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Chapter 15

Biology and Diseases of Swine

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I. INTRODUCTION

Swine have been increasingly used in biomedical research both as general large-animal biological models in teaching and research, and for the study of specific disease conditions due to their anatomic and physiologic characteristics (Swindle, 1998). Textbooks specific to the use of swine as laboratory animals are available (Swindle, 1998, 1983; Stanton and Mersmann, 1986; Bollen, Hansen, and Rasmussen, 2000). Proceedings books from symposia on the use of swine in research are also available (Swindle, 1992; Tumbleson, 1986; Tumbleson and Schook, 1996).

A. Taxonomy

Order: Artiodactyla (even-toed ungulates)
Family: Suidae
Species: *Sus scrofa domestica*

B. Availability and Sources

Commercial breeds of domestic swine raised for meat production are readily available worldwide. There is a wide variability in the health status of the various herds. In the United

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States the designation SPF (specific pathogen–free) has a proprietary connotation. It is a program based on management procedures that reduce or eliminate diseases that stunt growth. Pigs designated SPF are a good source for biomedical research; however, it must be remembered that the designation does not mean that the animals are completely free of diseases that may interfere with research. It is best to buy animals from a herd in which the institutional veterinarian has screened for complicating diseases. Commercial breeds have limited availability from commercial suppliers of laboratory animals (Saffron and Gonder, 1997; Swindle *et al.,* 1994).

When using domestic breeds of swine, the growth factors are a major consideration. Swine reach sexual maturity and a commercial slaughter weight of approximately 250–280 kg at 5–6 months of age. At birth, swine weigh approximately 3 kg (average); consequently, there is an exponential growth phase during the adolescent period. Most swine used in research programs are 15–30 kg and are 8–12 weeks of age. Weight gain during this period may be 2–5 kg per week. When selecting a model, the age and maturity factors must also be considered. Consequently, domestic swine are rarely used for long-term projects unless the study includes the effect of growth and maturity factors or the animals are involved in agricultural research. Generally, most projects involving a length of > 3 weeks would best be performed in miniature swine (Swindle, 1998; Swindle *et al.,* 1994; Fisher, 1993).

Miniature swine are available from commercial breeders of laboratory animals. Commonly used breeds include Yucatan, Hanford, Sinclair, Hormel, and Gottingen. Other breeds of miniature pigs are available in limited quantities from some market areas and include the Panepinto, Vietnamese potbellied, Ohmini, Pitman–Moore, and Chinese dwarf. Generally, the health status of these animals is higher than that of SPF animals, and they are suitable for most biomedical research projects. These animals range from 30 to 50 kg in body weight at sexual maturity and, consequently, are more amenable than larger commercial breeds to long-term projects (Swindle, 1998; Fisher, 1993; Panepinto, 1986).

C. Laboratory Management and Husbandry

Individual shipments of swine are best separated by time and distance and in particular, mixing animals from multiple vendors is poor practice. Swine should be purchased from vendor herds that are validated brucellosis-free and qualified pseudorabies-negative by the U.S. Department of Agriculture (USDA). Commercial sources typically implement a vaccination and parasite-control program beginning at weaning age and dependent on the intended experimental use of the animal, such efforts may or may not need additional attention at the research facility. Quality source herds will worm piglets at 4- to 6-week intervals and administer preventive treatments for ectoparasites. Weanling animals are commonly vaccinated against erysipelas and leptospirosis, and breeding-herd animals should be vaccinated in addition against porcine parvovirus, *Bordetella bronchiseptica, Pasteurella multocida,* and *Escherichia coli.* Newly received animals should be given a minimum of 72 hr to adjust to the new environment during which time physical exams and screening tests for parasites can be performed. Diet changes should be gradual over several days, with fiber increased if stress-induced diarrhea develops. Adult swine that are housed long-term should have, at a minimum, periodic physical exams that include weight and parasite checks. Vaccination programs for adult swine should be implemented based on risk assessment that considers how the animal will be used in research, what the housing conditions are, and how close the research herd is to new animals of uncertain health status. Ideally, pigs should be purchased from one source of established health status to take advantage of natural herd immunity. The value of good herd health management is illustrated by the observation that swine herds that maintain specific pathogen–free status have an odds ratio of 0.2 relative to that of conventional herds for the development of diarrhea (Moller *et al.,* 1998).

Swine are best housed in pens rather than cages. Pens may be constructed of either chain-link fencing or stainless steel or aluminum bars. Wood is best avoided because of pigs' ability to chew it and the difficulty of sanitation. The chosen material should be of sturdy construction because swine can be very destructive. It is best to provide them with indestructible toys or balls to preoccupy them and to satisfy their rooting instincts (Swindle, 1998).

Flooring for swine deserves special consideration. Smooth flooring, such as seamless epoxy, is best avoided. Swine have difficulty with firm footing on these floors, especially when the floors are wet. If contact flooring is used, it should either have a rough surface to provide traction and provide wear on the hooves or it should be covered with deep wood-chip bedding. Wood-chip bedding keeps swine clean and satisfies their rooting instinct. However, wood-chip bedding is eaten by swine, especially when they are fasted. Raised flooring has been found to be satisfactory in many laboratory situations. Plastic-coated metal grids are sturdy and easy to sanitize. However, if a cut becomes apparent in the plastic, swine will strip the flooring and eat the plastic. Slatted fiberglass floors with grit to provide hoof wear are generally ideal in most situations. They are lightweight and easy to remove from pens for sanitation (Swindle, 1998).

Swine readily use automatic watering systems. The system should be checked daily to ensure that the water supply is functional because swine are susceptible to "salt poisoning," which results in a neurologic syndrome when they are deprived of water. Food dishes should be secured to the cage or flooring. Swine will tip movable dishes and lose their feed, especially on raised flooring. They will also chew their feeders, which are best made of an indestructible material such as stainless steel (Swindle, 1998).

Swine prefer to have contact with other members of their species. They may be housed together in groups, but dominance fighting will occur unless animals are socialized. This social instinct may also be satisfied by providing cage walls that allow visual and snout contact between animals (Swindle, 1998; Fisher, 1993; Panepinto, 1986).

Swine can be restrained in slings, such as the Panepinto sling (Panepinto *et al.,* 1983). This method of humane restraint is preferable to agricultural methods such as snout tying. Small swine can also be restrained manually in a manner similar to that of dogs. Swine may be trained to walk on a leash and can also be restrained against the side of the cage with movable handheld panels (Swindle, 1998).

Intramuscular injections may be administered in the neck or hindlimb. Venous access sites include the following veins: auricular, cephalic, external and internal jugular, precava, lateral saphenous, cranial abdominal, and femoral (Figs. 1–9). Most of the peripheral vessels are deep and not visible; consequently, a knowledge of their anatomic location is essential. Most of the vessels can be accessed with standard-sized needles and a 20-gauge 1.5-inch needle is the largest size that will be required in swine up to 50 kg (Swindle, 1998; Bobbie and Swindle, 1986).

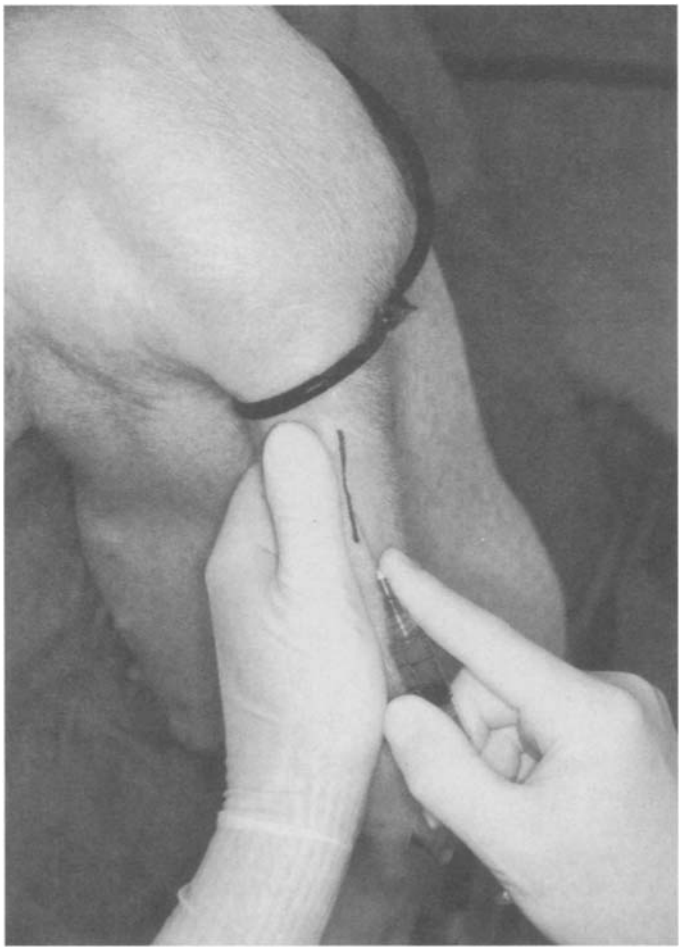

Fig. 1. Venipuncture of the cephalic vein.

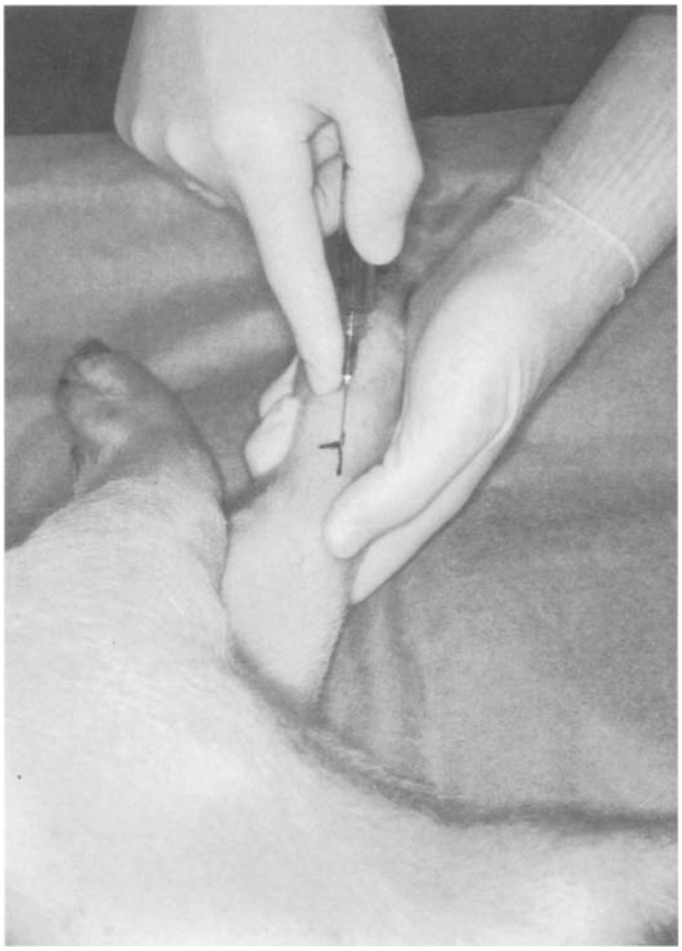

Fig. 2. Venipuncture of the digital vein.

Surgical procedures, anesthesia, and anatomy, including surgical approaches for vascular access and fistulation procedures, are described in detail in other references (Swindle, 1998).

D. Use in Research

Swine have been used mainly for research involving the cardiovascular system because of their unique anatomy and physiology, which makes them similar to humans (Swindle, 1998; Stanton and Mersmann, 1986). Cardiovascular diseases of interest include atherosclerosis, coronary arterial stenosis and infarction, congenital heart disease, volume- and pressure-overload heart failure, electrophysiology, and testing of grafts, stents, and interventional devices. Swine are uniquely susceptible to atherosclerosis, which may be induced by feeding of cholesterol and fat-enhanced diets. A more rapid form of atherosclerosis may be induced by damaging the endothelium with a

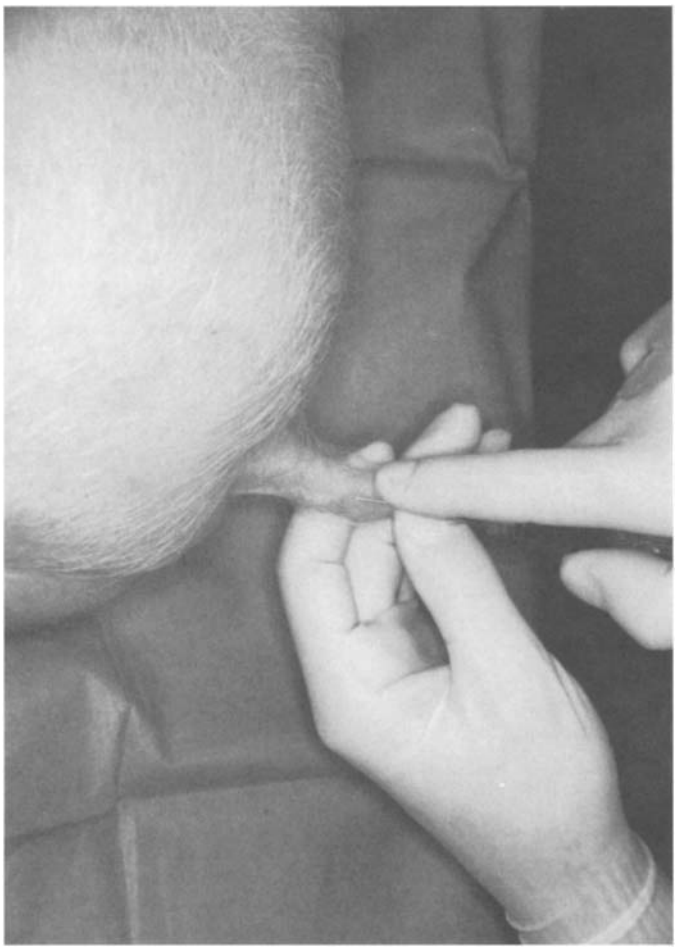

Fig. 3. Venipuncture of the tail vein.

balloon catheter. The induced form has the advantage of producing a lesion in a specific anatomic region. Genetic models of high membranous ventricular septal defect (VSD) and von Willebrand's disease are also available (Swindle *et al.*, 1996).

Nutritional and gastrointestinal models in swine are studied because of the physiology of their digestion, which is similar to that of humans, and their omnivorous diet. Areas studied include nutrient absorption and growth, gastrointestinal transport, hepatic metabolism, total parenteral nutrition, and necrotizing enterocolitis.

Renal diseases are another area of interest in research. Swine have been used in studies of renal hypertension, vesicoureteral reflux, intrarenal reflux, and urinary obstruction.

Swine have been increasingly used in research and teaching studies that involve surgery, both as a substitute for dogs and as a model based on physiologic characteristics (Swindle, 1986). Swine are the model of choice for most of the laparoscopic and endoscopic procedures because of their size and anatomy. Catheter delivery of interventional devices has also been studied extensively in swine. Transplantation research has been performed on heart, lung, liver, kidney, and viscera. The size of the organs, the surgical anatomy, and response to immunosuppressive therapy make them ideal for many of these studies. Swine are being developed as models and donors for xenotransplantation, which has included the development of transgenic strains (Swindle, 1998a). The anatomic and physiologic characteristics of the skin have made swine a definitive plastic surgical model. Swine have also been developed as models in a wide variety of other surgical procedures, including fetal surgery and procedures in the musculoskeletal, central nervous, gastrointestinal, urogenital, and cardiopulmonary systems.

Many other biological models have been developed in swine, including the areas of systemic and dermal toxicology, septic and hemorrhagic shock, immunology, diabetes, malignant melanoma, malignant hyperthermia, and gastric ulceration. An exhaustive list of all the developed and potential models in swine is beyond the scope of this chapter. Extensive reviews of that information may be found in general reference and proceedings books.

II. BIOLOGY

A. Unique Physiologic Characteristics and Attributes

References with complete descriptions of swine anatomy and physiology are available (Swindle, 1998). However, some of the unique characteristics of swine will be covered in this section.

The cardiovascular system is similar to that of humans, especially the coronary anatomy (Swindle, 1998). The blood supply from the coronary artery is right-side dominant and does not have preexisting collateral circulation. This makes the coronary blood flow situation similar to 90% of that of the human population, unlike that in other species such as the dog. The electrophysiologic system is more neurogenic than myogenic, and there are prominent Purkinje fibers. The left azygous (hemiazygous) vein drains the intercostal vessels into the coronary sinus unlike in most other species. This vessel may be ligated or blocked with a balloon catheter to provide total coronary venous drainage into the coronary sinus. The aorta has a true vaso vasorum like that of humans. Normal values for hematology and serum chemistry for Hanford miniature swine are listed in Table I, and Table II contains data on serum chemistry and urine physiology for Yucatan micropigs and domestic swine.

The gastrointestinal tract has unique anatomic characteristics (Swindle, 1998). The stomach has a muscular outpouching, the torus pyloricus, near the pylorus. The bile duct and pancreatic duct enter the duodenum separately in the proximal portion. The anatomic divisions between the duodenum, ileum, and jejunum are indistinct. The mesentery is thin and friable. The mesenteric branches form their vascular arcades in the subserosa rather than in the mesentery as in other species. The

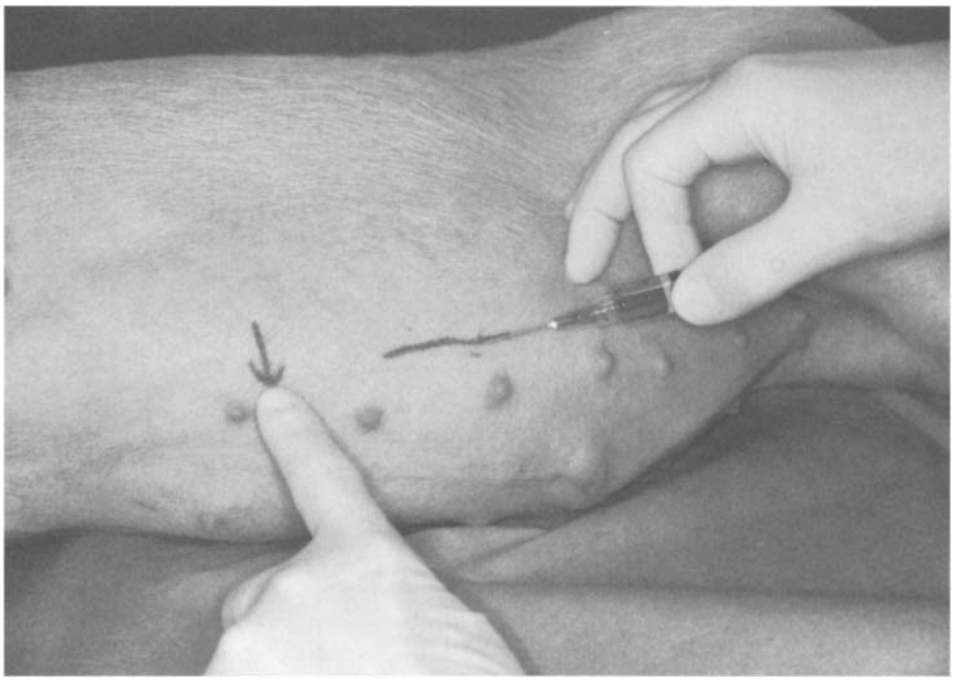

Fig. 4. Venipuncture of the mammary vein.

majority of the large intestine is arranged in a spiral colon in the left upper quadrant of the abdomen. This series of centrifugal and centripetal coils includes the cecum and ascending, transverse, and majority of the descending colon. Tenia and haustra are present on the cecum and large intestine. In spite of the anatomic differences from humans, the physiology of digestion and intestinal transport are very similar.

Other unique anatomic features need to be considered (Swindle, 1998). The lymph nodes are inverted with the germinal centers being located in the internal portion of the node. The

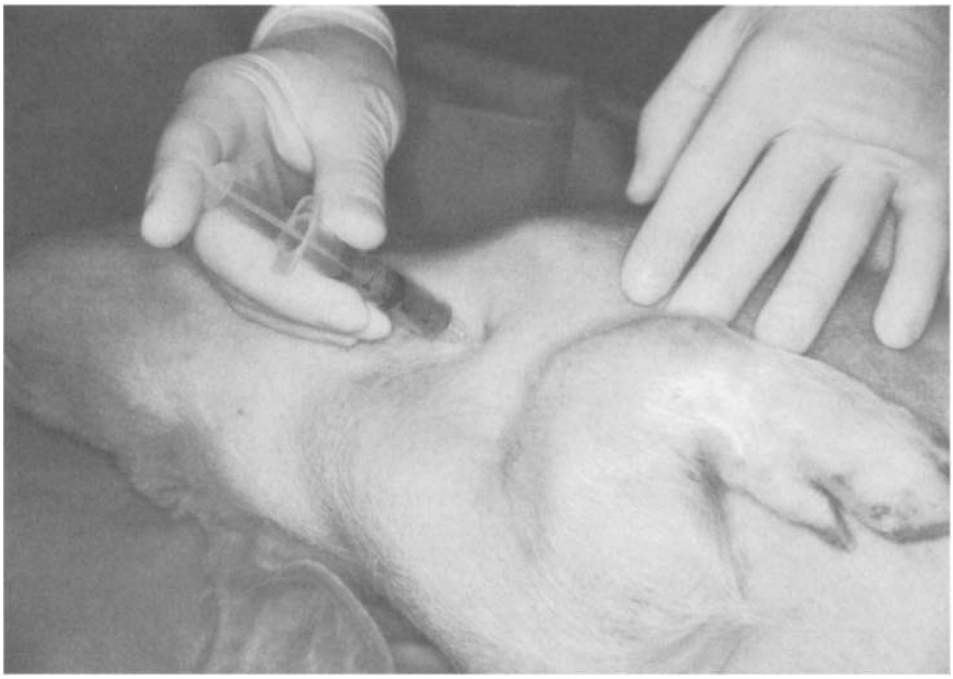

Fig. 5. Venipuncture of the anterior vena cava.

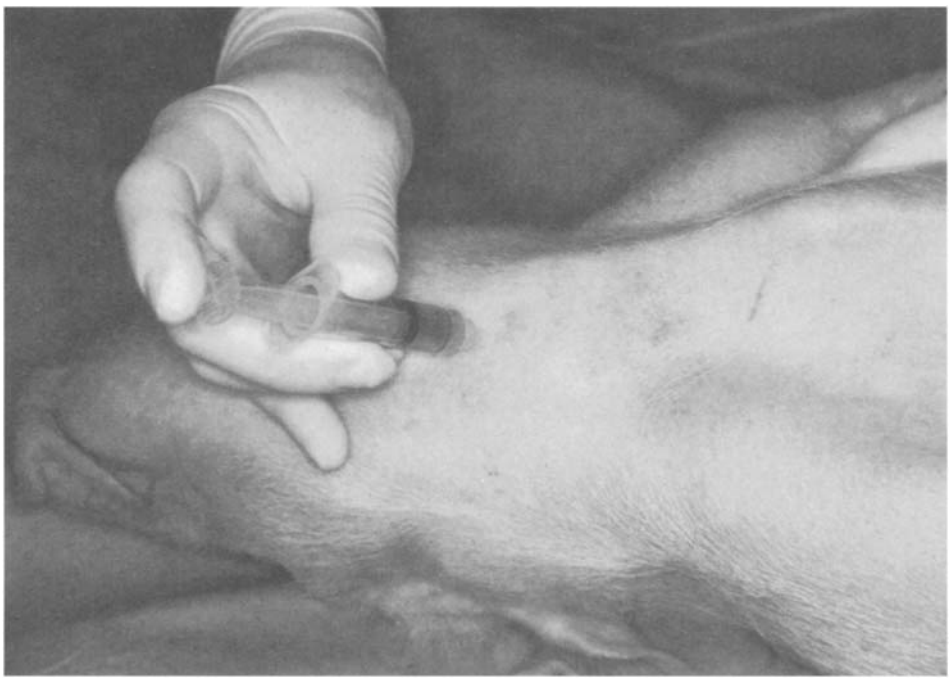

Fig. 6. Venipuncture of the external jugular vein.

thymus is located on the ventral midline of the trachea near the thoracic inlet rather than proximal to the larynx. A major portion of the thymus is located in the neck, and the single pair of parathyroid glands is located in the medial aspect of the proximal portion of this gland. The penis is fibromuscular with a corkscrew-shaped tip located in a preputial diverticulum near the umbilicus. The penis has a sigmoid flexure. The male accessory glands include the ductus deferens, prostate, vesicular gland, and bulbourethral gland. The female reproductive system is bicornuate with lengthy tortorus fallopian tubes. The pancreas is bilobed and surrounds and encompasses the superior mesenteric vein. The liver is divided into lobules by microscopic fibrous septae. The cytochrome P450 system is similar to that in humans.

B. Nutrition

A comprehensive text on swine nutrition has been published (Lewis and Southern, 2000). There is considerable variation of the genetic capacity for accretion of lean body mass among the various breeds of swine utilized in biomedical research. The "farm swine" include breeds developed for meat production and at 6 months of age may have a lean body weight 5- to 6-fold greater than that of a micropig breed. The published research on swine nutrition is focused on farm swine and maximization of lean growth (Table III). The majority of mini- and microswine nutritional research is proprietary and is reflected in the commercially available formulations offered by feed companies. In general, the nutrient requirements of these breeds are similar; however, the small breeds often require fixed-quantity feeding to control obesity, especially for long-term research studies. This in turn necessitates a higher margin of safety for many nutrient concentrations to prevent deficiencies, since most commercially available diets are designed for free-choice feeding. Diets formulated for the mini- and microbreeds generally have lower-energy and higher-fiber concentrations. The daily energy (Fig. 10) and quantity of feed (Fig. 11) required by farm pigs will predispose the mini- and microbreeds to obesity.

One nutrient requirement that is particularly important for newborn piglets is iron. Nursing piglets require 21 mg of iron for each kilogram of growth (National Research Council [NRC], 1998), and sow's milk contains approximately 1 mg of iron per liter (Brady *et al.,* 1978). Therefore, a microcytic, hypochromic anemia can develop. Nursing piglets can obtain some additional iron if allowed access to the feces of the sow; however, deficiency is still a common clinical problem. Consequently, it is routine practice in most swine herds to give 100–200 mg of iron dextran IM within 48 hr of farrowing to prevent iron deficiency anemia.

Swine, unlike ruminants, do not require elemental sulfur in their diets when adequate sulfur-containing amino acids (methionine and cystine) are available. Sulfur is essential for synthesis of various body compounds such as taurocholic acid, chondroitin sulfate, glutathione, and lipoic acid. Methionine alone can meet the total sulfur-containing amino acid re-

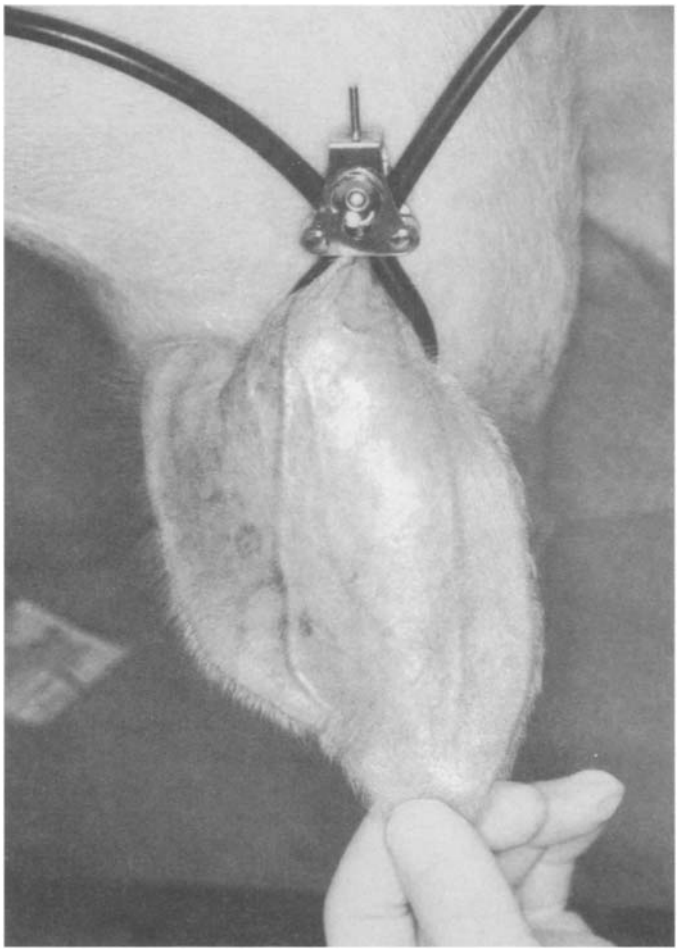

Fig. 7. Dilation of the lateral auricular vein, using a tourniquet.

quirement in swine because cystine can be synthesized from methionine. The amino acid requirements (Table III) refer to the L-isomer, which is the most biologically active form in swine and most common form found in plants and animals (NRC, 1988, 1998).

C. Reproduction

1. Reproductive Physiology

Swine reach sexual maturity at 3–7 months of age, with most miniature breeds becoming sexually mature at 4–6 months of age. Litter size varies among breeds, with domestic swine usually having an average of 8–12 pigs per litter and miniature breeds, 4–6 pigs. Litter size also varies with parity, being smallest at the first parity, increasing to a maximum between the third and seventh paritities, and then remaining stable or decreasing (Dial *et al.,* 1992).

