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 in the examination of pathophysiology and prevention/treatment of microbial-associated diseases and immune system disorders. A pig 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.
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. adipin, 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 characteristics and husbandry requirements, which must be taken into consideration when used as a laboratory animal (Swindell 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         | Domestic       | Minipig        | Rats           | References     |
| 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| Central Intelligence Agency (CIA) (2008) |
| Life expectancy                 | 70 years       | 25 years in wild| –              | 1 to 3 years   |                |
| 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          | –              | Similar¹       | Not similar¹   | Not similar¹   | 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                 | –              | Similar¹       | Not similar¹   |                | PWG Genetics Korea (2006) |
| Middle ear                      | –              | Similar¹       | Not similar¹   |                | Pracy et al. (1998) |
| Skin                            | –              | Similar¹       | Similar¹       |                | Bronaugh et al. (1982), Avon and Wood (2005) |
| Sweat glands                    | Apocrine and eccrine | Apocrine only   | Apocrine only  |                | Monteiro-Riviere (2005) |
| Atherosclerosis                 | –              | Similar¹       | Not similar¹   |                | Buettnier et al. (2007), Oron-Herman et al. (2008) |
| Kidney structure and function   | –              | Similar¹       | Not similar¹   |                | Sachs (1994) |

¹Similarity compared to humans.
<table>
<thead>
<tr>
<th>Model</th>
<th>Comments regarding swine model</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>Ossabaw minipig and Pietrain preferred as they exhibit obesity, insulin resistance and hypertension not seen in other breeds</td>
<td>See below</td>
</tr>
<tr>
<td>Developmental programming</td>
<td>Domestic pig preferred due to 2- to 3-fold variation in BW among littersmates (e.g. Large White)</td>
<td>Hoet and Hanson (1999), Clarke et al. (2000), Poore and Fowden (2003), 2004a and 2004b, Corson et al. (2009)</td>
</tr>
<tr>
<td>Placental and foetal growth and development</td>
<td>Pigs have epithelial chorial placentas allowing easy dissection</td>
<td>Tayade et al. (2005)</td>
</tr>
<tr>
<td>Maternal environment and foetal development</td>
<td>Little work done in the area; theoretically should give similar results to humans</td>
<td>Schoknecht et al. (1993 and 1994), Wu et al. (1999)</td>
</tr>
<tr>
<td>Size and shape at birth as indicator of health in later life.</td>
<td>Some studies done but only for Large White × Landrace.</td>
<td>Bauer et al. (1998), Corson et al. (2008a)</td>
</tr>
<tr>
<td>Cardiovascular disease: atherosclerosis</td>
<td>Atherosclerosis induced in domestic pig without other signs of metabolic syndrome</td>
<td>Gerrity et al. (2001), McDonald et al. (2007)</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Yucatan minipig shows good arterial response after balloon angioplasty even though it fails to exhibit insulin resistance and obesity</td>
<td>De Smet et al. (1998).</td>
</tr>
<tr>
<td>Obesity</td>
<td>Ossabaw minipig as atherogenic diet induces three or more signs of metabolic syndrome</td>
<td>Johansen et al. (2001), Spurlock and Gabler (2008)</td>
</tr>
<tr>
<td>Therapeutic angiogenesis</td>
<td>Minipig has similar coronary anatomy &amp; heart to body ratio to that of humans</td>
<td>Hughes et al. (2003 and 2004)</td>
</tr>
<tr>
<td>Collagen changes in the heart during hypertrophic cardiomyopathy</td>
<td>See above</td>
<td>Liu et al. (1994), Chiu et al. (1999)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>Pigs similar to humans for diabetes-induced accelerated atherosclerosis</td>
<td>Ruiz et al. (1997)</td>
</tr>
<tr>
<td>NIDDM</td>
<td>Pigs have similarities in structure and function of pancreas and pharmacokinetics following administration of trial drugs</td>
<td>Larsen and Rolin (2004)</td>
</tr>
<tr>
<td>Insulin dependent diabetes mellitus</td>
<td>Swine have physiological and anatomical similarities to humans</td>
<td>Larsen and Rolin (2004), Xi et al. (2004)</td>
</tr>
<tr>
<td>Digestive physiology and metabolism</td>
<td>Minipiglets can survive when delivered preterm &amp; can be used colostrums-deprived</td>
<td>See below</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>Piglet’s GI tract has high anatomical and physiological similarity to humans</td>
<td>Borum (1993), Mehrazar and Kim (1988), Sangild et al. (2002), Hyde et al. (2008)</td>
</tr>
<tr>
<td>Effects of dietary fat on brain growth</td>
