Animal (2010), **4:6**, pp 899–920 © The Animal Consortium 2010
doi:10.1017/S1751731110000200

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Porcine models for the metabolic syndrome, digestive and bone disorders: a general overview

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(Received 24 September 2008; Accepted 23 December 2009; First published online 22 February 2010)

The aim of this review article is to provide an overview of the role of pigs as a biomedical model for humans. The usefulness and limitations of porcine models have been discussed in terms of metabolic, cardiovascular, digestive and bone diseases in humans. Domestic pigs and minipigs are the main categories of pigs used as biomedical models. One drawback of minipigs is that they are in short supply and expensive compared with domestic pigs, which in contrast cost more to house, feed and medicate. Different porcine breeds show different responses to the induction of specific diseases. For example, ossabaw minipigs provide a better model than Yucatan for the metabolic syndrome as they exhibit obesity, insulin resistance and hypertension, all of which are absent in the Yucatan. Similar metabolic/physiological differences exist between domestic breeds (e.g. Meishan v. *Pietrain). The modern commercial (e.g. Large White) domestic pig has been the preferred model for developmental programming due to the 2- to 3-fold variation in body weight among littermates providing a natural form of foetal growth retardation not observed in ancient (e.g. Meishan) domestic breeds. Pigs have been increasingly used to study chronic ischaemia, therapeutic angiogenesis, hypertrophic cardiomyopathy and abdominal aortic aneurysm as their coronary anatomy and physiology are similar to humans. Type 1 and II diabetes can be induced in swine using dietary regimes and/or administration of streptozotocin. Pigs are a good and extensively used model for specific nutritional studies as their protein and lipid metabolism is comparable with humans, although pigs are not as sensitive to protein restriction as rodents. Neonatal and weanling pigs have been used to examine the pathophysiology and prevention/treatment of microbial-associated diseases and immune system disorders. A porcine model mimicking various degrees of prematurity in infants receiving total parenteral nutrition has been established to investigate gut development, amino acid metabolism and non-alcoholic fatty liver disease. Endoscopic therapeutic methods for upper gastrointestinal tract bleeding are being developed. Bone remodelling cycle in pigs is histologically more similar to humans than that of rats or mice, and is used to examine the relationship between menopause and osteoporosis. Work has also been conducted on dental implants in pigs to consider loading; however with caution as porcine bone remodels slightly faster than human bone. We conclude that pigs are a valuable translational model to bridge the gap between classical rodent models and humans in developing new therapies to aid human health.*

Keywords: porcine biomedical model, metabolic syndrome, digestive disorders, bone remodelling

Implications

This review article aims to provide an overview of the pig as a biomedical model for humans and specific categories of diseases are considered, metabolic, cardiovascular, digestive and bone in particular. Previous reviews have considered different disease categories and the relevant references are included here. The main limitation is the depth to which each disease can be considered, particularly with respect to space and the availability of information in the primary references.

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Introduction

Animals allow a multi-disciplinary approach to be taken aimed at improving our understanding of the pathophysiology of diseases in humans. The underlying physiological, biochemical and molecular biological mechanisms can be examined in animal models in a more invasive manner that would be unethical in humans, under controlled conditions and without the confounding genetic/social factors. It is acknowledged that there is generally not a direct numerical equivalence between animal and human experiments but responses to treatments are, on the whole, qualitatively similar allowing responses of animals to more extreme

treatments to be used to predict the anticipated response in humans.

Various species have been used as biomedical models to study human medicine (e.g. rat, mouse, guinea pig, dog, pig and sheep). Although rodents are small, inexpensive and are ideal in multivariate experiments, there are numerous differences between rodent models and humans. For example, such differences in adipose tissue characteristics (i.e. adipsin, leptin, resistin, tumor necrosis factor-α and other adipokines) have prevented the translation of data obtained from rodents into preventative/treatment strategies aimed at improving human health (Spurlock and Gabler, 2008). It is becoming increasingly apparent that pigs are a valuable translational model to bridge the gap between classical rodent models and humans in developing new therapies to aid human health (Schnieke and Wolf, 2008).

Pigs are an appropriate biomedical model for humans due to many genetic (Lunney, 2007), anatomical (Pracy *et al*., 1998; Prestige World Genetics Korea, 2006) and physiological similarities to humans (Book and Bustad, 1974; Miller and Ullrey, 1987; Mei and Xu, 2003) (Table 1). However, it should be noted that swine also have unique behavioural characteristic and husbandry requirements, which must be taken into consideration when used as a laboratory animal (Swindle *et al*., 2005). Other advantages of using the pig are that it is possible to use standard medical technologies to image internal organs and vessels, repeatedly collect blood samples and obtain an adequate quantity of tissue sample at slaughter without the need to pool samples. Pigs also share a high sequence and chromosome structure homology with humans, and genomic and proteomic tools are improving (Lunney, 2007). Furthermore, by using pigs from the same litter, or cloned or transgenic pigs, genetic variation is reduced making genetic mapping easier.

The two main categories of pigs used as biomedical models are the domestic pig (e.g. modern commercial breeds such as the Large White and Pietrain or ancient breeds such as the Meishan) and the minipig (e.g. Göttingen, Yucatan), both of which can differ in their suitability as a model for specific disorders. Some of the advantages of using the minipig compared with the domestic pig are its smaller and similar in size to humans, even at full maturity, slower growth during studies, ease of handling, and controlled genotype as well as its microbiological characteristics (Nunoya *et al*., 2007). However, one drawback of using minipigs is that they are in short supply and considerably more expensive to purchase. In contrast, domestic pigs are more costly to house, feed and medicate. Minipigs also have an advantage over traditional non-rodent animals, such as the dog, because of increasing ethical concerns about their use in experiments.

Apart from using whole animals, porcine cell lines have been established for studying metabolic function (e.g. Nishitsuka *et al*., 2007) in a wide range of tissue and these well-defined cell lines are readily available making it easier to examine gene expression and drug susceptibility for example. It should, however, be noted that some characteristics of porcine embryonic stem cells differ from murine and ovine embryos (Piedrahita *et al*., 1990). Cell lines can be used for some diseases, for example post-weaning diarrhoea (Pavlova *et al*., 2008) and the influenza virus (Seo *et al*., 2001), but this aspect will not be discussed further in this review.

Pigs have been used for research in a number of diseases (Table 2) including metabolic disorders (e.g. obesity and diabetes), cancer, chronic alcoholism, psychiatric disorders and regenerative therapies (e.g. use of stem cells). Recently, the transgenic pig has been developed for many uses within the areas of agriculture and biomedicine. For example, pigs have been modified to produce recombinant proteins in the mammary gland (Niemann and Kues, 2003), and anti-rejection work in xenotransplantation (Fodor *et al*., 1994). Genomic studies of melanoma and of infectious disease resistance, and issues for consideration in designing such genomic studies, have been recently reviewed by Lunney (2007) and will not be discussed further in the present review. The aim of this review article is to give an overview of the use of the pig as a biomedical model for humans, and in particular focuses on the Metabolic Syndrome, digestive tract-related dysfunction and bone disorders.

The metabolic syndrome

The metabolic syndrome consists of a cluster of risk factors for non-insulin dependent diabetes mellitus (NIDDM; Type II diabetes) and cardiovascular disease, which are generally classified as a combination of insulin resistance (DeFronzo and Ferrannini, 1991), central obesity, raised plasma triacylglycerol concentrations, reduced high-density lipoprotein cholesterol, increased low-density lipoprotein cholesterol and hypertension (Eckel *et al*., 2005; Pi-Sunyer, 2007). It is estimated that the current global prevalence of the metabolic syndrome is approximately 16% (95% confidence intervals 10 to 23; Wild and Byrne, 2005) and that this figure is growing at an alarming rate. A multitude of research has been undertaken to improve our knowledge of underlying causes and subsequent prevention and treatment of the metabolic syndrome, but much of this research has been conducted in rat models. One of the problems associated with rat models is that they rarely exhibit three of the clinical signs of this disorder, whereas in humans three or more of these symptoms are observed simultaneously; this is due to fundamental differences in metabolism and physiology between these two species. As a consequence, the porcine model, which exhibits three or more of the clinical signs, is now generally considered the optimum non-primate model for investigating the metabolic syndrome (Spurlock and Gabler, 2008). These authors have recently reviewed the development of porcine models of obesity and the metabolic syndrome in juveniles and adults, and so this aspect will not be covered in depth herein. The components contributing to the onset of the Metabolic Syndrome are discussed below.