The average estrous cycle is 21 days with a range of 17–25 days. Estrus typically lasts 48 hr (range 1–3 days). Prior to the onset of estrus, sows will exhibit signs of vulvar reddening and swelling, mucous discharge, nervousness, and increased activity. During estrus, sows will stand immobile when pressure is applied to the rump (Braun, 1993). Silent estrus is common in swine, but the presence of a boar can facilitate estrus detection (Dial *et al.,* 1992).

Optimal fertilization rates occur when insemination takes place 12 hr prior to ovulation. However, the variability in the interval between onset of estrus and ovulation makes it difficult to determine when females ovulate. As a result, commercial producers usually breed sows twice during estrus to maximize conception rates. Litter size also tends to increase with multiple matings per estrus. In pen mating, the sow and boar are left together during estrus. Hand mating involves placing the sow and boar in the same pen at 12–24 hr intervals during estrus until the female is no longer receptive (Dial *et al.,* 1992). Swine may also be bred by artificial insemination; however, conception rates are typically 10–15% lower than when natural service is used. Satisfactory results are obtained if sows are inseminated 10–30 hr after the beginning of estrus (Einarsson, 1980).

2. Pregnancy

Failure to return to estrus 18–24 days following mating is the first sign of pregnancy. Nonestrous sows are most easily detected by daily exposure to a boar during this time. Behavioral changes are seen in only 50% of sows in the absence of a boar. In the absence of a boar, determination of pregnancy can be based on whether or not the physical and behavioral changes of estrus are observed (Braun, 1993). Estrus detection has been reported to be 98% accurate and can be used to determine pregnancy status soon after failure of conception or death of a litter (Dial *et al.,* 1992).

Other pregnancy-detection procedures include the use of ultrasound and hormone assays. Ultrasound is $< 90\%$ accurate and cannot be performed prior to the fourth week of gestation Amplitude-depth ultrasound units can be used to detect pregnancy reliably between 30 and 90 days and as early as 18 days with some equipment. They are handheld devices that detect interfaces between fluid and tissues, which is the reason why they lose sensitivity at either early or late gestation. Doppler ultrasonography can be used from 4 weeks until farrowing and can also be used to determine litter size as well as fetal viability in late gestation (Dial *et al.,* 1992; Braun, 1993).

Activity of the corpora lutea can be measured by progesterone assays. Progesterone concentrations of < 1 ng/ml on days 17–19 of the estrous cycle are typical of nonpregnant females. An elevated progesterone concentration on day 18 after breeding is indicative of pregnancy. Estrone sulfate assays are more accurate for determining pregnancy status than progesterone assays. Estrone sulfate, produced by the fetus, reaches peak blood levels at 23–30 days gestation (Braun, 1993).

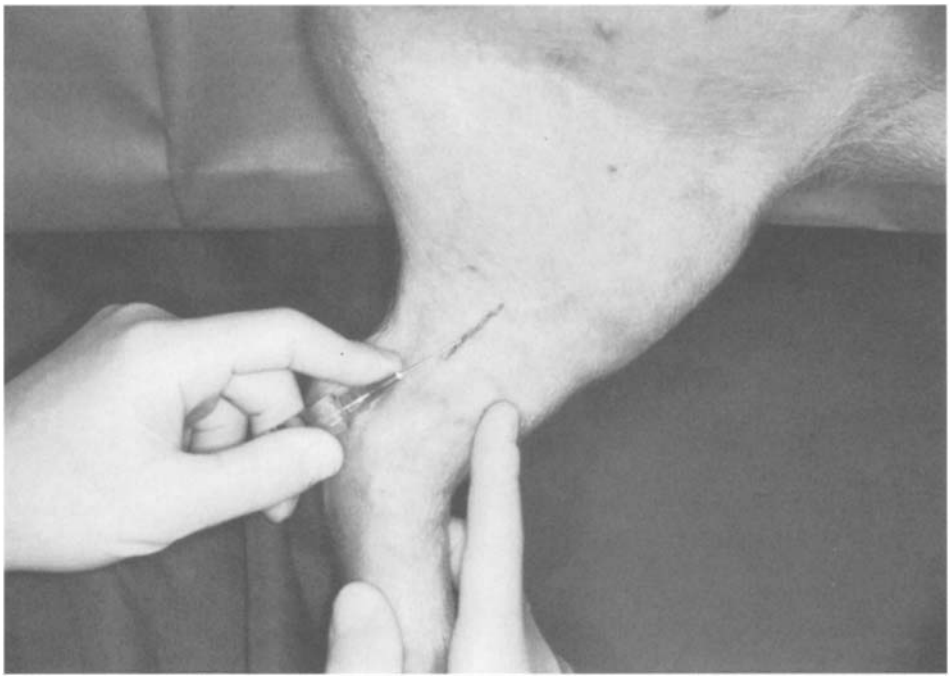

Fig. 8. Venipuncture of the medial saphenous vein.

3. Parturition and Neonatal Care

The gestation period of miniature pigs and commercial pigs is typically 114–115 days. Signs of impending parturition are usually evident during the last week of gestation. The vulva becomes swollen and more reddened during the last 3–4 days. Development and distension of individual mammary glands occur during the last 2–3 days of gestation, and drops of clear or straw-colored fluid can be expressed. This is followed by the initiation of milk secretion. Characteristically, abundant milk can be expressed at the onset of farrowing. The interval between the initiation of milk flow to parturition is typically 6–12 hr and provides a somewhat reliable sign of farrowing. Respiratory rate is most reliable. Behavioral changes occur during the 24 hr preceding farrowing and include restlessness and nesting. Frequent urination, defecation, and chewing or biting on surrounding objects may also be noted. However, just prior to birth, this activity diminishes and the sow becomes recumbent (Day, 1980; Braun, 1993).

Use of a farrowing crate is seldom necessary. The week prior to the anticipated farrowing date, sows should be placed in a quiet room in a stall with abundant bedding material for nest building. Wood chips are ideal for farrowing stalls since they allow the sow to engage in nesting behavior. They also help maintain the neonates' body temperature since newborn piglets lack the ability to effectively thermoregulate. Environmental temperature should be 85°–95°F with a supplemental heat source in the stall that results in a temperature of approximately 90°F at pig level (Fisher, 1993). Hanging heat lamps are commonly used and should be positioned to be effective without causing burns. The sow's comfort level is approximately 68°–70°F, which is the reason for having a supplemental heat source just for the neonates. Newborns should not be exposed to drafts or moisture.

The duration of farrowing ranges from less than 1 up to 8 hr, but typically lasts 3–4 hr. Larger litters may have a longer farrowing duration. The sow displays little physical exertion during the birth process. Sows generally remain laterally recumbent while giving birth but will occasionally change to a standing or ventrally recumbent position. The interval between the birth of piglets is typically 15 min. Assistance should be provided if more than 30–60 min elapse between the delivery of piglets (Day, 1980; Braun, 1993).

The most important factors that contribute to neonatal survival are the ability of the piglets to receive colostrum within the first 12 hr of birth, adequate nutrition, and appropriate environmental conditions (Reeves, 1993). Competition is normal among littermates during nursing and can result in inadequate colostrum and milk intake in less dominant animals. Neonates will compete for, and establish, teat order on their day of birth. This hierarchy remains until weaning (Sawatsky, 1993). If necessary, the technique of split suckling can be used to ensure that all animals can nurse. This involves removing half of the litter comprising the largest piglets 3–4 times a day to allow the smaller animals to nurse adequately (Reeves, 1993; Dial *et al.*, 1992). The sow's milk supply should be checked daily to

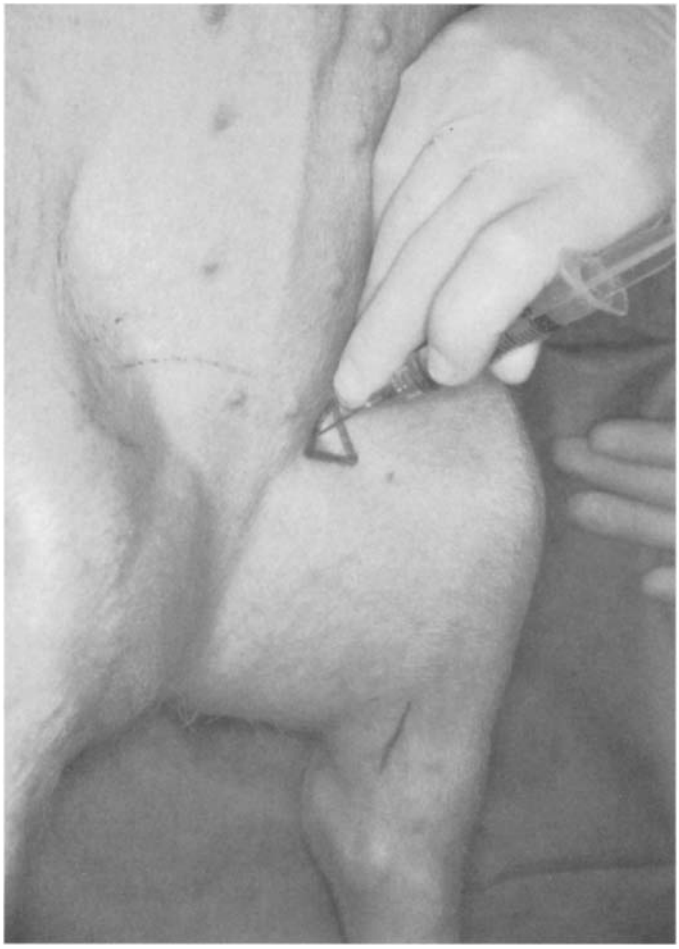

Fig. 9. Venipuncture of the femoral vein.

prevent piglet deaths from dysgalactia. Commercial pig milk replacers are available and should be provided to piglets by bottle or pan feeding if the sow is unable to produce an adequate milk supply.

Preweaning mortality is endemic in most herds, but mortality varies depending on the prevalence of the various causes, which include poor viability at birth, chilling, starvation, trauma, diarrhea, and other diseases (Dial *et al.,* 1992). Trauma includes incidences of piglets that are stepped on, suffocated when lain on, and savaged by the female. Savaging is a behavior observed occasionally in individual animals, resulting in injury to and/or death of the piglets. The only recourse is to remove the piglets from the sow and to cull her from the breeding herd.

Day 1 care for piglets includes disinfection of the navel, clipping of the canine or "needle" teeth, injection of an iron supplement, identification of individual animals, weighing, and clinical exam (Reeves, 1993; Fisher, 1993). The environmental temperature should remain at 85°–90°F for animals up to 3–4 weeks of age. Animals 4 to 8 weeks old can be housed in rooms with temperatures at 75°–80°F. Swine are generally weaned at 3–5 weeks by allowing them access to a solid ration.

D. Behavior

Swine are highly social and intelligent animals. They have a highly developed sense of smell, but poor eyesight. Group-housed swine are frequently observed vocalizing to each other. Pigs have an innate need to root, which can become destructive if they are not provided with an adequate outlet for expression. Housing strategies should accommodate swine behavioral needs as much as possible within the constraints of experimental design. Group housing or housing 2 animals per cage can be used to allow social interactions among animals. If individual housing is necessary, cages should be close together, and their design should include openings at the bottom to facilitate contact. Providing bedding material such as wood shavings is an excellent way to satisfy pigs' rooting behavior. Bedding material has the additional advantage of absorbing excreta but can be more labor-intensive for the husbandry staff than slatted or mesh flooring. Alternatively, a variety of toys, such as balls, chains, or hoses, can be supplied to help provide cage enrichment (Sawatsky, 1993; Fisher, 1993).

Swine are readily trained and respond well to positive reinforcement in contrast to conventional agricultural handling practices. This characteristic can be used to advantage in the research setting when animals must be handled or restrained for research manipulations. Acclimating and training swine to tolerate research equipment that will be used on them should be a standard procedure and can include the use of various types of food rewards given for reinforcing wanted behaviors. Gentle handling and the use of a humane restraint sling is warranted whenever swine need to be transported from their home cages or when restraint is necessary during noninvasive procedures. Many pigs respond to gentle rubbing of the ventral abdomen by rolling over onto their sides, enabling caregivers to perform such minor procedures as wound cleansing or suture removal without restraining the animals. This type of handling is very effective for positively reinforcing contact between pigs and their caretakers and has a calming effect on most animals.

E. Immunology and Use of Swine in Xenotransplantation

1. Immunology

Swine immunology is of increasing interest because of the potential for using pigs in xenotransplantation. The comparable anatomy and physiology of the pig and the human, the availability of inbred lines with a defined health status, and the emerging abilities to genetically modify the pig to lessen the risk of rejection make it an attractive source of much-needed

Table I

Hematology and Serum Chemistry for Hanford Miniature Swine[a]

Parameter	Males				Females			
	Mean	SD	Range	Quantity	Mean	SD	Range	Quantity
Hematology								
WBC (× 1000/μl)	25.1	3.4	21.3–32.4	9	20.8	3.0	16.8–26.7	10
RBC (× 10^6/μl)	7.4	0.8	6.6–9.3	9	7.0	0.7	6.4–8.3	10
Hemoglobin (gm/dl)	12.2	0.5	11.4–12.8	9	12.1	0.8	11.4–13.5	10
Hematocrit (%)	38.0	1.6	35–40	9	37.2	2.3	35–41	10
MCV (fl)	57.1	5.0	48.1–63.1	8	59.8	4.0	54.1–63.9	10
MCH (pg)	16.6	1.6	13.7–18.6	9	17.4	1.1	15.9–18.8	10
MCHC (gm/dl)	32.0	0.9	30.8–33.7	9	32.5	0.5	31.7–33.1	10
SEG N (× 1000//μl)	16.8	5.2	10.8–24.6	9	13.3	4.1	7.6–19.5	10
Lymphocytes (× •)	6.6	3.4	3.4–12.7	9	6.4	3.2	3.2–13.0	10
Monocytes (× •)	1.5	0.8	0.7–3.2	9	1.0	0.8	0.2–2.9	10
Basophils (× •)	0.1	0.2	0.0–0.7	9	0.0	0.1	0.0–0.3	10
Eosinophils (× •)	0.1	0.2	0.0–0.5	9	0.1	0.1	0.0–0.2	10
NRBC/100WBC	0.1	0.3	0.0–1.0	9	0.1	0.3	0.0–1.0	10
Chemistry								
Glucose (mg/dl)	104.6	9.3	94–118	10	108.7	11.0	91–123	10
BUN (mg/dl)	14.7	1.6	12–17	10	13.2	1.7	10–16	10
Creatinine (mg/dl)	0.8	0.2	0.5–1.1	10	0.7	0.1	0.6–0.8	10
Phosphorus	6.3	0.5	5.9–7.3	10	9.4	0.9	7.7–10.7	10
Calcium (mg/dl)	11.2	0.4	10.4–11.8	10	10.8	0.5	10.0–11.4	10
Total Protein	6.5	0.3	6.1–7.0	10	6.2	0.3	5.8–6.6	10
Albumin (gm/dl)	3.6	0.3	3.3–4.0	10	3.7	0.3	3.1–4.3	10
Globulin (gm/dl)	2.9	0.4	2.4–3.7	10	2.6	0.4	2.1–3.5	10
A/G	1.3	0.3	0.9–1.7	10	1.5	0.3	0.9–1.9	10
Sodium (mEq/liter)	142.2	1.9	140–146	10	142.5	1.7	139–144	10
Chloride (mEq/liter)	100.4	0.8	99–102	10	100.1	1.4	98–102	10
Potassium (mEq/liter)	5.7	0.7	4.7–6.8	10	5.6	0.6	4.6–6.3	10
CO_2	26.6	1.6	24–28	10	25.9	3.1	20–29	10
AGAP	15.2	1.5	12–17	10	16.5	2.2	14–20	10
Total bilirubin	0.2	0.1	0.11–0.41	10	0.1	0.0	0.09–0.16	10
Direct bilirubin	0.0	0.0	0.0–0.02	10	0.0	0.0	0.01–0.02	10
Indirect bilirubin	0.2	0.1	0.09–0.41	10	0.1	0.0	0.07–0.15	10
Alkaline Phosphatase (U/liter)	370.8	112.0	166–484	10	413.5	106.1	206–576	10
GGT (IU/liter)	47.4	14.1	31–75	8	37.7	6.6	29–49	10
AST (U/liter)	56.5	14.3	42–90	10	42.2	8.5	33–59	10
LDH (U/liter)	580.0	75.0	510–758	10	548.3	40.0	490–593	10
CK (U/liter)	456.8	185.7	270–735	10	358.9	144.2	221–628	10
Na/K	25.3	3.1	21–30	10	26.1	2.6	23–31	10

[a]Samples taken from unanesthetized 3-month-old animals. Unpublished data courtesy of Charles River Laboratories, Inc.

transplant organs. Comprehensive reviews of swine immunology (Pescovitz, 1998) and xenotransplantation (Gianello *et al.*, 1998) have been published.

In comparison to those of most other mammals, cortical and medullary areas of lymph nodes have an inverted relationship, a trait shared with the elephant, rhino, dolphin, hippo, and warthog (Pescovitz, 1998). Afferent lymph percolates from the central cortex to the outer paracortex (equivalent of medulla), where cells migrate through high endothelial venules and back into the blood; thus, efferent lymph is relatively acellular. Medullary areas of the porcine lymph node are denser in cell numbers than those of most other species, being rich in macrophages, plasma cells, and eosinophils. The pig also has prominent intraluminal macrophages within respiratory airways. Similar to ruminants, pigs have two types of Peyer's patches present in the small bowel. Although there is no clearly established functional distinction, the multiple (20±) discrete Peyer's patches found in the jejunum contain B and T cells, while the singular long ileal Peyer's patch contains B cells almost exclusively (Barman *et al.*, 1997). Due to a relative lack of specific antibodies, identification of cluster of differentiation (CD) markers to phenotype lymphocyte subsets has lagged such

Table II

Clinical Chemistry Reference Ranges for Swine[a]

Parameter	Yucatan Micropigs (Mature)		Yorkshire/Duroc (Immature)
	Female	Male	Female/Male
Serum analyte			
Glucose (mg/dl)	68.5 ± 10.1	65.2 ± 12.1	82.9 ± 11.9
BUN (mg/dl)	18.9 ± 3.0	19.4 ± 3.4	9.0 ± 3.2
Creatinine (mg/dl)	0.9 ± 0.13	0.85 ± 0.19	1.01 ± 0.22
Sodium (mEq/liter)	139.8 ± 2.90	139.8 ± 2.80	138.0 ± 3.49
Potassium (mEq/liter)	5.46 ± 0.84	5.50 ± 0.84	4.40 ± 0.37
Chloride (mEq/liter)	103.6 ± 6.9	101.8 ± 3.6	106.0 ± 7.80
Bicarbonate			29.0 ± 2.2
Calcium (mg/dl)	10.9 ± 0.64	10.9 ± 0.72	9.6 ± 0.58
Phosphorus (mg/dl)	6.66 ± 0.74	6.63 ± 0.74	
Iron (μg/dl)		169 ± 25	
GGT (IU/liter)	60 ± 9.6	60.0 ± 12.0	
AST (U/liter)	41.4 ± 27.6	40.2 ± 22.2	
Alkaline Phosphatase	63.0 ± 28.8	787.8 ± 178.8	
LDH	55.2 ± 19.8	759.6 ± 180.2	
CK (U/liter)	704.4 ± 1158	717.0 ± 995	
Total Protein (gm/dl)	74.9 ± 4.8	72.86 ± 4.4	
Albumin (gm/dl)		47 ± 3	
Cholesterol (mg/dl)	82.0 ± 15.1	73.1 ± 12.8	
Triglycerides (mg/dl)	31.9 ± 9.7	27.5 ± 8.9	
Total bilirubin (mg/dl)	0.338 ± 0.146	0.330 ± 0.288	
Urine analyte			
Urine flow (ml/min/kg)			0.1–0.16
Osmolality (mOsm/kg H_20)			115–546
Sodium (μmol/min/kg)			0.25–8.13
Potassium (μmol/min/kg)			0.09–3.31
Glomerular filtration rate (ml/min/kg)			1.0–4.5
Renal plasma flow filtration rate (ml/min/kg)			7.7–32.2

[a] Summarized from Loeb and Quimby (1999).

studies of the mouse and the human. Two International Swine Cluster of Differentiation Workshops have been held for comparison of novel antibodies to swine CD antigens and cross-reactive antibodies available from mouse and human studies (Saalmuller *et al.*, 1998). Many homologous CD markers have now been identified, and a limited number are available commercially from the American Type Culture Collection (Manassas, Virginia) and Pharmingen, Inc. (San Diego, California). A monoclonal antiporcine CD3 antibody has been identified that is capable of activating or depleting T cells *in vitro* and inducing an immunosuppressive state *in vivo,* which will greatly facilitate studies of the swine immune system, in particular, induction of tolerance in xenotransplantation research (Huang *et al.*, 1999). Bone marrow of swine is more similar to that of humans than of rodents in toxicity response to lethal irradiation, allowing studies that have demonstrated the benefit of T-cell depletion of donor tissues in preventing graft-versus-host disease.

Normative data for the swine immune system, such as lymphoid tissue weights and percentages of cell subsets represented in different tissues, are influenced by the animal health status, as data derived from animals of conventional health status (i.e., farm environments) differ significantly from data derived from those housed under specific pathogen–free, gnotobiotic, or axenic conditions. The pig has a large population of what were initially considered as "null" cells, lacking expression of CD2, CD4, or CD8, but now known to express CD3, classifying them as T cells. This lymphoid population is largely γδ T cells and is found in large numbers in various tissues, especially mucosal sites, as in ruminants (Davis *et al.*, 1998). Expression of CD4 (T helper) and CD8 (T cytotoxic or T suppressor) is mutually exclusive in most species, but swine have a unique lymphocyte subset that expresses both CD4 and CD8 (Thome *et al.*, 1994).

Table III

Daily Nutrient Requirements of Growing Swine[a]

Parameters	Body weight (kg)		
	10–20	20–50	50–80
Average weight in range (kg)	15	35	65
Digestible energy of diet (kcal/kg)	3400	3400	3400
Estimated digestible energy intake (kcal/day)	3400	6305	8760
Metabolizable energy of diet (kcal/kg)[b]	3265	3265	3265
Estimated metabolizable energy intake (kcal/day)[b]	3265	6050	8410
Estimated feed intake (gm/day)	1000	1855	2575
Crude protein (%)	20.9	18.0	15.5
Water (liters) (2.5 liters per kg feed consumed)	2.5	4.6	6.4
Fatty acid requirements			
Linoleic acid (gm)	1.00	1.86	2.58
Amino acid requirements (gm/day) (*Total basis*)			
Arginine	4.6	6.8	7.1
Histidine	3.7	5.6	6.3
Isoleucine	6.3	9.5	10.7
Leucine	11.2	16.8	18.4
Lysine	11.5	17.5	19.7
Methionine	3.0	4.6	5.1
Methionine + cystine	6.5	9.9	11.3
Phenylalanine	6.8	10.2	11.3
Phenylalanine + tyrosine	10.6	16.1	18.0
Threonine	7.4	11.3	13.0
Tryptophan	2.1	3.2	3.6
Valine	7.9	11.9	13.3
Mineral elements			
Calcium (gm)	7.00	11.13	12.88
Phosphorus, total (gm)	6.00	9.28	11.59
Phophorus, available (gm)	3.20	4.27	4.89
Sodium (gm)	1.50	1.86	2.58
Chlorine (gm)	1.50	1.48	2.06
Magnesium (gm)	0.40	0.74	1.03
Potassium (gm)	2.60	4.27	4.89
Copper (mg)	5.00	7.42	9.01
Iodine (mg)	0.14	0.26	0.36
Iron (mg)	80.00	111.30	129.75
Manganese (mg)	3.00	3.71	5.15
Selenium (mg)	0.25	0.28	0.39
Zinc (mg)	80.00	111.30	129.75
Vitamins			
Vitamin A (IU)	1750	2412	3348
Vitamin D_3 (IU)	200	278	386
Vitamin E (IU)	11	20	28
Vitamin K (menadione) (mg)	0.50	0.93	1.29
Biotin (mg)	0.05	0.09	0.13
Choline (gm)	0.40	0.56	0.77
Folacin (mg)	0.30	0.56	0.77
Niacin, available (mg)	12.50	18.55	18.03
Pantothenic acid (mg)	9.00	14.84	18.03
Riboflavin (mg)	3.00	4.64	5.15
Thiamin (mg)	1.00	1.86	2.58
Vitamin B_6 (mg)	1.50	1.86	2.58
Vitamin B_{12} (μg)	15.00	18.55	12.88

The values in this table are minimum reqirements only and are **not** recommended allowances. A margin of safety should be added for most of the nutrients with the exception of selenium. The National Research Council's (NRC) (1998) "Nutrient Requirements of Swine," 10th rev. ed., should be consulted by researchers developing their own diet formulations. Adapted from NRC (1998), with permission.

[a]Assumes allowed feed *ad libitum* that is 90% dry matter and corn–soybean based.

[b]Assumes that metabolizable energy is 96% of digestible energy.

Fig. 10. Expected daily digestible energy intake for growing farm swine. (Adapted from computer model program, NRC, 1998, with permission.)

This subset may represent a type of memory cell or a lineage that differentiates into $CD4^+CD8^-$, since CD8 expression is low and the CD8 dimer, normally αβ in chain structure, is αα in these cells.

Immunoglobulins (Ig) of the pig are the most studied of those in farm species (reviewed in Ober *et al.,* 1998). There is no transplacental transfer of maternal immunity; thus, neonates are colostrum-dependent. Access to IgG-rich colostrum within the first 6 hr postpartum is most critical for 3-week survival rate and weight gain. Colostral leukocytes, largely neutrophils and T cells, are also absorbed by intercellular migration. Intestinal closure for absorption of colostrum is complete by 24 to 48 hr of age. In contrast to most other species, the pig lacks the gene for IgD, which is a precursor immunoglobulin in the differentiation pathway to IgM. The pig does have a large number of IgG subclasses: IgG_1, IgG_{2a}, IgG_{2b}, IgG_3, and IgG_4. Immunoglobulin A circulates as a dimer in blood and tissues and as a monomer in mucosal secretions; IgE is found in serum and mucosal tissues. High endothelial venules of transplanted swine tissues express adhesion molecules, but information on the relative homology of these "addressins" is limited in scope due to lack of reagents.

Cytokines and lymphokines in the pig have been studied in models associated with inflammation, such as sepsis, atrophic rhinitis, erysipelas, arthritis, and viral infections (Murtaugh, 1994; Ober *et al.,* 1998). Reports on swine cytokine regulation and function suggest that the biology is similar to that of humans and mice and that there is some limited homology; swine lymphocytes will respond to recombinant human interleukin (IL)-2 *in vitro* (Whary *et al.,* 1995). Located on chromosome 7, swine leukocyte antigens (SLA), the equivalent of the mouse major histocompatibilite complex (MHC), have been cloned and sequenced. As they are in other species, SLA class I genes are universal in tissue expression and function to restrict T-cell activation, particularly antiviral immune responses, and are pivotal for inducing tolerance for "self." The SLA class II genes have been cloned and are restricted in expression to B cells, activated macrophages, a subset of $CD8^+$ T cells, and vascular endothelium. The number of SLA class III genes that have been cloned is lower than that found in other species. Member genes of the SLA class III complex function in the complement system, which in the pig is closely aligned with the human systems of classical and alternative pathways of complement activation. One difference is that elimination of antigen–antibody immune complexes occurs through the lung in the pig, in contrast to the target organs of liver and spleen in humans (Davies *et al.,* 1995). Red blood cell antigen classification is very complex in the pig, with 16 genetic systems having been developed that consist of 78 blood factors, which are either antigens of the red blood cell itself or become cell-associated from other tissues when serum concentrations are high (Pescovitz, 1998). Knowledge of red cell surface expression of carbohydrate antigens is important to xenotransplantation because of their role in complement activation, which mediates hyperacute rejection of transplanted tissues.

There are no primary immunodeficiencies that have been identified in the pig, but acquired immunodeficient states can be surgically induced (thymectomy, splenectomy). Spontaneous cases of immunodeficiency have been attributed to inadequate colostrum, stress, or poor nutrition (Pescovitz, 1998). Autoimmune disease in swine is largely undocumented except for hemolytic disease in neonates related to postnatal absorption of maternal immunoglobulins (erythroblastosis fetalis) and two forms of glomerulonephritis. One form appears to be inherited in Norwegian Yorkshire swine, and a second involves spontaneous IgA nephropathy reported in Japanese slaughter pigs (both reviewed in Ober *et al.,* 1998). Arthritis in pigs attributable to infection with *Mycoplasma hyorhinis* or *Erysipelothrix rhusiopathiae* has similar pathogenesis to human rheumatoid arthritis.

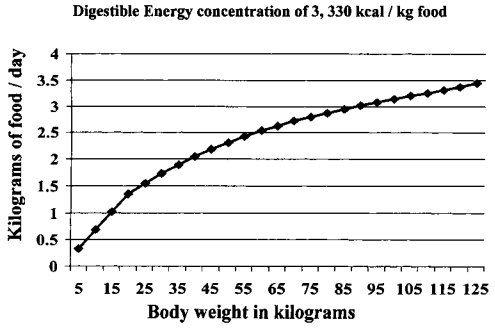

Fig. 11. Expected daily food intake for growing farm swine. (Adapted from computer model program, NRC, 1998, with permission.)