<td>Fatty acid profile of nutrients supplied to piglet influences fatty acid of tissues</td>
<td>Purvis et al. (1982), Lounsbery et al. (2009)</td>
</tr>
<tr>
<td>Fatty acid metabolism</td>
<td>Piglets like human infants are prone to diarrhoea</td>
<td>Shu et al. (2001), Meunier et al. (2008), Siggers et al. (2008)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Responses to probiotics similar in piglets and human infants</td>
<td>Shu et al. (2001), Sangild (2006), Meunier et al. (2008), Siggers et al. (2008)</td>
</tr>
<tr>
<td>Pre- and probiotics</td>
<td>Similar size of GI tract</td>
<td>Hu et al. (2004)</td>
</tr>
<tr>
<td>Testing of endoscopic equipment</td>
<td>Different techniques under investigation with some success but needs development</td>
<td>Hu et al. (2005), Ikeda et al. (2005), Chiu et al. (2006), Marks et al. (2006), Chen et al. (2008)</td>
</tr>
<tr>
<td>Ulcers</td>
<td>Limited at present as pigs used in one specific study only</td>
<td>Kantsevoy et al. (2005)</td>
</tr>
<tr>
<td>Topic</td>
<td>Description</td>
<td>References</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gastric cancer resection</td>
<td>Limited at present as pigs used in one specific study only</td>
<td>Ikeda et al. (2005)</td>
</tr>
<tr>
<td>GI tract damage through repeated use of non-steroidal anti-inflammatory drugs</td>
<td>Limited at present as pigs used in one specific study only</td>
<td>Rainsford et al. (2003)</td>
</tr>
<tr>
<td>Renal physiology</td>
<td>Kidneys similar in structure and function to humans</td>
<td>Borden and Vermeulen (1966), Assimos et al. (1986), Terris (1986), Paterson et al. (2002)</td>
</tr>
<tr>
<td>Bones</td>
<td>Pig bone remodelling is histologically more similar to human than rat or mouse</td>
<td>See below</td>
</tr>
<tr>
<td>Bones and osteoporosis</td>
<td>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</td>
<td>Spencer (1979), Mosekilde et al. (1993b), Boyce et al. (1995), Turner (2001), Tye et al. (2006), Walsh et al. (2009)</td>
</tr>
<tr>
<td>Dental research</td>
<td>PWG micro-pig® has a tooth structure which closely resembles that of humans</td>
<td>Robinson et al. (1987), Kirkham et al. (1988), Ko et al. (2002 and 2003), Bousdras et al. (2006), PWG Genetics Korea (2006), Mantesso (2008)</td>
</tr>
<tr>
<td>Examples of other models</td>
<td>The similar morphology of pigs to humans make them useful in many applications</td>
<td>Lunney (2007), Nunoya et al. (2007)</td>
</tr>
<tr>
<td>Xenotransplantation and hyperacute organ rejection</td>
<td>Transgenic pigs and minipigs used modified for research use</td>
<td>Fodor et al. (1994), Yamada et al. (2005)</td>
</tr>
<tr>
<td>Developmental immunology</td>
<td>Sinclair minipigs demonstrate cutaneous melanoma with a histopathology similar to humans</td>
<td>Rothkotter et al. (2002)</td>
</tr>
<tr>
<td>Wound healing</td>
<td>Pig skin very similar to human skin</td>
<td>Cynthia and Smith (2000)</td>
</tr>
<tr>
<td>Dermatoxicology</td>
<td>Pig skin has similar general morphology of skin to humans</td>
<td>Lavker et al. (1991), Svendsen (2006)</td>
</tr>
<tr>
<td>Infectious disease models</td>
<td>Pig skin has many physiological similarities to human skin</td>
<td>Gonzalez et al. (2004), Dawson et al. (2005), Elahi et al. (2005), Hassung et al. (2005), Houdebine (2005), Pomeranz et al. (2005), Butler et al. (2006), Cheetham et al. (2006), Dvorak et al. (2006), Lunney (2007)</td>
</tr>
<tr>
<td>Respiratory function</td>
<td>Minipigs have been demonstrated to be useful in the evaluation of respiratory response and disease</td>
<td>Koch et al. (2001), Turner et al. (2002), Watremez et al. (2003)</td>
</tr>
<tr>
<td>Biomechanical models</td>
<td>Similarity in size of pigs to humans facilitates use for the analysis of injury and for the development of imaging techniques</td>
<td>Ellner et al. (2004), Goldberg et al. (2004), Schmitt and Snedeker (2006)</td>
</tr>
<tr>
<td>Brain function</td>
<td>Limited use of minipigs in the examination of brain structure and disease</td>
<td>Minuzzi et al. (2005), Tambuyzer and Nouwen (2005), Imai et al. (2006)</td>
</tr>
<tr>
<td>Defects if growth hormone releasing hormone</td>
<td>Studies have used pigs to examine hypochondroplasia, intrauterine growth restriction, Crohn’s disease, renal insufficiency and Turner syndrome</td>
<td>Kues and Niemann (2004)</td>
</tr>
<tr>
<td>Human decompression sickness</td>
<td>Limited at present as pigs used in one specific study only</td>
<td>Reuter et al. (2000)</td>
</tr>
<tr>
<td>Ageing of bite marks for use in forensic science</td>
<td>The similarities between human and pig skin make it an ideal model</td>
<td>Avon and Wood (2005)</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>Pigs demonstrate similar responses to alcohol as seen in humans</td>
<td>Nakamura et al. (1992), Halsted et al. (2002)</td>
</tr>
</tbody>
</table>