Table 1 *A comparison of reproductive and general anatomical/physiological factors between human, swine and rats*

	Humans	Swine		Rats	References
		Domestic	Minipig		
Cost	–	Expensive	Very expensive	Inexpensive	Dunn and Mancoll (1992)
Newborn	28 days	14 days	n/a	0 to 4 days	Pond and Mersmann (2001), Tsutsumi *et al.* (2004), Hill (2008)
Infant	0.08 to 2 years	15 to 75 days	0 to 3 months	5 to 10 days	
Juvenile	3 to 13 years	76 to 150 days	3 to 5 months	11 to 17 days	
Age at puberty: male	13 to 16 years	5 to 18 months	140 to 170 days	6 weeks	Bivin *et al.* (1979), Jorgensen (1998)
Age at puberty: female	11 to 14 years	6 months			
Oestrous cycle (day)	28	21	21 to 22	4 to 5	Shaikh (1971), Bazer *et al.* (2001)
Menopause	48 to 55 years	–	–	15 to 18 months	Pavelka and Fedigan (1991), Alkayed *et al.* (2000)
Life expectancy	70 years	25 years in wild	–	1 to 3 years	Central Intelligence Agency (CIA) (2008)
Length of gestation	38 weeks	115 days	114 days	21 days	Stryker and Dziuk (1975), Jones and Summerlee (1986)
Maximum number of litters/year	1	2.3	2.3	6 to 8	Pond and Mersmann (2001)
Number of offspring/litter	1 to 2	8 to 12	5 to 6	10 to 12	Pond and Mersmann (2001)
Weight of offspring (kg)	3.2	1.5	0.35 to 0.5	0.007	Totora and Grabowski (2003), Robinson and Brumley (2005), Laws *et al.* (2009).
Adult BW (kg)	70	60 to 280	30	0.25 to 0.4	Pond and Mersmann (2001)
Heart size-to-BW ratio	–	Similar[1]		Not similar[1]	Hughes (1986)
Pooling of tissues (e.g. adipose)	Not required	Not required		Required	Spurlock and Gabler (2008)
Omnivore	Yes	Yes		Yes	Mei and Xu (2003)
Tooth structure	–	Similar[1]		Not similar[1]	PWG Genetics Korea (2006)
Middle ear	–	Similar[1]		Not similar[1]	Pracy *et al.* (1998)
Skin	–	Similar[1]		Similar[1]	Bronaugh *et al.* (1982), Avon and Wood (2005)
Sweat glands	Apocrine and eccrine	Apocrine only		Apocrine only	Monteiro-Riviere (2005)
Atherosclerosis	–	Similar[1]		Not similar[1]	Buettner *et al.* (2007), Oron-Herman *et al.* (2008)
Kidney structure and function	–	Similar[1]		Not similar[1]	Sachs (1994)

[1]Similarity compared to humans.

Table 2 *An overview of the use of the pig as a biomedical model*

Model	Comments regarding swine model	References
Metabolic syndrome	Ossabaw minipig and pietrain preferred as they exhibit obesity, insulin resistance and hypertension not seen in other breeds	See below
Developmental programming	Domestic pig preferred due to 2- to 3-fold variation in BW among littermates (e.g. Large White)	Hoet and Hanson (1999), Clarke *et al.* (2000), Poore and Fowden (2003), 2004a and 2004b), Corson *et al.* (2009)
Placental and foetal growth and development	Pigs have epithelial chorial placentas allowing easy dissection	Tayade *et al.* (2005)
Maternal environment and foetal development	Little work done in the area: theoretically should give similar results to humans	Schoknecht *et al.* (1993 and 1994), Wu *et al.* (1999)
Size and shape at birth as indicator of health in later life.	Some studies done but only for Large White × Landrace.	Bauer *et al.* (1998), Corson *et al.* (2008a)
Cardiovascular disease: atherosclerosis	Atherosclerosis induced in domestic pig without other signs of metabolic syndrome	Gerrity *et al.* (2001), McDonald *et al.* (2007)
Stenosis	Yucatan minipig shows good arterial response after balloon angioplasty even though it fails to exhibit insulin resistance and obesity	De Smet *et al.* (1998).
Obesity	Ossabaw minipig as atherogenic diet induces three or more signs of metabolic syndrome	Johansen *et al.* (2001), Spurlock and Gabler (2008)
Therapeutic angiogenesis	Minipig has similar coronary anatomy & heart to body ratio to that of humans	Hughes *et al.* (2003 and 2004)
Collagen changes in the heart during hypertrophic cardiomyopathy	See above	Liu *et al.* (1994), Chiu *et al.* (1999)
Abdominal aortic aneurysm	See above	Ruiz *et al.* (1997)
NIDDM	Pigs similar to humans for diabetes-induced accelerated atherosclerosis	Larsen and Rolin (2004)
Insulin dependent diabetes mellitus	Pigs have similarities in structure and function of pancreas and pharmacokinetics following administration of trial drugs	Larsen and Rolin (2004), Xi *et al.* (2004)
Digestive physiology and metabolism	Swine have physiological and anatomical similarities to humans	See below
Total parenteral nutrition	Minipiglets can survive when delivered preterm & can be used colostrums-deprived	Borum (1993), Mehrazar and Kim (1988), Sangild *et al.* (2002), Hyde *et al.* (2008)
Postnatal digestive physiology/nutritional studies	Piglets' GI tract has high anatomical and physiological similarity to humans	Moughan and Rowan (1989), Moughan *et al.* (1990 and 1992), Rowan *et al.* (1994), Darragh and Moughan (1995), Wu (1998), Reeds and Burrin (2000), Siggers *et al.* (2008), Spurlock and Gabler (2008), Lin *et al.* (2009)
Effects of dietary fat on brain growth	Piglets undergo growth spurt in the brain at a similar time to that in humans	Pond *et al.* (2002), Amusquivar *et al.* (2008), Hyde *et al.* (2008)
Fatty acid metabolism	Fatty acid profile of nutrients supplied to piglet influences fatty acid of tissues	Purvis *et al.* (1982), Laws *et al.* (2009)
Diarrhoea	Piglets like human infants are prone to diarrhoea	Shu *et al.* (2001), Meunier *et al.* (2008), Siggers *et al.* (2008)
Pre- and probiotics	Responses to probiotics similar in piglets and human infants	Shu *et al.* (2001), Sangild (2006), Meunier *et al.* (2008), Siggers *et al.* (2008)
Testing of endoscopic equipment	Similar size of GI tract	Hu *et al.* (2004)
Ulcers	Different techniques under investigation with some success but needs development	Hu *et al.* (2005), Ikeda *et al.* (2005), Chiu *et al.* (2006), Marks *et al.* (2006), Chen *et al.* (2008)
Transgastric endoscopic gastrojejunostomy	Limited at present as pigs used in one specific study only	Kantsevoy *et al.* (2005)

Gastric cancer resection	Limited at present as pigs used in one specific study only	Ikeda *et al*. (2005)
GI tract damage through repeated use of non-steroidal anti-inflammatory drugs	Limited at present as pigs used in one specific study only	Rainsford *et al*. (2003)
Renal physiology	Kidneys similar in structure and function to humans	Borden and Vermeulen (1966), Assimos *et al*. (1986), Terris (1986), Paterson *et al*. (2002)
Bones	Pig bone remodelling is histologically more similar to human than rat or mouse	See below
Bones and osteoporosis	Pigs show spontaneous vertebral fracture, are large enough to receive prosthetic implants and rates of bone removal and deposition (trabecular and cortical bones) similar to humans	Spencer (1979), Mosekilde *et al* (1993b), Boyce *et al*. (1995), Turner (2001), Teo *et al*. (2006), Walsh *et al*. (2009)
Dental research	PWG micro-pig® has a tooth structure which closely resembles that of humans	Robinson *et al*. (1987), Kirkham *et al*. (1988), Ko *et al*. (2002 and 2003), Bousdras *et al*. (2006), PWG Genetics Korea (2006), Mantesso (2008)
Examples of other models	The similar morphology of pigs to humans make them useful in many applications	Lunney (2007), Nunoya *et al*. (2007)
Xenotranslantation and hyperacute organ rejection	Transgenic pigs and minipigs used modified for research use	Fodor *et al*. (1994), Yamada *et al*. (2005)
Drug development	Minipigs possess the main human liver enzyme for drug biotransformation	Dorman *et al*. (1993), Oberle *et al*. (1994), Anzenbacherová *et al*. (2003)
Developmental immunology		Rothkotter *et al*. (2002)
Cancer	Sinclair minipigs demonstrate cutaneous melanoma with a histopathology similar to humans	Jones and Amoss (1982), Tissot *et al*. (1987), Amoss *et al*. (1988), Misfeldt and Grimm (1994), Nunoya *et al*. (2007)
Wound healing	Pig skin very similar to human skin	Cynthia and Smith (2000)
Dermatoxicology	Pig skin has similar general morphology of skin to humans	Lavker *et al*. (1991), Svendsen (2006)
Infectious disease models	Pig skin has many physiological similarities to human skin	Gonzalez *et al*. (2004), Dawson *et al*. (2005), Elahi *et al*. (2005), Hasslung *et al*. (2005), Houdebine (2005), Pomeranz *et al*. (2005), Butler *et al*. (2006), Cheetham *et al*. (2006), Dvorak *et al*. (2006), Lunney (2007)
Respiratory function	Minipigs have been demonstrated to be useful in the evaluation of respiratory response and disease	Koch *et al*. (2001), Turner *et al*. (2002), Watremez *et al*. (2003)
Biomechanical models	Similarity in size of pigs to humans facilitates use for the analysis of injury and for the development of imaging techniques	Ellner *et al*. (2004), Goldberg *et al*. (2004), Schmitt and Snedeker (2006)
Brain function	Limited use of minipigs in the examination of brain structure and disease	Minuzzi *et al*. (2005), Tambuyzer and Nouwen (2005), Imai *et al*. (2006)
Defects if growth hormone releasing hormone	Studies have used pigs to examine hypochrondroplasia, intrauterine growth restriction, Crohn's disease, renal insufficiency and Turner syndrome	Kues and Niemann (2004)
Human decompression sickness	Limited at present as pigs used in one specific study only	Reuter *et al*. (2000)
Ageing of bite marks for use in forensic science	The similarities between human and pig skin make it an ideal model	Avon and Wood (2005)
Chronic alcoholism	Pigs demonstrate similar responses to alcohol as seen in humans	Nakamura *et al*. (1992), Halsted *et al*. (2002)

