

Original Research

Physiologic Aspects of Pig Kidney Transplantation in Nonhuman Primates

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Xenotransplantation can provide a solution to the current shortage of human organs for patients with terminal renal failure. The increasing availability of genetically engineered pigs, effective immunosuppressive therapy, and antiinflammatory therapy help to protect pig tissues from the primate immune response and can correct molecular incompatibilities. Life-supporting pig kidney xenografts have survived in NHP for more than 6 mo in the absence of markers of consumptive coagulopathy. However, few reports have focused on the physiologic aspects of life-supporting pig kidney xenografts. We have reviewed the literature regarding pig kidney xenotransplantation in NHP. The available data indicate (1) normal serum creatinine, (2) normal serum electrolytes, except for a trend toward increased calcium levels and a transient rise in phosphate followed by a fall to slightly subnormal values, (3) minimal or modest proteinuria without hypoalbuminemia (suggesting that previous reports of proteinuria likely were due to a low-grade immune response rather than physiologic incompatibilities), (4) possible discrepancies between pig erythropoietin and the primate erythropoietin receptor, and (5) significant early increase in kidney graft size, which might result from persistent effects of pig growth hormone. Further study is required regarding identification and investigation of physiologic incompatibilities. However, current evidence suggests that, in the absence of an immune response, a transplanted pig kidney likely would satisfactorily support a human patient.

Abbreviations: GTKO, α 1,3-galactosyltransferase gene knockout; mAb, monoclonal antibody

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The increasing number of patients in need of organ transplants has stimulated research into the use of pig organs for transplantation,^{12,13} but numerous immunologic and physiologic barriers must be overcome. These barriers have developed due to the evolutionary divergence of the species over more than 80 million years.^{28–30} The immunologic aspects of xenotransplantation have been studied in considerable detail, but except for discrepancies in coagulation,^{15,20,56} physiologic compatibility between these species has received little attention.^{31,36,63} However, physiologic incompatibilities may have important implications for the success of pig-to-human kidney xenotransplantation.

The major immune barriers to xenotransplantation have largely been overcome by genetically engineering organ-source pigs: (1) by deleting antigens against which humans have natural (preformed) antibodies, the most important of which is galactose- α 1,3-galactose (Gal), and (2) by inserting human transgenes that help to protect the graft against human complement-mediated injury or human coagulation dysfunction, both of which contribute to graft failure (Figure 1). In addition, the pig antigens N-glycolylneuraminic acid (Neu5Gc) and Sda (β 4GalNT2) are known to play a role in xenograft rejection (Figure 1). In addition, novel immunosuppressive agents, such as those that block T cell costimulation (that is, signal 2), are more successful in suppressing the adaptive immune response

to xenografts than are the conventional pharmacologic agents that are used in current clinical allotransplantation and that suppress the recognition of donor antigens (that is, signal 1).

The transplantation of kidneys from genetically engineered pigs combined with effective immunosuppressive therapy has significantly increased the survival duration of life-supporting kidney grafts in NHP.^{32,33,38–40,46} For example, survival times of 160 and 310 d were achieved in 2 rhesus macaques after the transplantation of kidneys from α 1,3-galactosyltransferase gene-knockout (GTKO) pigs (which lacked the major target for primate antipig antibodies, Gal) that also expressed the human complement-regulatory protein CD55 (which provides additional protection from antibody-dependent complement-mediated rejection; GTKO-CD55 pigs).^{32,33} Immunosuppressive therapy was based on the blockade of a T-cell costimulation molecule, CD154, by using a monoclonal antibody. The same group also reported the 499-d survival of another GTKO-CD55 pig kidney graft in a rhesus monkey.⁴⁰ A rhesus macaque experienced extended survival (435 d) after the transplantation of a kidney from a GTKO- β 4GalNT2-KO pig (that is, lacking both Gal and Sda).⁴⁶ Our own group achieved prolonged survival (136, 237, and 260 d) of kidney grafts from pigs with multiple genetic modifications ('6-gene' pigs, although with different combinations of genetic modification) in 3 baboons that received antiCD40 monoclonal antibody as a costimulation blockade molecule.^{38,39} These prolonged survival times have allowed for observations regarding the function of pig kidneys in the 'foreign' NHP environment.

