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Physiologic studies in normal and uremic sheep: I. The experimental model

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Physiologic studies in normal and uremic sheep: I. The experimental model. A model of chronic renal failure was created in nine adult sheep by two-stage, subtotal nephrectomy. Carotid-jugular cannulas provided clot-free access for 72 to 274 days without exit-site infections. All sheep became uremic and anemic. Median survival, while uremic, was 145 days (72 to 327 days), although three were sacrificed. Five required dialysis within the first week of uremia, and median survival on dialysis was 70 days (41 to 177 days). Sheep that maintained adequate nutrition survived the longest on dialysis. Mean creatinine and BUN levels in the stable uremic and dialyzed sheep were 4.8/95 and 7.8/59 mg/dl, respectively. The other serum chemistries remained unchanged (mean values) from normal, although one sheep died of hypercalcemia (17.8 mg/dl). Renal blood flow correlated to GFR in both normal and uremic states. GFR fell more than serum creatinine rose, suggesting extrarenal excretion of creatinine.

Etudes physiologiques chez le mouton normal et urémique: I. Le modèle expérimental. Un modèle d'insuffisance rénale chronique a été créé chez neuf moutons adultes par néphrectomic subtotale en deux étapes. Des canules carotido-jugulaires ont permis un accès sans coagulation pendant 72 à 274 jours sans qu'il y ait d'infection aux lieux de pénétration. Tous les moutons sont devenus urémiques et anémiques. La survie médiane, au cours de l'urémie, a été de 145 jours (72 à 327 jours) bien que trois d'entre eux aient été sacrifiés. Cinq ont dû être dialysés dès la première semaine de l'urémie et la survie médiane en dialyse a été de 70 jours (41 à 177 jours). Les animaux qui ont eu une alimentation adéquate ont eu la survie la plus longue en dialyse. Les concentrations moyennes de créatinine et d'azote uréique dans l'urémie stable et chez les moutons dialysés étaient de 4,8/95 et 7,8/59 mg/dl, respectivement. Les autres valeurs plasmatiques moyennes n'étaient pas différentes de la normale bien qu'un mouton soit mort d'hypercalcémie (17,8 mg/dl). Le débit sanguin rénal était corrélé au débit de filtration glomérulaire dans ces situations normales et urémiques. Le débit de filtration glomérulaire a diminué plus que la créatininémie n'a augmenté, ce qui suggère une excrétion extra-rénale de créatinine.

Repetitive hemodialysis, introduced in 1960 by Scribner et al [1], is capable of reversing or stabilizing many of the complications of chronic renal failure (CRF). The pathophysiology of the abnormalities associated with renal dysfunction, however, is difficult to study in humans because of the type of experimentation required. Animal models of renal failure have been developed to investigate these problems [2, 3], but long-term studies are limited because chronic dialysis of animals is technically difficult.

Because of the need to study certain aspects of CRF in an experimental setting, we have established a large animal model for this syndrome in the sheep. This model of CRF allows repeated studies and physiologic manipulations to be performed, including animals on hemodialysis for up to 6 months, and animals can be used as their own controls prior to the establishment of CRF.

The sheep was chosen because of two advantages: *(1)* vascular access can be maintained for a prolonged period of time free of infection, and *(2)* by selecting animals for hemoglobin phenotype, it is possible to take advantage of an unusual hematopoietic property of certain ruminants, the appearance of a structurally distinct hemoglobin, hemoglobin C (HbC), in response to erythropoietin (ESF) stimulation [4]. In this report, the details of the model are described.

Methods

Surgery. Adult, dewormed female sheep, each weighing more than 100 pounds, were used. The surgical details of cannulation of the carotid and jugular vessels have been described elsewhere [5].

The spleen was removed at the same time the vascular access was created. This was carried out to exclude splenic red cell pooling and release, which might complicate quantitative studies of red cell production and destruction [6, 7].

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The uremic state was created by subtotal nephrectomy. In sheep, the renal artery divides at the renal hilus into posterior and anterior branches that supply approximately two thirds and one third of the kidney, respectively. Initially, the anterior branch of the renal artery was ligated along with all but one of the four to five secondary branches of the posterior division. This leaves approximately 8 to 10% of the blood supply to that kidney intact.