NIDDM = Non-insulin dependent diabetes mellitus; GI = gastrointestinal.

Developmental programming of the metabolic syndrome
Evidence from numerous epidemiological studies has suggested that there is a relationship between intrauterine growth restriction (IUGR) and the subsequent development of the metabolic syndrome (Hansen, 1999; Horvath and Bruning, 2006; Palinski, 2007; Taylor and Poston, 2007). Sheep, rats, guinea pigs and more recently pigs have extensively been used to investigate the mechanisms which link prenatal programming to adult diseases (Hoet and Hanson, 1999; Clarke *et al*., 2000; Poore and Fowden, 2004a).

Placental and Foetal growth and development. It is well established that in mammals the principal determinant of IUGR is placental nutrient supply, which in turn depends on the size, morphology, blood supply and transporter abundance of the placenta, and on synthesis and metabolism of nutrients and hormones by the uteroplacental tissues (Fowden *et al*., 2006). Both human and rat placentas belong to the general category of haemochorial placentas; however, there are fundamental differences (Table 3). For example, adiponectin and adiponectin receptor 2 (Adipo-R2) are present in cytotrophoblast and syncytiotrophoblast cells in humans, whereas adiponectin expression occurs in rat trophoblast cells and Adipo-R2 in giant cells and viteline membranes (Caminos *et al*., 2005). Pigs, on the other hand, have epithelial chorial (or diffuse) placentas making them a good model for studies during pregnancy as the maternal and foetal components of the placenta can be cleanly dissected without cross contamination (Tayade *et al*., 2005).

Foetal growth is a combination of numerous interrelated mechanisms that include cell replication and tissue differentiation, matrix formation and cell death, all of which need to be regulated (Gluckman, 1986). There is a well-defined, programmed, sequence of developmental changes that occurs at specific times in the growth of the embryo and foetus (Figure 1). The underlying principles of foetal maturation appear to be comparable between mammals, but it should be noted that quantitative differences occur between species. For example, stage 3 foetal development occurs *in utero* in humans and swine but postnatally in rats (Figure 1). In addition, rat pups are much smaller than either babies or piglets (Figure 1), which means that it is often necessary to pool tissue samples, thereby reducing indications of natural variation. When compared with the young of other commonly used research animals such as the dog, cat, goat and sheep, the piglet appears to show the greatest similarity to the human infant in terms of anatomy, physiology, nutrition and metabolism (Book and Bustad, 1974; Miller and Ullrey, 1987; Mei and Xu, 2003).

Measurements of embryos and foetuses are generally cited as crown-to-rump length (Figure 1), but while this parameter is quite reliable for man, it must be used with caution for domestic mammalian foetuses because of the longer neck and the increased chance in error due to changes in posture (Evans and Sack, 1973). In humans, the rate of foetal growth is relatively slow up to the 20th week of pregnancy and, as with the pig and rat; the majority of

Table 3 *Placental and metabolic comparisons between foetal and neonatal humans, swine and rats*

	Humans	Swine	Rats	References
Type of placenta	Haemochorial	Epithelial chorial	Haemochorial	Leiser and Kaufmann (1994)
Placental transfer				
Glucose	Occurs	Occurs	Occurs	Meschia (1982), Bazer *et al*. (2001), Ward Platt and Deshpande (2005)
Amino acids	Occurs	Occurs	Occurs	Ramsay *et al*. (1991), Ruwe *et al*. (1991)
NEFA	Occurs	Limited occurrence	Occurs	Shafrir and Khassis (1982), Mersmann and Pond (2001), Klingler *et al*. (2003)
Immunoglobulins	Occurs	Does not occur	Occurs	Schlamowitz (1976), Story *et al*. (1994), Saji *et al*. (1999), Blecha (2001)
Amino acid composition in utero	=	=	≠	Wu *et al*. (1999)
Protein accretion rates	13 g/kg BW/day	19 g/kg BW/day (after day 69)	25 g/kg BW/day	Goldspink and Kelly (1984), Chien *et al*. (1993), McPherson *et al*. (2004)
Maturity at birth	Precocious	Precocious	Altricial	Künkele and Trillmich (1997), Drake *et al*. (2008)
Possesses brown adipose tissue at birth	Yes	No	Yes	Mostyn *et al*. (2004)
Adipose tissue (% BW)	14	<2	<1	Mellor and Cockburn (1986)
Postnatal energy metabolism				
Total available lipid (g/kg BW)	150 (50)*	11	n/a	Mellor and Cockburn (1986)
Total available hepatic glycogen (g/kg BW)	3.78 (0.57)*	2.50	n/a	Mellor and Cockburn (1986)
Heat production (kJ/h per kg)				Mellor and Cockburn (1986)
32°C to 38°C	6.9 (5.9)*	9.5	n/a	
18°C to 26°C	13 (8.5)*	27	n/a	

NEFA = non-esterified fatty acids.
*Values in bracket are for premature human infants.

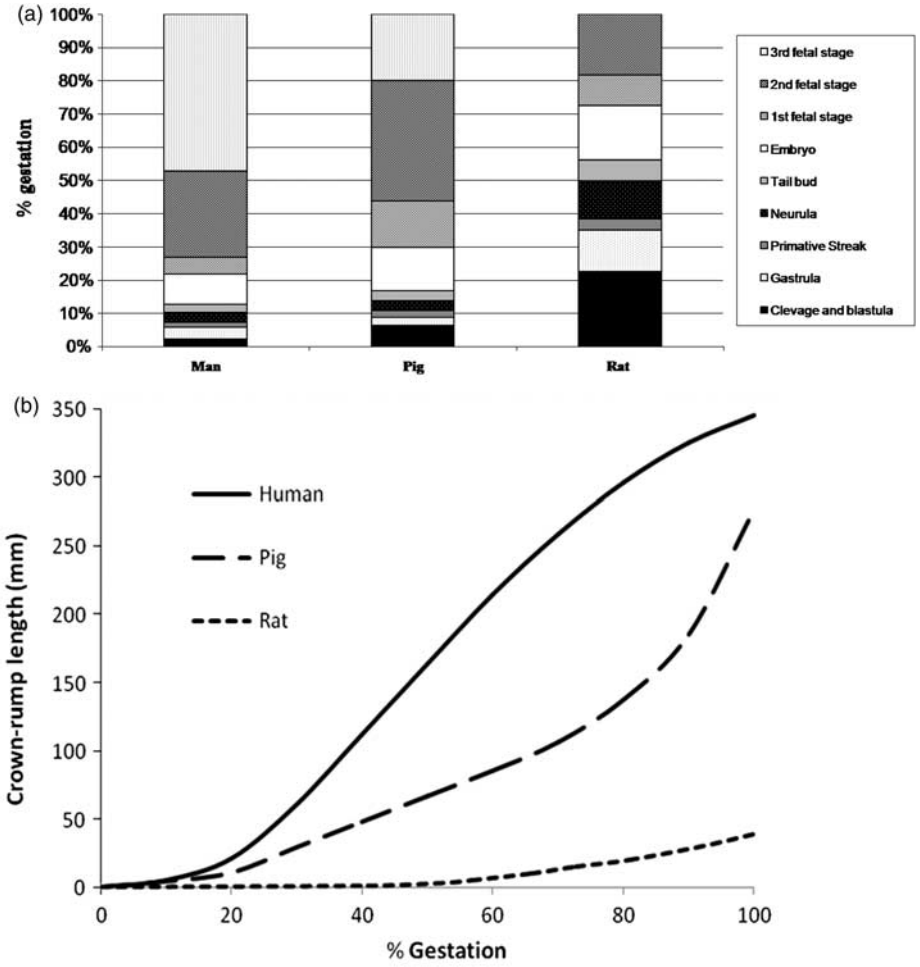

Figure 1 Comparison of prenatal development and crown-to-rump length of human (—), pig (– -) and rat (- - - -) foetuses throughout gestation. (a) Adapted from Book and Bustad (1974) and Hill (2008). (b) Adapted from Book and Bustad (1974), and Evans and Sack (1973).