The aim of the present brief review is to compare the known similarities and differences in physiology between pigs and

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	Year	Reference(s)
Transgenic expression of human complement-regulatory proteins (CD59, CD55, CD46)	1994, 1995, 2004	16, 25, 44
α 1,3-galactosyltransferase gene knockout (GTKO); deletion of expression of Gal	2002, 2003	42, 54
Transgenic expression of a human coagulation-regulatory protein (thrombomodulin)	2009	53
Cytidine monophospho-N-acetylneuraminic acid hydroxylase gene-knockout (CMAH-KO); deletion of expression of N-glycolylneuraminic acid (Neu5Ge)	2013	45
β (1,4)N-acetylgalactosaminyltransferase gene-knockout (β 4GalNT2-KO); deletion of expression of Sda	2015	23

Figure 1. Key advances in the genetic engineering of pigs

primates (including humans) and to discuss the feasibility of producing pigs whose kidneys are physiologically compatible with humans. Even if the pathobiologic problems of pig kidney xenotransplantation were overcome, clinical applications of this technology would remain unsuccessful unless the pig transplants are effective in performing the functions of a human kidney.

Are there physiologic incompatibilities between pig and primate? Pig kidneys are similar in structure, physiology (for example, glomerular filtration rate and total kidney blood flow), and relative size to human kidneys,^{6,12,41} but physiologic incompatibilities may arise.^{36,64} The kidneys are located in the highest part of the pig's body, which might influence renal blood flow; however, the renal blood flow of pigs is reported to be similar to that of humans.⁵⁷

Mean WBC and RBC counts are significantly ($P < 0.01$) higher in healthy pigs than in baboons and humans (Table 1).²² Whereas BUN, serum creatinine, sodium, and chloride values are comparable among all 3 species, pigs exhibit higher ($P < 0.01$) potassium, calcium, and phosphorus values than baboons and humans (Table 1).²² Levels of total protein and albumin appear to be significantly ($P < 0.01$) lower in pigs than in baboons and humans (Table 1).²²

Few data are available from experimental studies in pig-to-NHP models of kidney transplantation, but the following comments can be made in regard to specific aspects of renal function.

Serum creatinine. In reports of life-supporting pig kidney xenotransplantation in NHP extending back more than a decade, the serum creatinine level essentially remained stable and largely within the normal human range (Figure 2 A)^{16,32,38,39,70} but in early studies was higher than the normal range.⁶⁴ In view of the improved protection from immune-mediated injury provided by current genetically engineered pig kidneys, these data indicate that a persistently high creatinine is more likely to have been the result of immune-related graft dysfunction rather than of physiologic incompatibility, which is no longer seen.

However, we have observed that baboons with pig kidney grafts intermittently develop features of hypovolemia and dehydration (that is, transient increases in serum creatinine) in the absence of features of immune rejection. The infusion of normal saline reduces serum creatinine levels to the normal human range. We have now documented this phenomenon in 4 consecutive baboon recipients at various time points after pig kidney transplantation. The baboons remained fully alert and active, maintained a steady body weight, and did not drink or urinate more or less than usual, yet, when examined, had a low central venous pressure and dehydrated skin and tissues. The intravenous infusion of several hundred milliliters (approximately 100 mL/kg) of normal saline was required to raise the venous pressure of these animals to a normal level. Alternatively, we have administered saline subcutaneously on a daily basis to maintain our NHP recipients in a well-hydrated state. A possible cause of this intermittent phenomenon is discussed in the section *Plasma renin*.

Serum proteins. Proteinuria, even in small amounts, is considered pathologic (for example, in glomerulopathies and allograft rejection), because the human glomerular membrane normally is impermeable to proteins.⁴⁷ In contrast, in adult pigs, environmental and physical stresses can readily induce increased proteinuria.^{24,35} Furthermore, proteinuria occurs in healthy neonatal pigs, where it is associated with immature proximal renal tubules.²⁵ Proteinuria is, therefore, a feature of renal dysfunction, but it may be related to causes other than graft rejection.

In the early studies of pig-to-NHP kidney xenotransplantation, moderate to severe proteinuria and hypoalbuminemia were documented, necessitating frequent intravenous administration of human albumin to maintain the serum albumin concentration within the normal range.^{3,7,17,64,70} In another study, proteinuria and hypoalbuminemia occurred in NHP recipients at levels consistent with nephrotic syndrome, despite normal renal histology.⁷⁰

Our own more recent experience^{38,39} and that of other colleagues³² is of minimal or modest proteinuria (Figure 2 B), with no accompanying hypoalbuminemia (Figure 2 C)—probably because the recipient's immune response was well controlled due to genetic modification of the donor pig and because of pharmacologic intervention. This modest proteinuria was associated with prolonged graft survival in both studies.^{32,38,39} In another study of pig-to-NHP kidney xenotransplantation, despite normal renal function, recipients developed proteinuria with morphologic changes (podocyte effacement).⁶⁶ However, treatment with the antiCD20 (B cell) monoclonal antibody rituximab successfully delayed the development of proteinuria, possibly due to the prevention of pig podocyte disruption.⁶⁶ Although changes in serum creatinine and protein or albumin can be associated with changes in the recipient's body weight, none of our 3 baboons lost weight (data not shown), suggesting that loss of protein mass was not a feature in the lack of proteinuria.