At least 2 weeks after the animal had recuperated from the renal infarction, the contralateral kidney was removed. This intervening time allowed the renal remnant to hypertrophy and reduced the likelihood that dialysis would be required immediately postnephrectomy.

Metabolic studies. The sheep were kept in metabolic cages to collect urine and to prevent dislodging of the cannula by other sheep (Fig. 1). They were fed a daily diet of salt, up to 9 liters of water, and 1.0 to 1.5 kg of alfalfa pellets and hay. Blood samples for hematologic values and chemistries were obtained from the vascular access daily for the first postoperative week, and thereafter as dictated by the stability of the animal's renal function.

Several parameters of renal function were followed. RBF was determined by iodine-131 hippuran clearance [8, 9]; GRF was measured by iodine-125 iothalamate [10] or ytterbium-169 diethylene triamine pentacetic acid (DTPA) clearance [11]; overall renal function was monitored by the serum creatinine concentration.

Hemodialysis. Dialysis was initiated when the serum creatinine concentration exceeded 15 mg/dl or the serum potassium concentration was more than 7 mEq/dl. A standard 2-layer Kiil dialyzer (1 m^2) or a Gambro-Lundia dialyzer (1 m^2, 13.5-μm membrane) was used 6 to 8 hours and 4 to 5 hours, respectively, three times per week, utilizing a dialysate containing 145 mEq of sodium [12], 38 mEq of acetate, 3.5 mEq of calcium, 1.0 mg of magnesium, and 102.5 mEq of chloride per liter. Potassium was excluded.

Blood flow rates in the dialyzers were greater than 200 ml/min, and dialysate flow rates were 200 ml/min. Weights were obtained before and after dialysis to monitor fluid balance. During dialysis, the sheep were kept in metabolic cages but were partially immobilized by a stanchion (Fig. 1). Although the sheep were able to eat during dialysis, the blood tubing lines were inaccessible and could not be accidently punctured.

Results

Vascular access (Table 1). Cannula survival in previous studies of normal sheep averaged 46 days (range, 9 to 152 days) [5] and was prolonged to 104 days by Coumadin® anticoagulation [13]. The median survival of cannula function in 9 uremic sheep not receiving Coumadin was 142 days (range, 72 to 274 days). Three of these sheep clotted their cannulas. One (no. 53) died following surgical recannulation, another (no. 62) died 10 days after surgical recannulation, and the other had a cannula survival of 208 days while receiving Coumadin. Of the 6 sheep whose cannulas did not clot, 3 were sacri-

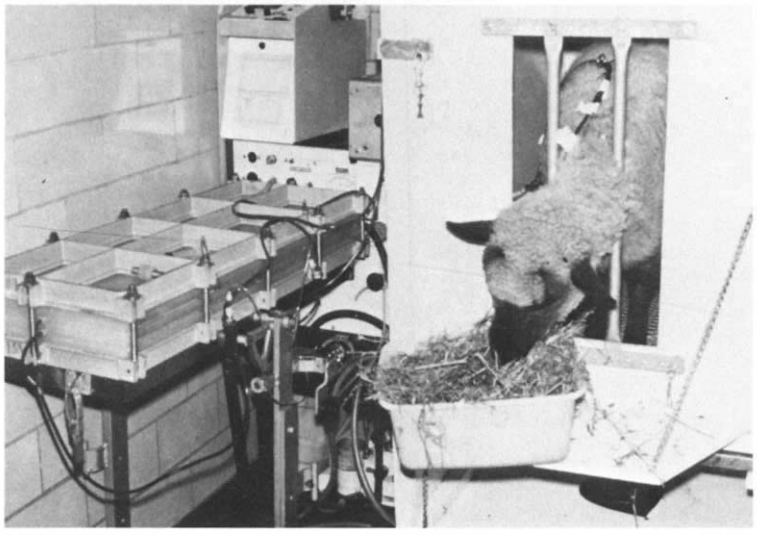

Fig. 1. *Sheep being dialyzed while in a metabolic cage.* The animal is retained in a stanchion, can stand or lie during dialysis, and can eat ad libitum.

