The kidneys and urological plumbing system acts as the primary excretory system of the body and has great importance to maintain body fluid volumes and homeostasis or balance of the milieu intérieur (the environment within). In general, the pig has urological anatomy and physiology similar to humans. Recognizing this similarity, biomedical researchers have applied miniature and domestic swine as research models for endourology, incontinence and overactive bladder, nephrolithotomy, cancer drug screening in bladder, non-surgical device (ureteral double-J stents) studies, surgical renal transplant, intra-renal surgery, renal reflux, hydronephrosis, renal hypertension, renal ischemia and reperfusion, and general urological functional studies.

Anatomy Review
The gross anatomic and histologic characteristics of the porcine and the human kidney are more similar than most other commonly used lab animals. The physiologic functions of the urinary system, including urodynamic parameters, are also similar to humans. The anatomy of the swine urological system (blood supply, kidneys, ureters, urinary bladder, urethrae) are schematically represented in Figure 1.

Pig and human kidneys are anatomically similar (characterized by multilobular structure in contrast to the unilobular rodent and dog kidneys). The swine internal kidney anatomy is a true multireniculate, multipapillate organ with a true calyceal system like humans (Smith & Swindle, 2006). Swine kidneys normally have 8-12 minor calices (Pond and Houpt, 1978). Few nephrons (3% vs 100% in dog or 14% in man) are long-looped or juxtamedullary which are involved in urine concentration (Pond and Mersmann, 2001). The kidneys of 25 kg Hanford miniature swine weigh 120g and measures
11 x 6 x 3 cm which is similar to the kidney of a 70 kg human (Schwalb et al., 1989). The average ureteral length in these minipigs is 22-26 cm, and the diameter of the ureterovesical junction is 4-6 F (1.3-1.9 mm). The bladder capacity is approximately 150 ml in this size Hanford. Access to the female minipig urethra is intravaginal in the Hanford which can potentially complicate dilatation.

Porcine renal blood flow is reported as 365 mg/min and medullary blood flow as 2.5-2.6 ml/min/g (Ludemann et al., 2009).

**Kidneys**

The left kidney is more cranial than the right (Figure 1). The intrarenal anatomy of the kidney is closer to man than in any other commonly used laboratory animals. An important difference and consideration for intrarenal surgery is that the avascular plane of the kidney is transverse in swine, not longitudinal as in dogs and humans (Swindle, 2007). Pigs develop both vesicoureteral and intrarenal reflux spontaneously and as a surgically produced model. Renal function [GFR, $C_{PAH}$, $T_{PAH}$, $Tm$ (glucose)] of pig vs minipig vs man was reviewed by Friis (1998).

![Kidneys in cross-section, from healthy 3.5 month old Male Yucatan.](image)

**Table 1. Individual and Averaged Kidney Weights (g) for Male or Female Miniature Yucatan**

<table>
<thead>
<tr>
<th>Linkage</th>
<th>Age (mon)</th>
<th>Gender</th>
<th>Body Weight (kg)</th>
<th>RI Kidney WT (g)</th>
<th>LI Kidney WT (g)</th>
<th>Avg Kidney WT (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min-Yucatan</td>
<td>1.1</td>
<td>M</td>
<td>6.5</td>
<td>12.1</td>
<td>13.5</td>
<td>12.8</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>1.8</td>
<td>M</td>
<td>21</td>
<td>36.0</td>
<td>39.2</td>
<td>38.1</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>3.4</td>
<td>F</td>
<td>22</td>
<td>32.4</td>
<td>31.7</td>
<td>31.8</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>3.6</td>
<td>F</td>
<td>28</td>
<td>42</td>
<td>43</td>
<td>42.5</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>5</td>
<td>M</td>
<td>35</td>
<td>47.3</td>
<td>46.5</td>
<td>46.9</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>5.1</td>
<td>F</td>
<td>33</td>
<td>45</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>6.5</td>
<td>M</td>
<td>35</td>
<td>59.3</td>
<td>58.0</td>
<td>58.7</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>9.2</td>
<td>M</td>
<td>47</td>
<td>83</td>
<td>82.4</td>
<td>82.7</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>9.2</td>
<td>F</td>
<td>33</td>
<td>115.4</td>
<td>114.8</td>
<td>115.4</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>10.1</td>
<td>M</td>
<td>57</td>
<td>122</td>
<td>120.8</td>
<td>121.9</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>27.4</td>
<td>M (castr)</td>
<td>70</td>
<td>77.02</td>
<td>75.91</td>
<td>76.47</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>37.4</td>
<td>M</td>
<td>70</td>
<td>124.8</td>
<td>126.5</td>
<td>125.9</td>
</tr>
<tr>
<td>Min-Yucatan</td>
<td>90</td>
<td>F</td>
<td>70</td>
<td>99.5</td>
<td>98.2</td>
<td>98.4</td>
</tr>
</tbody>
</table>