growth occurs during the second half of pregnancy (Manners and McCrea, 1963; Ashworth, 2006). Human foetal growth accelerates to reach a maximum around 30 to 36 weeks, declining thereafter until birth as the mother fails to meet the increasing energy demand of her growing foetus. On the contrary, the pig and rat have not reached their peak growth rate at birth and so the decline in growth rate observed during late gestation in humans does not occur (Figure 1). In litter-bearing species the number of developing foetuses is inversely related to the ultimate size of each individual at full term (Pond and Houpt, 1978). The pattern of foetal growth in pigs is determined by the genome of the foetus, maternal nutrition and health, uterine capacity and foetal position in the uterine horn (McCance and Widdowson, 1974; Antipatis *et al.*, 2008).

Protein accumulation tends to occur early in human foetal development to reach its maximum (~ 300 g) around week 35, and precedes fat accumulation, most of which is subcutaneous, and only exceeds the weight of protein deposition by week 38 (Prentice *et al.*, 1996). By term, there is approximately three-times more energy stored as fat than as protein in human infants. Unlike humans and sheep, both pigs and rats are born with little adipose tissue, but in this sense their early *post partum* development can be viewed as equivalent to the late development of human babies in utero (Table 3). It should be noted that the amino acid compositions differ appreciably among species that have relatively short periods of gestation such as the rat and species that have relatively long periods of gestation such as the pig and human for the amino acids: histidine, glycine, lysine, proline and hydroxyproline (Wu *et al.*, 1999).

The newborn pig's body fat is minimal and usually constitutes no more than 2% of total body weight (BW). However, this situation is reversed postnatally; piglets can double their birth weight due to high rates of protein deposition and lean tissue growth (Wood and Groves, 1965; Whittemore and Kyriazakis, 2006), and there can be a 10- to 20-fold increase in body fat in 7 to 10 days, whereas the human infant doubles its birth weight by about 5 months of age (Shulman, 1993; Pond and Mersmann, 2001). This means that piglets can provide an excellent model of accelerated growth and development (Odle, 1997), which is advantageous when studying the effects of postnatal nutrition on health in later life (Taylor and Poston, 2007). Moreover, the newborn piglet is more akin to the premature than to the

full-term human infant in several aspects, such as body composition (i.e. low fat and hepatic glycogen content) and a reduced thermoregulatory ability (Widdowson, 1971; Book and Bustad, 1974; Herpin *et al*., 2002; Mostyn *et al*., 2005).

Low birth weight (LBW) modern domestic pigs exhibit impaired mitochondrial metabolism in adipose tissue, which may in part explain their reduced body temperature (Mostyn *et al*., 2005). However, physiological studies have shown that porcine genotype must be taken into consideration when selecting an appropriate model because despite the minipig being smaller, it possesses more fat (0.117 to 0.158 kg fat for a 1.25 kg 5-day old neonatal piglet, (Sheng *et al*., 1988)) compared with modern domestic breeds (0.03 kg fat for a 1.5 kg 1 day old neonatal piglet, Shields *et al*., 1983)) and exhibits altered uncoupling protein (UCP) expression and endocrine profile at birth compared with modern domestic breeds of pigs (Knol *et al*., 2002; Mostyn *et al*., 2004, 2006). Compromised UCP abundance in adipose tissue may contribute to excess fat deposition in later life resulting in obesity, hence providing a natural model for obesity (Dyson *et al*., 2006).

Maternal environment and foetal development. Foetal metabolism and neonatal outcome are altered by factors such as maternal body composition, nutrition, endocrine environment (Gluckman and Pinal, 2002) and complications like gestational diabetes (Ray *et al*., 2001). Ethical restraints forbid the use of studies investigating human foetal metabolism. Size and length of gestation in rodents makes it difficult to study metabolic activity in the developing foetus. In contrast, piglets are large enough to catheterize in utero (Silver *et al*., 1986), and one further advantage is that since the pig is a litter-bearing species several different metabolic studies can be performed using replicates within a litter.

Protein intake determines placento-foetal growth (Godfrey *et al*., 1996). Rats are currently the best-characterized animal model with many studies showing maternal low protein diet (LPD) consumption throughout (Langley-Evans, 2001), or at specific gestational periods leading to hypertensive offspring (Kwong *et al*., 2000). The magnitude of effect is partly dependent on timing of exposure and in some (Kwong *et al*., 2000), but not all studies, is gender specific. The rat, however, may be particularly vulnerable to any nutritional imbalance during gestation given the exceptional rate of foetal protein accretion compared with the human foetus and the far larger total weight of the products of conception relative to maternal weight. For example, the rate of protein accretion (Table 1) is approximately 25 g/kg BW/day in the rat (Goldspink and Kelly, 1984) and 13 g/kg BW/day in the human foetus near-to-term (Chien *et al*., 1993). In the pig, the rate of foetal protein accretion is approximately 19 g/kg BW/day after day 69 of gestation (McPherson *et al*., 2004).

Maternal protein restriction during early pregnancy influences foetal and placental growth throughout pregnancy, whereas protein restriction throughout the whole of gestation stunts postnatal growth of swine progeny (Schoknecht *et al*., 1993 and 1994). Protein restriction during the first or last trimester, however, does not have a permanent effect upon postnatal growth of pigs once balanced nutrition is restored (Schoknecht *et al*., 1993). It has also been demonstrated that piglet size at birth is correlated to changes in the transport of leucine across the porcine placenta (Finch *et al*., 2004), which is in accordance with the findings that a low protein maternal diet induces foetal growth retardation in rats and humans (Metges, 2005). Although there is a somewhat limited amount of information on the effect of a LPD on the development of adulthood diseases in pigs, given the amino acid composition of the foetal pig is also similar to that of the human foetus (Wu *et al*., 1999), it seems feasible to suggest that results from porcine studies would be comparable to that observed in human epidemiological studies. Further work is required to determine the suitability of the pig as a model for studying the effects of a maternal LPD and the ontogeny of the metabolic syndrome in their offspring.

Essential fatty acids are known to be important for the maintenance of normal growth and development, as they form precursors for the components of the endocrine and immune systems (Milner and Allison, 1999; Wainwright, 2000). Supplementing the sow diet with lipids during pregnancy not only alters the lipid composition of the developing pig foetuses (Rooke *et al*., 1998), but also subsequent milk composition (Laws *et al*., 2008 and 2009). As observed in humans (Innis, 2004), the fatty acid composition of the milk mirrors that of the type of oil that is added to the sow diet, which can subsequently influence neonatal outcome in modern domestic breeds (Laws *et al*., 2008 and 2009). Supplementing the maternal diet with sunflower oil during the first half of gestation resulted in a greater proportion of LBW piglets ($20 \pm 3\%$), whereas supplementing with olive oil reduced the incidence of LBW offspring ($5 \pm 3\%$), and hence growth rate was higher in these piglets. Irrespective of the type of oil added to the maternal diet, LBW offspring of supplemented mothers possessed more fat compared with the offspring born to unsupplemented sows at birth. Follow-up studies on these LBW were not undertaken with respect to their glucose metabolism in later life. However, these results further support a role for the modern domestic pig as a biomedical model for understanding the relationship between maternal nutrition, birth weight and the development of the metabolic syndrome.

It is worth mentioning here the differences in milk composition between humans and pigs. There is no passive transfer of immunoglobulin across the porcine placenta as seen in humans (Table 3), and as such the sow-colostrum is rich in immunoglobulins (Laws *et al*., 2008). Modern domestic sow milk contains significantly higher amounts of fat and protein ($\sim 8\%$ and 6%, respectively; Laws *et al*., 2008) than human milk (4% and 1%, respectively; Mitoulas *et al*., 2002). This, in part, explains the higher rate of fat deposition observed during the neonatal period in pigs. In contrast, lactose is reduced in sows' milk ($\sim 4\%$) compared to human milk ($\sim 6\%$) (Mitoulas *et al*., 2002; Laws *et al*., 2008).