2. Use of Swine in Xenotransplantation

Experimental use of swine organs or tissues for humans faces significant scientific challenges of overcoming hyperacute and chronic rejection by the host as well as societal issues involving ethics, cost, and the risk of zoonotic diseases. Nonetheless, the

pig is considered to be the prime candidate for systematic production of suitable organs because of its many advantages. Miniature swine are readily available and have body weight, organ size, and physiology similar to those of humans. Additionally, their transplant potential is supported by emerging transgenic technology to minimize rejection and by a large database of technical information generated by their use in other areas of biomedical research (Swindle, 1992). Disease resistance of swine organs has also been promoted as a strategy to circumvent failure of transplanted organs resulting from infectious agents specific to the human, such as hepatitis B virus (Mueller *et al.,* 1999).

Three lines of miniature swine homozygous for a different set of SLA alleles have been developed by David Sachs of the Massachusetts General Hospital (Boston) (Lunney *et al.,* 1986). Designated as SLA^{aa}, SLA^{cc}, and SLA^{dd}, these lines are heterozygous at minor histocompatibility and other loci and thus are useful genetic models for studying rejection. Pairing donor and recipient within a line is used to model for transplants between identical human siblings, between lines as a model for nonidentical siblings, and between F_1 hydrids for parent–offspring transplants. Intra-SLA recombinant strains have permitted study of SLA class I and II differences and demonstrated the effect of SLA mismatches on graft survival of various tissues. Matching SLA skin grafts typically survive for 7 to 12 days, but vascular grafts and liver transplants survive much longer, some indefinitely. One-third of renal transplants have survived indefinitely, and when rejection did occur, it led to discovery of non-SLA-linked genes that promoted immune-mediated rejection. Acceptance of vascular grafts has been shown to induce tolerance to minor histocompatibility loci, and when performed prior to skin grafting, skin graft survival time was extended. Reversing this process (skin graft first) apparently sensitizes the host to reject vascular grafts hyperacutely.

The swine-to-baboon xenotransplantation model holds the promise of future technology transfer to enable swine-to-human donation. Lack of long-term success has generated multiple strategies to minimize rejection. Hyperacute rejection of organs occurs within minutes to hours and is mediated by complement when pig organs are perfused with human or nonhuman primate blood (Saadi and Platt, 1999). High titers of natural "xenoantibodies" in the human (or experimentally, in the nonhuman primate) target carbohydrate antigens, such as Gal(α1-3),Gal(α1-4),GlcNAc-R, expressed on donor tissue endothelium, resulting in complement activation and subsequent vascular injury and in severe cases, disseminated intravascular coagulation (DIC). One strategy has been to eliminate natural xenoantibodies from the circulation of baboons using α-Gal immunoaffinity columns or extracorporeal perfusion through pig liver; depletion is temporary, on the order of days to weeks (Kozlowski *et al.,* 1998). Sachs unsuccessfully attempted to identify an inbred swine genotype of low α-Gal expression with the objective of using selective breeding of pigs to decrease α-Gal expression (Chae *et al.,* 1999). Others have suggested screening specific donors for carbohydrate antigen expression levels as a means to diminish antigenic stimulation of the recipient (Papalois *et al.,* 1999). Brenner *et al.* (2000) reported that nonspecific depletion of the majority of recipient immunoglobulins of all isotypes by column immunoapheresis significantly improved graft survival of pig hearts in baboons.

In addition to the antibody-mediated hyperacute rejection, delayed rejection of xenografts through cell-mediated responses develops over 3 to 4 days, involving activation of endothelial cells of the graft as in the acute rejection response (Brouard *et al.,* 1999). Activation leads to loss of thrombomodulin and adenosine triphosphate diphosphohydrolase (ATPDase), which leads to prothrombosis, proinflammatory gene activation increasing the expression of adhesion molecules, prothrombotic factors, and cytokines. Adoptive cell transfer experiments in immunodeficient rodents have demonstrated that engrafted human $CD4^+$ T cells mediate rejection of porcine xenografts (Friedman *et al.,* 1999) as do natural killer cells and monocytes (Sandrin and McKenzie, 1999).

Early attempts to promote immunologic tolerance have included bone marrow ablation of the recipient, therapy with complement inhibitors (cobra venom factor or soluble complement receptor I), preadsorption of natural antibodies, immunosuppressive drug regimens, antithymocyte globulin, and splenectomy (Schmoeckel *et al.,* 1999). An attractive approach that has shown early promise is the induction of donor-specific tolerance using bone marrow transplantation to create chimeras. Tolerance to fully MHC-mismatched allografts has been demonstrated in mice and primates after first creating a mixed allogeneic hematopoietic chimerism by engrafting donor bone marrow cells into the recipient. However, this hematopoietic chimerism has been difficult to achieve in the discordant pig-to-primate xenogeneic model (Sablinski *et al.,* 1999), most likely due to species-specific differences in regulatory cytokines and elements of the stromal microenvironment (Emery *et al.,* 1999). Representative of a typical experimental protocol and illustrative of the complexities involved, recipient primates underwent whole-body irradiation on days 6 and 5 prior to infusion of pig bone marrow. Primate antipig xenoantibodies were immunoadsorbed by extracorporeal perfusion of recipient blood through a pig liver immediately before the intravenous infusion of porcine marrow (day 0). In addition to cyclosporine for 4 weeks and 15-deoxyspergualin for 2 weeks, recombinant pig stem-cell factor and interleukin 3 were given for 2 weeks. Recipient primates required 4 weeks to recover from pancytopenia from whole body irradiation, and antipig IgM and IgG antibodies were temporarily depleted by the liver perfusion for 12 to 14 days. About 2% of the myeloid progenitors in the bone marrow of the recipient were of pig origin, and the chimeric animal was less responsive by mixed lymphocyte reaction to pig-specific stimulators. This was the first report of long-term survival of discordant xenogeneic bone marrow in a primate recipient. Others have re-

ported on the poor function of porcine hematopoietic cells in primate marrow microenvironments. Warrens *et al.* (1998) found differences between swine and human bone marrow cultures in function of two well-characterized ligands known to be important in hematopoiesis, CD44 and very late antigen-4 (VLA-4), but they concluded that the differences were not significant enough to explain lack of effective porcine hematopoiesis in the primate marrow, suggesting that other unknown interactions may be important.

Gene therapy using retroviral transfer to minimize rejection has been investigated. In a mouse model, inhibition of xenoantibody production was accomplished by retroviral transfer into mouse bone marrow of a gene encoding the enzyme that synthesizes swine carbohydrate antigens (Bracy *et al.,* 1998). Gene therapy to express swine SLA class II antigens on baboon autologous bone marrow cells has had limited success (Ierino *et al.,* 1999). Transcription of the transgene was transient, and xenografts were rejected after 8 to 22 days. This experiment was important because it demonstrated that transfer and expression of xenogeneic class II transgenes can be achieved in baboons, and this therapy may prevent late T cell–dependent responses to porcine xenografts, which include induced non-α-Gal IgG antibody responses. Porcine thymic grafts in immunodeficient mice have been found to support normal development of polyclonal, functional human T cells, and these T cells were specifically tolerant to SLA antigens of the porcine thymus donor, suggesting thymic transplantation may be an approach to achieve tolerance in pig-to-human xenotransplantation (Nikolic *et al.,* 1999).

Transgenic science is the most promising approach to prevent rejection of xenotransplants. Transgenic expression of human α(1,2)-fucosyltransferase in different porcine cells and tissues, including the vascular endothelium, modifies the cell surface carbohydrate phenotype of the xenogeneic donor cell, resulting in the expression of the human universal donor O antigen and a concomitant reduction in the expression of the antigenic Gal(α1-3)Gal epitope (Costa *et al.,* 1999). Transgenic expression of CD59, a human complement regulatory protein, has promoted survival of swine lungs in a pig-to-primate model (Kulick *et al.,* 2000; Yeatman *et al.,* 1999). Swine endothelium has been genetically engineered to express other human complement regulatory proteins such as human decay-accelerating factor (Waterworth *et al.,* 1998), and membrane cofactor protein (MCP/CD46) (Perez de la Lastra *et al.,* 1999), both shown to be important in a swine model of xenogeneic lung and cardiac injury.

A major issue in xenotransplantation research is minimizing the risk for acquired zoonoses, particularly in recipients already immunosuppressed by illness and chemotherapy. Importantly, immunosuppression may take away the expected barrier of "species-specificity" of a potential agent. In addition to the anticipated risks associated with normal flora, environmental contaminants, and true pathogens, there is concern about the unknown risks of viral latency, viral recombination, and endogenous retroviruses (Levy *et al.,* 2000), which in the pig are known to infect human cells *in vitro* (Weiss *et al.,* 1999; Tacke *et al.,* 2000). In order to minimize risks, donor animals must be free of potential zoonoses and other complicating diseases (Ye *et al.,* 1994). The pig as a model has the advantage that it can be produced under gnotobiotic conditions, and management of newborn piglets from hysterectomy to donation has been described (Munoz *et al.,* 1999). Swindle has suggested that the term "xenograft-defined flora" rather than SPF be used to designate the appropriate health status of donor animals in order to avoid confusion with existing standards (Swindle, 1998).

There were 237 papers published on the use of swine in xenotransplantation between 1999 and mid-2000, which illustrates the intensity of research on the potential use of pigs in this vital area of human health. This amount of effort also represents the challenges to be overcome before xenotransplantation becomes a practical reality.

III. DISEASES

A. Infectious Diseases

If research pigs are typically purchased in relatively small numbers from herds with defined health status, newly introduced animals are adequately quarantined and conditioned, and husbandry conditions are optimum, the incidence of infectious disease in the research laboratory should be minimal. Nonetheless, veterinarians responsible for swine health need to be familiar with both classical swine diseases and the health problems that can emerge from opportunistic agents in animals stressed by experimental manipulation. Many of the diseases discussed below are in fact rare in the majority of modern commercial pigs and will not be found in the commercially supplied miniature swine herds of high health status.

Implementing treatment of infectious problems should be considered cautiously and is best reserved for those problems that are expected to resolve quickly with minimal impact on the research use or health status of the research herd as a whole. In the following discussion of infectious diseases, drugs of choice are identified, and the reader is referred to veterinary texts (Friendship, 2000; Hawk and Leary, 1995) for specific doses. Not all drugs mentioned are labeled for use in swine; thus if these drugs are used, the veterinarian must determine a dose from experience with other species and must ensure that treated domestic swine are not used for food.

1. Polysystemic Diseases

a. Salmonellosis

Etiology. There are over 2400 serotypes in the genus *Salmonella,* and each is conventionally referred to as a separate

species. All members of this genus are motile, non-spore-forming, facultative anaerobic gram-negative bacilli possessing peritrichous flagellae. There are 3 serotypes that are typically etiologic agents of clinical disease in swine and numerous others that are occasionally associated with disease.

Salmonella choleraesuis var. *kunzendorf* is the most frequent serotype causing disease in swine, and infection is usually manifested as septicemia and/or pneumonia. *Salmonella typhimurium* is the second most common isolate and typically causes enterocolitis. *Salmonella typhisuis* is associated with localized epizootics characterized by chronic wasting, caseous lymphadenitis, diarrhea, and pneumonia. It is very common to isolate more than one serotype from an individual pig; however, it is unusual that primary disease would be caused by a serotype other than *S. choleraesuis* or *S. typhimurium* (Schwartz, 1999).

Clinical signs and differential diagnoses. Signs characteristic of *Salmonella* septicemia include respiratory signs of cough, dyspnea, pneumonia, and cyanosis of the ears and ventral abdomen. Lethargy, anorexia, pyrexia of 105°–107°F (40.5°–41.6°C), and sometimes jaundice followed by watery yellow diarrhea are also evident. This form is usually caused by *S. choleraesuis* and can affect all ages, with swine aged 3 weeks to 5 months being the most commonly affected group. It can cause abortion in breeding sows. A differential list should include erysipelas and *Streptococcus suis* as other causes of septicemia.

The enteric form is characterized by an acute or chronic enterocolitis that is sporadically hemorrhagic. The initial diarrhea is usually watery and yellow and lasts less than a week but may recur. Anorexia, pyrexia, and dehydration are seen concurrent with diarrhea. Death may be the result in severely affected animals, and a distended abdomen due to rectal strictures can be a sequela to the chronic diarrhea. The majority of affected pigs recover; however, some will be carriers and shed the organism for several months. This form is usually caused by *S. typhimurium* and most commonly affects swine aged 3 weeks to 4 months.

A differential list should include other causes of bacterial, viral, and parasitic gastroenteritis in recently weaned swine. Bacterial agents include colibacillosis, porcine proliferative enteropathy (PPE) (*Lawsonia intracellularis*), and swine dysentery (*Serpulina hyodysenteriae*). The viral agents include transmissible gastroenteritis virus (TGE) and rotaviral enteritis. The parasitic agents include *Trichuris suis* and coccidiosis (*Isospora suis*).

Epizootiology and transmission. The source of *Salmonella choleraesuis* for swine is essentially other swine and environments contaminated by swine. Transmission is both vertical and horizontal by fecal–oral spread or nasal secretions. The incubation period ranges from 2 days to several weeks, and survivors become carriers that shed the bacteria in feces for at least 3 months. Some form of stress, including shipping, food deprivation, concurrent diseases, research protocols, temperature fluctuations, mixing pigs from different sources, and overcrowding, usually precedes clinical disease. The stress increases shedding by inapparent carriers. *Salmonella choleraesuis* is fairly host-specific for swine, but *S. typhimurium* is not host-specific (Schwartz, 1999). Therefore, other animal species in addition to swine are likely to be sources for *S. typhimurium.* Feed and feed ingredients have been shown to be a source of serotypes that can cause disease in swine (Harris *et al.,* 1997).

Necropsy. Gross lesions caused by *S. choleraesuis* are severe pleuropneumonia; cyanosis of the ears, feet, tail, and abdomen; splenomegaly and hepatomegaly; edematous enlarged mesenteric lymph nodes; erosion of the fundic mucosa in the stomach; and a focal to diffuse necrotic typhlocolitis with or without a necrotic ileitis (Turk *et al.,* 1992). Microscopic lesions include paratyphoid nodules in the liver; necrotic lesions involving the intestinal mucosa, submucosa, and lymphoid follicles; and a bronchopneumonia or hemorrhagic pleuropneumonia (Turk *et al.,* 1992; Wilcox and Schwartz, 1992).

Pathogenesis. Salmonella choleraesuis invades the mucosa of the ileum and is taken up by macrophages. It produces both Shiga-like and cholera-like endotoxins that are responsible for the microthrombosis and ischemia of vessels in the lamina propria and resulting necrosis of the enterocytes. Diarrhea is the malabsorption type with extensive fluid loss from the necrotic lesions (Wilcox and Schwartz, 1992).

Prevention and control. The most practical approach to preventing clinical salmonellosis is to remove stressors to minimize fecal shedding by carriers and to practice good sanitation to minimize exposure to the bacteria. These stressors include concurrent diseases, mixing of swine from different sources, poor environmental control, and nutritional deficiencies. Sanitary, pest-free facilities should be utilized for preparation, handling, and storage of swine feed. Common surface disinfectants that are efficacious for this bacterium include chlorine, iodine, and phenols.

A sensitive and specific multiplex polymerase chain reaction (PCR) assay has been developed that will identify salmonellae in feces and intestinal mucosa scrapings as well as in pure cultures (Elder *et al.,* 1997). This offers an alternative to conventional culture techniques and may be useful for confirming a clinical diagnosis or monitoring herd health.

Modified live attenuated vaccines for *S. choleraesuis* are protective and are thought to be effective because they stimulate cell-mediated immunity. An avirulent live *S. choleraesuis*–culture (SC-54) vaccine has shown a protective effect when applied by spraying the teats and udders of nursing sows. This vaccine reduced fecal shedding and mortality in suckling piglets (Burkhart and Roof, 1999). Killed bacterins for *S. typhimurium* are available and may provide some protection. Medication of feed or water with appropriate antibiotics

(e.g., carbadox, neomycin) in conjunction with improvements in husbandry, management, and environment may have a prophylactic benefit.

Treatment. Clinical salmonellosis should not be treated because recovered pigs will likely remain carriers and some isolates may be pathogenic for humans. If absolutely necessary, treatments should be based on susceptibility testing. Recommended antibiotics include ceftiofur (Burton, *et al.,* 1996) trimethoprim-sulfonamide, and gentamicin (Cowart, 1995; Poppe *et al.,* 1998; Seyfarth *et al.,* 1997).

Research complications. Salmonella is present at a low subclinical level in the majority of conventional swine herds. Outbreaks of clinical disease are associated with immunosuppression or stress, which probably includes experimental stress. Clinical disease caused by *S. choleraesuis* has a reported morbidity ranging to 60% and mortality to 30% (Schwartz, 1991), and this would seriously impact almost any research project.

b. Glasser's Disease (Haemophilus, Porcine Polyserositis, Infectious Polyarthritis)

Etiology. Haemophilus parasuis is a small gram-negative pleomorphic coccobacilli, which requires nicotinamide adenine dinucleotide (NAD or factor V) and exhibits satellitism when grown near *Staphylococcus epidermidis* on a blood agar plate. Serovars 2, 4, 5, 12, 13, and 14 are the most common in North America (Rapp-Gabrielson *et al.,* 1997) of the 15 currently recognized. Both pathogenic and nonpathogenic strains of the organism exist, and prior exposure to the nonpathogenic strain can induce protective immunity.

Clinical signs and differential diagnoses. This disease typically affects young pigs from 3 weeks to 4 months of age and varies in severity with the level of herd immunity. In conventional herds where *H. parasuis* is endemic, the clinical signs will be mild with low morbidity. In susceptible herds the clinical signs occur within a week after exposure and consist of pyrexia 104°–107°F (40°–41.7°C), anorexia, depression, lameness, neurological signs, dyspnea, and death. A markedly increased WBC and decreased packed cell volume (PCV) have been reported in experimentally infected SPF piglets (Wiegand *et al.,* 1997). Long-term sequelae include abortion and chronic arthritis. Differentials include *Mycoplasma hyorhinis* and other bacterial septicemic conditions that affect swine. These should include *Erysipelothrix rhusiopathiae, Salmonella choleraesuis,* and *Streptococcus suis.*

Epizootiology and transmission. Haemophilus parasuis is one of the earliest isolates to be cultured from the nasal cavities of swine in conventional herds. In endemic herds it can be cultured when animals are 1 week of age and is commonly cultured from the upper respiratory tracts of healthy pigs. Experimental evidence suggests that the first site of colonization in piglets is the nasal mucosa (Vahle *et al.,* 1995). It is only known to infect swine, and this suggests that introduction by other carrier species is unlikely. The role of *H. parasuis* as a respiratory pathogen is not well established. It is usually categorized as a secondary invader or predisposing factor; however, some report that it may be a primary etiologic agent in fibrinosuppurative bronchopneumonia (Rapp-Gabrielson, 1999).

Necropsy. Gross lesions may include cyanosis of the ears and tail, a polyarthritis with one or more swollen joints, fibrinous pleuritis, pericarditis and peritonitis, and a leptomeningitis (Little and Harding, 1971; Nicolet, 1992). Histopathologic lesions consist of fibrin thickening of alveolar walls, capillary thrombosis of glomerular tufts, fibrinopurulent arthritis and synovitis, a mononuclear epicarditis (Little and Harding, 1971), and a fibrinopurulent leptomeningitis (Nicolet, 1992).

Pathogenesis. This organism is part of the normal flora in the nasal passages of swine and is an opportunistic pathogen with swine influenza virus.

Prevention and control. A prevention and control program should include practices to increase immunity by the use of bacterins and reduction of experimental, environmental, and shipping stress. Herd-specific autogenous vaccines should be considered, as it is unlikely that any one commercial bacterin will induce immunity to all of the pathogenic strains in the population (Rapp-Gabrielson *et al.,* 1997). Elimination by early weaning is often unsuccessful because the piglets can be colonized by the time they are 1 week of age (MacInnes and Desrosiers, 1999). Medicated early weaning can be successful if high doses of both parenteral and oral antibiotics are utilized (Rapp-Gabrielson, 1999). Antimicrobial medication of feed or water of groups of swine at risk may be beneficial. An oligonucleotide-specific capture plate hybridization assay has been developed and is reported to be specific and more sensitive than culturing for *H. parasuis* from lesions and nasal swabs (Calsamiglia *et al.,* 1999). This may prove useful in a herd-health monitoring program or confirmation of a clinical diagnosis.

Treatment. Parenteral antibiotics should be started as soon as clinical signs become evident. Oral antibiotics are less effective. High doses of penicillin should be given to those with clinical signs and any other pigs in the affected group. Several other antibiotics (cephalosporins, fluoroquinolones, potentiated sulfas, tetracyclines, tylosin) are also effective. Resistance to tetracycline, erythromycin, and penicillin in some strains is increasing.

Research Complications. This disease will confound cardiovascular studies because the chronic form can produce congestive heart failure and fibrinous pericarditis.

C. *Erysipelas (Swine Erysipelas, SE)*

Etiology. *Erysipelothrix rhusiopathiae* (formerly *E. insidiosa*) is a gram-positive bacillus that has 26 serovars. The majority of isolates from swine are serovars 1 and 2.

Clinical signs and differential diagnoses. Animals with acute SE may have no clinical signs or present with a combination of classical rhomboid or diamond-shaped urticarial (pink to purple) skin lesions on the ventral abdomen and back; fever of 104°–108°F (40°–42°C); anorexia; depression; stiff, stilted gait; sitting posture; abortion; and sudden death. The skin lesions that appear 2–3 days postexposure are erythematous, raised, and palpable, and measure 1–8 cm across (Amass and Scholz, 1998); they vary in number from a few to numerous. The fever will usually resolve within 1 week. Differentials for the acute form include any bacterial septicemia. The diamond-shaped skin lesions are characteristic. There is also a subacute form, which is a mild version of the acute form and may pass unnoticed.

Enlarged, stiff joints resulting in slight to non-weight-bearing lameness characterize the chronic form of SE. The hock and carpal joints are usually the most visibly affected in those with chronic arthritis. In some cases cardiac insufficiency manifested by exercise intolerance and sudden death may result. Chronic SE may follow subclinical, subacute, and acute forms, sometimes within 3 weeks. Differentials for chronic SE include other causes of lameness in swine, including *Haemophilus* polyserositis, mycoplasmal polyserositis, and trauma and other bacterial septicemias such as *Actinobacillus suis.*

Epizootiology and transmission. The domestic pig is the primary reservoir of *E. rhusiopathiae,* and probably 30–50% of conventional swine are carriers (Wood, 1999; Cowart, 1995). These pigs harbor the bacteria in lymphoid tissues (tonsils, Peyer's patches) and shed it in nasal secretions, saliva, and feces. Individuals with acute SE will shed large quantities into the environment, and those with the chronic form are a long-term source of contamination. Additionally, contact with infected sheep, turkeys, chickens, ducks, and emus is a potential source of infection for swine. Swine older than 3 months and younger than 3 years of age are most likely to develop clinical disease. Passive antibodies obtained from the sow protect the young, and acquired immunity from subclinical infections protects the mature animals. This bacterium typically gains entry into the body through contaminated food and water (oral route) and skin wounds.

Necropsy. Acute phase gross lesions are those of a bacteremia and generalized coagulopathy (Wood, 1984). Characteristic rhomboid or rectangular-shaped, slightly raised, firm skin lesions are most commonly found on the skin of the abdomen but also on the thighs, ears, snout, throat, and jowls. There is congestion of the spleen, lungs, and liver, and there may be petechial hemorrhages on the surface of the kidneys, on the atrial myocardium, and within lymph nodes (Wood, 1984, 1992). Microscopic lesions in the acute phase are the result of damage done to endothelial cells in capillaries and venules. In the dermal papillae these lead to fibrin deposition, microthrombi and lymphocytic and plasmacytic perivascular infiltrates, and focal necrosis. Chronic lesions are manifested as a proliferative nonsuppurative synovitis and arthritis that results in enlarged joints, most commonly involving the stifle, hock, and carpal joints (Wood, 1984, 1992).

Pathogenesis. The organisms gain entry to the body via the palatine tonsils or gut-associated lymphoid tissue, and possibly from wounds in the skin. The pathogenesis of the lesions is not completely understood, but neuraminidase produced in large quantities by *E. rhusiopathiae* may be responsible for the production and deposition of the fibrin and for the vascular stasis (Wood, 1984).

Prevention. Initiation of a vaccination program in unvaccinated animals is very worthwhile although neither attenuated vaccines nor bacterins are successful at preventing chronic SE (Cowart, 1995). Immunization with purified protein antigen P64 has been found to be protective in an experimental challenge (Yamazaki *et al.,* 1999). The surface protein SpaA has shown good potential as an antigen for new vaccines (Makino *et al.,* 1998; Imada *et al.,* 1999; Shimoji *et al.,* 1999). Attenuated vaccines can be injected, given orally in drinking water, or delivered by aerosol with special equipment. Antibiotic treatment should be stopped 10 days prior to giving attenuated live vaccines. Experimental evidence has demonstrated that attenuated vaccines are still effective when porcine reproductive and respiratory syndrome (PRRS) is a concurrent infection (Sakano *et al.,* 1997a). Due to the ubiquitous nature of *E. rhusiopathiae* the ultimate prevention plan is to obtain SPF animals and maintain them in a barrier facility.

Control. Management, husbandry, and the environment in the facility should be improved. Chronically infected animals should be eliminated from the facility. Polymerase chain reaction (PCR) assays for the diagnosis of swine erysipelas can be used to advantage in a control program, since culture can be difficult (Brooke and Riley, 1999). Routine use of common disinfectants, including hypochlorite, quaternary ammonium, phenolic, and alkali, is important as these bacteria can survive in the environment for long periods.

Treatment. Penicillin is the treatment of choice for the acute form of SE. Tetracyclines (oxytetracycline and chlortetracycline), tylosin, and lincomycin are also effective. In one reported outbreak a combination of procaine penicillin and dihydrostreptomycin given for 3 days worked well (Wabacha *et al.,*

1998). Hyperimmune serum has been used historically and can be effective if given early in the course of the disease, especially in suckling piglets. This will provide about 2 weeks of passive immunity. Anti-inflammatory drugs can be used to treat the arthritis associated with chronic SE (Wood, 1999; Cowart, 1995).

Research complications. Acute SE can potentially complicate research protocols involving small numbers of swine by causing losses due to sudden death. The chronic form will affect orthopedic and cardiovascular studies since proliferative, nonsuppurative arthritis and vegetative proliferation on the heart valves can result.

d. Streptococcosis (Streptococcal Meningitis)

Etiology. Streptococcus suis (Lancefield's group D) is a gram-positive oval cocci found as diplococci or short chains. It is a facultative aerobe that produces a zone of hemolysis when grown on blood agar plates. Capsular types 1–8 are most often associated with clinical disease in swine, with type 2 being the most common (Aarestrup *et al.,* 1998a).

Clinical signs and differential diagnoses. Manifestations of meningitis are the most characteristic signs of *S. suis* type 2 infections in swine, and swine aged 5–16 weeks are most commonly affected. Pyrexia to 42.5°C is usually the initial sign, followed by anorexia, depression, ataxia, paddling, opisthotonus, convulsions, and death. Additional signs of *S. suis* infection include pneumonia, rhinitis, polyarthritis, stillbirths, abscesses, and vaginitis. Endocarditis and myocarditis may develop in some cases, and dyspnea, cyanosis, weight loss, and sudden death are typical clinical signs (Higgins and Gottschalk, 1999; Staats *et al.,* 1997). Differentials include other streptococcal infections, *Haemophilus parasuis, Erysipelothrix rhusiopathiae, Salmonella choleraesuis,* and salt poisoning or water deprivation.

Epizootiology and transmission. Transmission is by carriers and flies between herds; and sows infect newborns during parturition and suckling by direct contact, aerosols, and fomites. Most piglets of carrier sows are colonized before weaning age (Torremorell *et al.,* 1998). This bacterium has been cultured from a variety of other animals, including humans, birds, and wild *Sus scrofa* (Seol *et al.,* 1998), and theoretically these are potential vectors.

Subclinical carriers harbor the organism in their tonsilar crypts, nasal cavity, and reproductive and gastrointestinal tracts. When a carrier is introduced to a susceptible herd, the signs are usually first evident in recently weaned young between 5 and 12 weeks of age. Simultaneous infection with other pathogens, including PRRS and pseudorabies virus, can increase the severity of clinical signs (Cowart, 1995).

Necropsy Necropsy findings include lymphadenopathy, fibrinous pleuritis/pericarditis, polyserositis, and vascular congestion of organs (Erickson, 1987). Histopathologic findings include suppurative meningitis, fibrinous cranioventral bronchopneumonia, and suppurative polyarthritis. Another streptococcus species, *S. equisimilis,* may be recovered from cases of septicemia associated with subsequent development of swollen joints. At necropsy there is a hyperemic synovium and periarticular edema, and there may be periarticular abscesses and fibrosis as well as metaphyseal osteomyelitis and endocarditis. The organism may persist in the joints for 3–6 months (Sanford and Higgins, 1992).

Pathogenesis. The pathogenesis of *S. suis* is believed to begin via colonization of the palatine tonsil. It is then spread either by direct migration through the cribriform palate of the ethmoid bone or via a septicemia. Adult animals may be carriers and spread the organism from sows to neonatal piglets via nasal excretions or from the genital tract during farrowing (Clifton-Hadley *et al.,* 1984; Erickson, 1987).