Data from Sinclair BioResources LLC, 2011.

The Hanford miniswine is commonly used in GLP toxicology studies where urinalysis and organ weights are recorded. The 3.4-6 month old Hanford male kidneys (2) weighed 68.65-194.5g (N=34), while the female kidneys weighed 61.62-135.2g (N=26). Six-eight month old male
Hanford kidneys weighed 91.4-231.22g (n=24), while equivalent age female kidneys weighed 92.09-148.5g (n=25). This Hanford data was presented in poster format with kidneys as % body weight and as % brain weight, clinical pathology (hematology, chemistry) and urinalysis normal ranges. Individuals may request the SRC Hanford Normals Poster 2010. For some of the clinpath parameters we now have an N of over 300 animals for each gender. Minipig urinalysis normals are available from Sinclair BioResources, LLC (Book of Normals, 2011).

Urinary bladder retrograde catheterization using a flexible rubber Foley catheter is a readily used procedure for urine collection in females (Swindle, 2007). Catheter sizes 5-14 Fr will fit pigs between 10-70 kg (Swindle 2007). Females can be catheterized in either dorsal or ventral recumbency using a silicone Foley catheter with a stylette inserted into the lumen (Figures 3 & 4). The opening of the urethra is located at the caudal end of the brim of the pubis and the catheter can be advanced along the midline to enter the urethra. There is sometimes a diverticulum near the opening which causes a temporary blockage which can be overcome by gentle rotation of the catheter. Catheterization of the male bladder is more difficult due to the preputial diverticulum, cork-screw shaped tip of penis, and sigmoid flexure of the penis. Hite (2009) reported success on retrograde catheterizing male domestic swine. Ultrasound assisted cystocentesis puncture of the bladder may also be used to collect fresh urine samples. In some cases, metabolism cages are needed to collect urine for clinical pathology and measure the daily volume. Urine collection can also be accomplished for the short term by applying human pediatric adhesive urine collection bags over the vulva or the preputial diverticulum. This noninvasive method is only good for small volume single collections.

Urine production was studied for Domestic Danish Landrace pigs (9-13 wks age, 12-18 kg) (Deding et al., 2006). The mean urine production...
rate was $15.7 \pm 4$ ml/kg/h during day-time, as opposed to a night urine production rate of $8.2 \pm 2.6$ ml/kg/h. The mean voidings was $18.7 \pm 6$ per pig. The pig voiding frequency had a clear circadian rhythm with the highest hourly frequency around noon. The mean number of day-time voidings was $15.1 \pm 4.8$ while the mean number of night-time voidings was $3.6 \pm 1.1$. The total voided volume was between 572 ml to 8348 ml, giving a mean of $2845 \pm 900$ ml (day-time mean $1879 \pm 594$ ml, night-time mean $967 \pm 306$ ml). The average voided volume was $110 \pm 35$ ml during day-time and $222 \pm 70$ ml during night. The average urine flow was $12 \pm 3.8$ ml/s. The residual urine ranged from 0 ml to 136 ml. The average fluid intake during the 24 hour period was $4151 \pm 1313$ ml.

Link (1953) reported the renal glucose threshold for domestic pigs (3-14kg, avg 8.7kg) as mean 160 mg/dL (100mL). Larger pigs weighing 21-52kg (Avg 36.4) had a renal glucose threshold average of 147.2 mg/dL.