Size and shape at birth. More recently, human studies (Jarvelin *et al*., 1997; Laitinen *et al*., 2003 and 2004) have demonstrated that body shape at birth, rather than weight

per se, may be a better indicator of future health and development of the human infant. The modern domestic pig, rather than the ancient domestic pig or minipig, is an excellent model for developmental programming due to the 2- to 3-fold variation in BW among littermates, which provides a naturally occurring form of foetal growth restriction with less genetic variation than seen in man or other monotocous species (Bauer *et al.*, 1998; Corson *et al.*, 2008a). In addition, it is usually possible to identify asymmetrical and symmetrical body shapes within a domestic pig litter. Piglets that are long and thin at birth grow more slowly compared with those that are short for weight (i.e. fatter) over the first month of life and have a lower developmental score (Litten *et al.*, 2003). Moreover, LBW piglets that exhibited 'catch-up' growth had a higher neonatal developmental score than those animals that remained on their prenatal growth trajectory.

There is a growing body of evidence to suggest that postnatal 'catch-up' or 'catch-down' growth may also be a contributory factor to predisposition to adulthood diseases (Ong *et al.*, 2000 and 2002 and Ong and Dunger, 2004). Practically it is difficult to follow the growth of individual rat pups from birth and the importance of size at birth remains controversial. In addition, the programming of higher blood pressure appears to be greatly amplified in rats compared with human epidemiological and large animal studies (Langley-Evans, 2001). The pig provides an excellent model for longitudinal studies as individuals are easily identifiable, large volumes of blood can be taken and exogenous substances can be infused in both chronic and acute studies (Poore *et al.*, 2002; Poore and Fowden, 2003, 2004a and 2004b; Litten *et al.*, 2005 and 2008; Corson *et al.*, 2008a and 2009). Furthermore, the pig can be trained to remain conscious but relatively unstressed while procedures are carried out (Larsen and Rolin, 2004). Postnatal dietary studies can continue as individual feed intake can be recorded using feed intake recording equipment feeders without removing the pig from its social group (Litten *et al.*, 2004). The similarity of pathological response to high caloric intakes with humans supports the use of pig models for identifying genes and their variants associated with energy storage defects through the activation of both hormonal and biochemical pathways (Brambilla and Cantafora, 2004).

Centile charts for BW and height are routinely used to track the normal growth and development of children alongside their birth percentile, allowing their health and progress to be monitored. Many children deviate from their early percentile, but it is still not clear as to when the point at which they deviate becomes of pathological importance (Wright *et al.*, 1994). Percentile curves for pigs, similar to those used for human studies, have recently been developed, and allow an efficient method of following an individual pig's growth, particularly during experimental manipulations (Corson *et al.*, 2008a). Such curves could be used to determine if a pig's growth deviates from the expected normal growth curve, and identify when, or if, the point of deviation is of pathological importance. However, an air of caution must be taken if using these porcine growth curves as data were collected only for a specific domestic breed combination (i.e. Large White X Landrace), reared under standard commercial conditions, not experimental conditions; it is known that growth and development varies between porcine genotypes (Mostyn *et al.*, 2004) and also under different management regimes (Kusec *et al.*, 2007).

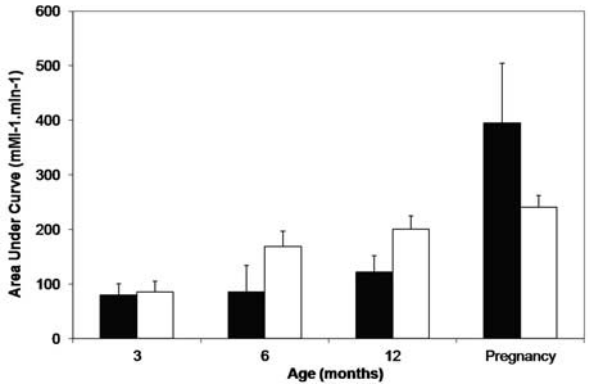

Figure 2 The effect of low (L) or normal (N) birth weight on the area under the curve following a glucose tolerance test (GTT) at 3, 6 and 12 months of age and during pregnancy. Values are presented as Mean ± s.e.m., L pigs are represented by black bars, N pigs by white bars. GTT: intravenous administration of 0.5 g/kg BW dextrose 40%. Data taken from Poore and Fowden, 2004a (3 and 12 months) and Corson *et al.*, 2008b (6 months and pregnancy).

Studies in older pigs have demonstrated that LBW is associated with glucose intolerance (Poore and Fowden, 2004a; Corson *et al.*, 2009), reduced insulin sensitivity and increased mean arterial blood pressure (Poore *et al.*, 2002) and altered Hypothalamo–pituitary–adrenal axis function (Poore and Fowden, 2003) in conjunction with changes in body composition and endocrine profile (e.g. plasma leptin) (Poore and Fowden, 2004b; Morise *et al.*, 2008). LBW pigs exhibit glucose intolerance (Figure 2), irrespective of whether they are reared under standard commercial (Corson *et al.*, 2009) or experimental conditions (Poore and Fowden, 2004b), and the methodology used for a glucose tolerance test (GTT). This suggests that their postnatal environment had little effect on their risk of developing adulthood diseases, and that the LBW pig provides a robust model for studying the metabolic syndrome.

Studies have shown that the birth weight of a human baby is related to both their mother's and maternal grandmother's birth weight (Hackman *et al.*, 1983; Klebanoff *et al.*, 1984). Women who were themselves small for gestational age (SGA) are twice at risk of having a SGA baby (Klebanoff *et al.*, 1989; Skjærven *et al.*, 1997) as well as being at a greater risk of developing adulthood diseases. Moreover, women who had parents with NIDDM had children with higher birth weights than women with non-diabetic parents. Grandchildren of grandparents with NIDDM are usually in the top percentiles in growth charts (i.e. 90th centile and above) compared with non-diabetic grandparents (McCarron *et al.*, 2004). In the past intergeneration

studies have been somewhat limited to rodent models (Harrison and Langley-Evans, 2009), but more recently it has been demonstrated that an intergeneration relationship between maternal size at birth and altered glucose tolerance in later life exists in the domestic pig (Corson *et al.*, 2009). The added advantage of using a porcine model for intergeneration investigations is that it allows both LBW and high birth weight piglets within a litter to be studied, further reducing the number of animals required as well as decreasing genetic variation.

Cardiovascular disease and the metabolic syndrome

Pigs are frequently used as models for the study of cardiovascular disease and atherosclerosis as the morphology and physical function of the cardiovascular system in swine are similar to humans' (Smith and Swindle, 2006; Tables 1 and 2). Exceptions are that the swine heart has a left azygous vein that contains systemic blood from the inter-costal vessels; the conduction system is more neurogenic than myogenic; and the nerve cells within the atrioventricular node also differ. Having said that, the blood supply to the myocardium and the conduction system of the swine is similar to 90% of the human population (Smith and Swindle, 2006). Atherosclerosis in the pig develops both spontaneously and when induced by an experimental atherogenic, high-cholesterol diet in pigs (Gerrity *et al.*, 2001). Plaque histology and pathogenesis in the atherogenic swine appears to be similar to that of humans (Gal and Isner, 1992; Rand, 2009). Atherogenic diets offered to rodents result in some of characteristics of atherosclerosis and the metabolic syndrome observed in humans (Buettner *et al.*, 2007; Oron-Herman *et al.*, 2008), however they generally provide poor models of the changes in plasma lipids associated with coronary heart disease.

Some metabolic and cardiovascular disorders occur naturally in domestic pigs as a consequence of intense selective breeding and selection for increased growth rate and leanness (Brambilla and Cantafora, 2004). Feeding the modern domestic pig excess amounts of lard and cholesterol can induce atherosclerosis (Gerrity *et al.*, 2001; McDonald *et al.*, 2007; Table 4) without some of the other clinical signs of the metabolic syndrome. The minipig, particularly the ossabaw swine, has proved to be an excellent model because an atherogenic diet induces three or more of the clinical signs of the metabolic syndrome (Johansen *et al.*, 2001; Spurlock and Gabler, 2008).

The natural history of restenosis (i.e. the reoccurrence of stenosis) in pigs, both with respect to neointimal formation and remodelling, resemble the human disease closely. A combination of denudation and atherogenic diet can be used to induce atherosclerosis in pigs. Although the Yucatan breed of minipig is not a successful model for metabolic-syndrome-induced atherosclerosis, as it fails to exhibit insulin resistance and obesity, it does provide a model for studying the arterial response after balloon angioplasty and natural remodelling (De Smet *et al.*, 1998).