These observations suggest that the proteinuria reported in early studies was due to a low-grade immune response (for example, activation or injury of the vascular endothelium by complement or antipig antibodies) rather than from physiologic incompatibilities between pig and primate.

Serum electrolytes. Studies of pig-to-NHP kidney xenotransplantation have indicated that most serum electrolytes (for example, sodium, chloride, potassium, calcium) remain within normal limits in recipients with well-functioning pig kidney grafts, although serum calcium can rise.^{11,32,36,38,39,64} Serum phosphate can rise transiently immediately after transplantation, but thereafter falls and remains in the low-to-normal range;^{32,36,38,39,64} this effect may be due to the slightly greater glomerular filtration rate in pigs. However, kidney allotransplantation in NHP has likewise been associated with a reduction in serum phosphate (Figure 2 D).⁵⁸ The cause of decreased phosphate levels during the period of stable pig xenograft function is uncertain.

Serum uric acid. In humans, uric acid is an end-product of purine metabolism, but in lower mammals, including pigs, it is further oxidized by urate oxidase.⁵¹ Hyperuricemia is unlikely to be problematic in pig kidney xenotransplantation, because

Table 1. Normal hematology and clinical chemistry values in pigs, baboons, and humans²²

	Pigs (mean ± 1 SD)	Baboons (mean ± 1 SD)	Humans (range)
Hematology			
WBC (no./mm ³)	18.6 ± 6.4 ^a	10.0 ± 1.7	3.8–10.6
RBC (×10 ⁶ /mm ³)	6.9 ± 1.1 ^a	5.1 ± 0.1	3.73–4.89
Hgb (g/dL)	10 ± 1.4	12.7 ± 0.3	11.6–14.6
Hct (%)	37.9 ± 8.7 ^b	39.9 ± 1.3	34.1–43.3
Platelets (×10 ³ /mm ³)	507 ± 156	419 ± 61	156–369
Clinical chemistry			
BUN (mg/dL)	12.4 ± 5.1	14.3 ± 4.0	8.0–26.0
Creatinine (mg/dL)	1.0 ± 0.1	0.7 ± 0.1	0.5–1.4
Sodium (mmol/L)	143 ± 4.0	146 ± 2.0	136–146
Potassium (mmol/L)	5.3 ± 1.0 ^a	3.8 ± 0.5	3.5–5.0
Chloride (mmol/L)	105 ± 1.9	108 ± 4.0	95–110
Calcium (mg/dL)	11.0 ± 0.8 ^a	9.5 ± 0.5	8.4–10.2
Phosphorus (mg/dL)	8.6 ± 3.2 ^a	4.3 ± 1.8	2.5–4.5
Total protein (g/dL)	5.2 ± 1.1 ^a	6.8 ± 0.3	6.3–7.7
Albumin (g/dL)	2.6 ± 0.6 ^a	4.1 ± 0.3	3.4–5.0

^aSignificant ($P < 0.01$) difference between pigs compared with baboons and humans

