before weaning (4 to 6 weeks of age) because huge cysts form in the kidney and liver, actually swelling the abdomen. These cysts are believed to originate from the external capsule of the kidney and the liver. In the kidney, the nephrons themselves are normal, but they are progressively destroyed by pressure from the cysts. In contrast, the Basenji is an animal model for human Fanconi syndrome in which tubular disease causes mineral imbalances and loss of glucose. The dog suffers from Fanconi-type mineral imbalances and loss of glucose before the later signs of renal failure such as vomiting, diarrhea and dehydration appear.

Finally, affected Lhasa Apso and Shih Tzu puppies have misshapen kidneys with additional microscopic abnormalities. The kidneys may be dumbbell-shaped with normal tissue absent from the middle of the kidneys. Under the microscope, nephrons may be small, irregular and not fully developed, looking more like the immature nephrons present in the kidney of a canine fetus.

Beyond genetics and birth defects, poisons and infections can injure any or all parts of the nephrons. Ethylene glycol (the primary ingredient in antifreeze) destroys the kidney only after it has been metabolized to oxalic acid in the liver. In that form, it precipitates as calcium oxalate crystals in the tubules, effectively blocking and destroying them.

Infectious bacteria also can attack the nephrons, invading through either the bloodstream and into the glomerular capillary tuft or directly from the urine itself, migrating up from the bladder through the tubules and deep into the kidney. Blood clots can effectively destroy kidney tissue as well. Finally, the glomerulus may even filter circulating antigens and antibodies, depositing these noninfectious but still reactive complexes in the glomerulus, leading to its destruction.

Regardless of the specific location or cause of kidney damage, once 60 percent to 75 percent of the kidney is destroyed, abnormal blood values generally develop, and as likely as not, there will be an inexorable progression of kidney destruction after that point, leading eventually to death from renal failure. It is believed that once the kidney is significantly diseased, nephrons are lost at a constant rate due to the excessive work demands placed on those nephrons still remaining.

In fact, graph studies have shown the course of the disease can be roughly predicted if several creatinine measurements are taken. Creatinine was selected for one particular study because it is a waste byproduct of muscle breakdown and repair, and its production is nearly constant. The other two compounds most constantly monitored are urea (blood urea nitrogen) and phosphorus, but both of these are affected by diet. Essential minerals such as calcium, sodium and potassium also may be abnormal in renal failure, but this generally occurs only after BUN (blood urea nitrogen), CREAT (creatinine) and PHOS (phosphorus) are elevated several times above the normal range.

Clearly, successful management of the renal failure patient requires attention to every derangement. Nitrogenous protein wastes must be minimized, sodium must be restricted to help lower blood pressure, phosphorus must be withheld and any anemia reversed. When dietary management fails to accomplish these objectives, specific drugs are prescribed to bind phosphorus in the intestines, minimize phosphorus and calcium release from bone, lower blood pressure and stimulate the bone marrow to produce red blood cells.

When specific drugs should become part of the management plan for a patient is a matter of medical judgment and great debate today among veterinary clinical researchers, and much remains unanswered. Finally, it is crucial that the patient's urine is checked frequently with chemical testing and microscopy for any sign of bacteria.   An animal with few nephrons cannot afford an infection so urine testing and even bacterial culturing on a regular basis often are recommended.