Prevention. Rederivation by hysterectomy or hysterotomy and maintenance in a barrier facility will eliminate *S. suis* from an infected herd (Higgins and Gottschalk, 1999). Probably the most satisfactory method is depopulation and repopulation with clean animals since it is feasible to eliminate the modes of transmission in research facilities. Antimicrobial therapy and early weaning did not eliminate the tonsillar carrier state (Amass *et al.,* 1996). A PCR assay developed for the detection of strains of serotypes 1 and 2 in tonsillar specimens (Wisselink *et al.,* 1999) and an ELISA based on a purified polysaccharide antigen (Kataoka *et al.,* 1996) have been found to be specific and sensitive and may be useful for monitoring of herd health.

Control. Minimization of environmental and experimental stress, good sanitation, prophylactic antibiotics, and use of bacterins will help control clinical disease. *Streptococcus suis* is susceptible to common disinfectants. Medicated early weaning and segregated early weaning programs are unlikely to be useful because the neonates are colonized very early after birth (MacInnes and Desrosiers, 1999). Mixing swine from different sources and of different ages should not occur. Oral medication of feed or water has been shown to be beneficial in controlling streptococcal meningitis. Penicillin, ampicillin, and amoxicillin antimicrobials are recommended (Awad-Masalmeh *et al.,* 1999); however, it must determined that clinically efficacious serum concentrations with the particular dose and route of administration would be achieved. Bacterins of different designs, including autogenous and whole-cell, have had variable success. Live avirulent strains (Busque *et al.,* 1997) and vaccines against cell-wall proteins or extracellular proteins, particularly suilysin (Jacobs *et al.,* 1996), have produced protective immunity in swine (Higgins and Gottschalk, 1999).

Treatment. Early treatment with a parenteral antibiotic to which the particular herd strain has been shown to be susceptible by testing or prior experience is the treatment of choice. Drugs to consider include ceftiofur (Burton *et al.,* 1996), enrofloxacin, amoxicillin, ampicillin, and penicillin. Resistance to several antibiotics, including tetracycline, tylosin, and sulfonamides, is a developing concern (Aarestrup *et al.,* 1998b; Rasmussen *et al.,* 1999).

Research complications. Direct losses from fatal meningitis will certainly affect all types of research. Cardiovascular studies will be confounded by the development of endocarditis and myocarditis. *Streptococcus suis* type 2 is zoonotic to humans (Erickson, 1987).

e. *Pseudorabies (PR)*

Etiology. Pseudorabies, also known as Aujeszky's disease, was not considered important in the United States prior to 1960. However, since that time it has been significantly elevated in stature due to the emergence of new and more virulent strains and changes in husbandry practices that have potentiated its spread among swine. The virus belongs to the alphavirus subfamily of the Herpesviridae. This classification of viruses is known for the ability to establish latent infections, particularly in the sensory ganglia of the nervous system.

The virus can affect a variety of animals, including pigs, cattle, sheep, goats, dogs, cats, rodents, macaques, and marmosets. Reports of human infection have been limited and are poorly documented (Kluge *et al.,* 1992). Infection of all animals other than the pig results in death. Pigs are capable of hosting subclinical and latent infections.

Clinical signs and differential diagnoses. The clinical signs associated with this disease are primarily related to the age of the swine affected, although the strain of virus and the infectious dose also play a role. The virus predominantly impacts the respiratory and nervous systems with related clinical signs. Neonatal pigs typically respond to exposure with acute signs related to the central nervous system (CNS). Affected pigs will tremble, hypersalivate, stumble, and exhibit nystagmus and opisthotonus, often with epileptiform-like seizures. Because of posterior paresis, the animals may be observed actually sitting like a dog. Other signs include circling and paddling, vomiting, and diarrhea. Once CNS signs start, death usually follows within 24–36 hr, and mortality approaches 100%. As the pigs age, the clinical signs become less severe, fewer pigs develop CNS involvement, and mortality declines. Respiratory signs characterized by sneezing, nasal discharge, and cough become the hallmark of pigs that are infected at greater than 9 weeks of age. Morbidity rate is high, but mortality is low with uncomplicated CNS signs such as muscle tremors that occur only sporadically. The duration of clinical signs is usually 6–10 days, with rapid recovery unless the disease has progressed to pneumonia or a secondary bacterial pneumonia has been initiated. Sows and boars also develop primarily respiratory signs, although pregnant animals in the second to third trimester abort and in the first trimester, resorb the fetus.

The main differential diagnosis is swine influenza.

Epizootiology and transmission. The virus is spread within a herd in various ways. The single most important mechanism contributing to disease spread is the movement of swine who are shedding the viral particles. Transmission can occur via direct contact, insemination, or transplacental transmission. Indirect transmission can occur by inhalation of aerosolized particles or by contact with contaminated surfaces. Fomite transmission is also possible. Infective levels of virus can persist for up to 7 hr in air with relative humidity of 55% (Schoenbaum *et al.,* 1990). Infective levels of viral particles can also be present in tissues of animals that have died from the disease. Consuming infected carcasses or feed that has been contaminated with the virus is another means of transmission. Evidence indicates that avian species are not a significant contributor to the spread of the virus, and the role of insects in the transmission process has not been adequately evaluated (Zimmerman *et al.,* 1989). Animals other than pigs, which are considered dead-end hosts, typically die within 3 days of being infected.

Diagnosis. Pseudorabies in older animals can easily be confused with swine influenza, especially if the only clinical signs manifested are respiratory in nature. When CNS signs are exhibited, the clinical diagnosis of PR becomes much clearer. Serology is not the ideal choice for defining acute infections, as there is a delay in humoral antibody development; and interpretation of serologic results can be difficult, especially in younger animals, as maternal antibodies are present until piglets are up to 4 months of age. If serology is used to diagnose an active infection, it is recommended that paired serum samples be collected at a 2-week interval to demonstrate a rise in antibody titer (Kluge *et al.,* 1992). Virus isolation allows for a definitive diagnosis, with brain, spleen, and lung being the organs of choice.

Necropsy. Gross lesions may be minimal or may include a fibrinonecrotic rhinitis; necrotic foci in the tonsils, liver, spleen, and lungs; and an endometritis and necrotizing placentitis (Thomson, 1988). Microscopic lesions includes a nonsuppurative meningoencephalitis and ganglioneuritis involving both gray and white matter, and intranuclear inclusions may be found in neurons, astrocytes, oligodendroglia, and endothelial cells (Thomson, 1988). There is a necrotizing bronchitis and alveolitis, necrotizing tonsilitis, lymphohistiocytic endometritis, and necrotizing placentitis with inclusion bodies in both necrotic cells and epithelial cells around the foci of necrosis (Kluge *et al.,* 1992).

Pathogenesis In natural infections, the virus enters via the mucosal epithelium in the nasopharynx and tonsils and then spreads via the lymphatics to regional lymph nodes where it replicates and results in a viremia (Thomson, 1988). The virus also spreads via the axoplasm of the trigeminal, glossopharyngeal, and olfactory nerves to the medulla and pons where it replicates in neurons and then spreads to other parts of the brain and results in latent infection of the trigeminal ganglia (Kluge *et al.,* 1992).

Prevention and treatment. Modified live, killed, and gene-deleted vaccines with foreign-gene insertions are available to aid in the control of pseudorabies (Mulder *et al.,* 1997). The vaccines protect pigs against clinical signs and mortality but do nothing toward eradicating the disease; the vaccine does not eliminate the virus in infected animals, nor does it prevent animals from becoming infected with the virus. Animals that are vaccinated, however, do shed lesser amounts of virus and have a limited tissue invasion by the organism. The gene-deleted vaccinations offer the advantage of producing vaccinated animals that lack antibody against the specific protein coded for by the deleted gene. This allows the vaccinated pig to be differentiated serologically from an infected pig.

Pseudorabies is a reportable disease, and in January 1989, a national pseudorabies virus-eradication program was implemented in the United States (Ormiston, 1988). This program includes test and removal, offspring segregation, and depopulation and repopulation. The majority of industrialized nations support the concept of and are planning eradication programs.

2. Respiratory Diseases

a. Atrophic Rhinitis (AR, PAR, NPAR)

Etiology. Toxigenic strains of *Pasteurella multocida, Bordetella bronchiseptica,* and *Haemophilus parasuis* are the bacterial agents of this multifactorial disease. Porcine cytomegalovirus (CMV), which is the cause of inclusion body rhinitis, does not cause nasal turbinate atrophy; however, it may damage the nasal mucosa, predisposing it to colonization with one of these bacterial agents. Environmental air pollutants, namely, high ammonia levels (50–100 ppm) and dust (Hamilton *et al.,* 1999), and genetic factors also play a role. *Pasteurella multocida* strains A and D produce a thermolabile dermonecrotic toxin (DNT), which severely damages the nasal mucosa, producing a progressive form of nasal turbinate atrophy. *Bordetella bronchiseptica* also produces a heat-labile DNT and alone will produce a moderate self-limiting form of the disease in which damaged tissues may regenerate in time (Tibor, 1999). *Haemophilus parasuis* reportedly causes a mild turbinate atrophy (Cowart, 1995). Combined infections of toxigenic *P. multocida* and *B. bronchiseptica* produce the most severe form. Typically, two or more infectious organisms are required to produce clinical disease with permanent nasal distortion and turbinate atrophy. Recently, the term "nonprogressive atrophic rhinitis" (NPAR) has been applied to the form caused by *B. bronchiseptica* alone, and the term "progressive atrophic rhinitis" (PAR) to *P. multocida* alone and combined infections of *P. multocida* and *B. bronchiseptica* (De Jong, 1999).

Clinical signs and differential diagnoses. The clinical signs of pure *B. bronchiseptica* infection (NPAR) generally appear in nursery pigs less than 4 weeks of age and consist of sneezing, snuffling, and a mucopurulent nasal discharge. In older pigs these signs are milder or nonexistent. In very young pigs (3–4 days old) a severe bronchopneumonia can result. This form is much more rare than the nasal infections. The signs are a mild fever (103°–104°F or 39.5°–40°C), marked "whooping" cough, and dyspnea, with high morbidity and mortality possible if untreated. This organism is frequently isolated from pneumonic lesions of older pigs; however, its role as a pathogen in this situation is questionable (De Jong, 1999). Other diagnoses to rule out for *B. bronchiseptica* include CMV and other causes of sneezing and rhinitis.

The clinical signs of *Pasteurella multocida* (PAR) typically begin at 1 to 3 months of age and consist of sneezing and snuffling, which progresses to more violent sneezing with mucopurulent nasal discharge. In some cases epistaxis is seen. Inflammation of the nasolacrimal duct, which causes occlusion of the duct and subsequent tear staining visible at the medial canthus, frequently occurs. The most characteristic clinical sign is the dorsal and/or lateral deviation of the snout as the pig grows. This is caused by the abnormal bone growth, which occurs as a result of unequal nasal turbinate atrophy. Brachygnathia superior (BS) is the most common form seen and is due to slower bone growth in the upper jaw which gives it an upturned appearance. Significant turbinate atrophy can be present without visible snout abnormalities. Commonly, this atrophy is subjectively measured at necropsy by visual scoring of a section at the level of the second premolar. Techniques for objective quantification of this atrophy by digital image analysis or digitization (Gatlin *et al.,* 1996) and computed tomography (Shryock *et al.,* 1998) have been published. The latter method allows morphometric analysis of live pigs. In the more severe cases, whole-body growth rate will be decreased (De Jong, 1999), and this may be due in part to the possibility that the toxin produced affects the growth of the skeletal system (Ackermann *et al.,* 1996). Differentials for PAR include other causes of facial deformities, including paranasal abscesses and breed variations.

Epizootiology and transmission. *Bordetella bronchiseptica* is spread from pig to pig by aerosol droplets, which probably first occurs with snout-to-snout contact between a sow and a newborn piglet. This is followed by horizontal spread among littermates; however, spread can occur at any age. Piglets infected in the first week of life will generally develop more severe lesions

than those infected at 4 weeks or later. Those infected at 9 weeks show almost no lesions (De Jong, 1999). The quantity and quality of passive antibody obtained from the sow also affects the severity of lesions. In SPF herds the mode of transmission is often the introduction of new carrier animals to the herd. *Bordetella bronchiseptica* can be isolated from many domestic and wild species; however, these strains are usually nonporcine and less pathogenic for swine. This bacterium is commonly cultured from most swine herds and is not always associated with disease.

Pasteurella multocida infection in SPF herds typically occurs by the introduction of carrier pigs. Once introduced into a seronegative herd, these bacteria will quickly spread by direct contact and aerosols. The pharynx, especially tonsils, and vagina of sows are sources of infection for piglets. Age of first infection inversely affects the severity of lesions; however, older pigs (3–4 months) will still develop lesions, which is in contrast to infection with *B. bronchiseptica* (De Jong, 1999).

Necropsy (Pasteurella multocida). There are varying degrees of deformity of the snout and the nasal septum. Distortion and atrophy of the turbinates are most severe in the ventral scroll of the ventral turbinates but also involve the dorsal scroll of the ventral turbinates, dorsal turbinates, and ethmoid turbinates. Microscopic changes include atrophy of the osseous cores of the turbinates and replacement by fibrous connective tissue, metaplasia of respiratory epithelium to stratified squamous, and inflammatory cell infiltrates in the lamina propria (De Jong, 1992).

Pathogenesis (Pasteurella multocida). Production of lesions in this disease is dependent on the presence of toxigenic *P. multocida* and/or *B. bronchiseptica* colonization of the nasal epithelium with elaboration of toxins (De Jong, 1992). These toxins incite inflammatory cell infiltrates in the lamina propria and cause atrophy of mucosal glands, osteolysis, and replacement of turbinate bones by fibrous connective tissue.

Necropsy (Bordetella bronchiseptica). Lesions in young pigs are catarrhal rhinitis, varying degrees of atrophy of the turbinates (most severe in the ventral scroll of the ventral turbinate), and a bilateral bronchopneumonia involving the apical and cardiac lobes (Giles, 1992; Duncan *et al.,* 1966a). Microscopic lesions in the turbinates are metaplasia of the respiratory epithelium to stratified squamous, and an inflammatory cell infiltrate in the lamina propria with atrophy of the osseous cores and replacement by fibrous connective tissue. There is a severe vasculitis, endothelial cell hyperplasia, hemorrhage, and alveolar and perivascular fibrosis in the lung (Duncan *et al.,* 1966b).

Pathogenesis (Bordetella bronchiseptica). Bordetella bronchiseptica colonizes the ciliated epithelial cells in the nasal epithelium, where it results in loss of cilia. It also produces a toxin that is believed to penetrate the lamina propria and initiate an inflammatory infiltrate and atrophy of the osseous cores (Giles, 1992).

Prevention. Development and maintenance of an SPF swine facility using cesarian section, medicated early weaning, and segregated early weaning are the most satisfactory methods of prevention. The focus should be on assuring freedom from toxigenic *P. multocida* since this is the most pathogenic etiologic agent of this multifactorial disease. Polymerase chain reaction (PCR) assays directed at the gene that encodes for the dermonecrotic toxin produced by toxigenic strains of *P. multocida* are reportedly specific and sensitive when used on nasal and tonsillar swabs (Kamp *et al.,* 1996; Lichtensteiger *et al.,* 1996) and colostrum (Levonen *et al.,* 1996). Assays of this type and enzyme-linked immunosorbent assays (ELISAs) may be used for herd-health monitoring, facility biosecurity, and clinical diagnosis.

Control. The majority of conventional swine herds are infected with *B. bronchiseptica,* and a smaller proportion also have strains A and D of *P. multocida,* the bacterial etiologic agents of atrophic rhinitis, but it is possible to keep these herds free of significant clinical disease through good sanitation, husbandry, and management. Experimental evidence has shown that continuous exposure of piglets to 20 ppm ammonia for 2 weeks will markedly exacerbate *P. multocida* colonization in the upper respiratory tract (Hamilton *et al.,* 1998). Practices such as disinfection between groups of animals housed in a facility; adequate air changes to reduce ammonia levels; good temperature control; adequate nutrition and pen space; and control of concurrent diseases, dusty conditions, and experimental stress will help. *Pasteurella multocida* and *B. bronchiseptica* are sensitive to most common disinfectants.

Vaccines for both *P. multocida* and *B. bronchiseptica* are available as bacterins and toxoids and are considered effective against atrophic rhinitis (Sakano *et al.,* 1997b). These are generally given to the sow prefarrowing, as improved colostral immunity is considered more important than piglet vaccination.

Treatment. A treatment plan for NPAR and PAR should include a combination of environmental and husbandry improvements followed by a vaccination and antibiotic program tailored to the particular facility. One approach is to medicate the feed of sows during the last month of gestation to reduce the bacterial load and source of initial exposure for suckling piglets. The oral antibiotics of choice include tilmicosin (Olson and Backstrom, 1999), sulfonamides, and tetracyclines. Piglets can be given weekly or biweekly parenteral injections of oxytetracycline, potentiated sulfonamides, ceftiofur, or penicillin/streptomycin, preferably based on culture and susceptibility, for the first month of life. Medication of feed or water in older weaned pigs at risk for PAR for periods of at least 4–5 weeks will help control clinical signs (De Jong, 1999).

Research complications. The toxin produced by severe infections of toxigenic strains of *P. multocida* will induce liver and kidney lesions as well as damage nasal turbinates. *Bordetella bronchiseptica* can induce pneumonic lesions in very young piglets. Therefore, PAR has the potential to affect most chronic research studies.

b. *Pasteurellosis*

Etiology. *Pasteurella multocida* is a gram-negative coccobacillus and a facultative anaerobe. Capsular serotypes A, B, and D have been reported in swine, with A being the most common in pneumonic lungs and B causing the most severe disease. Serotype B has not been reported in natural outbreaks in Europe and the United States (Pijoan, 1999). The role of toxin production by *P. multocida* as a virulence factor in pneumonic pasteurellosis is not clear; however, it has a defined role in causing atrophic rhinitis.

Clinical signs and differential diagnoses. The predominant signs of the acute form of the disease are dyspnea ("thumping"), cough, anorexia, and fever to 107°F (41.7°C). Sudden death is not typical unless rare serotype B strains are involved. Morbidity and mortality are variable, and typically pigs will lose weight and have a decreased rate of growth. The chronic form of the disease is characterized by intermittent cough, thumping, and low fever of 103°–104°F (39.5°–40°C) or no pyrexia. The acute form is clinically similar to pleuropneumonia (APP) without the frequency of sudden death; the chronic form is similar to mycoplasmal pneumoniae of swine (MPS). *Salmonella choleraesuis* should also be considered. *Metastrongylus elongatus* and *Ascaris suum* are additional differentials for the chronic form (Cowart, 1995; Pijoan, 1999).

Epizootiology and transmission. *Pasteurella multocida* is a common inhabitant of the upper respiratory tract of swine. It can be cultured from the nose and tonsils of healthy pigs from most herds, including SPF herds (Pijoan, 1999). The transmission is by direct contact and aerosols.

Necropsy. Gross findings in the lungs are usually confined to the cranioventral aspects of the lobes and include red to gray areas of consolidation, frothy exudate in the trachea, suppurative pleuritis and pericarditis (Pijoan and Fuentes, 1987), pleural adhesions, and pulmonary abscesses (Pijoan, 1992). The histopathologic lesions in the lungs are a severe suppurative bronchopneumonia, pleuritis, and abscess.

Pathogenesis. *Pasteurella multocida* serotype A adheres to ciliated respiratory epithelial cells, while serotype D adheres to nonciliated cells (Pijoan, 1992). It is usually not a primary agent but results in disease when adherence is facilitated by the presence of other agents. *Pasteurella multocida* has been shown to produce a toxin that results in necrosis of osteoblasts and stimulation of osteoclastic bone resorption in the nasal turbinates, leading to turbinate atrophy (Dominick and Rimler, 1988).

Prevention. It is essential to identify and treat or manage any concurrent pathogens since *P. multocida* is usually the secondary agent. Typically, pasteurellosis is a complication of *Mycoplasma hyopneumoniae* infection. High quality control of environmental air temperature, humidity, and ammonia levels is critical.

Control. Vaccination and medicated feed (tetracyclines, tylosins) and water may be beneficial. Any concurrent respiratory pathogens, especially *Mycoplasma hyopneumoniae,* PRRS, swine influenza, *Actinobacillus pleuropneumoniae,* and parasites should be controlled. The role of PRRS in exacerbating pasteurellosis is still uncertain and probably has only a mild effect (Carvalho *et al.,* 1997).

Treatment. Animals showing clinical signs should be treated with a parenteral antibiotic based on susceptibility testing. Alternatively, oxytetracycline, ceftiofur (Burton *et al.,* 1996), penicillin, florfenicol, enrofloxacin, or doxycycline dosed in the feed has been shown to be effective at controlling pneumonia caused by *P. multocida* and *M. hyopneumoniae* (Bousquet *et al.,* 1998). Development of resistance to antibiotics among Pasteurellae is a concern (Hormansdorfer and Bauer, 1998).

Research complications. Bronchopneumonia-associated accumulation of purulent fluid in airways will complicate general anesthesia. Severe infections produce fibrinous pleuritis and pericarditis, which will confound most cardiovascular and respiratory system research studies.

c. *Pleuropneumonia (APP)*

Etiology. *Actinobacillus pleuropneumoniae,* previously designated as *Haemophilus pleuropneumoniae* or *H. parahaemolyticus,* is the cause of pleuropneumonia of swine. Extracellular hemolytic toxins ApxI, ApxII, and ApxIII are some of the more important virulence factors of the *A. pleuropneumoniae* strains that produce them (Reimer *et al.,* 1995; Kamp *et al.,* 1997). All serotypes secrete one or more Apx toxins. There are currently 12 recognized serotypes (1–12) (Burkhardt *et al.,* 1999); however, serovars 1, 5, and 7 are isolated most frequently (Cowart, 1995). This bacterium is a gram-negative encapsulated coccobacillary rod, which requires nicotinamide adenine dinucleotide (NAD or factor V) for growth. Primary isolation may be achieved by cross-streaking on a blood agar plate with a staphylococcus, which produces NAD. Termed "satellitism" or "satellite phenomenon," this will allow growth near the staphylococcus colonies. Chocolate agar media, which is supplemented with NAD, is commonly utilized. This organism also

shows the Christie-Atkins-Munch-Petersen (CAMP) phenomenon or reaction when colonies are grown near a β toxigenic *Staphylococcus aureus.* This consists of an increased zone of hemolysis greater than the partial lysis created by the *S. aureus* and is due to cytolysins (Taylor, 1999).

Clinical signs and differential diagnoses. The clinical signs of APP can be categorized into peracute, acute, and chronic forms. The peracute form is characterized by sudden death. In the acute form, pigs have fevers of 105°–107°F (40.6°–41.7°C), depression, anorexia, cyanosis, severe dyspnea with a marked abdominal component ("thumping"), and sometimes death within 36 hr. The chronic form is characterized by variable cough, decreased rate of body-weight gain, and other complications (pleuritis, abortion, endocarditis, arthritis, abscesses). Serotype 2 has been connected with lameness due to necrotizing osteomyelitis and fibrinopurulent arthritis in 8- to 12-week-old pigs (Jensen *et al.,* 1999). All three forms may be found in the same group of animals. A list of diagnoses to rule out would include other causes of pneumonia, primarily MPS, pasteurellosis, PRRS, *Salmonella choleraesuis,* and combinations of these agents.

Epizootiology and transmission. Transmission is primarily by snout to snout and by aerosol. Recovered swine become chronic carriers and are a source of transmission within the herd and between herds. Pleuropneumonia is more prevalent in facilities that bring in swine from multiple sources on a regular basis. Typically, in herds where APP is endemic, the piglets are infected in the farrowing pen and a carrier sow is the source. All age groups are affected, and morbidity and mortality are linked to environmental quality, stress, and concurrent infection with other pathogens. The disease is prevalent worldwide, different countries tend to have a different set of serovars, and multiple serovars can be found in one facility. The spread is likely related to the movement of animals since artificial insemination and embryo transfer are unlikely sources of introduction (Taylor, 1999).

Necropsy. The gross findings in pigs with *A. pleuropneumoniae* are a fibrinous pleuritis, pulmonary edema, and the presence of bloody froth or clotted fibrin plugs in the trachea and bronchi (Fig. 12). The lungs contain bilateral lesions that are dark red and firm with a predominance of lesions in the dorsal aspects of the caudal lobes, and there may be a bloody nasal discharge (Didier *et al.,* 1984; Bertram, 1985; Nielsen, 1973). Histopathologic lesions are a necrotizing, fibrinous, and hemorrhagic pneumonia that is predominantly lymphocytic and histiocytic, as well as a vasculitis with thrombosis of vessels and lymphatics (Didier *et al.,* 1984; Nielsen, 1973).

Pathogenesis. Primary damage to the capillary endothelium in alveoli may be the result of endotoxin produced by *A. pleuropneumoniae* in acute and peracute infections. This results in severe edema and fibrin deposition as well as in thrombosis of capillaries and ischemic necrosis of pulmonary parenchyma (Bertram, 1985).

Prevention. The most satisfactory prevention program is to maintain a closed, APP-free herd through strict isolation. Ar-

Fig. 12. Yucatan microswine lung infected with *Actinobacillus* (formerly *Haemophilus*) *pleuropneumoniae.*

tificial insemination and embryo transfer can be utilized when introduction of new genetics is required. Alternatively, only known SPF animals that have been validated by serologic testing (ELISA, CF, or PCR) can be added. An ELISA utilizing the *A. pleuropneumoniae* ApxII antigen has been shown to be useful for this purpose (Leiner *et al.,* 1999). In addition, PCR on mixed bacterial cultures from swine tonsils may be more sensitive than culture for detection (Gram *et al.,* 1996). Vaccination of seronegative animals prior to introduction and maintaining optimal ambient temperature, ventilation, and humidity are useful for minimizing clinical disease in infected herds (Taylor, 1999). Segregated early-weaning practices can potentially eliminate APP; however, this is difficult because this bacterium is an early colonizer (MacInnes and Desrosiers, 1999). Depopulation and restocking with hysterectomy-derived SPF animals is the most satisfactory means of prevention.

Control. Vaccines of the killed whole cell, cell-free antigens (Oishi *et al.,* 1995), or subunit type (Burkhardt *et al.,* 1999) may reduce morbidity and mortality and extent of treatment. Oral immunization with live or inactivated *A. pleuropneumoniae* serotype 9 has been shown to provide partial clinical protection from aerosol challenge (Hensel *et al.,* 1995). A vaccine strain of *A. pleuropneumoniae* produced by insertional inactivation of the ApxII operon can be delivered live intranasally and provide cross-serovar protection (Prideaux *et al.,* 1999). Additional control measures include good husbandry practices, including use of disinfectants and minimization of stress.

Treatment. Parenteral antimicrobials, including ceftiofur (Burton *et al.,* 1996), penicillin, tetracyclines, and enrofloxacin, can reduce mortality in the acute stage of the disease. Marked resistance has been reported for amoxicillin, oxytetracycline, and metronidazole (Gutierrez *et al.,* 1995). Medicating feed and water with an antimicrobial at a low minimum inhibitory concentration (MIC) for members of an affected group that are still eating and drinking may be successful. Oral chlortetracycline (CTC) has been found to offer better protection from clinical disease than oxytetracycline (OTC) in experimental APP serotype 1 clinical challenge. This is probably due to the greater bioavailability of CTC in medicated feed (del Castillo *et al.,* 1999). Tilmicosin phosphate added to feed 5 days prior to clinical disease has been shown to lower APP mortality and clinical impression scores (Moore *et al.,* 1996; Bane *et al.,* 1999). A combination of parenteral and oral medication often yields the best results. Antimicrobial therapy will not eliminate the chronic form or carrier animals from the herd (Taylor, 1999).

Research complications. APP will affect any research involving the respiratory or cardiovascular systems since pleurisy, pneumonia, and pericarditis may result. The mortality associated with the acute form may terminate most studies.

d. Mycoplasmal Polyserositis and Arthritis

Etiology. Mycoplasma hyorhinis is probably the easiest of the porcine mycoplasmas to isolate and is a common contaminant of cell culture lines.

Clinical signs and differential diagnoses The age group most commonly affected is 3 to 10 weeks of age. Clinical signs typically begin about 1 week after some form of stress or initial exposure to the etiologic agent. The acute signs are lethargy, anorexia, labored respirations, arched back with tucked-up abdomen, lameness, and fever of 104°–105°F (40°–40.6°C). These signs abate in about 2 weeks except that the lameness with swollen joints may persist for several months. Experimental *M. hyorhinis* intranasal inoculation has been shown to cause eustachitis and occasionally otitis media (Morita *et al.,* 1998, 1999). *Haemophilus parasuis* should be ruled out for this clinical disease.

Epizootiology and transmission. This organism is harbored in the respiratory tract of carrier swine, often without clinical disease. The most likely first exposure for baby pigs is from aerosolization or direct contact with nasal secretions from the sow prior to weaning. The organism will spread rapidly through group-housed pigs and typically will not cause clinical disease unless the animals are stressed. Stress will induce a septicemia and the resulting lesions.