^bSignificant ($P < 0.01$) difference between pigs compared with baboons

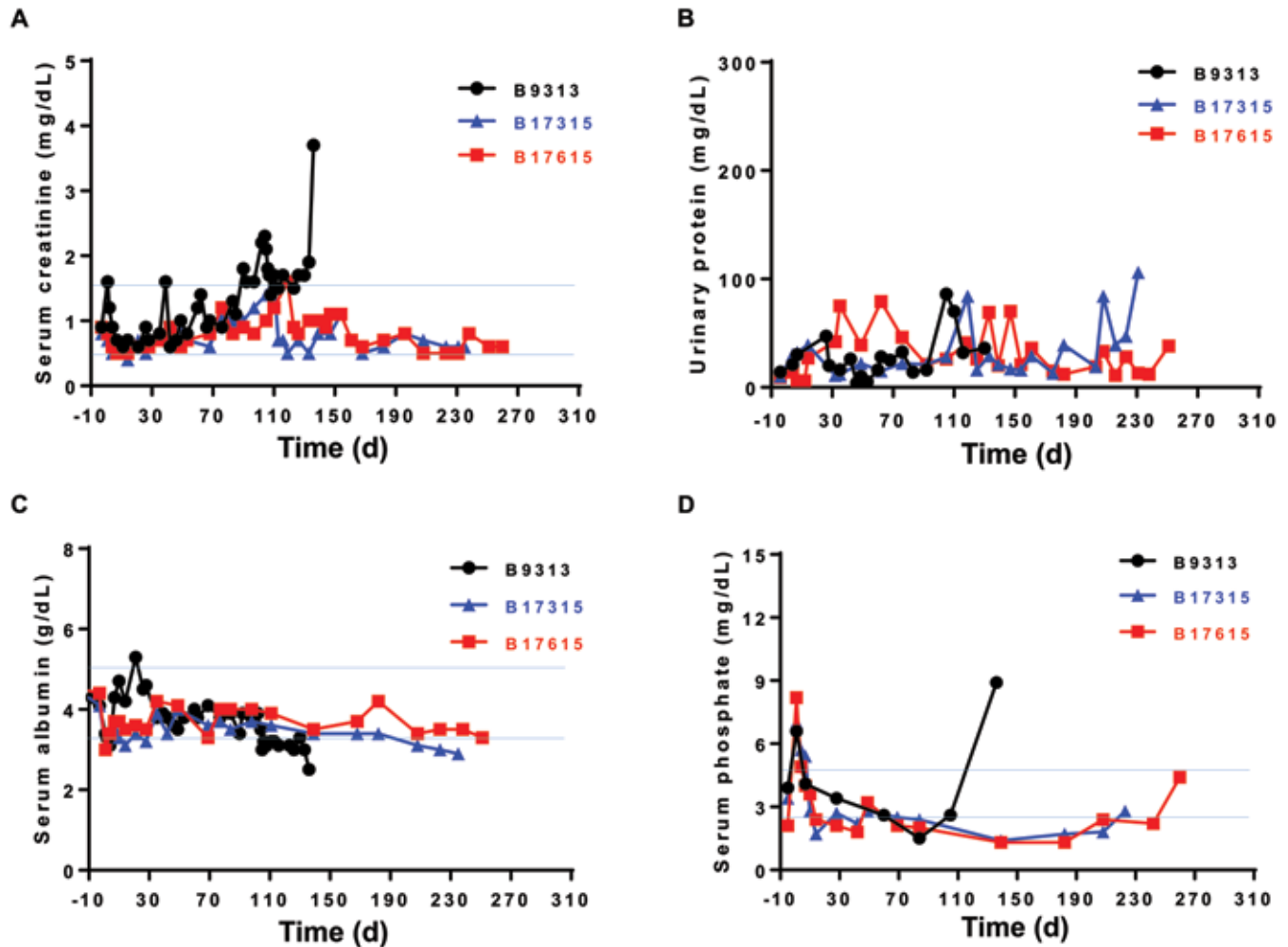


Figure 2. (A) Serum creatinine, (B) urinary protein, (C) serum albumin, and (D) serum phosphate levels in 3 baboons (nos. 9313, 17315, and 17615) whose genetically engineered pig kidney grafts functioned for 136, 237, and 260 d, respectively, before infectious complications necessitated termination of the experiments. Blue lines indicate the normal range of serum creatinine in humans. Reprinted with permission from reference 39.

pig kidneys can eliminate uric acid both by filtration and secretion.⁶² This added function of pig kidneys should prove an advantage over human kidneys, which cannot oxidize uric acid.

Plasma renin. Renin (produced by the kidney),²⁷ cleaves angiotensinogen (produced by the liver) to angiotensin I, which is further cleaved to angiotensin II, which regulates body fluid volume and potassium balance. Pig renin cannot cleave human angiotensinogen.^{59,68} The relatively normal fluid balance and maintenance of body weight in NHP with well-functioning life-supporting pig kidney grafts^{32,38,39,64} may indicate an alternative regulatory mechanism to maintain fluid balance despite decreased renin activity (for example, antidiuretic hormone).

Alternatively, the state of intermittent hypovolemia or dehydration that we have documented and that results in an increase in serum creatinine (see earlier) may be associated with abnormalities of renin function. Baboons with pig kidney grafts apparently are unaware that they are becoming dehydrated, because their fluid intake does not match their clinical need (even though their urinary output isn't excessive). Patients with pig kidney grafts, therefore, may need to drink large volumes of fluid, even though they do not feel thirsty.

Erythropoietin. The amino-acid identity between pig and human erythropoietin (produced by the kidney) is approximately 82%.^{18,69} Life-supporting pig-to-NHP renal xenotransplantation was associated with the gradual development of normocytic, normochromic anemia in the absence of treatment with recombinant human erythropoietin.⁶⁴ This effect possibly resulted from molecular incompatibility between pig erythropoietin and the primate erythropoietin receptor.⁶⁴ Alternatively, drug-associated myelosuppression combined with frequent blood draws for laboratory tests might have induced the observed anemia.