Table 1. Cannula function and survival

Sheep no.	No. of cannulations	Days of uremia	Cause of death
53	2	188[a]	Trichobezoar
62	2	101[b]	Hypercalcemia
65	1	274[c]	Pulmonary embolism?
182	1	142[c]	Exsanguinated
318	1	74[b]	Sacrificed
324	1	72[b]	Pneumonia
353	2[d]	327[a]	Sacrificed
362	1	145[b]	Pneumonia
363	1	180[b]	Sacrificed

[a] Dialysis not needed
[b] Dialysis required within 8 days after subtotal nephrectomy.
[c] Dialysis not needed until 210 and 101 days after subtotal nephrectomy
[d] Initial cannulation functioned 208 days, associated with Coumadin therapy.

ficed, so the true duration of their cannula survival is unknown.

Survival (Table 1). Of the 9 sheep made uremic, 5 required dialysis within 3 to 8 days after nephrectomy; the other 4 maintained a stable degree of uremia (creatinine, 4.8 ±[SD] 0.4 mg/dl) for 101 to 327 days (median, 199 days). Hemodialysis was eventually required in 2 of these after 210 and 101 days of renal failure, possibly because progressive fibrosis led to further destruction of the renal remnant [14] The median survival time, once hemodialysis was initiated, was 70 days (range, 41 to 177 days). The median survival for all 9 sheep from creation of the azotemic state was 145 days (range, 72 to 327 days).

The causes of death in the uremic sheep varied and are indicated in Table 1. Three sheep were sacrificed at the termination of the studies.

Metabolic studies. Table 2 gives the blood chemistries observed in the normal, prenephrectomy state, during the period of stable uremia, and during dialysis. In dialyzed animals, the mean predialysis serum creatinine was 7.8 ± 3.0 mg/dl, which was higher than values in sheep with stable uremia. BUN levels, however, were lower in dialyzed sheep than they were in stable uremic animals because food intake was less. This is illustrated in Fig. 2, which shows the mean weights of the two groups. Mean serum albumin concentrations did not differ, however, between the normal, stable uremic, or

Table 2. Blood chemistries in normal and uremic sheep[a]

Sheep no.	S_{Cr} *mg/dl*	BUN *mg/dl*	S_{Alb} *g/dl*	S_{Na} *mEq/liter*	S_K *mEq/liter*	CO_2 *mEq/liter*	S_{Ca} *mg/dl*	S_P *mg/dl*	$S_{Alk\ Pase}$ *IU/liter*	*N*
					A. Normal sheep (prenephrectomy)					
53	1.1	26	2.3	148	4.6	23	9.6	6.9	70	2
65	1.1	23	2.7	149	4.7	25	10.4	—	80	1
182	1.3	29	2.4	148	4.4	27	10.3	—	55	2
318	1.1	23	2.0	146	4.3	27	8.9	6.4	69	12
324	1.0	21	2.3	145	4.3	25	9.1	6.5	33	8
353	1.1	23	1.9	142	4.7	25	9.4	5.3	53	3
362	1.0	21	1.8	145	4.9	26	8.2	8.8	45	5
363	0.7	20	1.9	144	4.7	26	8.6	6.3	51	32
Mean	1.1	23	2.2	146	4.6	26	9.3	6.7	57	
± SD	±0.2	±3	±0.3	±2	±0.2	±1	±0.8	±1.2	±15	
					B. Uremic, stable sheep					
53	5.2	88	2.2	148	4.6	31	9.9	8.6	147	22
65	4.4	90	2.3	147	5.1	29	10.2	7.5	98	39
182	4.5	100	2.3	146	5.5	30	11.0	—	107	24
353	5.2	103	2.6	146	5.0	29	9.6	5.0	55	37
Mean	4.8	95	2.4	147	5.1	30	10.2	7.0	102	
± SD	±0.4	±7	±0.2	±1	±0.4	±1	±0.6	±1.8	±38	
					C. Sheep on dialysis					
62	10.8	61	1.9	138	4.5	22	12.4	—	51	38
65	9.8	47	1.7	143	4.5	25	8.0	10.2	37	20
182	11.7	56	2.0	145	4.8	28	8.5	5.6	42	9
318	4.1	58	2.9	147	4.8	24	9.1	8.9	62	33
324	7.5	44	2.3	141	5.8	29	10.4	6.8	36	7
362	5.4	78	2.2	145	5.9	27	8.1	11.9	42	54
363	5.1	70	3.1	145	5.5	28	9.0	6.4	50	48
Mean	7.8	59	2.3	143	5.1	26	9.4	8.3	46	
± SD	±3.0	±12	±0.5	±3	±0.6	±3	±1.6	±2.5	±9	

[a] *N* denotes the number of determinations. In group B, *N* was obtained weekly beginning 1 month after surgery; in group C, *N* was obtained before dialysis or three times per week.