Necropsy. Acute lesions include a serofibrinous or fibrinopurulent pleuritis, pericarditis, and peritonitis, as well as a serofibrinous arthritis with increased synovial fluid and swollen reddish yellow synovial membranes (Ross *et al.,* 1971). The joints most frequently involved are the stifle joints, but the tibiotarsal, cubital, coxofemoral, and shoulder joints may also be involved (Ross *et al.,* 1971). This agent has also been reported to cause otitis media in swine (Morita *et al.,* 1995).

Pathogenesis. Mycoplasma hyorhinis is commonly found in the nasal passages of young pigs and is believed to be an opportunist following a stressful event, with a septicemia and seeding of the organism in the joints (Ross, 1992).

Prevention and control. Eliminating stress of any type can best prevent clinical outbreaks of disease. This includes eliminating other diseases, controlling temperature and humidity fluctuations, and avoiding shipping and invasive research protocols. Concurrent infection with *M. hyorhinis* and PRRSV has been found to cause severe pulmonary lesions with respiratory distress (Kawashima *et al.,* 1996) and underscores the need to eliminate other pathogens.

Treatment. Prophylactic treatment of the entire herd by medicating food or water with lincomycin or tylosin may be

beneficial. Antimicrobial treatment of clinically affected swine is unrewarding (Ross, 1999a; Cowart, 1995).

Research complications. Although mortality is low and morbidity typically less than 25%, clinical disease will confound cardiovascular studies and surgical models because it causes pericarditis, pleuritis, and peritonitis.

e. Mycoplasmal Pneumonia: Enzootic Pneumonia, Virus Pig Pneumonia, Mycoplasmal Pneumoniae of Swine (MPS)

Etiology. *Mycoplasma hyopneumoniae* is a common pathogen that colonizes the ciliated epithelium of the porcine respiratory tract. Mycoplasmas are small (0.2–0.3 mm), lack a cell wall, and are nonmotile, fastidious, gram-negative facultative anaerobes. They belong to the class Mollicutes and are the smallest free-living cells.

Clinical signs and differential diagnoses. Although younger pigs may be affected, generally clinical signs are not obvious until pigs are 3–6 months of age. Uncomplicated MPS is generally characterized by a reduced growth rate and a chronic cough precipitated by exercise. In some affected animals the cough may not be readily evident. Morbidity is typically high and mortality low unless complicated by concurrent viral infections, secondary bacterial or other mycoplasmal diseases, or stress of any form. It plays an important role in porcine respiratory disease complex (PRDC) when concurrent infection with porcine reproductive and respiratory syndrome (PRRS) occurs (Thacker *et al.,* 1999); however, additional experimental evidence indicates that this is not true for very young (3-week-old) pigs (Van Alstine *et al.,* 1996). In these complicated infections, malaise, anorexia, fever, labored respirations ("thumping"), and possibly death may result (Ross, 1999b). Bacteria that frequently complicate MPS and are clinical differentials include *Pasteurella multocida, Bordetella bronchiseptica, Actinobacillus pleuropneumoniae, Salmonella choleraesuis,* and *Streptococcus suis* (Bousquet *et al.,* 1998; Cowart, 1995). Pneumonias due to other etiologic agents such as swine influenza, *Ascaris suum,* and *Metastrongylus elongatus* are additional differentials and complicating agents.

Epizootiology and transmission. The spread of MPS is primarily by direct contact with respiratory secretions and aerosols from carrier swine. Generally it is transmitted from infected sows to suckling piglets prior to weaning; however, pigs of all ages are susceptible. It is probably the most common cause of chronic pneumonia in swine, and most conventional herds are affected.

Necropsy. Grossly, the lungs contain pale gray or dark red foci of consolidation that are most commonly found in the apical lobes and the cranioventral aspects of the middle, accessory, and caudal lobes. Additionally, there may be a purulent exudate in the bronchi. Microscopic lesions consist of perivascular, peribronchial, and peribronchiolar infiltrations of large numbers of lymphoreticular cells, which in chronic lesions may include lymphoid nodules (Piffer and Ross, 1984; Ross, 1992). Additionally, differentiation of cuboidal epithelium to pseudostratified epithelium in bronchioles occurs (Ackerman *et al.,* 1991).

Pathogenesis. *Mycoplasma hyopneumoniae* adhere to the cilia and apical plasma membrane of the respiratory epithelium in the trachea, bronchi, and bronchioles and result in loss of cilia, ciliostasis, and filling of alveoli with cell debris and exudate (Ackerman *et al.,* 1991).

Prevention. The most satisfactory form of prevention is to allow only SPF swine into the facility. *Mycoplasma hyopneumoniae*–free herds may be derived by hysterotomy or hysterectomy, medicated early weaning, or segregated early weaning (Dritz *et al.,* 1996). The success of these techniques should be monitored by a combination of ELISA testing of serum or milk, PCR assay of bronchoalveolar lavage fluids (Baumeister *et al.,* 1998) or lung tissue (Stemke, 1997), clinical observation, and examination of lungs at necropsy. Culture is not usually feasible since mycoplasmas and *M. hyopneumoniae,* in particular, are difficult to isolate and grow.

Control. Control of clinical disease in infected animals is best accomplished by providing optimal environmental conditions with respect to ammonia levels, humidity, temperature control, air changes, overcrowding, and reduction of stress. Protective immunity will develop in swine recovered from MPS, and vaccines are beneficial in some herds (Ross, 1999b). Maternally derived antibodies have been found to inhibit response to *M. hyopneumoniae* vaccination, and the timing of the dosing to avoid this interference varies from herd to herd (Daniels *et al.,* 1999).

Treatment. Antimicrobials, including lincomycin, tetracyclines, especially doxycycline in feed (Bousquet *et al.,* 1998), tiamulin, and several quinolone antibiotics, have been shown to be efficacious in reducing the severity of pneumonia and weight reduction due to MPS. This beneficial effect is generally attributed to controlling complicating bacterial infections. Experimental evidence has shown that doxycycline has greater *in vitro* activity than oxytetracycline against *M. hyopneumoniae, A. pleuropneumoniae,* and *P. multocida* (Bousquet *et al.,* 1997). Recent *in vitro* susceptibility studies have shown that valnemulin has exceptional activity against *M. hyopneumoniae,* and perhaps *in vivo* trials will validate this as another effective antibiotic treatment for MPS (Hannan *et al.,* 1997).

Research complications. Uncomplicated infection with *M. hyopneumoniae* will directly interfere with research involving the

respiratory system, and complicated infections will also interfere with cardiovascular studies since pericarditis may result.

f. Inclusion Body Rhinitis (IBR)

Etiology. Inclusion body rhinitis, a disease caused by porcine cytomegalovirus, is found throughout the world. The causative viral agent is a member of the subgroup of slow-growing herpesviruses, beta herpesvirinae, which produce cytomegaly with hallmark intranuclear inclusions. The agent is species-specific and is able to induce latent infection, with shedding of the organism occurring even in the presence of circulating antibodies.

Clinical signs and research complications. This disease is usually subclinical in pigs more than 3 weeks of age and may even be totally inapparent in young animals if good management practices are being followed. The clinical sequelae typically associated with this disease include unexpected fetal and piglet death, runting, mild rhinitis, pneumonia, and poor weight gain in young pigs. Some piglets may be born anemic, with edema noted around the jaw and tarsal joints. Adult animals that are exposed to this agent for the first time may develop mild anorexia and lethargy. The virus has been documented to modify the host defensive mechanism through inhibiting T-cell function (Kelsey *et al.,* 1977). A differential diagnosis is parvovirus.

Epizootiology and transmission. The virus can be recovered from nasal and ocular secretions, urine, and fluids associated with pregnancy, as well as from male reproductive organs. Dissemination of the agent most commonly occurs via nasal secretions and urine. The majority of virus is excreted from animals at 3–8 weeks of age; however, reactivation of excretion can occur when the animals are stressed. Lung macrophages are the reservoir of infection. The virus can be transmitted transplacentally, and congenital infection often manifests as fetal/neonatal death and runted pigs with rhinitis (Edington *et al.,* 1977).

Diagnosis. The presence of this disease can be confirmed using a serum ELISA. The virus can be isolated from the nasal mucosa, lung, and kidney. Histologic identification of inclusions and cytomegaly in epithelial tissues is also pathognomonic. Differential diagnoses include those diseases that result in an impact on the reproductive system, such as parvovirus and pseudorabies.

Necropsy. Gross lesions in piglets are found in the nasal passages, where there is a serous rhinitis in early stages of the disease and a purulent exudate in older lesions (Thomson, 1988). There may also be a sinusitis, and if the disease becomes systemic, there are petechial hemorrhages and edema in the lungs, lymph nodes, subcutaneous tissues, and pericardial and pleural effusions. The kidneys may contain large numbers of petechia, or they may be dark purple (Edington, 1992). Histologic findings characteristic for this disease are the presence of large basophilic intranuclear inclusions in the epithelial cells in both the mucosa and the mucosal glands (Thomson, 1988; Edington, 1976). If the disease has become systemic, there may be a pneumonia and foci of necrosis in the liver, kidney, CNS, and adrenals, with inclusions in capillary endothelium and sinusoidal cells throughout the body (Thomson, 1988).

Pathogenesis. The virus appears to enter the body through the mucosa, where it replicates inside the epithelial cells of the mucosal, Harderian, and lacrimal glands. The subsequent viremia results in seeding of mucosal glands, renal tubular epithelium, hepatocytes, duodenal epithelium, and in neonates or fetal pigs, the reticuloendothelial cells and capillary endothelium (Edington, 1992, 1976).

Prevention and treatment. Supportive therapy to prevent the occurrence of secondary bacterial infections is always helpful in the face of a viral disease outbreak. Caution should always be taken when introducing new animals into an established grouping as new animals may expose susceptible animals or may stress existing groupings to stimulate resurgence of a latent infection.

g. Swine Influenza

Etiology. Swine influenza, first identified in 1918, is caused by a type A influenza virus. The agent is distributed worldwide, and antibodies to the virus are found in about 45% of the sampled pig populations. The influenza A viruses belong to the family of RNA viruses, Orthomyxoviridae. The type A viruses are further classified based on the glycoprotein spikes that extend from the viral particle (hemagglutinin [H] and neuraminidase [N]). The antigenic characteristics of these spikes provided the basis for dividing these viruses into subtypes. Antigenic comparison of the H1N1 swine viruses has shown, in contrast to human strains, that there has been little antigenic variation over the last 50 years (Sherrar *et al.,* 1989). This could be attributed to the fact that the virus is able to propagate in an ever-present population of nonimmune pigs. Strain H3N2 is also very prevalent in swine.

Clinical signs and differential diagnoses. This disease typically spreads rapidly throughout susceptible herds, with morbidity close to 100%. The animals appear very ill with signs including anorexia, labored open-mouthed breathing, and a strong reluctance to move. The animals have fever, conjunctivitis, rhinitis, and nasal discharge, and will exhibit a barking cough. Despite the apparent severe clinical signs, the animals typically recover rapidly after 5–7 days of developing clinical signs. Mortality is usually less than 1%. Occasionally, abortions, stillbirths, and infertility have been reported to occur concomitantly with infection; however, studies have shown that the virus was

not directly responsible (Brown *et al.,* 1982.) The main differentials include bacterial pneumonias.

Diagnosis. A definitive diagnosis can be made through isolation of the virus by swabbing nasal mucosa, or by demonstration of seroconversion. Serologic diagnosis requires paired serum samples (disease onset, then 4 weeks later) demonstrating an increase in antibody titer. Diagnosing weanling pigs via serology is difficult as maternal antibody persists up to 4 months. Young pigs carrying maternal antibody may still be infected and shed viral particles.

Epizootiology and transmission. Swine influenza typically appears as a result of population movement, i.e., new animals entering the herd. Outbreaks can be described as explosive, rapidly spreading through all animals within a grouping. Once the virus gains purchase within a population of swine, the disease is likely to recur unless the grouping is totally depopulated.

The primary route of transmission is via direct contact with the viral particles that are found in high concentrations in nasal secretions. There is no evidence that supports a carrier state, and the widespread occurrence and persistence of the virus is attributed to its continued passage to young susceptible animals or animals that have lost protective antibody titers obtained from previous infections.

The H1N1 viruses have a very wide host range, including humans and birds, and interspecies transmission readily occurs. The H1N1 viruses can cause acute respiratory disease in humans, with evidence indicating that this virus, transmitted from pigs, was responsible for the 1918 influenza epidemic that killed an estimated 20 million people throughout the world. The more recent cases of documented H1N1 transmission have been in younger people, resulting in morbidity but no mortality. These cases also implicate birds, especially turkeys, as important sources of the virus. The strain of influenza virus identified in humans, H3N2, has also been shown to be infective to pigs, resulting in significant disease.

Necropsy. There is a fibrinous to mucopurulent exudate in the nasal passages, trachea, bronchi, and bronchioles (Thomson, 1988), and there are dark red to purple firm foci of consolidation in the apical and cardiac lobes of the lung and interlobular edema (Easterday and Hinshaw, 1992). Microscopic lesions are those of a necrotizing bronchitis, bronchiolitis, and bronchointerstitial pneumonia, and the airways are filled with cell debris and neutrophils (Thomson, 1988).

Pathogenesis. The virus enters via the epithelium throughout the respiratory tract. There may be secondary infection by *Haemophilus* or *Pasteurella.*

Prevention and control. Currently, there are several vaccines licensed for use in the United States and Europe. Other means of control include preventing influx of animals from unknown contaminated sources and preventing contact with birds and infected humans.

Treatment. Although not field-tested, amantadine has been shown to reduce the febrile response and the shedding of virus in experimentally infected pigs. This therapeutic drug is used for treatment and prevention of influenza in humans. Solid nursing care, avoidance of stress, and antibiotics to prevent secondary bacterial infections are suggested.

h. Verminous Pneumonia (Verminous Bronchitis)

Etiology. Natural infections of swine with *Metastrongylus* spp. include one or more of *M. salmi, M. pudendotectus,* or *M. elongates apri,* with the latter being the most common. Adults are white, with males averaging 25 mm in length and females, 50 mm. Their eggs are oval, 40–50 mm in diameter, and larvated.

Adult *Ascaris suum* (ascarids) are pinkish yellow nematodes. Males are 15–25 cm in length and females, 20–40 cm. The eggs are oval, 40–60 mm in width and 50–80 mm in length (Corwin and Stewart, 1999).

Clinical signs and differential diagnoses. The clinical signs consist of dyspnea, "thumping," and decreased weight gain. Icterus can be seen if ascarids migrate into the common bile duct. Differentials should include all bacterial, mycoplasmal, and viral causes of pneumonia in swine.

Epizootiology and transmission. Metastrongylus elongatus (lungworm) has an indirect life cycle and requires an earthworm as an intermediate host. Several species, including *Lumbricus terrestris, Helodrilus foetidus* (Lapage, 1968b), and *Eisenia foetida* (Kumar, 1978), can serve this function (Lapage, 1968b). Eggs are coughed up from the lungs, swallowed, and excreted in the feces. Swine eat an earthworm that contains infective larvae, which then migrate to the mesenteric lymph nodes and on to the right heart and lungs. They mature in the bronchi and bronchioles of the diaphragmatic lung lobes. The prepatent period is 28 days.

Ascarids have a direct life cycle and therefore can be a problem even in indoor facilities. Ingested larvated eggs hatch in the small intestine and invade the wall of the cecum and colon (Murrell *et al.,* 1997); the larvae then migrate through the liver and lungs. In the lungs the larvae enter the alveoli and migrate up the airways. They are coughed up and swallowed and then return to the small intestine where they molt into adults. The prepatent period ranges from 40 to 53 days. The presence and migration of these two parasites exacerbate the clinical signs and disease of other viral and bacterial pneumonias of swine.

Necropsy. Adult *M. elongatus* can be found in the trachea, bronchi, or bronchioles, and larvae may be found in the lung

parenchyma at necropsy (Jones and Hunt, 1983). Characteristically, mucoid plugs containing adults and eggs obstruct the bronchioles in the diaphragmatic lobes, producing atelectasis (Corwin and Stewart, 1999).

Adult *A. suum* are found in the small intestine, including the common bile duct, and white focal hepatic lesions (scarring) indicative of ascarid migration and sometimes called "milk spots" are typically found at necropsy (Wagner and Polley, 1997). Larval migration through the lungs produces hemorrhage, inflammation, emphysema, and secondary bacterial pneumonia (Corwin and Stewart, 1999).

Pathogenesis. *Metastrongylus elongatus* larvae migrate through the lung parenchyma, causing alveolar hemorrhage followed by inflammation and consolidation of the lungs. This consists predominantly of leukocytes of which the majority are eosinophils. Maturing larvae continue migrating to the bronchioles and bronchi as they mature into adults, where they copulate and lay eggs which produces more irritation and inflammation and further lung consolidation (Jones and Hunt, 1983). Secondary bacterial pneumonia can also result, and *Pastuerella* and *Staphylococcus* spp. were common isolates in one report (Copland, J. W., 1976).

Migrating *A. suum* create liver lesions, which are seen grossly as white spots that peak at about 1 week postinfection and heal in 3–8 weeks (Roepstorff, A., 1998). The pathogenesis of the lung lesions is similar to that of *M. elongates;* however, the larvae are coughed up and then swallowed and mature into adults in the small intestine.

Prevention and control. In indoor research facilities, the life cycles of both these parasites can be broken by frequent and thorough sanitation procedures that minimize contact with feces. The provision of bedding material is associated with a higher incidence of *A. suum* infection than in bedding-free housing systems (Dangolla *et al.,* 1996). Neopredisan (*p*-chloro-*m*-cresol) disinfectant has been shown to be a very efficacious ovicide and larvicide for *A. suum* (Mielke and Hiepe, 1998). This coupled with a strategic or continuous anthelmintic treatment program should eliminate clinical disease. If outdoor pens are utilized, housing on concrete or bringing the animals indoors to prevent access to earthworms and to facilitate sanitation and anthelmintic treatment is worthwhile. Feral *Sus scrofa* in the United States and Europe have been found to have *A. suum* and *Metastrongylus* spp. (Gipson *et al.,* 1999; Henne *et al.,* 1978) and are a potential reservoir in areas where contact is possible. It is recommended that health monitoring for these pathogens be done on any wild populations. An indirect ELISA for anti–*A. suum* IgG is more sensitive and probably provides a more realistic assessment of the prevalence than fecal examination for oocysts (Roepstorff, 1998).

Treatment. *Ascaris suum* is susceptible to numerous anthelmintics, including avermectins (doramectin (Logan *et al.,* 1996; Stewart *et al.,* 1996; Saeki *et al.,* 1997), ivermectin, the benzimidazoles (fenbendazole, albendazole, oxfendazole), pyrantel, piperazine, levamisole, dichlorvos, and hygromycin B. Doramectin SQ has been shown to have persistent activity of at least 7 days against a challenge with embryonated *A. suum* eggs (Lichtensteiger *et al.,* 1999). *Metastrongylus elongatus* is susceptible to doramectin (Logan *et al.,* 1996; Yazwinski *et al.,* 1997), ivermectin, benzimidazoles, and levamisole (Cowart, 1995). Antibiotic therapy may be indicated to treat secondary or primary bacterial pneumonia in swine showing respiratory signs.

Research complications. If untreated, these infections will damage the lungs, liver, and other tissues during migration.

3. Gastrointestinal Diseases

Young swine commonly develop diarrhea associated with shipping stress, changes in diet, primary or mixed infection with a variety of enteric pathogens, or the perioperative use of antibiotics that may upset the balance of normal gut microbiota (Table IV). The morbidity and mortality associated with enteritis make clinically affected pigs unsuitable for experimental use, and residual lesions in recovering animals may interfere with experimental assessment of the gastrointestinal tract. The following is a summary of the infectious diarrheas that may be encountered when young swine are managed within research facilities. The reader is referred to comprehensive texts for detailed information on historical perspective, epidemiology, diagnosis, and treatment of these diseases (Leman, 1992; Hawk and Leary, 1995).

a. Swine Dysentery

Swine dysentery is a severe mucohemorrhagic diarrhea of pigs of postweaning age.

Etiology. *Brachyspira hyodysenteriae,* a gram-negative anaerobic spirochete, is the primary etiologic agent of swine dysentery and is one of five *Brachyspira* spp. known to infect swine (Boye *et al.,* 1998). Because disease is less severe when gnotobiotic pigs are experimentally infected, other anaerobic microorganisms normally found in the lower bowel are believed to contribute to lesion development. Additionally, nutritional factors may be important; diets rich in rapidly fermentable carbohydrates may exacerbate clinical signs (Pluske *et al.,* 1996). Diagnosis of *B. hyodysenteriae* infection can be confirmed by culture or PCR (Atyeo, 1998).

Clinical signs and differential diagnoses. Rarely, swine dysentery may cause peracute death without premonitory signs. More commonly, severe diarrhea and fever with accompanying dehydration, weight loss, and weakness develop over several days. Diarrhea of acute onset is usually watery with large amounts

Table IV

Common Infectious Causes of Enteritis in Newborn to Postweaning Age Swine

Disease	Clinical signs	Age	Etiology	Gross lesions	Histologic lesions	Diagnosis
Colibacillosis	Acute death, watery to white-yellow or hemorrhagic diarrhea	Newborn to postweaning	*Escherichia coli* ETEC, EPEC (AEEC), EHEC	Nonspecific dilation and congestion of small intestine, blood-tinged contents	Congestion, hemorrhage, acute inflammation, villous atrophy, adherent bacteria	Culture, serotyping
Swine dysentery	Watery, mucoid, and hemorrhagic diarrhea, rarely acute deaths	1 week and older	*Serpulina hyodysenteriae*	Large bowel edema, hyperemia, mucofibrinous exudate on mucosa	Mucosal edema, mucofibrinous enteritis with superficial erosions, hemorrhage	Culture, Warthin–Starry positive spirochetes in colonic crypts, PCR
Proliferative enteropathy	Acute death, mucoid to hemorrhagic diarrhea	Postweaning	*Lawsonia intracellularis*	Gross thickening of distal ileum, cecocolic junction, cecum, edema, exudate	Hyperplasia of glands and epithelium, intracellular bacteria on EM	*In situ* hybridization, tissue culture isolation, electron microscopy
Clostridial enteritis	Acute death, severe hemorrhagic diarrhea	Newborn to postweaning	*Clostridium perfringens*	Severe hemorrhagic involvement of small intestine, gas, bloody fluid in abdomen	Necrotic villi, adherent gram-positive bacilli, profuse hemorrhage	Culture, toxin assays on cecal contents, Gram stain of mucosal smears
Salmonella enterocolitis	Watery, yellow diarrhea with fever, anorexia, depression	Postweaning	*Salmonella typhimurium, S. choleraesuis*	Focal or diffuse necrotic typhlocolitis, enlarged mesenteric lymph nodes, other organ involvement	Necrosis of enterocytes, inflammatory infiltrates, thrombi, lymphoid atrophy or hyperplasia	Culture, clinical signs, necropsy lesions
Transmissible gastroenteritis	Vomiting, severe diarrhea, high mortality	Any age	TGE virus	Thin-walled small intestine distended with yellow fluid	Villous atrophy ulceration of Peyer's patch dome epithelium	Rising serum titers, viral isolation, PCR
Rotavirus	Profuse watery, white/yellow diarrhea	Most severe within days of birth	Porcine rotavirus	Nonspecific dilation of small and large intestine with yellow to gray watery fluid	Villous atrophy	Rising serum titers, viral isolation, PCR, *in situ* hybridization
Balantidiasis	Asymptomatic to severe ulcerative enterocolitis	Any age	*Balantidium coli*	Variable, secondary to other primary diseases	Ciliated trophozoites, flask-shaped ulcers	Histology, fecal direct smears
Giardiasis	Asymptomatic to anorexia with diarrhea	Any age	*Giardia intestinalis*	None to nonspecific enteritis	None to nonspecific enteritis, adherent comma-shaped flagellates	Histology, fecal direct smears
Coccidiosis	Asymptomatic to severe diarrhea	1–2 weeks of age	*Isospora suis*	None, severe cases may have fibrinonecrotic membrane in jejunum and ileum	Villous atrophy, villous fusion, hyperplasia of crypts, necrosis	Fecal flotation
Whipworms	Asymptomatic to severe mucoid or hemorrhagic diarrhea with nortality	Postweaning	*Trichuris suis*	Edema, nodules containing exudate, fibrinonecrotic membrane, hemorrhage, anemia, adult worms attached to mucosa	Migrating larva in submucosa, adult worms attached to mucosa	Fecal flotation, necropsy
Small intestinal threadworm	Asymptomatic to severe diarrhea with mortality	Nursing pigs	*Strongyloides ransomi*	Nonspecific, presence of adult worms in small intestine	Encysted larvae	Fecal flotation, necropsy

of mucus accompanied by flecks of blood and white, mucofibrinous exudate. Pigs with chronic diarrhea may pass red to black soft stools that contain mucus. Nursing pigs are typically not affected but may develop catarrhal enteritis without hemorrhage. Hemorrhagic diarrhea in piglets that are newborn to several weeks of age could also be caused by *Clostridium perfringens.* In older pigs, other causes of hemorrhagic enteritis include *Salmonella* spp., *Lawsonia intracellularis,* and *Trichuris suis.* Mixed infections with *Yersinia pseudotuberculosis, Salmonella typhimurium,* or *B. pilosicoli* commonly result in more extensive lesions, affecting the cecum as well as the colon, and may prolong recovery time from swine dysentery (Thomson *et al.,* 1998). *Brachyspira pilosicoli* is a newly recognized species of pathogenic intestinal spirochete (Duhamel *et al.,* 1998) that causes porcine colonic spirochetosis, a nonfatal diarrheal disease that affects pigs during the growing and finishing stages of production.

Epizootiology and transmission. In natural outbreaks of swine dysentery, *B. hyodysenteriae* is transmitted by fecal–oral contact, either by direct contact between naive and infected pigs or by use of contaminated housing, equipment, or clothing. The organism will survive up to 60 days in moist ground or feces but is readily eliminated by disinfection in the absence of organic material. Recovered pigs may continue to shed *B. hyodysenteriae* in their feces.

Necropsy. Pigs that have died from swine dysentery are dehydrated and may have rough or fecal-stained coats. The gross lesions vary in distribution but are confined to the large bowel (Hughes *et al.,* 1977). Early lesions include reddening and edema of the gut wall, mucosa, and mesenteric lymph nodes, as well as the presence of a fibrinous, blood-flecked membrane covering the mucosa (Harris *et al.,* 1997). The exudate in the lumen is red-brown and watery and contains exudate (Hughes *et al.,* 1977). Older lesions are less edematous, but there is a thick pseudomembrane composed of fibrin, mucus, and blood covering the mucosa (Harris and Lysons, 1992). Microscopic lesions consist of elongated colonic crypts, hyperplasia of goblet cells, and necrosis of sheets of epithelial cells that results in damage to exposed capillaries and exudation of fluid, fibrin, blood, and inflammatory cells from the lamina propria (Hughes *et al.,* 1977). Large amounts of this exudate accumulate in the mucosal crypts and on the mucosal surface, forming a fibrinous pseudomembrane. Large number of spirochetes can be found in the crypts as well as in the lumen.

Pathogenesis. Brachyspira hyodysenteriae is very efficient at penetrating mucus or other material and attaching to the colonic epithelium. These organisms do not invade the gut wall below the lamina propria. The organism has been shown to produce a hemolysin that is cytotoxic and an endotoxin. The diarrhea is the result of colonic malabsorption from failure of colonic epithelial cells to transport sodium and chloride from the lumen to the blood (Schmall *et al.,* 1983). The mechanism of diarrhea is therefore very different from that of *Salmonella, Shigella,* and *Escherichia coli* (Schmall *et al.,* 1983). The dehydration and fluid loss are due to the failure to reabsorb the pig's endogenous secretions (Harris and Lysons, 1992).

Prevention. Swine dysentery is usually introduced to a facility by the purchase of an asymptomatic carrier pig. Wild rodents are also reservoirs. Pigs should be purchased from herds SPF for *B. hyodysenteriae* or alternatively, from herds in which drugs or vaccines that may only suppress the infection are not used.

Control. In the biomedical research setting, pigs affected with swine dysentery should be quarantined and treated or euthanatized. Sanitation of the facility and associated equipment along with review of rodent control and vendor health status should be adequate for avoidance of re-introduction. Valuable pigs can be segregated by health status and treated with antibiotics. Nursing pigs are protected by colostrum from previously infected sows and can be a source of *Brachyspira*-free pigs if weaned early and housed in a clean facility.

Treatment. If indicated, therapy should consist of fluid and electrolyte replacement along with antibiotics. Carbadox, tiamulin, and lincomycin have all been reported to be effective in treatment and/or prevention of swine dysentery.

Research complications. The morbidity and mortality associated with swine dysentery make clinically affected pigs unsuitable for experimental use.

b. Proliferative Enteropathy

Based on inflammatory and proliferative lesions found at necropsy in the terminal ileum, proliferative enteropathy (PE) of the pig has been historically referred to as porcine intestinal adenomatosis, terminal or regional ileitis, regional enteritis, intestinal adenoma, porcine proliferative ileitis, and muscular hypertrophy with stenosis of the ileum. Proliferative enteropathy affects multiple species, and the comparative aspects have been reviewed (Cooper and Gebhart, 1998).