Whether pig erythropoietin functions adequately in humans or NHP is unclear. In our own studies, we relatively frequently draw considerable volumes of blood from pharmacologically myelosuppressed recipient NHP; we therefore routinely administer recombinant human erythropoietin to recipient baboons and have maintained a stable hematocrit. However, even if pig erythropoietin does not adequately function in humans, the administration of recombinant human erythropoietin should resolve any deficiency, as it does in NHP. Furthermore, an alternative solution is to genetically engineer pigs to produce human erythropoietin, which thus would interact with the human erythropoietin receptors of recipients.

Kidney size and growth. Early studies reported an increase in kidney graft size (Figure 3).⁶³ We observed a similar increase in our recent studies, but in every case a partial stricture of the ureter had developed; this stricture was not always related to the ureterovesical anastomosis and therefore may have been due to the immune response, thus potentially complicating interpretation of the increase in graft size.^{38,39} In addition, relief of the partial stricture achieved only a minimal reduction in pig kidney size.^{38,39} Other investigators have not mentioned an increase in kidney graft size,^{16,32,61,71} nor has rapid growth been reported after heterotopic pig heart xenotransplantation in baboons.^{37,48,49}

In our recent report, pig kidney grafts increased markedly in length (at least 2-fold; less so in other dimensions) during the first 1 to 2 mo, after which growth slowed and then plateaued (Figure 4 A through C).^{38,39} This time-scale correlates relatively well with the original observation,⁶³ although kidney graft growth in that study plateaued slightly sooner than in ours. The changes in our animals^{38,39} were not a result of an acute cellular or antibody-mediated immune response, when interstitial hemorrhage, thrombosis, and cellular infiltrates might increase graft weight and size, because histology of the grafts showed no

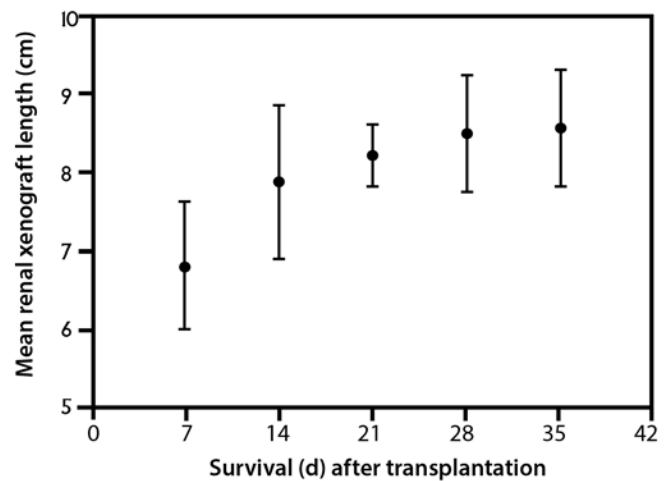


Figure 3. Growth of pig kidney grafts in cynomolgus monkey recipients ($n = 6$). Based on the data from reference 63.

features of rejection (Figure 5) but revealed considerable interstitial expansion and fibrosis.

The cause of the initial rapid growth in size (which in our experience seemed disproportionate to the effect of a partial stricture of the ureter) remains uncertain. This effect might be associated with compensatory enlargement when one immature kidney (taken from a 6- to 8-wk-old pig) takes the place of 2 relatively mature kidneys excised from an 8-kg baboon. Relatively rapid growth in kidney allografts occurs when kidneys from infants or children are transplanted into adult recipients.^{26,52}

However, there is a recognized discrepancy in the rate of organ growth between pig and NHP. Pigs (and pig organs) grow at a much faster rate than primates,⁶³ with Yorkshire swine reaching a body weight of more than 50 kg by 6 mo of age (Figure 6),^{8,72} whereas baboons, rhesus monkeys, and cynomolgus monkeys (all Old World NHP) are unlikely to weigh more than 4 to 6 kg at that age.^{1,9,43}

Recently, growth of a transplanted miniature swine kidney after GTKO pig-to-baboon kidney xenotransplantation ($n = 6$) was similar to that of the contralateral kidney that was retained in the miniature swine donor, which was maintained to measure autologous kidney growth (Figure 7 A).⁶⁵ Furthermore, in a pig allotransplantation model ($n = 5$), a Yorkshire pig kidney graft exhibited rapid growth after transplantation into a miniature swine, reaching 3.7 times its initial volume over 3 mo. This growth rate compared with an increase in volume of only 1.2 times over the same period when a miniature swine kidney was transplanted into another miniature swine (Figure 7 B).⁶⁵

One group^{60,65} has suggested that the rapid growth of pig kidney xenografts in small baboons is largely associated with intrinsic (that is, graft-associated) factors rather than with factors in the recipient environment. From our own observations, we agree with this conclusion, even though partial ureteric stricture may have played a minor role. The other authors suggested that rapid growth may result in deterioration of renal function due to a form of 'abdominal compartment syndrome.' That is, the rapid growth of the kidney in the confined space of the abdomen may have led to insufficient intragraft blood flow, leading to cortical ischemia and graft dysfunction. This effect might be associated with a rise in serum creatinine without evidence of rejection. However, although we have seen a rapid growth of the pig kidney, we have not observed any persistent decrease in its function.