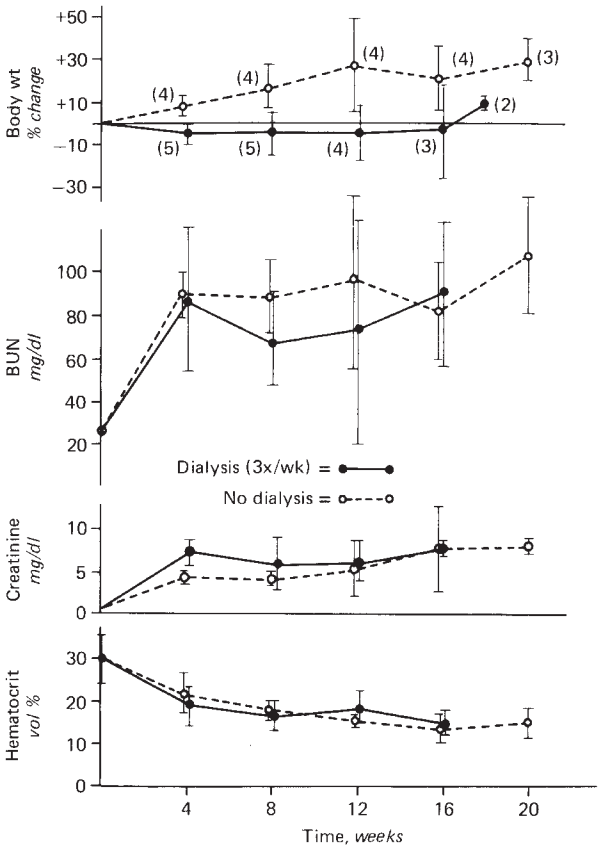

Fig. 2. *Hematocrit, serum creatinine, blood urea nitrogen, and body weight changes observed in 9 uremic sheep, 5 of which required dialysis shortly after the uremic state was surgically created.* The nondialyzed uremic sheep remained anabolic. The hematocrit declined during the first month after surgery to a similar degree in both the dialysis-dependent and stable uremic sheep. Numbers in brackets indicate number of sheep.

dialyzed sheep, although the variation was greater in the last group.

Hyperkalemia, a serious problem in dialyzed, totally nephrectomized animals [15], was well controlled with three-times-weekly dialysis in animals subtotally nephrectomized. Hypercalcemia greater than 12 mg/dl developed transiently in 3 animals and persisted in another. This last sheep died with a serum calcium concentration of 17.8 mg/dl while on dialysis. Nevertheless, the mean serum calcium concentrations were similar in all three study stages.

Serum phosphate concentrations varied widely in the dialyzed sheep (8.3 ± 2.5 mg/dl), although the mean value was also similar at all three study stages. This may be explained by the decreased intake of grain, which contains high quantities of phosphates, by the dialyzed, uremic sheep. Even the normal sheep had levels that ranged between 3.7 to 7.8 mg/dl. Alkaline phosphatase concentrations were higher in 3 of the uremic sheep, but did not increase when hypercalcemia was present. These values subsequently normalized over a 3-month period.

Renal function changes. Figure 3 shows the relationship between serum creatinine and GFR in 11 sheep. The mean GFR in 7 normal sheep (12 determinations) was 161.1 ± 44.3 ml/min, and was associated with a mean serum creatinine of 0.88 ± 0.28 mg/dl. One to two weeks after the unilateral seven-eights renal infarction procedure, the mean GFR in 4 sheep was 74.0 ± 20.8 ml/min and was associated with a mean serum creatinine of 0.98 ± 0.21 mg/dl. The 12% rise in the serum creatinine, associated with a 45% reduction in the GFR, is consistent with the fact that there may be extrarenal excretion of creatinine in sheep [16]. Serial studies in several animals indicated that the GFR must be reduced to less than 15 ml/min before the serum creatinine rises above 4 mg/dl.