Over the past decade, pigs have been increasingly used to study changes in the collagen of the extra cellular matrix of

Table 4 *A comparison of diet-induced metabolic syndrome in different breeds of pig*

	Domestic	Göttingen minipigs	Ossabaw minipigs	Chinese Guizhou minipigs	Yucatan
Diet	15% Lard and 1.5% cholesterol	55% energy from fat with no cholesterol for 5 weeks	45% energy from fat and 2% cholesterol for 9 weeks	High carbohydrate (42% starch; 37% sucrose) with only 16% energy from fat but with 2% cholesterol for 6 months	n/a
Obesity	Not determined	Yes	Yes	Yes	No
Insulin resistance	Not determined	Yes	Yes	Yes	No
Glucose intolerance	Yes	Yes	Yes	Yes	No
Hypertension	Not determined	Yes	Yes	Not determined	No
Dyslipidemia	Yes	Yes	Yes	Yes	Yes
Atheroslcerotic lesions	Yes	Yes	Yes	Yes	No
References	Gerrity *et al.* (2001), McDonald *et al.* (2007)	Yasuda *et al.* (1983), Johansen *et al.* (2001), Larsen *et al.* (2002b), Christoffersen *et al.* (2007)	Dyson *et al.* (2006)	Xi *et al.* (2004), Yin *et al.* (2004)	De Smet *et al.* (1998)

Yes indicates whether the animal expresses diseases.

Table 5 *Response to increasing dose rates of streptozotocin in juvenile pigs*

Dose (mg/kg)	Effect	Authors
35 to 40	No major effect in domestic or minipigs	Marshall *et al.* (1975), Gabel *et al.* (1985)
50	Diabetes induced (initially 8 to 10 weeks of age)	Natarajan *et al.* (2002)
85	Diabetes induced reversible within 2 weeks	Gabel *et al.* (1985)
100 to 150	Complete and permanent induced insulin-dependent diabetes in domestic and minipigs (mortality rate 0% after 7 months)	Gabel *et al.* (1985), Wilson *et al.* (1986), Barb *et al.* (1992), Canavan *et al.* (1997), Grussner *et al.* (1993), Larsen *et al.* (2002a)
150	Diabetes induced in landrace pigs but not in Göttigen minipig (mortality not reported)	Liu *et al.* (1998)
200	Insulin-dependent diabetes induced in Göttigen Minipig (mortality not reported)	Liu *et al.* (1998)

the heart during hypertrophic cardiomyopathy (Liu *et al.*, 1994; Chiu *et al.*, 1999); abdominal aortic aneurysm (Ruiz *et al.*, 1997) and chronic ischaemia because their coronary anatomy, with minimal preexisting coronary collateral vessels (Maxwell *et al.*, 1987), cardiac physiology, and cardiac conduction systems are very similar to humans (Swindle *et al.*, 1986). Likewise, the heart weight to BW ratio for the typical 30 kg minipig used in most laboratory studies is identical to that of humans at around 0.005:1 or 5 g heart tissue per kilo of BW (Joseph, 1908; Hughes, 1986; Kist *et al.*, 1999**)** and from a metabolic standpoint non-esterified fatty acids (NEFA) are the preferred substrate of myocardial energy production in both species (Abdel-Aleem *et al.*, 1999). The development of a porcine model of myocardial ischaemia to evaluate the efficacy of therapeutic angiogenesis in the preclinical setting is ongoing (Sodha *et al.*, 2008). Despite the success in some of these models (Hughes, 2003), randomized placebo controlled clinical trials failed to demonstrate a similar degree of success (Kastrup *et al.*, 2005). There are multiple reasons for the disparate results seen between animal models and human patients, including the presence of comorbidities such as hypercholesterolemia and diabetes, and medication usage, which may alter the milieu of signalling molecules involved in the angiogenic cascade (Simons *et al.*, 2000).

Diabetes and the metabolic syndrome

NIDDM. Atherosclerosis is accelerated in diabetic patients and contributes to the majority of deaths of diabetic patients (Ruderman *et al.*, 1992). Pigs represent a valuable model for diabetes-induced accelerated atherosclerosis. Administration of streptozotocin (STZ) induces DNA strands to break within β-cells. The activation of repair mechanisms leads to a reduction in cellular nicotinamide adenine dinucleotide and adenosine triphosphate levels to below physiological levels, resulting in cell death and ultimately diabetes (Yamamoto *et al.*, 1981). Various studies have investigated the effectiveness of different dose rates of STZ to induce diabetes (Table 5) and the differences in response have been attributed to age and gender variations (Larsen and Rolin, 2004).

Insulin dependent diabetes mellitus. Pigs provide a good model for Type I or insulin-dependent diabetes as there are many similarities between pigs and humans in terms of the structure and function of the pancreas (Larsen and Rolin, 2004) and pharmacokinetics following administration of trial drugs. However, the spontaneous development of Type-I diabetes is very rare in pigs and so this condition must be induced experimentally either via surgery, chemical administration, such as STZ (Larsen and Rolin, 2004) or diet as described above (Xi *et al.*, 2004).

The severity of Type I diabetes after surgical-induction by pancreatectomy is dependent on the degree of excision/ablation. For example, a 40% pancreatectomy results in mild changes, 80% in significant alterations (Lohr *et al.*, 1989) and 100% in severe hyperglycemia (Wilson *et al.*, 1986; Stump *et al.*, 1988; Mellert *et al.*, 1991 and 1998). The problems associated with using this method are that surgery involves the removal of exocrine and endocrine tissue, which is not characteristic of the disease in humans (Wilson *et al.*, 1986), and that it is an extremely invasive technique with huge welfare implications.

Digestive physiology and metabolism

Total parenteral nutrition

When an infant is born prematurely, although its gastrointestinal (GI) tract is fully formed at about 20 weeks of pregnancy, it is not fully functional at that time; for example peristalsis does not commence until around 29 weeks of gestation and it may not be able to synthesize the enzymes required to digest milk and formula (Sangild, 2006). As a consequence, it can often not tolerate enteral feeding due to its immature GI tract and so must be fed intravenously (known as total parenteral nutrition (TPN)). As nutrition provided by TPN bypasses the gut and absorption at the intestinal mucosa, it results in varying degrees of gut atrophy, depending on the period of treatment and whether the individual is receiving any nutrient enterally. Most infants on TPN are subject to numerous clinical problems, which complicate the nutritional and metabolic requirements and make interpretation of any experimental results difficult (Jadhav *et al.*, 2007). The presence of central venous catheters and mechanical ventilation associated with TPN may increase the incidence of late-onset sepsis in these very LBW (<1500 g) babies (Kansagra *et al.*, 2003). TPN results in deprivation of

luminal nutrition that also adversely affects the mucosal integrity and may compromise the barrier function of the neonatal gut, resulting in 'gut-derived' sepsis, and the subsequent translocation of luminal bacteria and toxins into the blood (Berg, 1995).

Rat pups are not a suitable model for studying human premature infants receiving TPN due to their immaturity. When rats have reached a BW of around 180 g (~ 60% mature BW), they can be used as a model to study gut function and epithelial regeneration following TPN after GI trauma, surgery or cancer (Jordinson *et al*., 1999). As mentioned above, piglets possess poor thermoregulatory mechanisms, have high metabolic rates and are prone to hypoglycemia, thus providing an excellent model for premature human neonates receiving TPN (Mei and Xu, 2003). Although immature at parturition, piglets have the ability to survive when delivered preterm allowing modelling of different levels of prematurity visible in human infants. Piglets can also be used with or without being given colostrum to provide immunoglobulins (Shulman, 1993). Work with colostrum-deprived (i.e. receiving no colostrum and so immumocompromised) minipiglets was first carried out by Mehrazar and Kim (1988) who used germfree colostrum-deprived piglets delivered 3 to 5 days preterm to study the ontogeny of the immune system. Borum (1993) developed their work by using non-germfree (i.e. born and housed in non-sterile conditions), colostrum-deprived pigs as a model for studies into human TPN. This model has been further developed by Sangild *et al*. (2002), with the use of colostrum-deprived piglets with limited immunity gained via an infusion of maternal serum; they also delivered the piglets at 93% of gestation (i.e. 8 days preterm) with a good degree of success. Pigs in a germfree (i.e. sterile) environment can be administered TPN successfully for up to 21 days (Mehrazar and Kim, 1988; Borum, 1993).

Apart from anything else, piglets have a large enough body size to allow the same TPN methods and procedures to be used as in humans and for regular blood sampling without significant diminution of the total blood volume. At the same time, their body size is small enough to limit experimental costs (Burrin, 2001). Pigs have the advantage of a large litter size and 2 to 3 litters per sow per year (Pond and Mersmann, 2001) making repeat experiments easily achievable, and reducing, to some extent, genetic influences. A typical TPN solution (energy content 1.67 kJ/ml) is usually administered with 20% lipid emulsion (8.36 MJ/l) (Hyde *et al*., 2008). One factor important to emphasize is that premature piglets, as with premature human babies, are prone to fluid retention and so infusion rates must be altered accordingly (Hyde *et al*., 2008) by gradually stepping up the infusion rates over the first 24 h of life. Infusion rates also differ between piglets delivered by Caesarean section (112 days of gestation) and vaginally at term (115 days) (Hyde *et al*., 2008 and 2010).