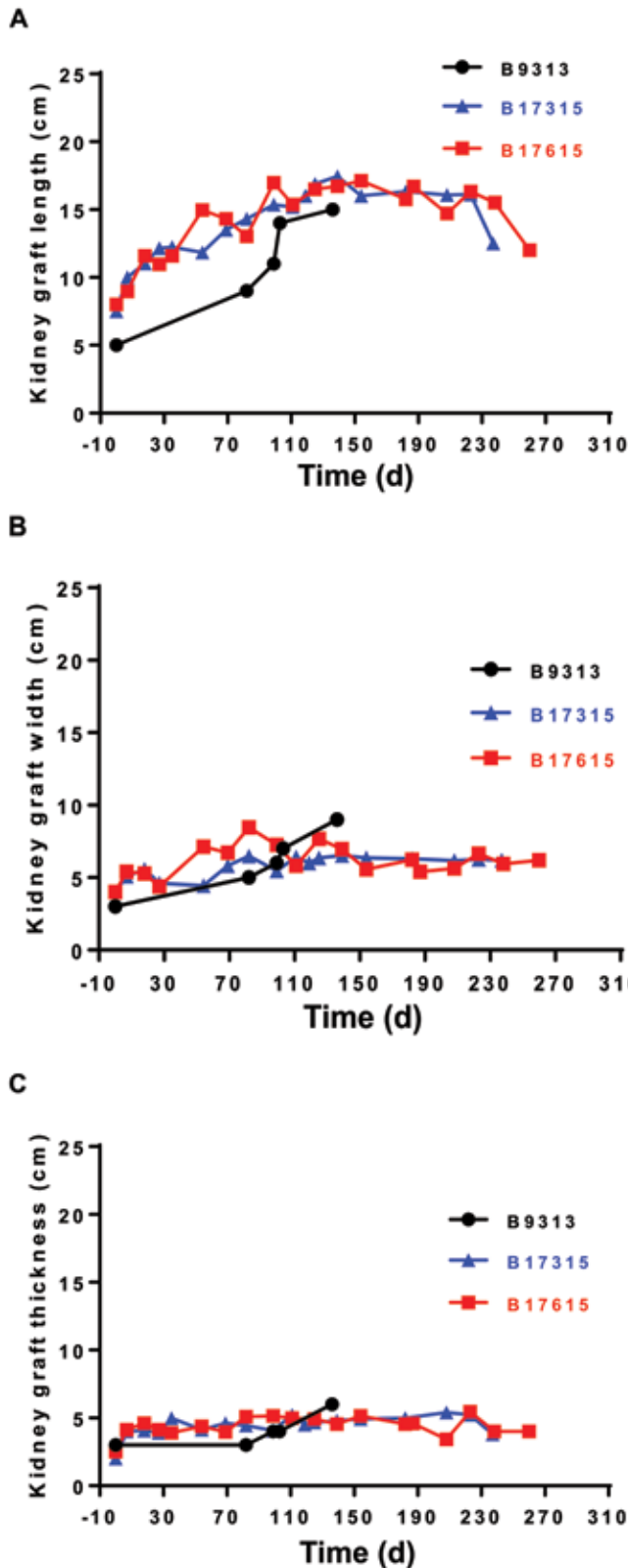


Figure 4. Increases in the (A) length, (B) width, and (C) thickness of the pig kidneys in 3 baboons (nos. 9313, 17315, and 17615) with genetically-engineered pig kidney grafts that functioned for 136, 237, and 260 d, respectively; all of the experiments were terminated due to infectious complications.

Although the intermittent dehydration (discussed earlier) might represent transient impairment of function, it is rapidly and entirely reversible. By increasing the circulating blood