The correlation between GFR and RBF is shown in Fig. 4. The RBF was calculated by dividing the measured renal plasma flow by the plasmacrit (100

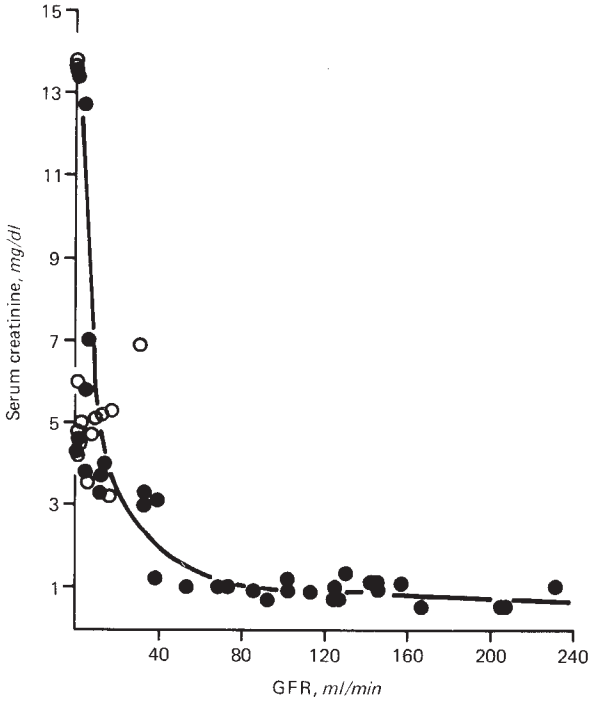

Fig. 3. *Relationship of the GFR to serum creatinine in 11 sheep at different levels of renal function, including the normal state and after subtotal nephrectomy.* The *open circles* indicate values obtained in dialyzed sheep. The fact that the serum creatinine remained normal despite marked reductions in GFR is compatible with extrarenal excretion of creatinine.

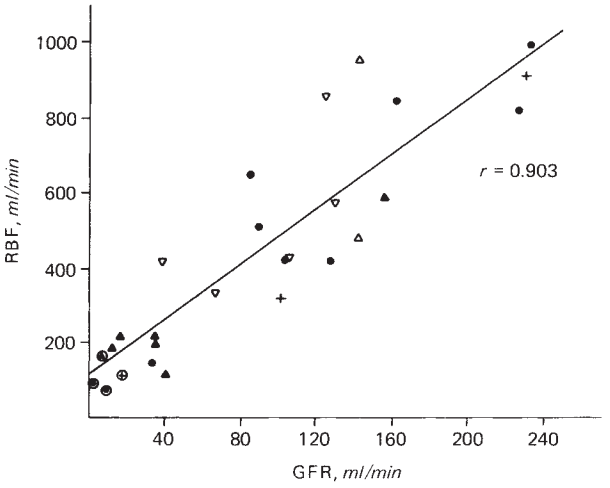

Fig. 4. *Relationship of GFR to RBF in 5 sheep studied at all levels of renal function.* Each sheep is represented by a different symbol, and the four *open circles* represent sheep requiring dialysis. There is a direct correlation (r = 0.90) between these two parameters.

– hematocrit). A close correation (r = 0.90) between GFR and RBF was found at all levels of GFR.

Urine volumes fell below 1 liter/day for several days after nephrectomy, but then varied between 2 to 9 liters/day, depending on fluid intake. When urine volumes remained less than 700 ml/day, maintenance dialysis was subsequently required.

Discussion

A large-animal model of chronic renal failure, produced by subtotal nephrectomy, has been created specifically to study the pathophysiologic changes of CRF. With this approach, about one half of the experimental animals developed a stable, but moderately severe uremia for 3 to 11 months before requiring dialysis. The remaining animals required dialysis within 3 to 8 days after the surgical establishment of uremia. These sheep were maintained with thrice-weekly dialysis for 1 to 5 months. As seen in Fig. 2, anemia developed within 1 month and was similar in degree, whether or not dialysis was required. Nutrition appeared adequate in the nondialyzed uremic sheep, and body weight increased 27 ± 22% by 12 weeks. When renal function was poor enough to warrant dialysis, body weight fell a mean of 5.2 ± 4.7% after 4 weeks of dialysis. There was longer survival in those sheep that maintained their nutrition and weight. The 2 sheep that lived 18 weeks on dialysis had eventually gained 9 and 14% above their original body weight, whereas the 3 sheep that died earlier had lost 15, 16, and 29% of their body weight. Dialysis ultrafiltration was able to prevent peripheral or pulmonary edema in all but one animal.