Etiology. Proliferative enteropathy had long been associated with the presence of abundant intracellular *Campylobacter*-like organisms (CLO) in enterocytes that were antigenically distinct from known *Campylobacter* species (McOrist and Lawson, 1989). Due to its obligate intracellular parasitism of enterocytes, this CLO has been difficult to work with because it can be grown only in tissue culture. Sequence analysis of 16S ribosomal RNA identified the causative bacterium as a close relative of *Desulfovibrio desulfuricans,* and the bacterium has since

been definitively identified as the microaerophilic bacterium, *Lawsonia intracellularis* (McOrist *et al.,* 1995b).

Clinical signs and differential diagnoses. Clinical disease attributed to PE is most often observed in the postweaned pig between 6 and 20 weeks of age. Infected animals may show clinical signs ranging from none to severe hemorrhagic diarrhea following a stress such as shipping or weaning. Failure to grow at a normal rate may be the only clinical sign that is detectable antemortem. More severe necrotic enteritis, most commonly found in young adult swine rather than in those just weaned, may present as acute death, anemia secondary to acute hemorrhagic diarrhea, or a more chronic form associated with passage of black tarry feces. Differential diagnoses for hemorrhagic diarrhea in piglets that are newborn to several weeks of age should include *Clostridium perfringens* and *B. hyodysenteriae.* Other causes of hemorrhagic enteritis, particularly in older pigs, include *Salmonella* spp., *Lawsonia intracellularis,* and *Trichuris suis.* Fluorescent *in situ* hybridization targeting 16S ribosomal RNA in formalin-fixed tissue has been used for specific and fast detection of *Lawsonia intracellularis* in enterocytes from pigs affected by PE (Boye *et al.,* 1998).

Epizootiology and transmission. Proliferative enteropathy is worldwide in distribution and affects other species, including the hamster, dog, fox, ferret, horse, rat, and rabbit. Consequently, other animals, such as rodents, could be the sources of new infection. *Lawsonia* is shed in feces, and transmission is by fecal–oral contact. In endemic areas, 15 to 30% of the herds are estimated to be affected with a 5 to 20% infection rate within a herd. There is risk of environmental contamination, but little is known about how long *Lawsonia* can remain infectious outside of the animal.

Necropsy. The gross lesions of PE are found in the ileum, cecum, and the most proximal one-third of the spiral colon and consist of a markedly thickened gut wall and the mucosa containing multiple transverse or longitudinal folds (Rowland and Lawson, 1992); there may be polyps in the colon. Microscopic lesions consist of markedly elongated branching crypts lined by immature epithelial cells and lack goblet cells. Varying numbers of silver-staining organisms that also exhibit acid-fast staining with a modified Ziehl–Neelsen stain are found free in the apical cytoplasm of the lining cells (McOrist, 1995b). Inflammatory response in the lamina propria may be minimal.

The gross lesions of proliferative hemorrhagic enteropathy are confined to the ileum and rarely involve the large bowel. These consist of a thickened, reddened mucosa that does not contain erosions but may be covered by a fibrinous membrane, and the lumen may contain blood clots (Love and Love, 1979). Colon contents may be black and tarry (Rowland and Lawson, 1992). Histologic findings include extensive degeneration and necrosis of the ileal epithelium, crypt abscesses, and extensive accumulation of proteinaceous fluids in the lamina propria of the villi, resulting in distortion of the villi (Love and Love, 1979).

Lesions of regional ileitis consist of a very firm thickened wall of the ileum, which has multiple foci of erosions and ulcerations of the mucosal surface and marked hypertrophy of the outer muscle layers (Rowland and Lawson, 1992).

Pathogenesis. Lawsonia intracellularis is an obligate intracellular organism. Animals become infected as a result of consuming fecal-contaminated material (McOrist *et al.,* 1995b). The organisms enter the immature, proliferating crypt epithelial cells and multiply within the apical cytoplasm. The infected crypt cells fail to mature and are not shed, so the crypts become elongated and tortuous (Rowland and Lawson, 1992).

Prevention. Swine should be purchased from a vendor with a herd-health history that is free of clinical PE. Newly introduced pigs should be quarantined and housed separately to avoid contact with feces of other swine that may be shedding *Lawsonia.*

Control. Clinically affected pigs should be quarantined and treated or euthanatized, based on severity of disease and the intended use of the animal. Control efforts should include sanitation of equipment and the housing area, review of rodent control, and treatment with antibiotics of pigs at risk of clinical disease (McOrist *et al.,* 1996).

Treatment. Proliferative enteropathy can be self-limiting with spontaneous improvement after several weeks. Antibiotics are commonly used to control clinical signs. Treatment of this disease is problematic because of the lack of *in vivo* or *in vitro* data on antibiotic sensitivities of *Lawsonia.* In tissue culture, penicillin, erythromycin, difloxacin, virginiamycin, and chlortetracycline were the most effective antibiotics, followed by tiamulin and tilmicosin (McOrist *et al.,* 1995a). Tylosin phosphate can be effective for prevention and for treatment of PE (McOrist *et al.,* 1997).

Research complications. The morbidity and mortality associated with PE make clinically affected pigs unsuitable for experimental use. Lesions typically resolve over time.

c. Colibacillosis

Enteric colibacillosis is the most important diarrheal disease of newborn to postweaning-age swine (Leman, 1992). Diarrhea attributable to colibacillosis is commonly observed in neonates born to nonimmune sows or in piglets housed in heavily contaminated environments. Susceptible animals include recently weaned piglets that are experiencing the waning of passive maternal immunity, are being stressed by new housing, or are adjusting to dietary changes.

Etiology. Colibacillosis is caused by pathogenic *Escherichia coli,* a gram-negative facultative anaerobic rod. The species *E. coli* includes members that are normal gut flora as well as enteric pathogens that are further classified by antigenic serotype: somatic (O), capsular (K), flagellar (H), and fimbrial adhesins (F). Pathogenic *E. coli* also possesses one or more virulence factors encoded on either the bacterial genome or plasmids. Various classifications associated with different modes of pathogenesis include enterotoxigenic strains of *E. coli* (ETEC), which produce heat-stabile (ST) or heat-labile (LT) enterotoxins. Enteropathogenic *E. coli* (EPEC), also referred to as attaching and effacing strains (AEEC), which attach to the enteric epithelium using fimbrial adhesins, efface the microvilli and invade the epithelial cells. Strains of *E. coli* that cause hemorrhagic gastroenteritis are referred to as enterohemorrhagic *E. coli* (EHEC) (Tzipori *et al.,* 1989). As an example, neonatal diarrhea in piglets from 0 to 4 days of age is commonly caused by an enterotoxigenic (ETEC) strain of *E. coli* that possesses F4-type fimbrial adhesins, produces ST or LT enterotoxin, and belongs to the classical serotypes O149, O8, O147, or O157.

Clinical signs and differential diagnoses. Colibacillosis presents as diarrhea that will vary in severity based on the virulence factors present in the *E. coli* strain involved and the age and immune status of the piglets. Severe dehydration, metabolic acidosis, and weight loss may accompany the diarrhea, or peracute deaths without diarrhea may be seen. Neonatal colibacillosis can develop within hours of birth if piglets are born to gilts in contaminated environments and is characterized by either clear, watery diarrhea or loose stools that vary in color from white to brown. Severe outbreaks are associated with high morbidity and mortality in neonates; older pigs have less severe disease. Hemorrhagic gastroenteritis from colibacillosis can occur peracutely (sudden death) or acutely (rapid decline with severe diarrhea) in previously healthy unweaned or recently weaned pigs. The differential diagnoses for yellow to white, watery diarrhea in piglets that are newborn to several weeks of age should include colibacillosis, salmonellosis, transmissible gastroenteritis virus, rotavirus, nematodiasis, and coccidiosis.

Epizootiology and transmission. Clinical disease results from interaction between the causative bacteria, adverse environmental conditions, and select host factors. Newborn pigs encountering large numbers of *E. coli* carrying the appropriate virulence factors will develop colibacillosis if colostrum is not available because of competition for teats, if the sow develops agalactia, or if the sow is not immune to *E. coli.* Some pigs are inherently resistant to colibacillosis because they lack receptors on their epithelial cell brush borders to which the fimbriae bind (Baker *et al.,* 1997).

Necropsy. Gross lesions of the edema disease syndrome may include marked edema of the mesenteric lymph nodes and mesentery, the wall of the stomach, large intestine, subcutaneous lymph nodes, eyelids, subcutaneous tissues, lungs, liver, and gallbladder. The mucosa of the small intestine and stomach may contain extensive hemorrhages (Bertschinger and Pohlenz, 1983). Microscopic lesions in the lamina propria of intestinal villi include vascular congestion with some hemorrhages into the lumen, endothelial swelling, perivascular edema, necrosis of the tunica media, microthrombi, subendothelial deposition of fibrin, an inflammatory infiltrate consisting of neutrophils and macrophages, and villus atrophy (Bertschinger, 1983). Some ETEC isolates can be found adhered to the mucosal epithelium on the villi, while other isolates colonize the crypts of Lieberkuhn (Bertschinger *et al.,* 1992).

Pathogenesis. Enteropathogenic *E. coli* has numerous virulence factors. The AEEC porcine organisms attach to enterocyte microvilli by means of an attachment factor and then efface the microvilli and invade the epithelial cells (Gyles and Thoen, 1993). The ETEC organisms contain a mucopolysaccharide capsule that is antiphagocytic and not very antigenic. The K1 polysaccharide enhances bacterial resistance to complement mediated killing by inhibiting the alternative pathway to complement activation. The very long O chain polysaccharide chains in the cell wall bind the membrane attack complex resulting from complement activation distant from the cell membrane so that it cannot lyse the cell (Gyles and Thoen, 1993). Specialized fimbriae, K88(F4), K99(F5), F6, and F41, permit the adherence and colonization of the enterocytes. The ETEC also produce heat-labile toxins, which elevate levels of adenylate cyclase leading to the efflux of Na and Cl ions and water out of the cell. In addition, SLT-IIe, a heat-labile, Shiga-like toxin, binds to and damages vascular endothelium, resulting in edema, hemorrhage, and thrombosis (Gyles and Thoen, 1993). The heat-stable toxins Sta and Stb cause elevated levels of prostaglandins in enterocytes, which may enhance diarrhea (Gyles and Thoen, 1993).

Prevention. Farrowing management should be "all in, all out" to provide for adequate sanitation between litters. In problem herds, gilts and sows should be immunized with a commercial vaccine or an autologous bacterin during gestation.

Control. To minimize environmental stress, piglets should be housed on warm floors to prevent hypothermia and in clean conditions to avoid ongoing ingestion of bacteria. Housing should be draft-free and maintained at temperatures of 30° to 34°C for very young pigs. Nursing pigs will derive protection from colostrum feeding from immune sows. Vaccination of breeding stock is indicated if problems are recurrent.

Treatment. A broad-spectrum antibiotic should be started pending culture and sensitivity results. Most isolates are sensitive to amikacin, gentamicin, spectinomycin, and enrofloxacin.

Oral fluid therapy consisting of electrolyte replacement solutions containing glucose should be instituted to correct dehydration, energy depletion, and ongoing fluid and electrolyte losses.

Research complications. Morbidity and mortality from colibacillosis in neonatal pigs clearly interfere with their experimental use. Once recovered, animals should be clinically normal.

d. Clostridial Enteritis

Clostridial infection of the intestinal tract of young swine commonly results in a necrotic enteritis with high mortality.

Etiology. Clostridium perfringens type A is a normal inhabitant of the swine intestine and causes an enteritis generally associated with low mortality. In contrast, fatal necrotic enteritis is caused by *C. perfringens* type C. *Clostridium perfringens* is an encapsulated, gram-positive bacillus that produces a variety of enterotoxins that are responsible for clinical signs and lesions (Buogo *et al.,* 1995).

Clinical signs and differential diagnoses. Clinical manifestations of infection with *C. perfringens* will depend on the immune status of the swine herd and the age of naive exposed piglets. Clinical disease may be peracute with death of piglets aged 12 to 36 hr that may or not have developed hemorrhagic diarrhea. Acute disease is characterized by 2 days of reddish brown diarrhea containing gray, necrotic debris, with ensuing death by 3 days of age. Subacute disease develops as persistent nonhemorrhagic diarrhea that is yellow initially and then changes to clear liquid with flecks of necrotic debris. Piglets with subacute disease remain alert but commonly die from dehydration by 5 to 7 days of age. Chronic enteritis may involve intermittent or persistent diarrhea for several weeks, with feces yellow-gray in color and mucoid in consistency. Pigs may die after several weeks of clinical signs or be culled based on failure to grow. Differential diagnoses for hemorrhagic diarrhea in piglets that are newborn to several weeks of age should include *C. perfringens* and *Brachyspira hyodysenteriae.* Other causes of hemorrhagic enteritis, particularly in older pigs, include *Salmonella* spp., *Lawsonia intracellularis,* and *Trichuris suis.*

Epizootiology and transmission. Clostridum perfringens is usually introduced by purchase of a carrier sow or by use of contaminated housing, equipment, or clothing. Although disease is most common in pigs aged 12 hr to 7 days and peaks in incidence at 3 days of age, disease has also been observed in older pigs aged 2 to 4 weeks and in postweaning pigs. Disease is explosive, with 100% mortality in pigs born to nonimmune sows. Subsequent litters are protected by maternal immunity. The bacillus is transferred from sow to pigs and between pigs by fecal–oral contact. *Clostridium perfringens* exists in the environment as a vegetative form or as spores that persist for a least a year.

Necropsy. Piglets may be found dead, or hemorrhagic diarrhea may be noted in acute and peracute cases. Death is the result of a severe necrotizing enteritis. The affected segments of gut vary from involvement of only several centimeters to extension from a point 14 cm distal to the pylorus to the cecum. The affected gut wall is dark red to black, and there may be gas bubbles. Enteric lymph nodes are red. The mucosa is dark red, and the intestinal contents in affected segments contain hemorrhagic and necrotic debris. There may also be blood-tinged ascitic fluid. Microscopic lesions consist of severe necrosis of villi and crypts, and severe and extensive hemorrhages throughout the lamina propria and mucosa. There may be a necrotic membrane composed of bacteria, sloughed epithelium, fibrin, and inflammatory cells lying over the submucosa (Taylor, 1992).

Pathogenesis. Disease due to *C. perfringens* type A occurs when large numbers of organisms build up in the jejunum and ileum and produce an alpha (α) toxin that can cause necrosis of enterocytes, leading to a profuse loss of both electrolytes and fluids. These organisms do not invade the enterocytes. Sporulating forms also produce an enterotoxin that forms a complex with a specific cell-membrane protein and alters the cell-membrane permeability, leading to loss of sodium, chloride, and fluid while inhibiting glucose uptake (Nilo, 1993).

Clostridium perfringens type C organisms produce a trypsin-sensitive beta (β) toxin that is responsible for much of the necrotizing lesions. These organisms attach to enterocytes and result in initial loss of microvilli on the enterocytes at the tips of the villi and damage to terminal capillaries, with increased capillary permeability. This is followed by a rapid, progressive necrosis of the remaining villus enterocytes, the crypt cells, and mesenchymal structures in the lamina propria and muscularis mucosa (Nilo, 1993). Some organisms may penetrate to the muscle layers and produce emphysema of the gut wall and thrombosis of vessels (Taylor, 1992).

Prevention. Routine vaccination of sows will prevent disease (Kelneric *et al.,* 1996). Sows can be vaccinated with a toxoid at the time of breeding or midgestation and then again 2 weeks prior to farrowing. Piglets from immune sows will be protected by colostrum.

Control. Clinically ill pigs should be isolated and treated and the premises sanitized. Individual piglets and pregnant swine that are at risk from recent exposure should be vaccinated with toxoid. Medicated feed has been shown to control clinical signs (Kyriakis *et al.,* 1996).

Treatment. Once clinical signs develop, disease is extensive and often unresponsive to therapy. Oral antimicrobials such as ampicillin given soon after birth and repeated daily for the first 3 days of life may prevent clinical disease. Pigs with severe diarrhea should receive supplemental fluids containing glucose and electrolytes.

Research complications. Clostridial enteritis causes acute death and severe morbidity among survivors. Overgrowth of *C. perfringens* from perioperative use of antibiotics may cause acute losses and interrupt surgical studies.

e. Salmonella Enterocolitis

Salmonellosis can be subclinical or present with multiorgan involvement, including septicemia, pneumonia, meningitis, lymphadenitis, abortion, and enterocolitis (Leman, 1992). Enterocolitis can be acute or chronic. Salmonellosis is a zoonotic disease.

Etiology. *Salmonella* enterocolitis is usually attributed to *Salmonella typhimurium* and less frequently, *S. choleraesuis.*

Clinical signs and differential diagnoses. Signs of *Salmonella* enterocolitis begin with watery, yellow diarrhea associated with fever, anorexia, and dehydration and will last several days to a week, sometimes with intermittent relapses. Diarrhea containing blood or mucus is not a prominent feature as in diseases such as swine dysentery. The differential for watery, yellow diarrhea in weaned pigs should include salmonellosis, colibacillosis, transmissible gastroenteritis, coccidiosis, and nematodiasis.

Prevention. Pigs proven to be clinically ill or shedding *Salmonella* should not be maintained in a research facility because of chronic fecal shedding and the zoonotic risks associated with husbandry and research use.

Control. Infected swine may shed *Salmonella* for 5 months or more. Clinically affected swine should be euthanatized and the facility sanitized.

Treatment. Treatment is contraindicated because of the shedding status of clinically recovered animals and the zoonotic risks associated with husbandry and research use.

Research complications. Infected stock should be depopulated and the facility sanitized. Ideally, research use would not resume until it can be demonstrated that new stock will remain free of infection.

f. Transmissible Gastroenteritis

Transmissible gastroenteritis (TGE) is a viral enteritis associated with vomiting, severe diarrhea, and high mortality in piglets less than 2 weeks old.

Etiology Transmissible gastroenteritis virus (TGEV) is a pleomorphic enveloped virus containing a positive-sense, single-stranded RNA genome. This virus is one of four members of the family Coronaviridae (Sirinarumitr, 1997) that are known to naturally infect pigs: TGEV, hemagglutinating encephalomyelitis virus, porcine respiratory coronavirus, and porcine epidemic diarrhea virus (Kweon *et al.,* 1997), which has been reported only in Europe and Taiwan. The TGE virus is antigenically related to feline infectious peritonitis virus and canine coronavirus. Swine can be experimentally infected with both cat and dog coronaviruses, and likewise, dogs and cats can be experimentally infected with TGEV, suggesting that cats and dogs may be reservoirs for swine TGEV.

Clinical signs and differential diagnoses. Anorexia, vomiting, and/or diarrhea develop within days in susceptible animals of all ages, particularly in the winter. Nursing pigs develop transient vomiting and yellowish diarrhea, with dehydration and rapid loss of weight. Malodorous diarrhea will contain milk curds. Piglets less than 2 weeks old experience high mortality secondary to dehydration from enteritis, which can be compounded by agalactia if the sow is also ill. Differential diagnoses for yellow to white watery diarrhea in piglets that are newborn to several weeks of age should include colibacillosis, transmissible gastroenteritis, rotavirus, and coccidiosis.

Epizootiology and transmission. Epizootic TGE develops within days when the majority of animals are susceptible. A pattern of enzootic TGE will follow if viral challenge exceeds protection afforded by maternal immunity or as passive immunity wanes in the postweaning period. In herds with enzootic TGE, older animals will be asymptomatic, but diarrhea will develop in pigs 1 to 2 weeks old. Usually morbidity and mortality are lower, making diagnosis more difficult and requiring discrimination between other common causes of neonatal diarrhea, such as rotavirus and colibacillosis.

Necropsy. Gross lesions are confined to the gastrointestinal tract and consist of a stomach distended with milk; foci of hemorrhages on the diaphragmatic side of the mucosa, varying in size from several millimeters to 2 cm in diameter; and a distended thin-walled small intestine, which is filled with watery material and curds of undigested milk. The piglets are usually severely dehydrated, and there is no chyle in the lymphatic channels in the mesentery (Hooper and Haelterman, 1966, 1969). The most striking microscopic lesion is the severe villus atrophy in the jejunum and ileum, which causes a massive loss of mature absorptive enterocytes. The villus crypt ratio is 1:1, compared to a normal of about 7:1 (Hooper and Haelterman, 1966, 1969). The enterocytes are vacuolated and low-cuboidal or flattened, there is lymphoid depletion of Peyer's patches, and there is a minimal inflammatory response in the lamina propria (Hooper and Haelterman, 1969). Virus particles can be found in

the cytoplasm of villus enterocytes, M cells, lymphocytes, and macrophages within Peyer's patches (Saif and Wesley, 1992).

Pathogenesis. The virus multiplies in villus enterocytes, which are then sloughed as the villi begin to shrink. Normally, crypt cells divide rapidly to produce a constant supply of enterocytes that develop their absorptive enzyme capacity as they move onto the villus. In TGE this process is impeded due to the massive loss of enterocytes from villus atrophy, and the remaining crypt cells lack these enzyme systems. The secretory flux exceeds the ability to resorb. In addition, the hyperplasia of crypt cells results in increased secretory flux, which further adds to the diarrhea (Hooper and Haelterman, 1966; Moon, 1978).

Prevention. Naive swine should not be introduced into potentially contaminated environments or into established herds known to harbor enzootic TGEV. Vaccination of boars, gilts, and sows will moderately reduce clinical signs.

Control. Entrance of TGEV into production herds in the winter months is difficult to prevent because of probable reservoir transmission by wild birds, which should be excluded in laboratory animal housing. A moratorium on purchase of new animals and vaccination of reproductive stock will eventually contain an outbreak as the herd develops immunity.

Treatment. There is no specific treatment for piglets infected with TGEV. Supportive care with fluids containing glucose and electrolytes is indicated. Antibiotics may be protective against concurrent primary or opportunistic bacterial pathogens.

Research complications. Clinical signs of TGEV are severe enough to make animals unsuitable for experimental use unless sufficient time is available for clinical recovery.

g. *Porcine Rotavirus*

Porcine rotavirus is a major cause of morbidity and mortality from acute diarrhea in very young pigs, particularly if piglets are colostrum-deprived or raised under gnotobiotic conditions in which the herd is free of natural infection (Bridger *et al.*, 1998).

Etiology. Four (A, B, C, E) of seven serogroups (A–G) of rotavirus have been described in swine, but group A rotavirus appears to be the most common. Within these serogroups, rotaviruses fall into two major serotypes based on expression of two surface antigens, VP4 and VP7. Rotaviruses are nonenveloped with a double-stranded RNA genome. They are stable in the environment and are relatively resistant to effects of temperature, pH, and disinfectants.

Clinical signs and differential diagnoses. Disease is most severe in naive pigs first exposed at 1 to 5 days of age. Typical signs include anorexia, lethargy, some vomiting, and profuse watery diarrhea that is white to yellow in color and contains flocculent material. In pigs that will recover, consistency of feces slowly returns to normal after 3 to 5 days of diarrhea. Death loss due to dehydration can reach 50–100% of affected piglets. Clinical signs and losses are less severe if exposure occurs after piglets are 7 days of age, and infection is commonly subclinical if it occurs after they are 21 to 28 days of age. Disease is usually mild and self-limiting if other enteric pathogens are absent. If rotaviral infection is detected in clinically ill pigs of postweaning age, mixed infection with other agents such as TGEV should be suspected. Differential diagnoses for yellow to white, watery diarrhea in piglets that are newborn to several weeks of age should include rotavirus, colibacillosis, transmissible gastroenteritis, coccidiosis, and nematodiasis.

Epizootiology and transmission. Rotaviral infection is enzootic in most swine herds, and clinical disease will be apparent only if viral challenge exceeds the capacity of passive maternal immunity. Piglets born to gilts are at greater risk than those farrowed by older sows, who are more likely to have naturally high virus neutralizing titers that protect the nursing piglets. Rotaviruses are resistant to environmental extremes and disinfection. Subclinical infection may persist in adult animals, with periodic shedding.

Necropsy. Gross lesions are confined to the small bowel. The wall of the distal half of the small intestine is typically thin and dilated and contains watery material, while the mesenteric lymph nodes are tan and small (Paul and Stevenson, 1992). The cecum and colon are dilated, with watery contents similar to those in the small intestine. Gross lesions in pigs over 21 days of age are variable or absent. Microscopic lesions include degeneration and loss of enterocytes on the tips of the villi, increased thickness of the lamina propria due to large numbers of neutrophils and mononuclear cells, reduction in villus height from the duodenum to the ileocecal juncture, and fusion of villi due to exposed lamina propria in villus cores (Pearson and Me Nulty, 1977).

Pathogenesis. Rotaviruses replicate in the cytoplasm of enterocytes and M cells overlying Peyer's patches, as well as in the lining epithelium of the colon and cecum (Butler and Moxley, 1988). The diarrhea is the result of destruction of enterocytes on the tips of the villi and villus atrophy, which reduces the mucosal surface area available for resorption. An osmotic diarrhea ensues due to decreased resorption of sodium, water, and disaccharides in the jejunum and ileum, which causes a hyperosmolarity to the intestinal contents (Graham *et al.*, 1984).

Prevention. Because porcine rotavirus is enzootic in most herds, exclusion is difficult. Management should concentrate on minimizing the viral challenge for susceptible pigs through good sanitation and boosting passive immunity by exposing replacement gilts to feces from the herd prior to their first parturition.

Control Modified live- and inactivated-virus vaccines are commercially available for immunization of sows and nursing pigs. Immunity is serotype-specific, and the duration is unknown.

Treatment. No specific treatment is available. To minimize losses, supportive therapy should include replacement fluids containing glucose and electrolytes, antibiotics to treat or prevent secondary bacterial infections, and warm, clean housing.

Research complications. Morbidity and mortality of porcine rotaviral infection will impact studies using very young piglets and will probably be subclinical in postweaning animals.

h. *Balantidiasis*

Because *Balantidium coli* invades necrotic tissue, clinical balantidiasis may be a sequela to other primary causes of enteritis. Balantidiasis is a zoonotic disease.

Etiology. Balantidiasis is caused by trophozoites of *Balantidium coli,* a ciliated protozoan that colonizes the cecum and anterior colon of swine, usually as a commensal. Trophozoites are large (25 × 150 μm), ciliated ovoid structures containing a macronucleus and micronucleus in addition to contractile and food vacuoles. Trophozoites of *B. coli* isolated from pigs affected by acute disease and from pigs with subclinical balantidiasis, as well as trophozoites cultured *in vitro,* have been shown to differ in nucleic acid content, suggesting clinical disease may be associated with different strains of *B. coli* (Skotarczak and Zielinski, 1997).

Clinical signs. Infection with *B. coli* may present as an acute typhlitis or colitis or more commonly, the host is colonized without apparent effect. Infection can cause severe ulcerative enterocolitis, which can be fatal. Clinical signs include weight loss, anorexia, weakness, lethargy, watery diarrhea, tenesmus, and rectal prolapse.

Epizootiology and transmission. Infection with *B. coli* is contracted by ingestion of trophozoites or cysts that are shed in feces. Most infections are subclinical, so if clinical enteritis can be associated with *B. coli,* other infectious agents or management problems that may be cofactors in disease development should be investigated.

Necropsy. Balantidium coli is not considered a primary pathogen in pigs (Manwell, 1968) but may be a secondary invader. *Balantidium coli* has been shown to invade lesions caused by *Oesophagostomum, Trichuris suis* (Beer and Lean, 1973), and some types of colitis produced by infectious agents.

Pathogenesis. Secondary invasion occurs when the integrity of the colonic mucosa is compromised.

Prevention. Herd-health management that minimizes the risk of enteritis from any cause will help prevent clinical balantidiasis.

Control. Clinically ill pigs should be isolated and treated or necropsied to rule out other predisposing causes of enteritis.

Treatment. Balantidiasis can be successfully treated with metronidazole, tetracycline, and diiodohydroxyquin.

Research complications. Although *B. coli* is usually nonpathogenic, severe ulcerative enterocolitis can develop. Because of zoonotic potential, it may be advisable to euthanatize piglets shedding *B. coli* in high numbers.

i. *Coccidiosis*

Swine can be naturally infected with three genera of coccidia. While disease is commonly absent or subclinical, significant morbidity and mortality can result from severe diarrhea in neonatal piglets.

Etiology. Eimeria spp., *Cryptosporidium parvum,* and *Isospora suis* are three genera of coccidia that infect swine and other mammals. There are eight species of *Eimeria* that infect up to 95% of the swine housed in the United States on dirt lots. *Eimeria* spp. are considered to be nonpathogenic in swine. *Cryptosporidium parvum* typically causes subclinical infection in swine that are 6 to 12 weeks of age. Clinical disease is associated with nonhemorrhagic diarrhea and either no histologic lesions or mild villous atrophy. Clinical neonatal coccidiosis is caused by the intracellular parasite, *I. suis,* and is the most important protozoal disease of nursing piglets that are 1 to 2 weeks of age (Lindsay *et al.,* 1997).

Clinical signs and differential diagnoses. Isospora suis causes clinical disease in nursing piglets that are 1 to 2 weeks old. Yellowish to gray diarrhea that varies in consistency from watery to pasty will develop, although piglets will usually continue to nurse. Weight loss and dehydration secondary to coccidiosis can be exacerbated by concurrent infections with other parasites, bacteria, or viruses. The differential should include colibacillosis, *Clostridium perfringens,* transmissible gastroenteritis, rotavirus, and *Strongyloides ransomi.*

Epizootiology and transmission. Isospora suis is transmitted by fecal–oral contact. Warm temperatures and high humidity associated with indoor farrowing favor rapid sporulation of oocysts. Infection rates of sows vary from 1 to 3%, although carrier sows are not the major source of new infections. Contaminated environments pose the greatest risk to naive piglets.