Over the last two decades the newborn piglet has proved to be a good model for studying: (i) calcium metabolism (Draper *et al*., 1991); (ii) growth and development of the gut and gut barrier function (Burrin *et al*., 1991; Van Aerde *et al*., 1997; Kansagra *et al*., 2003); (ii) the immune system (Mehrazar and Kim, 1988); (iv) amino acid metabolism (House *et al*., 1997 and 1998); and (v) non-alcoholic fatty liver disease (Hyde *et al*., 2005) in TPN-fed human infants. More recently, the effects of the fatty acid composition of the lipid emulsion on fatty acid profiles of tissues from Caesarean-sectioned delivered piglets has shown that the fatty acid composition of key tissues mirrors the fatty acid profile of the lipid emulsion supplied (Amusquivar *et al*., 2008); this could have important consequences, particularly for neurodevelopment, in premature human babies.

Postnatal digestive physiology

The piglets' GI tract has a high degree of anatomical and physiological similarity to that of the human infant (Siggers *et al*., 2008), and their protein and lipid metabolism are comparable with humans (Canavan *et al*., 1997; Davis *et al*., 2008). Therefore, pigs are an accepted and extensively used model for specific types of nutritional studies (Moughan and Rowan, 1989; Spurlock and Gabler, 2008). For example, pigs have been used to study protein digestion in human infants (Darragh and Moughan, 1995; Lin *et al*., 2009); digestibility of dietary amino acids (Rowan *et al*., 1994; Wu, 1998; Reeds and Burrin, 2000) and the effect of infant milk formulas on organ development and digestive enzyme activities (Moughan *et al*., 1990 and 1992). A review of the pig as an experimental model for elucidating the mechanisms governing dietary influence on mineral absorption has recently been published by Patterson *et al*. (2008), and so this aspect of digestion will not be considered herein.

Another area of interest is the effect of dietary fats on the growth and development of the human infant, particularly the brain (Innis, 2004). Piglets undergo a growth spurt in the brain at a similar time as that observed in humans; the porcine brain is relatively well developed at birth, having achieved 38% of its adult brain weight (Pond *et al*., 2002). This growth spurt is accompanied by subcutaneous lipid accumulation and research shows that the fatty acid profile of the nutrients supplied to the developing piglet postnatally can influence the fatty acid profile of the brain and other tissues (Amusquivar *et al*., 2008; Hyde *et al*., 2008). Hence, the piglet is an excellent model for the studies on fatty acid metabolism during the perinatal period (Purvis *et al*., 1982; Laws *et al*., 2009).

In addition to the physiological changes associated with the transition from the intrauterine to extrauterine environment, pig and human infants both are also prone to diarrhoea. Diarrhoea during this phase of development is usually associated with rotavirus and *Escherichia coli*, although Coronavirus (Transmissible Gastroenteritis) and *Clostridium perfringens* type C also cause enteritis in pigs. The beneficial effect of the probiotic lactic acid bacteria in human or animal health has interested scientists over the last century. Probiotics are essentially 'living microorganisms which favourably influence the health of the host by improving the indigenous microflora' (Fuller, 1989). The World Health

Organization (WHO, 2002) defines them as 'live microorganisms which, when administered in adequate quantities, confer a health benefit to the host'. Positive health effects may also be obtained by 'prebiotics' – non-digestible substances that increase the growth or the activity of specific microorganisms in the gastro-intestinal tract. Potential effects of prebiotics and probiotics include increased nutritional value of food due to improved digestibility and absorption, improvement of the immune system, and prevention of intestinal tract infections, cancer, atherosclerosis and osteoporosis (Ziemer and Gibson, 1998; Gill and Guarner, 2004).

Necrotizing enterocolitis (NEC) is a medical condition primarily seen in premature infants in which portions of the bowel undergo necrosis, and this condition has been investigated using Caesarean-delivered preterm pigs as a model for premature human infants (Sangild, 2006). A probiotic-containing formula can reduce the severity of NEC in this model. Probiotic administration immediately after birth appears to promote the colonization of a beneficial commensal microbiota capable of limiting the formula-induced mucosal atrophy, dysfunction, and pathogen load in preterm neonates, thereby reducing the incidence and severity of NEC (Siggers *et al*., 2008).

Weaning piglets at an age of 3 to 5 weeks changes the flora, morphology and function of the porcine intestine (Nabuurs, 1998). The effectiveness of feeding probiotic (*Bifidobacterium lactis* HN019 concentration 10^8 cfu/mL) against naturally acquired enteric infectious diseases caused by rotavirus and *E. coli* has been studied using a piglet model (Shu *et al*., 2001). Results suggest that diarrhoea was significantly reduced in probiotic-administered weanlings. It is of interest to note that the reduction in the incidence and severity of diarrhoea in neonatal and weanling pigs receiving probiotics is comparable, further supporting the pig as a good model for neonatal GI infection in human infants (Figure 3).

Alternative animal models have been used, for example probiotics have been shown to reduce bacterial infection in the acute pancreatitis rat model, the major advantage of this model is that it resembles the human to such an extent that bacteriologic results, reaction to treatment and disease course can all be predicted (Van Minnen *et al*., 2007). Supplementation with *Bifidobacterium infantis* in the rat model resulted in intestinal colonization and a significant reduction in intestinal colonization and a significant reduction in the incidence of necrotising enterocolitis in comparison to the controls (Caplan *et al*., 1999). However, due to the small size of the rat, the tissues samples obtained are also small and often require pooling.

It is well documented that diet modulates immune functions in different ways and affects host resistance to infections. In addition to the essential nutrients, non-digestible carbohydrates such as inulin (IN) and oligofructose (OF) modulate the systemic immune system (Seifert and Watzl, 2007). IN and OF are classified as prebiotics, which occur naturally as plant storage carbohydrates in vegetables, cereals and fruits. Results from human intervention studies suggest that the intake of IN and OF has beneficial effects on

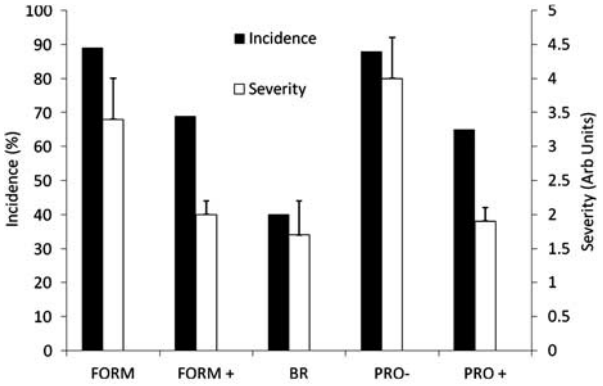

Figure 3 The incidence and severity of diarrhoea as influenced by breast (colostrum) milk (BR), milk formula (FORM) and milk formula with probiotics (FORM+) in caesarean-delivered preterm pigs and weaned pigs orally administered either a placebo (PRO−) or probiotic (PRO+). Values are presented as means for incidence & mean ± s.e.m. for severity. FORM+ = *Bifidobacterium animalis* and *Lactobacillus: L. acidophilus, L. casei, L. pentosus, L. plantarum.* PRO+ = *Bifidobacterium lactis* HN019 (10^9 colony-forming units (cfu)/piglet per day). Caesarean-delivered preterm pigs data adapted from Siggers *et al.* (2008). Weaned pigs data adapted from Shu *et al.* (2001).

the gut-associated lymphoid tissue. Both porcine and rat models have demonstrated similar anti-inflammatory changes in the gut-associated lymphoid tissue as those observed in humans and give more insight into the immune tissue-specific effects of IN and OF (Roller *et al*., 2004; Seifert and Watzl, 2007). More recently an *in vitro* dynamic model to simulate porcine ileal digestion (Meunier *et al*., 2008) has been developed, but the potential benefits of using a similar system to investigate the effects of probiotics/prebiotics remains to be established.

Ulcers

Damage to the human GI tract can be caused by a number of different conditions such as repeated use of non-steroidal anti-inflammatory drugs (NSAID) or surgery due to cancer and other GI tract-related diseases. Bleeding peptic ulcers remain a major cause of upper-GI bleeding (Laine and Peterson, 1994) and although endoscopic haemostasis is now the primary treatment for bleeding peptic ulcers (Sacks *et al*., 1990; Cook *et al*., 1992) there remains a subgroup of patients with bleeding who are not amenable to endoscopic control, and in this cohort salvage surgery carries a mortality of ~25% (Rockall, 1998).