The female Hanford miniature swine model has been described as an excellent endourologic model (Schwalb et al., 1989). Cystourethroscopy using a rigid ureteroscope was possible as was ureteral catheterization and ureteral dilatation.

**Other Urological Models**

Cancer drug intravesicular instillation: Hendricksen et al. (2006) used domestic female pigs to study Penetrexed pharmacokinetics and toxicity following intravesicular administered drug.

Pigs have also been used for bladder wall bulking agent studies (Clementson Kockum et al., 1999) for human incontinence and other studies for overactive bladder (Parsons and Drake, 2011).

Braun et al. (2003) reported on a porcine minipig model of bladder urodynamics and detrusor neuro-muscular model for researching treatment of voiding dysfunctions.

**Surgical Models**

Swindle (2007) has addressed the urinary system of the laboratory swine. Nephrectomy,
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partial nephrectomy, intrarenal surgery, renal transplant, cystotomy and ureteral diversion, urinary tract obstruction, reflux nephropathy and hydronephrosis, and perineal urethrostomy are subjects covered in this reference book (2nd Ed Swine in the Laboratory, CRC Press, 2007).

The strong human correlation to porcine physiology and immune systems provides a basic knowledge of graft recovery and inflammatory physiopathology through in vivo studies. In addition, the porcine body size allows surgical procedures similar to those in humans, repeated collections of peripheral blood or renal biopsies making pigs ideal for medical training and for the assessment of preclinical technologies. These studies support potential future xenotransplantation efforts.

Swine have been used extensively as models of urologic conditions in humans, most commonly in obstructive urologic syndromes. A large number of investigative procedures can be performed in one experiment both in acute and chronic models. Recently, a new technique of surgically induced antenatal lower urinary tract obstruction in swine has been developed (Dalmose et al., 2000).

Surgical and Perioperative Care Procedures (Swindle, 2007)
Although the kidneys may be approached via a midline abdominal procedure, it may be preferable in many instances to use a retroperitoneal flank approach. The flank approach negates having to deal with retraction and packing off of the gastrointestinal tract which is substantial in the pig. A curvilinear incision is made caudal to the last floating rib. After the latissimus dorsi is transected the other abdominal muscles may be bluntly divided and retracted from the ventral surface of the lateral vertebral wings. The muscles may be retracted manually to expose the kidney within the retroperitoneal space. Using this approach the kidney may be exteriorized by performing a lateral rotation of the cranial head of the kidney and gently retracting it to the surface of the incision. This provides access to the body of the kidney, the renal vessels and the ureter.
Surgical gauze or umbilical tape can be utilized to sling the exposed kidney and retract it in any direction without interfering with the blood supply.

If the ventral approach is utilized, for example when bilateral renal procedures are required, it is imperative to fast the pig for 24 hours to reduce the contents of the intestines. This is particularly important in the case of the spiral colon which obscures the left kidney for this approach. Water should never be restricted preoperatively for these procedures because the pig is prone to the development of an eosinophilic meningoencephalitis (salt poisoning) if it
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becomes dehydrated. This neurologic condition is frequently fatal if allowed to develop.

Figure 5. The flank approach to the right kidney has been performed to attach inflatable balloon occlusal catheters to the renal vessels. The pig’s head is towards the right side and the surgeon’s finger is in the flank incision.

As stated above the division of the blood supply to the kidney is transverse rather than longitudinal. The avascular plane of the kidney may be identified by temporarily occluding on branch of the renal artery as it divides between the cranial and caudal pole. There will be a clear division of the ischemic pole from the pole which still has arterial blood supply. For intrarenal surgery an incision is made along this line and the kidney is spatulated down to the calyceal region. Intrarenal surgery allows the implantation of renal calculi or other foreign objects which simulate calculi. The technique can also be utilized to perform a heminephrectomy; however, hemostasis will be a problem if it is performed as a survival procedure. The use of horizontal mattress sutures through the edges of the entire renal parenchyma and hemostatic agents such as oxycellulose sponges must be utilized.

Reduction of total renal blood flow of approximately 75% is necessary to produce a model of renal hypertension. Typically a left nephrectomy is performed and the right kidney which has the larger artery has the blood supply reduced by partial occlusion of the main renal artery. This may be accomplished by partial ligation or use of an occlusal device such as a circumferential occlusal balloon. Use of an occlusal balloon device offers the advantage of being able to titrate the occlusion postoperatively by gradual inflation of the balloon.