Necropsy. The gross lesions are confined to the jejunum and ileum and consist of a necrotic enteritis involving the entire

thickness of the mucosa. A yellow fibrinonecrotic pseudomembrane may be present over foci of mucosal ulceration. Microscopic lesions consist of moderate to severe segmental villous atrophy and a necrotic enteritis. The variable reduction in villous heights ranges from slight to severe, and the villous enterocytes are flattened and irregularly shaped. There may be crypt epithelial hyperplasia, and the lamina propria is condensed and infiltrated with large numbers of mononuclear cells. The least involved sections of the mucosa contain varying stages of coccidia in vacuoles in the enterocytes on the distal two-thirds of the villi (Eustis and Nelson, 1981).

Pathogenesis. Ingestion of sporulated oocysts by the pig permits development to sporozoites in the intestinal lumen. These invade enterocytes and form trophozoites, which then form merozoites, resulting in rupture of the cell membranes when they are released into the intestinal lumen.

Prevention. Piglets should be purchased from vendors with an established herd-health profile that is free of coccidiosis. Newly received piglets should be routinely quarantined and tested for coccidia by fecal flotation.

Control. Coccidiosis can be controlled by "all in, all out" husbandry and thorough cleaning of housing areas, which should include removal of organic debris, chemical disinfection, steam cleaning and/or change of flooring from solid concrete to woven wire or Tri-bar. Coccidiostatic drugs can be administered for control of clinical disease.

Treatment. Piglets should be individually dosed orally with amprolium or furazolidone. Sulfonamides and trimethoprim-sulfa are also effective (Lindsay *et al.,* 1997). Drug therapy may only delay the onset of clinical signs. Electrolyte and water-balance disturbances should be treated with either oral or parenteral fluids.

Research complications. Morbidity is high, but mortality is usually low to moderate in piglets affected by neonatal coccidiosis. Growth may be stunted.

j. Giardiasis

Etiology. Giardia trophozoites are commonly found in domestic swine and belong to the *Giardia intestinalis* group (Olson *et al.,* 1997). Trophozoites colonize the surface of intestinal crypts of the small intestine from the duodenum to the ileum, with maximum numbers in the cranial part of the upper jejunum (Koudela *et al.,* 1991). Giardiasis is a zoonotic disease.

Clinical signs and differential diagnoses. Clinical signs include anorexia, depression, and formless feces. *Giardia* may be the primary cause of enteritis or may be found coincidental to other causes of enteritis (see Table IV).

Epizootiology and transmission. Giardia is commonly present in domestic swine (Olson *et al.,* 1997). *Giardia* cysts are intermittently shed in feces and transmitted to other pigs by fecal–oral contact.

Necropsy. No pathologic lesions were found in the small intestines of groups of pigs experimentally infected with *Giardia intestinalis* (Koudela *et al.,* 1991). Detection of these can be done using Giemsa-stained fecal smears or Giemsa-stained histologic sections.

Pathogenesis. Transmission is via the fecal–oral route. Most organisms are found in the jejunum, with fewer present in the duodenum and ileum (Koudela *et al.,* 1991).

Prevention. Sanitation protocols should include removing feces daily or housing pigs on slatted floors to minimize fecal contact.

Control. Giardia exists as a commensal in the vast majority of domestic swine. Clinical enteritis can be controlled by quarantine and treatment.

Treatment. Metronidazole is commonly used for 5 days to control giardiasis. Diagnostic steps to rule out other causes of enteritis are indicated.

Research complications. Giardiasis can cause debilitation from diarrhea and dehydration but usually responds readily to treatment that is both supportive and specific (metronidazole). Attention to zoonotic aspects of giardiasis is warranted.

k. Nematodiasis

Young swine can be infected with the nematodes *Hyostrongylus rubidus, Globocephalus urosubulatus, Macracanthorhynchus hirudinaceus, Oesophagostomum* spp., *Ascaris suum, Trichuris suis,* and *Strongyloides ransomi* (Leman, 1992). Only *Trichuris suis* and *Strongyloides ransomi* will be discussed here because the other parasites are either discussed elsewhere (*Ascaris*), they require intermediate hosts (*Macracanthorhynchus*), or infection is associated with pasture maintenance (*Hyostrongylus, Globocephalus, Oesophagostomum* spp.), which renders them unlikely to be common problems in laboratory animal research facilities.

i. Trichuris suis

Etiology. The swine whipworm, *Trichuris suis,* colonizes the small intestine and cecum. Besides causing morbidity and possibly mortality in young, postweaning swine, this parasite can infect humans and other primates.

Clinical signs and differential diagnoses. Trichuris suis may cause anorexia, mucoid to hemorrhagic diarrhea, dehydration, and in severe infections, death. Differential diagnoses for hem-

orrhagic diarrhea in piglets that are newborn to several weeks of age should include colibacillosis, *Clostridium perfringens,* and *Brachyspira hyodysenteriae.* Other causes of hemorrhagic enteritis, particularly in older pigs, include *Salmonella* spp. and *Lawsonia intracellularis.*

Epizootiology and transmission. Bipolar, thick-shelled eggs are intermittently shed in feces. After 3 to 4 weeks in the environment, eggs are infective for as long as 6 years. Ingested eggs hatch in the small intestine and cecum, with newly released larvae penetrating cells lining the crypts. Larvae gradually migrate from the lamina propria into the submucosa over several weeks. After a series of molts, adult worms can be found at necropsy with their anterior end buried in the mucosa and the posterior end free in the intestinal lumen. Prepatency is 6 to 7 weeks, and the life span of the adult worm is 4 to 5 months.

Necropsy. There is evidence of a profuse bloody diarrhea, dehydration, emaciation, and growth retardation (Batte *et al.,* 1977; Beer and Lean, 1973). Gross lesions are found primarily in the cecum and colon. The wall of the large intestine is thickened, the mesentery may be thickened and appear as bands between coils of gut, and there may be foci of hemorrhages on the serosal surface (Beer and Lean, 1973). The mesenteric lymph nodes are enlarged and congested. The lumen of the gut is filled with bloody fluid, and there is a hemorrhagic catarrhal colitis and typhlitis, with portions of the mucosa being replaced by a yellow crumblike, fibrinonecrotic membrane (Batte *et al.,* 1977; Beer and Lean, 1973). Microscopic examination reveals parasites embedded in the mucosa between villi and in crypts, which may be cystic, or they may have penetrated to the muscularis mucosa (Batte and Moncol, 1972). Enterocytes with degenerative changes are present surrounding the embedded parasites, and the lamina propria is infiltrated by large numbers of mononuclear cells. Foci of hemorrhage may be found in the mucosa, as well as ulcers, which are covered by a thick fibrinonecrotic material (Beer and Lean, 1973).

The severe watery and bloody diarrhea results in severe dehydration and death. Scanning electron microscopy (EM) has shown that the penetration of the mucosa by the tunneling parasite results in formation of nodules and disruption of mucosal integrity. Damage caused to the mucosa permits colonization by pathogenic bacteria and *Balantidium coli.*

Prevention. *Trichuris suis* eggs passed in feces require 3 to 4 additional weeks to develop to an infectious stage; hence, indoor housing with good sanitation that includes regular removal of feces and organic debris should prevent environmental contamination and reinfection.

Control. Newly received swine should be tested for *Trichuris* by fecal flotation and treated with anthelmintics during the quarantine period. Housing areas and equipment should be steam-cleaned to destroy eggs and infective larvae.

Treatment. Effective anthelmintics for trichuriasis include fenbendazole, dichlorvos, and levamisole hydrochloride, all of which are formulated for administration in feed. Although ivermectin is considered to be efficacious for elimination of *Ascaris, Oesophagostomum,* and *Metastrongylus,* it is less effective for *Trichuris.*

Research complications. Severe infection with *Trichuris* will cause bloody scours in young pigs, with associated morbidity and some mortality.

ii. Strongyloides ransomi

Etiology. *Strongyloides ransomi* is the small intestinal threadworm of swine that is most prevalent in warm climates and causes morbidity in suckling pigs (Leman, 1992).

Clinical signs and differential diagnoses. Transcolostral infection of newborn pigs can cause clinical signs of diarrhea, with secondary dehydration and potential death within the first 2 weeks of life. Poor growth commonly results. The differential diagnosis for nonhemorrhagic diarrhea in piglets aged upward of 14 days should include colibacillosis, salmonellosis, rotavirus, transmissible gastroenteritis, giardiasis, coccidiosis, and nematodiasis.

Epizootiology and transmission. Larvae of *S. ransomi* can infect pigs *in utero* as well as by the oral, percutaneous, and transcolostral routes. Eggs shed in feces hatch within hours to release larvae that are directly infective within 24 hr or develop into males and females that then reproduce, resulting in more larvae within 72 hr. Larvae encysted in the mammary gland of the sow gain access to newborn piglets via colostrum.

Necropsy. Pigs may be dehydrated or may be stunted and unthrifty. Pigs less than 10 days old may die. Adult forms of the parasite are found in the small intestine, and ova are present in the feces. There are no pathognomonic findings in parasitized pigs.

Pathogenesis. Transmission of ineffective larvae may occur prenatally, with larval migration into the small intestine shortly after birth. Transcolostral, percutaneous, and oral routes of infection also occur.

Prevention. Breeding animals should receive anthelmintics to control the shedding of *S. ransomi* eggs and the transmitting of larvae through colostrum. Removing feces daily or housing on slatted floors should minimize exposure of neonates to infective larvae.

Control. Treatment with ivermectin several weeks before farrowing will prevent transmission of *S. ransomi* to piglets.

Treatment. Young swine can be treated with paste formulations of thiabendazole. Other effective drugs are ivermectin and levamisole.

Research complications. *Strongyloides ransomi* is an important cause of parasitic debilitation in nursing pigs in the southeastern United States. Routine diagnostic screening and timely use of anthelmintics should minimize any impact on research.

4. Circulatory Disease

Eperythrozoonosis

Etiology. *Eperythrozoon suis,* a rickettsia of the family Rickettsiaceae, tribe Rickettsieae, is the etiologic agent for this disease in swine and is host-specific. These are obligate, intracellular, coccoid to coccobacillary organisms (0.2–2 μm) that are found within or attached to the outer surface of erythrocytes and in the plasma. They change size and shape as they mature, which gives the microscopic appearance of infection by two different rickettsiae. They stain well with Giemsa but not with Gram stain.

Clinical signs and differential diagnoses. The acute form is usually seen in suckling or newly weaned piglets or other pigs that have been stressed, and consists of fever of 40°–42°C, anemia, jaundice, pale mucous membranes, cyanosis of the ears, allergic skin reactions, weakness, and poor weight gain. All ages of swine can be clinically affected; however, the very young are most likely to be clinically affected. Acutely affected sows will become anorexic and febrile, and will have decreased milk production and poor maternal behavior. Vulvar and mammary gland edema may also be seen in sows.

The chronic form affects older pigs and is usually subclinical, or it may adversely affect reproductive parameters in sows (Solignac *et al.,* 1996). The reproductive problems include anestrus, low conception rates, abortions, weak piglets, and small litters. Mortality due to eperythrozoonosis is extremely low.

Differentials include iron deficiency anemia and other causes of anemia in piglets, other infectious diseases, and toxicity producing icterus or anemia.

Epizootiology and transmission. The reservoir for *E. suis* is domestic swine, and serologic studies have not detected it in wild swine (Heinritzi, 1999). However, current serologic tests will not detect every latent carrier. The various species of this parasite are considered host-specific. Transmission is mechanical by blood-sucking arthropods, primarily lice, or reuse of blood-contaminated needles and surgical or tattoo instruments. It can be directly transmitted by the oral route when swine lick fresh wounds or any fluids containing blood.

Necropsy. Gross findings include icterus, distended gallbladder filled with gelatinous bile, splenomegaly, pale mucous membranes, watery blood, swollen edematous lymph nodes, ascites, and hydrothorax, and the liver may be swollen and yellow-brown (Smith, 1992; Splitter, 1950). One or more of the organisms can be found within RBCs in a smear of peripheral blood, where they appear as 0.8–1 μm diameter rings with a pale center (Thomson, 1988). Microscopic lesions in other organs include hemosiderosis in hepatocytes and Kupffer's cells, fatty degeneration and centrolobular necrosis of hepatocytes (Splitter, 1950), and a hyperplastic bone marrow (Smith, 1992).

Pathogenesis. Arthropod transmission from pig to pig is believed to be the mode of spread, but this has not been proven. *In utero* and oral transmission have been reported.

Prevention and control. Control measures include eliminating ectoparasites, never reusing needles, and sterilizing surgical instruments thoroughly. Additionally, any concurrent disease should be eliminated, and environmental, nutritional, and experimental stress reduced. The most satisfactory prevention is to allow only known *Eperythrozoon suis*–free swine into a facility. A PCR assay for *E. suis* in blood has been developed, which may be useful for herd-health monitoring as well as clinical diagnosis (Messick *et al.,* 1999). In acute cases, a fresh blood smear can be stained with Giemsa to visualize the organisms.

Treatment. Oxytetracycline either parenterally or in food or water will control the clinical signs but does not eliminate the rickettsiae. Iron dextran should be given to each clinically affected pig. In severely anemic animals, administration of whole blood may be beneficial. Additionally, any form of environmental, experimental, or physical stress should be eliminated.

Research complications. Eperythrozoonosis causes an autoimmune hemolytic anemia, which will be precipitated or exacerbated by the stress of experimental protocols. This also predisposes affected animals to respiratory and gastrointestinal disease, which will further confound research protocols.

5. Skin Diseases

a. Exudative Epidermitis (EE): Greasy Pig Disease

Etiology. *Staphylococcus hyicus* is a gram-positive cocci that produces an exfoliative toxin (SHET). Three antigenically different exfoliative toxins (ExhA, ExhB, ExhC) have been identified (Andresen, 1998) and are thought to correlate with clinical disease (Tanabe *et al.,* 1996). All three of these toxins are metalloproteins (Andresen, 1999a,b). A fourth toxin has recently been identified, and its proposed designation is SHETB (Sato *et al.,* 1999).

Clinical signs and differential diagnoses. The early clinical signs of EE are lethargy and erythematous skin in a variable number of pigs in a litter. Pigs aged 5 days to 2 months are susceptible, and older pigs are more resistant. The signs progress to an exudative dermatitis characterized by exfoliation and crust-

ing, which begins in the groin, in the axillae, behind the ears, and in areas of damaged skin. Anorexia, dehydration, and poor weight gain are characteristic; however, pyrexia and pruritis are not typical signs. Erosions at the coronary band of hooves and vesicles or ulcers in the mouth and on the tongue and snout are common findings. The dermatitis may progress to cover the majority of the body in 3–5 days and becomes exfoliative and crusty. Severely affected members of the litter may die in 24 hr to 10 days, and others may not be affected or be chronically affected with small, localized patches of EE. Adult animals may be mildly affected with small areas of EE on their backs and sides (Wegener and Skov-Jensen, 1999; Cowart, 1995). *Staphylococcus hyicus* has also been reported to be an etiologic agent for arthritis in piglets less than 12 weeks old (Hill *et al.,* 1996).

Differential diagnoses should include swine pox, mange, ringworm, and pityriasis rosea.

Epizootiology and transmission. *Staphylococcus hyicus* in carrier swine is harbored in the nasal cavity and conjunctiva, and vagina of sows and prepuce of boars. Outbreaks are seen following introduction of a carrier animal to a nonimmune herd. The newborn piglets are probably infected during parturition, and cross-contamination can occur when weanlings from different litters are group-housed. This bacterium is very persistent in the environment, and aerosol transmission is possible. Damage to the skin by abrasions from pen surfaces, fighting, mange mites, and concurrent vesicular diseases facilitates entry of *S. hyicus.* Spread by other species is of little concern (Wegener and Skov-Jensen, 1999). The morbidity can reach 20%, and mortality can reach 80% in affected piglets (Cowart, 1995).

Necropsy. The skin in the area of the erosive lesions may be reddened, edematous or thickened, and covered with an exudate composed of sebum, serum, and sweat (Jones, 1956). These lesions are most commonly found on the ears, around the eyes, on the ventral thorax, and on the abdomen. Microscopic findings are the presence of both a superficial and deep pyoderma that may extend to involve the subcutis, with multiple coalescing foci of necrosis of the stratum corneum; and the presence of a brownish exudate, as well as the formation of rete pegs by the hyperplastic stratum germinativum (Jones, 1956; Thomson, 1988; Taylor, 1992).

Pathogenesis. *Staphylococcus hyicus* is an opportunist that readily invades traumatic wounds of the skin.

Prevention and control. Autogenous bacterins made from strains cultured from a particular herd and given to nonimmune sows are useful to protect the litters of newly introduced sows. The exfoliative toxin and the bacterial cells should be included as antigens when the vaccine is made. An indirect ELISA or phage typing can be utilized to select a toxigenic strain for vaccine production (Andresen, 1999a). The environment should be improved, including temperature and humidity control and, especially, sanitation of the farrowing pens. The sows can be washed with appropriate antibacterials (chlorhexidine or povidone–iodine shampoos) prior to parturition, and any sharp or abrasive surfaces removed from the pens. The animals should be checked to be sure that they are free of mange and lice, as these may irritate the skin. Isolation of affected animals and housing animals in socially compatible groups to avoid fighting may help. Reviewing the diet to be sure that it meets NRC minimum requirements is indicated.

Treatment. Treatment with antibiotics will reduce the severity of the dermatitis and aid recovery. This bacteria is potentially susceptible to several antibiotics; however, plasmid-mediated resistance is common. The choice should be based on sensitivity testing whenever possible. The list includes trimethoprim-sulfonamides, cephalosporins, lincomycin, amoxicillin, erythromycin, tylosin, and penicillin. Topical treatment of the affected skin with antibiotics and antiseptic shampoos or dips in conjunction with the antibiotics are also beneficial. Treatment is most effective when started early in the course of the disease, and severely affected young piglets may be slow to recover (Wegener and Skov-Jensen, 1999; Cowart, 1995).

Research complications. Exudative epidermitis will complicate most studies involving young piglets due to the potentially significant morbidity and mortality.

b. Swine Pox

Etiology. Swine pox virus is the only member of the genus *Suipoxvirus,* family Poxviridae. The virus is found worldwide, primarily in herds with poor sanitation, and chiefly affects pigs less than 4 months of age.

Clinical signs. The lesions associated with this virus mimic other pox diseases. Initially, macules form (reddening); followed by 1–6 mm diameter papules (reddening with edema); then vesicles (fluid within the lesion); then pustules (umbilicated, ischemic); and finally, crusts (brown to black in color). The progression of the lesions occurs over a 3- to 4-week period. Younger animals are affected more severely than adults, and they may have lesions covering the entire body surface. Older animals tend to have lesions in more focal locations. If vector transmission has occurred, the location of the lesions follows the vector preferences, i.e., the pig louse attacks the lower parts of the body, while flies feed predominantly over the top of the body. Adults have lesions primarily on their belly, udder, ears, snout, and vulva.

Epizootiology and transmission. The virus, although worldwide in distribution, exists primarily in herds where poor sanitation is practiced. The reservoir is infected swine, as the virus

is host-restricted. The virus may persist in an active form in dry skin scabs for up to 1 year. Horizontal transmission may occur via nasal and oral secretions coming in contact with abraded skin. The primary method of transmission, however, is the pig louse. Flies and mosquitoes can also carry the viral particles. Once the virus is established within a herd, it usually persists. Outbreaks can result in high morbidity if young animals are present, although mortality is very low.

Necropsy. Gross lesions are most commonly found on the ventral and lateral abdomen and chest and the medial aspects of the legs, and only in severe cases involve the oral cavity and main airways (Jubb *et al.,* 1985). Early lesions consist of erythematous macules and papules, and later lesions progress to pustules and scabbing. Microscopic findings are related to viral replication in the stratum spinosum, causing hydropic degeneration, intercellular edema, necrosis of epithelial cells, and formation of pustules that involves the full thickness of the epidermis with 1–3 eosinophilic intracytoplasmic poxvirus inclusion bodies in epithelial cells (House and House, 1992).

Pathogenesis. The virus gains entry to the body by traumatic injuries and by bites from the pig louse, as well as from flies. It replicates in the cells of the stratum spinosum and is spread from cell to cell in the epidermis (House and House, 1992). A viremia is believed to occur and results in transplacental infection and disease in neonates (Jubb *et al.,* 1985).

Diagnosis. The diagnosis is primarily made by identifying the typical lesions in the typical locations. Differential diagnoses include any of the vesicular diseases, pityriasis rosea, allergic skin reactions, sunburn, or staphylococcal or streptococcal epidermitis. The presence of intracytoplasmic inclusion bodies along with central nuclear clearing in affected epithelial cells is a hallmark sign of this disease.

Prevention and treatment. Supportive care should be given to prevent secondary bacterial skin infections. Affected animals should be isolated, and sanitation and pest control should be improved.

c. *Mange (Scabies)*

Etiology. Sarcoptes scabiei var. *suis* is the cause of sarcoptic mange in swine. This is probably the most significant ectoparasite of swine. This mite is 0.5 mm in length, has 4 pairs of legs, and completes its entire life cycle within the layers of the epidermis. The time necessary for an egg to hatch and develop into a mature egg-laying female is 10–25 days. This is one of the more common swine diseases, but it is frequently overlooked, probably because the clinical signs may be perceived as normal and losses are not readily apparent. Demodectic mange caused by *Demodex phylloides* can also occur in swine; however, it is a rarity.

Clinical signs and differential diagnoses. There are two clinical forms of sarcoptic mange in swine. The acute pruritic or allergic hypersensitive form affects younger, growing pigs. This is characterized by an intensely pruritic, erythematous papular dermatitis on the ventral abdomen, flank, and rump. Pigs with this form will rub the affected areas, often causing hair loss, abrasions, and thickened, keratinized skin. A reduced growth rate will be seen if the dermatitis is severe (Davies, 1995). It is difficult with this form to find the mites on skin scrapings.

The chronic or hyperkeratotic form is typically found in mature sows and boars. Thick, crusty scabs begin on the pinnae and spread to the neck and head, and contain numerous mites that are relatively easy to find on skin scrapings. Mortality is unlikely unless concurrent disease is severe.

Differentials should include causes of dermatitis in swine, such as exudative epidermitis, dermatomycosis, swine pox, parakeratosis, niacin and biotin deficiencies, sunburn, photosensitization, and insect bites (Cargill and Davies, 1999).

Epizootiology and transmission. Mange infestations are fairly common in small conventional swine herds in the United States. Nursing piglets first obtain the mites from an infected sow through direct contact. These breeding sows with hyperkeratotic encrustations in their ears are the primary reservoirs of *S. scabiei* var. *suis* mites. Group housing of pigs, especially from various sources, will facilitate spread of mites. Spread of mites through environmental contamination is less likely but still possible, as mites can survive off the host for a few days or even longer if ambient temperatures are cool. Herd-to-herd transmission is by introduction of a carrier pig; other species are not known to harbor this mite.

Necropsy. Papular dermatitis will be seen in growing swine with or without positive skin scrapings for the sarcoptid mites. The papules, which are manifestations of the hypersensitivity reaction, contain eosinophils, mast cells, and lymphocytes (Cargill and Davies, 1999) and have an associated eosinophilic perivasculitis (Hollanders and Vercruysse, 1990). In mature animals, thick, crusty scabs with positive skin scrapings are typical findings. Histologic sections will reveal offending mites burrowing to the level of the deep stratum corneum and stratum malpighii, producing hyperkeratosis and acanthosis (Jones and Hunt, 1983).

Pathogenesis. Young pigs or newly exposed older animals become pruritic due to a hypersensitivity response to the mites burrowing into the dermis and laying eggs (Davis and Moon, 1990). This generally occurs several weeks postinfection. The first 3 weeks postinfection, the females burrow into the skin and a covering of keratinized encrustations develops. These crusts fall off after 7 weeks, and the mites leave the burrows (Morsy *et al.,* 1989). This is seen clinically as rubbing and development of encrustations containing mites, followed by papular dermatitis as hypersensitivity develops. If the rubbing is severe, persist-

ent hyperkeratosis will develop. The hyperkeratotic form is seen more often in mature animals (Cargill and Davies, 1999).

Prevention. Allowing only mange-free SPF animals into the facility is the most effective and satisfactory method of prevention. *Sarcoptes scabiei* can be eliminated by hysterotomy rederivation. Alternatively, mange-free herds can be made by elimination of mites with acaricides such as ivermectin. It is feasible to maintain a herd free of *S. scabiei* if a good biosecurity and surveillance program is developed (Cargill *et al.,* 1997).

Control. Swine with unusually severe chronic hyperkeratosis should be culled from the group if possible. Every pig in the group should be treated twice, with a 1- to 2-week interval. This should be followed by thorough cleaning of the environment, removing any bedding, and spraying the area with an acaricide.

The success of the control program can be monitored by using an ELISA for serum antibody levels to *S. scabei* (Hollanders *et al.,* 1997; Bornstein and Wallgren, 1997; Wallgren and Bornstein, 1997; Jacobson *et al.,* 1999; Zimmermann and Kircher, 1998), using periodic skin scrapings, and monitoring for prevalence of scratching and papular dermatitis lesions (Davies *et al.,* 1996).

Treatment. Ivermectin is effective orally or subcutaneously (Hollanders *et al.,* 1995; Cargill and Davies, 1999) and should be repeated in 14 days. Doramectin intramuscularly has also been reported to be very effective (Cargill, 1996; Logan *et al.,* 1996; Saeki *et al.,* 1997; Yazwinski *et al.,* 1997). Experimental evidence has demonstrated that doramectin has a greater persistent efficacy than ivermectin (Arends *et al.,* 1999). There are several other acaricides, including amitraz, phosmet, and diazinon, that are also effective. Two or more treatments at 1- to 2-week intervals are usually necessary to eliminate these mites.

Research complications. Sarcoptic mange should not result in direct loss of animals in a study since this disease is rarely associated with mortality unless there is concurrent disease. The intense rubbing associated especially with the acute form is a potential threat to surgical incisions and implants in these models.

d. Lice (Pediculosis)

Etiology. Haematopinus suis females are 4–6 mm in length and males, 3.5–4.75 mm. These lice belong to the order Phthiraptera and suborder Anoplura, or sucking lice, which possess specialized mouth parts to penetrate swine skin and feed on their blood. It is the only species of louse that affects swine (Lapage, 1968a).

Clinical signs and differential diagnoses. Pruritus, poor growth, and anemia in young pigs are the clinical signs. These lice can be found almost anywhere on the body but have a predilection for the skin on the flank area, neck, axilla, groin, and the inner ears. Their eggs, or nits, are 1–2 mm in length and attach to the hair shafts.

Epizootiology and transmission. Transmission is by direct pig-to-pig contact, as this louse is host-specific and will not survive very long (less than 2–3 days) off the host. The life cycle is 23–32 days and is entirely in and on the skin. It is considered a vector for swine pox and *Eperythrozoon suis.*

Necropsy. The entire life cycle of *H. suis* occurs on the skin surface; therefore, adults can be visualized around the inner ear, face, and neck without special techniques. The nits can be found attached to hair shafts. Allergic dermatitis and mechanically induced skin lesions with hemorrhage may been found on some affected pigs (Nickel and Danner, 1979).

Pathogenesis. The three instars of the nymph stage and egg-laying females suck blood, causing irritation and pruritus, manifested clinically as rubbing, and possibly as anemia in heavy infestations of young pigs.

Prevention, control, and treatment. The most reasonable and effective means of lice prevention is to allow only swine known to be lice-free into the research facility. Feral populations of *Sus scrofa* have been found to be reservoirs for *H. suis* (Gipson *et al.,* 1999), and certainly contact with domestic populations should be prevented. However, this condition is easier to treat than scabies. The same treatments that are effective for mites also work well for lice. These include several sprays, dips, dusts, and oral and injectable ectoparasiticides. Most are very effective when given as 2 treatments 2 weeks apart. Treatments that are typically administered as sprays include malathion, methoxychlor, permethrin, diazinon, and coumaphos. Phosmet, fenvalerate, and amitraz are typically administered as pour-on solutions for swine treatment. The avermectins (primarily doramectin) (Logan *et al.,* 1996) and ivermectin are available as an oral or injectable treatment and are also effective for ascarids and lungworms.

Research complications. Severe infestations may cause anemia in young swine, and the rubbing may damage surgical incisions. Furthermore, the use of potentially toxic treatments to remove the lice may interfere with some research studies.

6. Reproductive Diseases

a. Brucellosis

Etiology. Brucella suis, particularly biovars 1, 2, and 3, is the only species of *Brucella* that causes systemic infection and clinical disease, including infertility, in swine. Biovar 3 is currently the most common cause of this disease in swine. Morphologically, this genus is a nonmotile, non-spore-forming, small gram-negative aerobic bacillus or coccobacillus.

Clinical signs and differential diagnoses. The clinical signs of *B. suis* infection vary with the herd and range from no obvious disease to the classical signs, which include abortion, infertility, metritis, orchitis, lameness, spondylitis, and posterior paralysis. Clinical disease in piglets of weaning age usually consists of spondylitis and posterior paralysis (MacMillan, 1999). Differentials include other causes of infertility and abortion in swine, such as porcine parvovirus and leptospirosis.