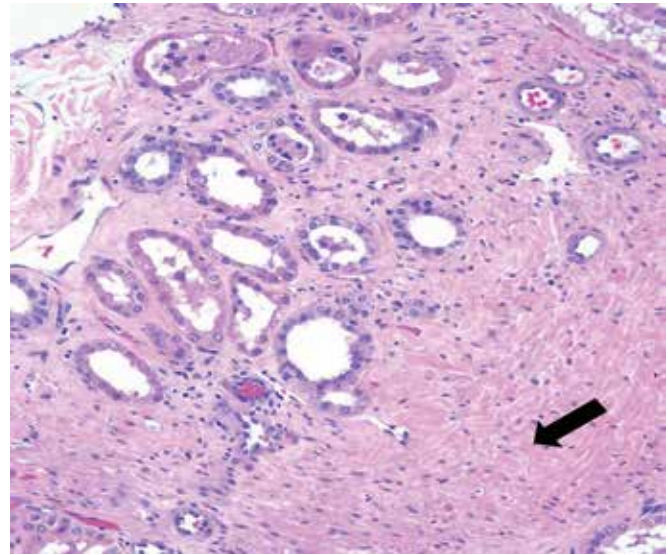


Figure 5. Microscopic appearance of a genetically engineered pig kidney graft in a baboon at necropsy (at 260 d after transplantation), showing expansion of the interstitial tissue, with some fibrosis (arrow), but no features of rejection. Reprinted with permission from reference 39.

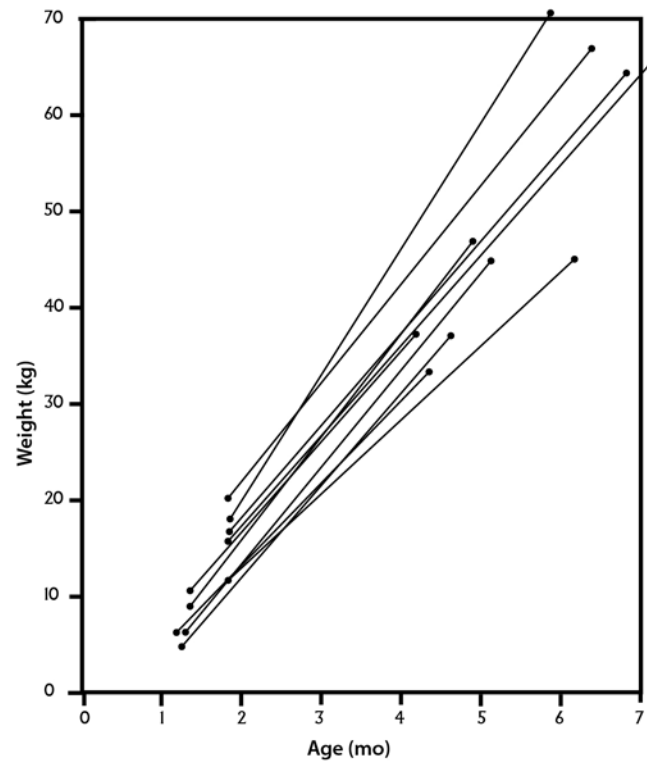


Figure 6. Increase in weight of healthy Yorkshire pigs during the first 6 mo of life. Reprinted with permission from reference 72.

volume through the administration of intravenous or subcutaneous fluid, the intragraft blood flow can be improved, at least temporarily, resulting in a reduction in serum creatinine. We think it unlikely that abdominal compartment syndrome would be so easily reversible. Together, these studies suggest that the pig kidney graft continues to grow at its normal rate (as it would in the native donor pig) for several weeks after transplantation