The pig provides a good model for testing the efficacy and safety of new endoscopic equipment before clinical trials (Hu *et al*., 2004). A feasibility study using a porcine model for endoscopic plication of massively bleeding peptic ulcer by using the Eagle Claw VII device has recently been conducted (Chiu *et al*., 2006). Although this model simulated bleeding ulcers with a large vessel at the base, the chronicity of such an ulcer could not be reproduced primarily because it is often matted with hard and fibrotic tissue (Hu *et al*., 2005). Consequently, although the authors suggest that the Eagle Claw VII provides a feasible and reliable technique in achieving

endoscopic plication on bleeding peptic ulcers, it remains to be established whether a needle of the Eagle Claw VII device would be able to penetrate such ulcer (Chiu *et al*., 2006).

A non-survival porcine model that simulates acute peptic ulcer bleeding has recently been established that can be used to develop future endoscopic therapies and for training purposes (Chen *et al*., 2008). Similarly, a porcine model is currently being used to investigate the possible role of high-intensity focused ultrasound in the treatment of acute peptic ulcer haemorrhage (Marks *et al*., 2006).

Many unresectable primary (gastric, duodenal, pancreatic) or metastatic (colorectal, renal, etc.) malignancies can cause gastric outlet and duodenal obstruction in humans (Alam *et al*., 2003; Cogliandolo *et al*., 2004; Mittal *et al*., 2004). Moreover, open surgery for palliation of this obstruction is associated with high morbidity and mortality (DeMaria *et al*., 2002; Reed *et al*., 2003). Although the laparoscopic approach is less traumatic than open surgery, the laparoscopic creation of a gastrojejunostomy is technically difficult, requires extensive surgical and laparoscopic skills, and is associated with numerous complications, primarily anastomotic stricture (3.1% to 8.8%) and leak (1.2% to 3.0%) (Hamad *et al*., 2003; Sundbom and Gustavsson, 2004). The safety and feasibility of transgastric endoscopic gastrojejunostomy, with survival, has recently been studied in a porcine model, and has demonstrated the potential advantages of this procedure in comparison with surgical or laparoscopic gastroenteric anastomosis. Benefits include minimal invasiveness, no need for an anterior abdominal wall and skin incisions, thereby eliminating the risk of skin wound infection and post-operative hernias (Kantsevoy *et al*., 2005). A common treatment for gastric cancer is a resection; the pig has been effectively used to study an endoscopic full-thickness resection with sutured closure before clinical trials (Ikeda *et al*., 2005).

As mentioned earlier, humans often suffer GI diseases following repeated daily enteral administration of NSAID, but it is often difficult to study certain regions of the GI tract for example, the proximal regions of the large intestine using routine endoscopic investigations. A pig model has successfully been developed to assess the resultant damage to the GI tract from long-term use of NSAID (Rainsford *et al*., 2003).

Renal physiology

In the past canines have been successfully used as a large animal model for kidney investigative work. The larger animals are often selected as their size makes arterial catheter navigation easier; pigs have the additional benefit over dogs of possessing kidneys which are similar in anatomy and physiology to the human kidney (Yokota *et al*., 1985; Tumbleson and Schook, 1996). Similar to humans, the porcine kidney is multipyramidal with an undivided cortex and has several different medullary structures. Each medullary pyramid forms a separate papilla and fusion results in the formation of some compound papillae. The rat kidney has a single papilla, and the medulla and cortex are undivided. Pig and Man have similar maximal urine concentration (pig 1080 and man 1160 mOsmol/l), maximal urine-to-plasma osmolal ratio (pig 3.7 and man 4.0), glomerular filtration rate (pig 130 and man 126 to 175 ml/min per 70 kg) and total renal blood flow (pig 4 and man 3.0 to 4.4 ml/min per g; Sachs, 1994).

When atherosclerosis causes stenosis or an abnormal narrowing of blood vessels, the pig has been successfully used to study not only atherosclerosis but also renal artery stenosis. Angioplasty (widening of the blood vessel) work has been completed using magnetic resonance to guide the procedure and while the authors state that the work is preliminary, these authors believe that future hardware, and software advances will improve the performance of the procedures further (Omary *et al*., 2006; Park *et al*., 2007a and 2007b).

Swine have also been shown to be an excellent model for urological studies, including the formation of renal calculi (Borden and Vermeulen, 1966; Assimos *et al*., 1986; Terris, 1986). Papillary calcifications have been induced in pigs fed oxamide (Borden and Vermeulen, 1966) and the implantation of kidney stones into pig kidneys has been used as a model for lithotripsy research (Paterson *et al*., 2002). To-date the rat has been used as the main reproducible animal model of calcium oxalate crystalluria and urolithiasis. However it is desirable to have an animal model, such as the pig, of oxaluria and urolithiasis with physiological, anatomical and nutritional characteristics that more closely resemble man. It has been shown that feeding pigs trans-4-hydroxy-l-proline causes hyperoxaluria and calcium oxalate crystalluria in which calcium oxalate papillary deposits form that may be precursors of kidney stones (Mandel *et al*., 2004). Consequently, further development of the pig as a model of human hyperoxaluria and stone formation should be successful for studying these human diseases.

Bones

Bones and osteoporosis

Osteoporosis is a multigenic complex disorder. Though the mouse and rat are used as experimental models for human osteoporosis, the pig bone remodelling cycle is histologically more similar to human than the rat or mouse. Moreover, livestock genomics have many advantages over model organisms and human studies for complex trait dissection (Onteru *et al*., 2008). In addition to other features mentioned elsewhere in this review, the reproductive cycle of the pig is similar in duration to the human (18 to 21 days) and is continuous, also like the human (Turner, 2001).

A syndrome of spontaneous vertebral fracture has been reported in the pig, a rarity in the animal world (Spencer, 1979), pigs are large enough to receive prosthetic implants, withstand serial bone biopsies and large volumes of blood sampling (Turner, 2001). The rate of bone removal and deposition of the trabecular and cortical bone is also similar to that observed in humans (Mosekilde *et al*., 1993b). A porcine model has also been used to evaluate the initial fixation strength of a biodegradable interference screw in

anterior cruciate ligament reconstruction using a bone-patellar tendon-bone graft (Seil *et al*., 1998; Walsh *et al*., 2009).

Findings suggest that the Sinclair Si minipig fed a 0.75% calcium restricted diet may be a good model to study the bone remodelling and perimenopausal bone loss in women when an ovariectomy is performed (Mosekilde *et al*., 1993a and 1993b; Boyce *et al*., 1995). Lafage *et al*. (1995) have also used minipigs to investigate bone active agents such as sodium fluoride, assessed on bone quality and remodelling. Dynamic ^{18}F-fluoride ion positron-emission tomography (PET) has demonstrated that porcine bone loss after total gastrectomy is related to a high-turnover bone disease without associated changes in bone blood flow. It is thought that the increased bone metabolism observed in minipigs is probably related to an elevated parathyroid hormone secretion, thus maintaining serum calcium homeostasis at the expense of the bone mineral content. Normalizing bone metabolic activity by the specific bone mass increases the sensitivity in the detection of osteopenic high turnover bone diseases. Therefore, the combination of quantitative computed tomography and ^{18}F-fluoride ion PET seems to be the method of choice for the classification of metabolic bone diseases and for monitoring treatment effects quantitatively (Piert *et al*., 2003).

Dental research

Since the tooth structure of the Prestige World Genetics (PWG) Micro-pig® closely resembles that of human more than any other species, the pigs are valuable in dental research. Adult stem cells originated from pulp show that new dental material can be created and implanted. As the size of the Micro-Pig® jawbone is as thick as humans, these pigs are frequently used in dental surgery, especially in the testing of dental implants and the use of dental stem cells to grow new teeth (PWG Genetics Korea, 2006; Mantesso, 2008).

By examining the ontogeny of porcine enamel our understanding of human enamel deposition and maturation has been significantly improved (Robinson *et al*., 1987 and 1988; Kirkham *et al*., 1988). Work has been completed on implants in pigs to consider loading, however caution needs to be used here as porcine bone remodels slightly faster than human bone. That noted this work provides a valuable insight into micro damage strains following implants (Ko *et al*., 2002 and 2003). A novel device for a bite force measurement system in a porcine model has recently been described (Bousdras *et al*., 2006) which enables the biomechanical adaptation of the bone-implant interface to masticatory loads to be assessed with either natural dentition or single implant crowns.

Conclusions

In conclusion, the pig is an extremely useful biomedical model for improving our understanding of the pathophysiology and for investigating potential treatment/prevention strategies under rigorously controlled conditions for many human diseases and ailments. The optimum porcine model to use is often dependent on the specific disease being studied. For example, the domestic pig can be used to study developmental programming due to the natural variation in BW within a litter, while the minipig is considered the best breed for investigation on the metabolic syndrome. Pigs provide a valuable translational model to bridge the gap between classical rodent models and humans in developing new therapies to aid human health.

Acknowledgements

The authors would like to thank Dr Colin Litten-Brown for his assistance in the preparation of this manuscript.

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