The partially nephrectomized model has proved much easier to maintain and study than the anephric model [15]. Despite daily dialysis of 15 anephric sheep, catabolism could not be controlled, and death occurred within 39 days (mean, 15 days). The differences between the two models indicate the importance of the renal remnant. Potassium balance was generally preserved and remained normal during dialysis even while renal failure progressed. Salt and water balance was also easily maintained, and the intake of sodium did not need to be restricted. Appetite remained good as long as the azotemia was stable, but decreased once dialysis was necessary, a finding similar to that in uremic man. The degree of anorexia, however, was much worse in the anephric sheep requiring dialysis. These differences suggest that in the sheep even a small residual of renal tissue may contribute to overall nutrition.

Renal function tests of RBF and GFR were predictable and correlated well with one another. The serum creatinine was a good measurement of serial changes in renal function despite the possible existence of extrarenal creatinine excretion.

Detectable hematologic changes were confined to erythropoiesis. During the first month of uremia, the hematocrit gradually fell from a mean of 30 vol% to 22 and 19 for nondialyzed and dialyzed animals, respectively. The hematocrits of dialyzed sheep ranged between 15 and 18% thereafter. According to Fig. 2, the hematocrits of the stable uremic sheep continued to decline, but this was because of study-related phlebotomies. The hematocrits of the 2 stable uremic sheep, just before dialysis was initiated, were 13 and 19%.

The advantages of the sheep model are that carotid-jugular, silastic-teflon cannulas function for many months and provide for easy blood sampling and hemodialysis with minimal clotting and infection. The large blood volume is similar to that in humans and permits relatively large quantities of blood to be removed or shifted extracorporeally during dialysis without significant blood pressure changes. Renal failure can be reliably created with subtotal nephrectomy, and animals can be studied serially, both before and after the establishment of uremia, and thus serve as their own controls.

Other animal models do not have all of these advantages. Although anephric dogs can be kept alive by daily peritoneal dialysis for up to 69 [2] and 111 [17] days, malnutrition and peritonitis limit long-

term effectiveness [17, 18]. Partial nephrectomy in dogs can create a uremic milieu without the need for dialysis [19], but because erythroid function is almost absent in anephric dogs [20, 21] in contrast to anephric humans [22], the uremic dog model is not appropriate to investigate disorders of erythropoiesis in CRF. In addition, cannula survival in nonuremic dogs is poor, due to frequent wound infections (Eschbach and Cole, unpublished observations). Anephric rabbits have only been kept alive with peritoneal dialysis for up to 9 days [3], or with hemodialysis for 1 week [23]. In both situations, infections of the access site limit long-term effectiveness.

Anephric rats have been successfully peritoneally dialyzed for up to 12 days without developing peritonitis through the use of a permanent, dacron-cuffed, peritoneal catheter [24]. Anemia develops rapidly leading to a 50% reduction in red cell mass by the 12th day of uremia. This technique should allow for the maintenance of a more chronic uremic state, so that repeated studies would then be feasible. Nevertheless, because of the difficulties of successfully dialyzing anephric rats, most rat models are based on the two-stage, five-sixths nephrectomy originally described by Chanutin and Ferris [25] in which the upper and lower thirds of one kidney are surgically removed, followed by the removal of the contralateral kidney 1 week later. Ibels et al observed that death from uremia usually occurred within 168 days unless phosphate depletion was induced [14].

A stable level of anemia developed within 6 to 8 weeks in a similar model studied by two other investigators [26, 27]. There was, however, eventually a spontaneous improvement in the anemia and azotemia of some nonphosphate-depleted, five-sixths nephrectomized rats [28], making studies difficult to interpret in this setting. An ingrown strain of mice with polycystic kidney disease that progresses to renal failure has been studied by Reissmann and Werder [29], but as yet chronic dialysis has not been used. Recently, small anephric goats have been chronically maintained on hemodialysis for up to 93 days, but the anemia failed to stabilize, and weight loss continued despite normal food intake [30].

Because it is difficult to study the same small animals repeatedly in both control and uremic conditions, let alone keep them alive and stable with dialysis, if it is required, the subtotally nephrectomized sheep provides an advantageous model in which the physiologic changes of chronic renal failure can be studied.

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