*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 vitelline 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 |
|----------------------|------------------|------------------|------------------|------------------|------------------|
| Type of placenta     | Humans           | Swine            | Rats             |
| Glucose transfer     | Occurs           | Occurs           | Occurs           |
| Amino acids          | Occurs           | Occurs           | Occurs           |
| NEFA                | Occurs           | Occurs           | Occurs           |
| Immunoglobulins      | Occurs           | Does not occur   | Occurs           |
| Amino acid composition in utero | = 19 g/kg BW/day | = 19 g/kg BW/day | = 19 g/kg BW/day |
| Protein accretion rates | = 13 g/kg BW/day | = 13 g/kg BW/day | = 13 g/kg BW/day |
| Maturity at birth    | Precocious       | Precocious       | Precocious       |
| Adipose tissue (%)   | 0.62             | 1.19             | 1.51             |
| Postnatal energy metabolism |
| Total available lipid (g/kg BW) | 1.50 (0.50)* | n/a              | n/a              |
| Total available hepatic glycogen (g/kg BW) | 3.78 (0.57)* | n/a              | n/a              |
| Heat production (kJ/kg per kg) | 6.9 (5.9)* | n/a              | n/a              |

NEFA = non-esterified fatty acids.
*Values in brackets are for premature human infants.
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 (Kno 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., 2005).

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 (Goldsink 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). Supplemeting 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). Supplemetning the maternal diet with sunflower oil during the first half of gestation resulted in a greater proportion of LBW piglets (20 ± 3%), whereas supplementing with olive oil reduced the incidence of LBW offspring (5 ± 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 un-supplemented 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 biomedicai 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 (~ 8% and 6%, respectively; Laws et al., 2008) than human milk (4% and 1%, respectively; Mitoula 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 (~ 4%) compared to human milk (~ 6%) (Mitoula 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 monotonous 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). Centile 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).