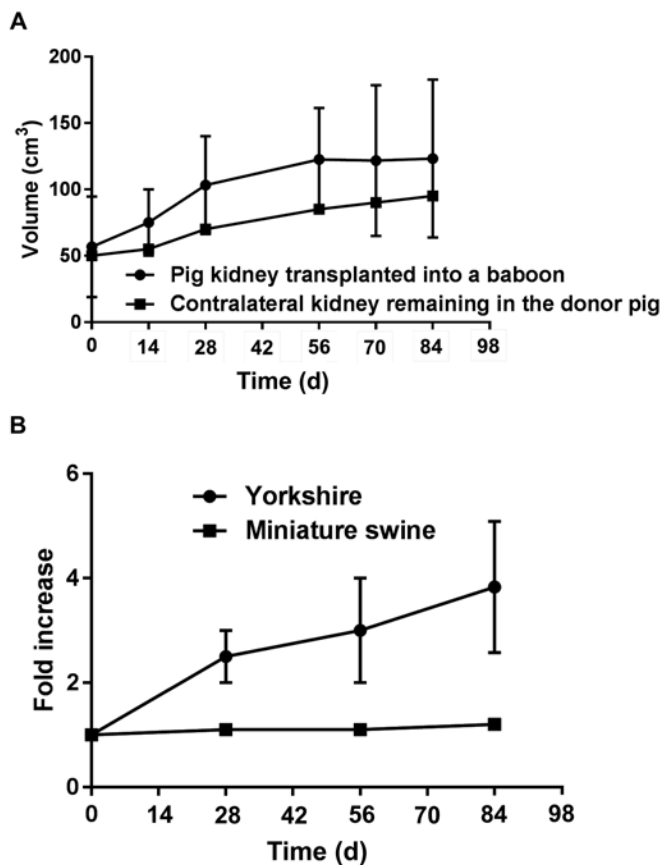


Figure 7. (A) The growth of a miniature swine pig kidney graft transplanted into a baboon was similar to that of the contralateral kidney, which was retained in the donor. The graft in the baboon increased in volume by 2.1-fold, whereas the kidney that remained in the donor increased 1.6-fold, suggesting maintenance of a growth stimulus after transplantation. Longitudinal data obtained from 3 of 6 baboons with pig kidney grafts formed the basis of this study. Based on data from reference 65. (B) Growth of a Yorkshire pig kidney graft compared with that of a miniature swine kidney graft during the first 3 mo after transplantation into miniature swine recipients. The volume of the graft from the Yorkshire pig increased 3.7-fold, whereas that from the miniature swine increased only 1.2-fold. Based on data from reference 65.

into an NHP. Thereafter, its growth correlates with the growth rate of the recipient NHP. The mechanism behind this sequence of events remains uncertain. Although rapid growth of a pig kidney in the abdomen of the recipient may not be problematic, rapid growth of a pig heart within the confines of the recipient's chest would likely restrict function.

In view of the observations regarding the initial rapid growth of the transplanted kidneys, it could be argued that all grafts for clinical xenotransplantation should be from miniature swine (of which there are several different breeds that reach adult sizes ranging from 30 to 200 kg), rather than from domestic pigs, such as Large White Landrace. However, several points require consideration. First, miniature swine grow more slowly than domestic pigs; therefore, if an organ is required for a large human recipient, miniature swine would need to be housed for a much longer period, thus adding to logistics and cost. Second, some miniature swine do not grow to the size required to provide an organ sufficient for a large human adult. Third, domestic swine are currently available that carry 6 genetic manipulations, and it might be easier to inhibit the growth of these pigs by further genetic manipulation (discussed later) than continue to genetically

engineer miniature swine, in which this field is less advanced. Nevertheless, with further experimental experience, a case might be made that miniature swine may become advantageous in this regard. In a recent study,³⁴ inactivation of the growth hormone receptor gene in pigs led to markedly decreased levels of insulin-like growth factor 1 and thus to decreased body and organ growth. This group is inactivating the growth hormone receptor gene in GTKO/hCD46/hThrombomodulin pigs to reduce the growth of the pig heart after orthotopic cardiac xenotransplantation in baboons.³⁴

Differences between pig and primate growth hormone may be a critical factor for organ growth after transplantation. One group reported that pig growth hormone does not activate human growth hormone receptors due to amino acid differences in growth hormone structure between the 2 species.⁴ In contrast, human growth hormone has a biologic effect in pigs.⁵⁵ Perhaps residual pig growth hormone is present in the graft after transplantation and leads to the initial increase in size (as it would if the kidney had remained in the rapidly growing juvenile pig). This rapid growth may cease when the residual pig growth hormone is depleted. The subsequent more gradual increase in pig kidney graft size might be associated with the effect of human (or NHP) growth hormone. Further investigation of these observations and of this hypothesis is required.

Although both growth hormone (produced by the anterior pituitary gland) and insulin-like growth factor 1 are growth stimulants for many organs, including kidney,^{10,21,67} a key question is why these hormones might be retained after transplantation in the kidney but not the heart, which, in the abdominal heterotopic position, apparently does not continue to grow rapidly.^{37,48-50} The fact that the kidney grafts are life-supporting, whereas heterotopic (that is, abdominally placed) heart grafts do not support a vascular circulatory system (and therefore are not fully functional), may be relevant.¹⁹ Recently, survival after orthotopic heart transplantation (in which the heart supports the entire circulation) has been extended to 90 d, during which the heart graft grew abnormally rapidly.^{19,34}

In summary, pigs might be a solution to the problem of organ donor shortage. Recent progress in the survival of kidneys transplanted from genetically engineered pigs into NHP that were supported with effective immunosuppressive regimens and antiinflammatory therapy indicates that the immunologic barriers are being overcome and that clinical trials of pig kidney xenotransplantation are likely to be considered soon.¹⁴ Although few to date, most experimental data from pig-to-NHP models of kidney xenotransplantation imply that the pig kidney will function satisfactorily within a human recipient, provided that the patient's hydration and volemic states are monitored carefully. However, further evaluation of the ability of pig erythropoietin to maintain adequate erythrocyte numbers in primate recipients is required. Questions also remain regarding the cause of the rapid growth of pig kidneys early after transplantation and whether this phenomenon will be problematic when pig kidneys are transplanted into humans.

Acknowledgments

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