Renal transplantation for the study of immunosuppressive and/or organ preservation and transport systems is one of the more common models utilizing pig kidneys. There are many variations in the technique that may be found in the literature. For example total bilateral nephrectomy and reimplantation of a preserved kidney from another animal may be used. Alternatively a kidney may be reimplanted into the abdomen while leaving one or both native kidneys intact to provide uncompromised renal function for the animal until the transplanted kidney is harvested for study. Most commonly
transplanted kidneys are located in the retroperitoneal space in the caudal abdomen and the blood supply is provided by anastomosis of the renal vessels to the iliac vessels of the recipient. Using this technique gives the advantage of having a shorter length of ureter to implant into the bladder. Having too lengthy a ureter carries a high risk of inadequate blood supply to the structure which would result in necrosis. Use of a Carrel patch on the transplanted kidney is recommended for attachment to the iliac vessels to help prevent stricture of the anastomosis. A ventral midline approach provides the most optimal surgical exposure for this procedure. Intraoperatively it is recommended that a continuous infusion of iv fluids and a bolus flush of 50% mannitol or glucose be administered to hasten the blood flow and micturition function of the transplanted kidney. The immunosuppressive regimen is frequently the aspect of transplantation that is being studied and can vary considerably in terms of the types of drugs and their dosages which are administered. In terms of clinical chemistry values to be followed to determine whether the transplant is losing function the BUN and Creatinine will frequently be elevated for a few days postsurgically. However, a Creatinine value >6.0 which is persistent is a good indicator of organ failure and is less variable than the BUN. As indicated above nonsurgical catheterization of male pigs is likely impossible in most situations. If a permanent catheter is to be implanted surgically it is necessary to use a rounded catheter tip with multiple holes because the thin wall of the bladder is easily sucked into the end of a catheter creating a periodic blockage during cystocentesis. A perineal urethrostomy can also be performed caudal to the sigmoid flexure of the penis. The anatomy of the perineum will indicate the best location to perform the procedure. The stoma can be created anywhere from the ventral brim of the pubis to the ventral midline over the pubis. Veterinary advice should be sought to determine the proper location to prevent urine scalding and medicated gels should be applied around the opening.

Figure 6. Anatomy of the male pig urinary and reproductive tract.
Surgical procedures of the ureters are performed to produce models of hydronephrosis and intrarenal reflux. Using the flank approach a portion the ureter in young pigs can be implanted within the psoas muscle. As the pig grows the gradual compression of the ureter will result in a chronic model of hydronephrosis. Intrarenal reflux only occurs in the human and swine due to the similar intrarenaal anatomy. It can be created surgically in young pigs by excising the ureteral entrance to the bladder with a small patch of bladder and then reimplanting the ureteral roof at a straighter angle. Both of these procedures will result in pediatric models over a period of weeks.

Many variations of the renal and bladder procedures can be found in the literature and those procedures have been reviewed (Dalmose et al, 2000). Miniature pigs of various breeds can be used for these procedures and offer the advantage of a slower growth rate. Some of these procedures will result in surgical failure is they are attempted in domestic swine because of the growth of the blood vessels, the ureters and the kidneys.

Reviews
Dr James M. Terris (1986) of USUHS reviewed the use of swine as a model in renal physiology and nephrology at the Conference on Swine in Biomedical Research held at University of Maryland, Columbia, MD, June 17-20, 1985. This review contains 126 cited references. Hodson (2 papers), Constantinou et al. (2 papers), Jorgensen and Djurhuus, Mortensen and Djurhuus, Cuttino et al., Buckley et al., Zatzman et al., O’Hagan and Zambraski, Bloor et al., and Braunberg et al. also presented papers at this 1985 conference. The 3 volume proceedings containing 13 renal papers is a good place to start for investigators contemplating nephrology research using the porcine model.

Conclusions
Miniswine models offer similar anatomy and physiology to humans, are excellent workable models for urological studies, and of reasonable
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size and economy for the large animal research budget.

Cited References


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