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 hypothalamic–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

<table>
<thead>
<tr>
<th>Diet</th>
<th>Chinese Guangzhou minipigs</th>
<th>Ossabaw minipigs</th>
<th>Domestic Gottingen minipigs</th>
<th>Yucatan clubhouse minipigs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>15% Lard and 15% cholesterol</td>
<td>Yes</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Gerrity et al. (1983), Johansen et al. (2001), Larsen et al. (2002b), Christoffersen et al. (2007)</td>
</tr>
<tr>
<td>55% energy from fat and 2% cholesterol for 5 weeks</td>
<td>Yes</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Xi et al. (2004), Yin et al. (2004), De Smet et al. (1998)</td>
</tr>
<tr>
<td>45% energy from fat and 2% cholesterol for 9 weeks</td>
<td>Yes</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Dyce et al. (2006)</td>
</tr>
<tr>
<td>42% starch; 37% sucrose with only 16% energy from fat but with 2% cholesterol for 6 months</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yassala et al. (2001), Johansen et al. (2002b), Christoffersen et al. (2007)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Not determined</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Garry et al. (2011), McDonald et al. (2007)</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Not determined</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Garry et al. (2011), McDonald et al. (2007)</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>Not determined</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Garry et al. (2011), McDonald et al. (2007)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Not determined</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Garry et al. (2011), McDonald et al. (2007)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Not determined</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Garry et al. (2011), McDonald et al. (2007)</td>
</tr>
<tr>
<td>Atherosclerotic lesions</td>
<td>Not determined</td>
<td>Yes</td>
<td>Not determined</td>
<td>Yes</td>
<td>Garry et al. (2011), McDonald et al. (2007)</td>
</tr>
</tbody>
</table>

Yes indicates whether the animal expresses diseases.
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).

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

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 gestation, 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 (Jordonson 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 immunocompromised) 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); (iii) the immune system (Mehrazar and Kim, 1998); (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 extraterine environment, pig and human infants both are also prone to diarrhea. 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 Guermer, 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 communal 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 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 (Chenet 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 laparo-
scopic creation of a gastrojejunostomy is technically difficult,
requires extensive surgical and laparoscopic skills, and is
associated with numerous complications, primarily anastomo-
static 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 gastro-
jejUNostomy, with survival, has recently been studied in a
porcine model, and has demonstrated the potential advan-
tages 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 suc-
cessfully 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 navi-
gation easier; pigs have the additional benefit over dogs of
possessing kidneys which are similar in anatomy and physiol-
ology to the human kidney (Yokota et al., 1985; Tumbleson
and Schook, 1996). Similar to humans, the porcine kidney is multi-
pyramidal 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 osmolar 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 pre-
liminary, 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
oxamid (Borden and Vermeulen, 1966) and the implanta-
tion 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). Conse-
quently, 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
(Onterus 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 18F-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 18F-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 remodelling 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.

References
Papers 147, 155–159.

The pig as a biomedical model


The pig as a biomedical model


Kues WA and Niemann H 2004. The contribution of farm animals to human diabetes, with special focus on Type 1 diabetes research. ILAR Journal 45, 302–313.


Larsen MO and Rolin B 2004. Use of the Göttingen minipig as a model of diabetes, with special focus on Type 1 diabetes research. ILAR Journal 45, 302–313.


Meschia M 1982. The function of the placenta as it relates to the transport of metabolic substrates to the foetus. In Biochemical development of the foetus and neonate (ed. CT Jones), pp. 495–513. Elsevier Biomed Press, Amsterdam, NL.

Metges CC 2005. Long-term effects of pre and postnatal exposure to low and high dietary protein levels. Evidence from epidemiological studies and controlled animal experiments. Advances in Experimental Medicine and Biology 569, 64–68.


Schlamowitz M 1976. Membrane receptors in the specific transfer of immunoglobulins from mother to young. Immunological Investigations 5, 481–500.


Shulman R 1993. The piglet can be used to study the effects of parenteral and enteral nutrition on body composition. Journal of Nutrition 123, 395–398.