Epizootiology and transmission. Domestic swine populations are the primary sources for *B. suis.* The European hare (*Lepus capinensis*) is a carrier for biovar 2 and has been linked to brucellosis in European swine facilities. Feral pigs are also reservoirs in areas where contact with domestic swine can occur. *Brucella suis* biovar 2 has been reported in wild boars in Germany (Heinritzi *et al.,* 1999).

Transmission is most frequently through contaminated discharges from infected swine being ingested by a susceptible animal. This takes place from direct contact with aborted fetuses and fetal membranes or with contaminated food or water. Additionally, nursing piglets frequently become infected while suckling infected sows. *Brucella suis* is present in semen of infected boars and can be spread by natural breeding or artificial insemination.

Necropsy. Gross lesions are variable in site and extent but generally consist of one or more abscesses, and there may be erosions of mucous membranes (MacMillan, 1992) and seminal vesiculitis (Deyoe, 1967). Aborted fetuses may appear normal, or there may be edema or evidence of a suppurative placentitis. Microscopic lesions consist of inflammatory cell infiltrates in the endometrium, uterine glands, and placentas (MacMillan, 1992); suppurative seminal vesiculitis (Deyoe, 1967); pyogranulomatous foci in the liver; caseous necrotic foci adjacent to growth plate cartilages in the vertebrae; and abscesses in the kidneys, spleen, ovaries, lungs, brain, and other tissues (MacMillan, 1992).

Pathogenesis. The precise mechanisms by which this organism attaches to and penetrates mucosal epithelium is not known. However, once the organisms have penetrated to the submucosa, they travel to the local lymph nodes, gain entrance to macrophages and neutrophils, and multiply, resulting in a bacteremia with seeding of organisms in other lymph nodes, the genital tract, placenta, joint fluids, and bone marrow (MacMillan, 1992). Differential diagnoses should include leptospirosis and any bacterial agent that may cause abortion.

Prevention and control. The best prevention is to allow only brucellosis-free swine from validated herds into a facility. A control program in infected herds with valuable genetics might be achieved by test and elimination of all seropositives. This is difficult because of problems with specificity and sensitivity of serologic assays (Ferris *et al.,* 1995). This plan works only if there are very few animals in the herd actually infected. The most satisfactory method is to depopulate infected herds and repopulate with validated animals. If a closed herd is maintained with a good biosecurity program, it is feasible to keep it brucellosis-free. Brucellosis is a zoonotic and reportable disease in the United States.

Treatment. Infected swine should be euthanatized. Antimicrobials are unlikely to eliminate the bacteria from swine, and vaccines that can safely produce a lasting immunity have not been developed. Fortunately, the incidence of brucellosis among domestic swine in the United States has declined to a very low level.

Research complications. Research protocols involving any aspect of swine reproduction are at highest risk for brucellosis. *Brucella suis* is one of the most common species implicated in cases of human brucellosis. Investigators and veterinarians performing necropsies on infected animals are at risk for becoming infected.

b. Leptospirosis

Etiology. The etiologic agent for this disease in swine consists of several serovars of *Leptospira interrogans.* All are gram-negative, motile aerobic spirochetes. The serovar *pomona* is the most common cause of clinical leptospirosis in swine, and the serovar *bratislava* is commonly found in serologic surveys and sometimes correlated with clinical disease. There are several other serovars, which are typically maintained in other mammalian hosts but are occasionally found to infect swine. These include *icterohaemorrhagiae* from the brown rat (*Rattus norvegicus*); *sejroe* from small rodents; *hardjo* from cattle; *canicola* from dogs; *grippotyphosa* from wildlife; and *tarassovi* from opossums, skunks, and raccoons (Ellis, 1999 and Cowart, 1995).

Clinical signs and differential diagnoses. The acute form is characterized by a mild transient anorexia, listlessness, diarrhea, and pyrexia that resolves within a week and usually goes unrecognized. Rarely seen are piglets < 12 weeks of age infected with strains from the serogroup *icterohaemorrhagiae,* hemoglobinuria, and jaundice. The chronic form is characterized by late-term abortions, stillbirths, and weak newborn piglets. This is particularly true of serovar *pomona* infection. Infertility of the sow is seen following infections due to serovar *bratislava;* however, reproductive performance following abortions due to *pomona* is not affected (Ellis, 1999). Differential diagnoses include parvovirus, brucellosis, and pseudorabies.

Epizootiology and transmission. Transmission from animal to animal is by direct or indirect contact with a carrier animal, which harbors the leptospires in the renal tubules or genital

tract. Leptospires are shed from carrier animals in urine and genital fluids into the environment. Feral swine are potential sources of serovars *pomona* and *bratislava* for outdoor facilities where contact can occur (Saliki *et al.*, 1998; Mason *et al.*, 1998). Venereal transmission is thought to be the mode of spread for serovar *bratislava* because sows and boars harbor it in the reproductive tract and urinary excretion is relatively low. Survival of the bacteria out of the host is favored by warm, moist conditions. Entry into the new host is through mucous membranes of the eye, snout, mouth, and genital tract or through damaged skin.

Swine are typically maintenance hosts for serovars of the serogroups *pomona, australis* (serovars *bratislava* and *muenchen*), and *tarassovi.* Infection with other serovars is considered incidental. Typically, only a limited number of serovars will be endemic in a given area and host species (Ellis, 1999).

Necropsy. There may be petechial or echymotic hemorrhages in the lungs and kidneys, which may be swollen, along with small gray lesions on the renal cortex. Microscopic lesions in the kidney include an interstitial nephritis with inflammatory cells, lymphocytes, and plasma cells. Glomeruli may be swollen or atrophic and cellular casts may be found in the lumen of renal tubules lined by atrophic epithelial cells (Ellis, 1992).

Pathogenesis. The route of infection is believed to be via the mucous membranes of the mouth, nasal passages, eye, and vagina. A bacteremia develops that results in seeding of *Leptospira* organisms in most organs, including the liver, the pregnant uterus, and the proximal renal tubules, where they persist, multiply, and are voided for varying periods in the urine (Thomson, 1988).

Prevention and control. A biosecurity program that prevents potential vectors, such as rodents and feral swine, from making direct or indirect contact with the swine in the facility is essential to prevent introduction and minimize spread. The microscopic agglutination test (MAT) is commonly utilized for serologic monitoring of herds. Artificial insemination can be used to advantage to prevent spread or introduction of serovar *bratislava.* Vaccination with bacterins will reduce the incidence of infection but not eliminate the disease from the herd. Immunity is short-lived, which necessitates revaccination at least every 6 months (Ellis, 1999; Cowart, 1995).

Treatment. Medicating feed for periods of 4 weeks or more with oxytetracycline or chlortetracycline will help control clinical signs until a vaccination program can be established. Individual dosing of pigs with dihydrostreptomycin–penicillin G, oxytetracycline, erythromycin, or tylosin may help eliminate serovar *pomona* from the renal tubules (Alt and Bolin, 1996; Ellis, 1999).

Research complications. Leptospirosis will interfere with studies involving swine reproduction or fetal surgery, due to the increased rate of late-term abortions associated with the chronic form of the infection.

c. *Parvovirus*

Etiology Porcine parvovirus (PPV) is a disease of swine characterized by embryonic and fetal infection and death when susceptible sows and gilts are exposed to the virus during the first 70 days of gestation. The infection typically causes no observable clinical signs in the infected female, and its major impact on animal health relates to the agent's ability to interfere with live births. Porcine parvovirus is one of the major infectious causes of embryonic and fetal death (Mengeling *et al.*, 1991).

The disease is caused by a single-stranded DNA virus classified in the genus *Parvovirus,* family Parvoviridae. All isolates of the virus found in swine have been antigenically similar, if not identical, and are also antigenically related to other members of the genus. Although the viral particles have actually been identified in pig feces, there is no evidence implicating that PPV replicates in the intestinal crypt epithelium or causes enteric disease in swine, as the agent does in other species (Brown *et al.*, 1980).

Clinical signs. Acute infection of both postnatal and pregnant dams is subclinical; however, the pigs will have a transient, mild leukopenia within 10 days after the initial exposure. The only clinical sequela to exposure is maternal reproductive failure. Dams can cycle back into estrus, farrow fewer pigs per litter, or farrow a large proportion of mummified fetuses. Typically, an epizootic of PPV starts as a subclinical infection and culminates with the delivery of mummified fetuses, usually at or near term. Most of the infected fetuses have a crown–rump length of 17 cm or less because those infected after day 70 are able to respond to the viral assault and survive (Mengeling *et al.*, 1993). Infertility, abortion, stillbirth, neonatal death, prolonged gestations, and reduced neonatal viability have also been attributed to PPV.

There is no evidence that PPV impacts on either fertility or libido of boars (Thacker *et al.*, 1987).

Epizootiology and transmission. Porcine parvovirus is ubiquitous among swine worldwide. In general, infection is enzootic in most herds, and with rare exception, sows are immune. Also, gilts usually contract PPV before conception and develop an active immunity that persists through life. Disease occurs when there is a large population of gilts that have not developed immunity prior to conceiving. Gilts are most commonly infected via the oronasal route, and prenatal pigs are infected via the transplacental route.

Nursing pigs absorb protective PPV antibody from colostrum. These titers diminish to levels that are not protective when the

piglets are 3–6 months of age. The significance of the passively acquired antibody is that it interferes with the development of active immunity until the 3- to 6-month mark (Paul and Mengeling, 1980).

The major reservoir for PPV is environmental. The virus is thermostable and resistant to many disinfectants. It has been shown that pigs transmit PPV for about 2 weeks after exposure, but the pens they were housed in remained infectious for up to 4 months (Mengeling and Paul, 1986).

It is also possible that immunotolerant carriers of PPV, resulting from early *in utero* infection but not death, are carriers (Johnson, 1973). Boars may also play a role in dissemination of the disease. During acute infection with the agent, the virus can be shed in semen. Virus can also be isolated from scrotal lymph nodes up to 35 days postexposure.

Necropsy. Gross lesions are confined to the placenta, which may be edematous and have white, chalklike deposits (Joo *et al.,* 1977) and stunted fetuses with prominent blood vessels on their surfaces, petechial hemorrhages, edema, enlarged dark liver and kidneys, serosanguinous fluid in body cavities, and mummification (Joo *et al.,* 1977; Hogg *et al.,* 1977). Microscopic findings in the fetuses include vasculitis with hypertrophy of endothelial cells; and perivascular accumulations of mononuclear cells around vessels in the gray matter and white matter in the cerebrum, brain stem, and meninges, in the interstitial area around glomeruli, the portal areas of the liver, and the placenta (Joo *et al.,* 1977; Hogg *et al.,* 1977).

Pathogenesis. Viral infection of the pregnant sow results in a viremia and allows transplacental passage of the virus to the fetuses (Joo *et al.,* 1976; Mengeling, 1975). Once infected, a fetus can then transmit the virus to other fetuses (Mengeling, 1975).

Differential diagnoses. Differential diagnoses should include porcine reproductive and respiratory syndrome (PRRS), brucellosis, and leptospirosis.

Diagnosis. Porcine parvovirus is one of the primary diagnostic considerations when swine exhibit embryonic or fetal death. Gilts are the population primarily at risk. The lack of maternal illness, abortions, or fetal developmental anomalies differentiate this disease from other causes of reproductive failure. In addition, identifying mummified fetuses that have a crown–rump length of $\leq$ 17 cm is a strong indicator that PPV is the infectious agent at play.

The definitive diagnosis can be made by identifying viral antigen by immunofluorescent (IF) microscopy from sections of fetal tissues. Serologic testing for antibodies (i.e., ELISA) are recommend only when tissues from mummified fetuses are not available. Results from serum are of value if antibody is not detected or if samples are collected at intervals that document seroconversion for PPV. Since PPV is ubiquitous, the presence of antibody in a single sample is meaningless. Detection of antibody in sera of fetuses/stillborns before they nurse is evidence of *in utero* infection, as the maternal antibody does not cross the placenta (Chaniago *et al.,* 1978).

Prevention and treatment. There is no treatment for the reproductive failure associated with PPV. Prevention involves either naturally infecting gilts with PPV or vaccinating them prior to pregnancy. Through herd-management practices, natural infections can be promoted. Seronegative gilts can be housed with seropositive sows. Vaccines are used extensively in the United States. They are administered several weeks before conception but after the disappearance of passively acquired colostral antibody. In essence, the window for vaccination is small in herds keyed for production. Vaccination for boars is also recommended.

d. Porcine Reproductive and Respiratory Syndrome

Etiology. A new swine disease was first identified in the United States in the late 1980s. Hallmark signs included reproductive disorders, high piglet mortality, and respiratory disease seen in a wide age range of animals. The disease became known officially as PRRS (porcine reproductive and respiratory syndrome) but is often referred to in the literature as SIRS (swine infertility and respiratory syndrome). The disease has now spread into many countries and has escalated into one of the major causes of reproductive losses and respiratory disease in swine.

The causative agent is a single-stranded RNA virus classified in the order Nidovirales, family Arteriviridae, genus *Arterivirus.* This agent shares structural and functional organization with others in the genus, including lactate dehydrogenase–elevating virus, equine arteritis virus, and simian hemorrhagic fever virus. These viruses in general are known to have high rates of mutation. The isolates found in the United States (VR-2332) and Europe (Lelystad) have genomic and serologic differences, although it is believed they merged from a common ancestor. The U.S. isolates differ genomically but cross-react serologically. Current efforts are being directed toward determining if infection with a single isolate provides immunologic cross protection. Recent infections in vaccinated herds lend suspicion that immunization does not provide protection across all isolates (Collins *et al.,* 1992, 1997).

Clinical signs. The clinical presentation of PRRS infection depends on the age of the pig and the gestation status when infected. In addition, the clinical presentation can vary depending on complicating infections with viruses or bacteria. Late gestational abortions typically occur when animals are infected during the third trimester and can occur sporadically or sweep throughout the population of animals. Other reproductive manifestations that have been documented include delayed parturi-

tion and premature farrowing resulting in mummified or stillborn fetuses. Clinical signs in infected females vary from none to anorexia, fever, pneumonia, agalactia, red/blue discoloration of ears and vulva, subcutaneous edema, and a delayed return to estrus.

Clinical signs in PRRSV-infected newborn pigs also vary in frequency and severity. Dyspnea and tachypnea are the most characteristic clinical signs, with other signs including periocular and eyelid edema, conjunctivitis, blue discoloration of the ears, diarrhea, and CNS signs. Mortality can reach 100%. As the pigs reach postweaning age, the clinical signs shift to include fever, pneumonia, failure to thrive, and significant mortality caused by otherwise non-life-threatening concurrent bacterial infections.

The susceptibility and resulting impact of secondary bacterial infections in pigs infected with PRRSV depends on the PRRSV isolate, the swine genetic composition, management practices, and environmental factors. Subclinical infections occur commonly as the pig continues to mature, with the only indication of infection being seroconversion to the virus. Occasionally a transient fever and inappetence or loss of libido can be observed.

Hematologic parameters congruent with infection include a decrease in lymphocytes, neutrophils, and monocytes at 4 days postinfection, with a concurrent increase in band neutrophils. Four-week-old pigs had decreased RBC counts, hemoglobin levels, and hematocrits (Rossow et al., 1994).

Differential diagnoses include parvovirus, pseudorabies, and leptospirosis.

Epizootiology and transmission. This virus is spread predominantly through direct contact between infected and naive pigs, although the route of fetal PRRSV infection has not been identified. The virus is carried in blood, oropharyngeal fluids, semen, feces, and urine. Transmission by aerosolization is possible, though routinely occurs only over short distances. The virus establishes a foothold by infecting macrophages located within mucosal surfaces. The virus infection is limited to domestic swine with the exception of a single report occurring in mallard ducks (Zimmerman *et al.,* 1995). The agent is considered to be a "slow spreader." The virus can be identified in semen prior to seroconversion as well as after cessation of viremia, indicating that virus isolation from serum and serology may not be an adequate indicator of infection status in boars. The disease does persist in infected swine in a transmissible, viable state, often without stimulating antibody production, thereby making serologic screening for the disease inaccurate. Pigs subclinically infected with PRRSV are thought to be the key factor in disease transmission within herds (Rossow, 1998).

Diagnosis. The viral infection is most accurately diagnosed through the demonstration of PRRS by virus isolation, fluorescent antibody examination, immunohistochemistry, or PCR in concert with clinical signs and characteristic histologic lesions. Exposure to the virus can be documented through the use of serology testing for anti-PRRSV antibodies; however, if pigs are vaccinated with the modified live-PRRSV vaccine, the current serologic tests cannot differentiate between vaccine virus and field PRRSV isolates. It is also important to note that pigs vaccinated with the modified live vaccine can transmit vaccine virus to naive pigs, resulting in infection and seroconversion of the naive animal (Rossow, 1998).

The virus can most easily be located in lung tissue, lymphoid tissue, heart, brain, nasal turbinates, and reproductive organs. Again, it is important to note that modified live-PRRSV vaccine virus can also be identified from these tissues, and pathogenic PRRSV isolates must be differentiated from the vaccine virus.

Necropsy. Gross lesions in young piglets include mottled lungs with tan foci of consolidation; lymphadenopathy of the mesenteric and middle iliac nodes, which are tan and may contain cysts; moderately enlarged and rounded hearts; and clear fluid in the pericardial space and abdominal cavity.

Microscopic lesions consist of a multifocal lymphohistiocytic myocarditis; an interstitial pneumonia with mononuclear cell infiltrates, resulting in septal thickening; peribronchial and peribronchiolar lymphohistiocytic cuffing; hypertrophy and hyperplasia of type II pneumocytes; and filling of alveolar spaces with necrotic and normal macrophages. There is also follicular hypertrophy, hyperplasia, and necrosis in lymphoid tissues and a mild lymphohistiocytic choroiditis with cuffing of vessels in the meninges, choroid plexus, and brain (Halbur *et al.,* 1995). Lesions in fetuses consist of myocarditis with fibrosis, arteritis, and encephalitis (Rossow *et al.,* 1996a).

Pathogenesis. The virus has been demonstrated in urine, feces, nasal secretions, semen, saliva, and serum, and all are potential routes of exposure (Rossow, 1998). The virus has been shown to enter via the nasal epithelium, bronchial epithelium, and tonsillar and pulmonary macrophages, followed by replication in macrophages, with a subsequent viremia (Rossow *et al.,* 1996b). Migration of infected macrophages across the placenta may be one of the mechanisms for transplacental infection of fetuses.

Prevention and control. Vaccination of pigs with a modified live-PRRSV vaccine has protected pigs from clinical disease when the pigs were challenged with heterologous PRRSV isolates; however, other reports have shown that the vaccine is not universally protective against all isolates of PRRSV. Efforts should be made to obtain pigs from sources that are free of PRRSV. Pigs coming from different sources should be isolated from each other.

Treatment. Once pigs show signs of disease, supportive therapy should be implemented. This can include antibiotics to

control concurrent bacterial infections and vitamin and food supplements until animals regain their appetite.

B. Metabolic/Nutritional Diseases

a. Porcine Stress Syndrome

Etiology. Porcine stress syndrome (PSS) refers to a cascade of physiologic events and clinical signs that occur in pigs that have a mutation in the calcium-release channel protein (ryanodine receptor [RYR]). This mutation results in a hypersensitive triggering mechanism of the calcium-release channel in skeletal muscle sarcoplasmic reticulum in response to various stressors, such as gas anesthetics or stressful environmental conditions. The lack of proper calcium control within the membranous portions of the sarcoplasmic reticulum and mitochondria is thought to initiate the cascade of events that results in the syndrome (O'Brien *et. al.,* 1991; Fujii *et al.,* 1991). Stress-susceptible pigs are also known to overrespond to stressful stimuli, with excessive β-adrenergic receptor stimulation, lower rates of lactate, alanine, and aspartate conversion to carbon dioxide by the liver, abnormal phosphorus metabolism, and a much higher cortisol and thyroxine turnover rate.

Animals carrying the genetic defect are found throughout the world with a frequency varying between 0 to 89% among herds (Webb *et al.,* 1992). Genotypic analyses have indicated that the mutation arose from a single founder animal. The mutation is found in five major breeds of swine: Landrace, Yorkshire, Duroc, Pietrain, and Poland China. However, there are reports of this disease occurring in other breeds, including miniature potbellied pigs (Claxton-Gill *et al.,* 1993). The mode of inheritance is autosomal recessive with variable penetrance. This syndrome has also been reported in humans, dogs, cats, and horses.

Clinical signs. In a laboratory setting, development of PSS has most commonly been associated with exposure to halothane and succinylcholine; however, methoxyflurane, enflurane, and isoflurane have all been shown to be capable of eliciting a reaction in susceptible swine. The course of the disease is variable, ranging from abatement of clinical signs when anesthesia is stopped to fatality.

Initial signs include tachycardia, tachypnea, muscle rigidity, and hyperthermia. Clinicopathologic changes include metabolic acidosis, myoglobinemia, hyperkalemia, and hyperglycemia. These metabolic derangements frequently lead to cardiovascular collapse and death. In addition to the typical manifestation, nonrigid and normothermic forms have been described. Signs of this disease are less pronounced in young pigs and those that are heterozygous for the trait. In nonanesthetized pigs, stressful situations will lead to the early signs of the disease, which include muscle and tail tremors. Progression of the syndrome leads to dyspnea, blanched and reddened areas on the skin, increased body temperature, and cyanosis. Muscle rigidity and cardiovascular collapse follow.

Necropsy. Pigs exhibiting this syndrome present with a very rapid development of rigor mortis. In addition, many of the animals will have muscles that appear very pale and are very soft, almost watery in texture, due to the high lactic acid content in muscles that occurs postmortem. Antemortem histologic changes have not been identified in these animals.

Prevention and control. The disease is best controlled by identifying those animals who carry the genetic mutation and eliminating them from the breeding stock. A readily available, inexpensive DNA-based test can be used to screen for the mutation (O'Brien *et al.,* 1993).

Treatment. Early recognition of the disease is the key to treatment. Anesthetic delivery should be discontinued immediately and 100% oxygen delivered. Additional treatment includes sodium bicarbonate to combat the metabolic acidosis and hyperkalemia. Active cooling of the animal may be done by ice packing and IV administration of cooled fluids, or by gastric and/or rectal lavage with iced saline. Dantrolene, an agent that prevents PSS by decreasing release of calcium from the sarcoplasmic reticulum while allowing calcium uptake to continue, is highly effective in stopping the progression of the syndrome when administered at the onset of signs. After the crisis is alleviated, the animal must be monitored closely for 48 hr; redevelopment of the syndrome in response to minor stressors can occur. Dantrolene can also be given as preventive therapy in animals known to be susceptible.

b. Salt Poisoning

Etiology. Salt poisoning, also known as sodium ion toxicosis, is a condition that can easily occur in swine. It can be caused directly by the animal consuming excessive amounts of sodium. This happens infrequently, as animals are rarely presented with feed that has excessively high sodium content. However, feeding milk by-products such as whey, which has a high sodium content, has been shown to cause the disease. By far, the most common initiator for the condition is water deprivation. Usually, signs are initiated after a minimum of 24 hr of deprivation, but the condition can also occur after just a few hours of deprivation.

Clinical signs. Initially, the animal presents as being very thirsty and constipated. Central nervous system (CNS) involvement, which may be delayed for several days after the insult, follows. The pigs will appear tense and apprehensive, with ears pricked and staring ahead with the head slightly elevated. The nose will then twitch, the eyes will close, and a rhythmic chomping of the jaws follows. Animals may also appear blind

and deaf. Pigs near death may paddle continuously. If the condition occurs because of excessive salt consumption rather than water deprivation, vomiting and diarrhea may be part of the presentation.

Pathogenesis. Salt poisoning is caused by hyperosmolarity of the CNS. When the animal rehydrates, the osmotic pressure causes water to be drawn into the CNS, resulting in swelling and edema.

Diagnosis and pathology. The diagnosis can easily be made if the clinical signs are matched with known water deprivation. Histologic evaluation reveals eosinophilic cuffing of the meningeal and cerebral vessels. Supporting findings include gastritis, constipation, or enteritis. A laminar subcortical polioencephalomalacia may occur if pigs are subacutely affected. The animal may present with hypernatremia; however, if the animal has had a chance to rehydrate, this finding will not be present. Differential diagnoses include pseudorabies, hog cholera, and edema disease. Other causes of toxicoses, such as food poisoning, should also be considered.

Treatment. Unfortunately, treatment is generally ineffective, and in fact, the condition is likely to be exacerbated by rehydration.

c. *Gastric Ulcers*

Etiology. Gastric ulceration in pigs refers to a condition in which ulceration of a specific region of the pig's stomach, the pars oesophagea, occurs. This condition has been diagnosed with increasing frequency since the 1950s, with the distribution being worldwide and varied in occurrence. To date, the pathogenesis of the disease remains speculative.

Clinical signs and differential diagnoses. The clinical signs vary depending on duration of the ulceration. In the peracute form, apparently healthy animals are simply found dead. In the acute form, pigs will become pale and weak, with an increased respiratory rate. Vomiting of blood and passage of bloody, tarry feces are seen. In the subacute or chronic form, the animal will be anemic and anorexic, with passage of dark feces that may be intermittent or persistent. Occasionally, the only sign observed may be the passage of dark, hard feces. Pigs of either sex and any breed may be affected. Usually, single pigs are affected, and body temperature is normal or slightly subnormal. Anemia can be detected hematologically if the chronic/subacute form is present. Differential diagnoses include swine dysentery, *Salmonella choleraesuis,* transmissible gastroenteritis, and intestinal hemorrhagic syndrome. These diseases can be differentiated relatively easily, as they impact on groupings of animals and result in high body temperatures, except in the hemorrhagic syndrome.

Epizootiology. Although this condition has been identified for decades, the definitive pathogenesis is unknown. Nutritional factors, such as increased concentrations of copper and unsaturated fatty acids, and decreased concentrations of tocopherols and selenium, have been shown to induce the condition. Fasted pigs exposed to stressful environmental conditions had a higher incidence of ulcers compared to controls. An increased incidence of ulceration was produced when pigs were fed finely ground diets. Many species of bacteria and fungi have been isolated from ulcer lesions, but none have been shown to be causative. One study investigated the prevalence of *Gastrospirillum suis* in pigs with gastric ulcer but found no correlation between its presence and the occurrence of ulceration (Barbosa *et al.,* 1995). Further investigations are needed to better define the etiology of this condition.

Pathology: Gross. The pars oesophagea contains no glands and is covered by stratified squamous epithelium continuous with the esophagus. In a healthy animal, this surface appears white and smooth. Lesions can first be detected as a roughened, irregular surface. Ulceration follows, with a disruption in the epithelium that may be small, discrete, and single to multiple, large, and irregular. Blood or blood clots can be seen at the ulceration site, as well as in the stomach or in the gastrointestinal tract. If the subacute/chronic form of the condition is present, chronic ulceration usually ensues. This is characterized by the presence of fibrous tissue and the contraction of the area of ulceration.

Pathology: Microscopic. The pars oesophagea in the pig is covered by stratified squamous epithelium. In the early stages of the ulcer formation, parakeratosis of the epithelium occurs. Occasionally, infiltration of some polymorphonuclear cells occurs, but usually inflammatory cells are absent. The epithelium is weakened, and erosion of the tissue eventually occurs as a result of the parakeratosis. Once the underlying tissues are exposed to the gastric juices, diffuse necrosis and bleeding characteristic of any ulcer occurs. Chronic ulcers develop as fibrous connective tissue forms in the underlying lamina propria. The muscularis mucosae may hypertrophy or may degenerate and be replaced by collagenized fibrous tissue. Occasionally, the ulcer may penetrate the serosa.

Prevention. Providing pigs with appropriate feed is a prudent measure to take toward disease prevention. The diet should be more coarsely ground (not less than 700 μm in size), not contain excessive unsaturated fatty acids, and have the right balance of vitamin E and selenium. Stressful conditions such as overcrowding, fasting, and unstable social groupings should be avoided.

Treatment. Early stages of ulceration are not typically identified, so treatment is often not initiated until the condition has

progressed to a point where treatment is ineffective. Options include administering nonabsorbable antacids, and vitamin E and selenium, as well as H-2 blockers (cimetidine, Zantac, etc.).

C. Iatrogenic Diseases

Catheter Infections

Etiology. A wide variety of either venous or arterial vascular-access lines are commonly used in swine and maintained for variable periods. Bacteria can be easily introduced into these lines if strict adherence to sterile technique is not observed during flushing. Improper maintenance of the catheter can also result in seeding of thrombi.

Clinical signs. Swine with a catheter infection will be febrile, have decreased appetite, and have a discharge from around the vascular access port.

Necropsy. A suppurative exudate may be present around the external access port or around subcutaneous implants. The entire catheter tract should be dissected to observe for any gross evidence of infection. Cultures should be taken of any suspicious sites. There may be a suppurative pneumonia with consolidation, suppurative emboli in multiple organs, renal infarcts (Fig. 13), or infarcts in other organs. Microscopic lesions may include a cellulitis, myositis, suppurative pneumonia, suppurative emboli in one or more organs, or infarcts in the kidneys or other organs.

Pathogenesis. Bacteremia with seeding of multiple organs can result in septic emboli in the lungs, kidney, spleen, and other sites. Thrombi dislodged from catheters during flushing can result in infarcts in multiple tissues, including the kidney.

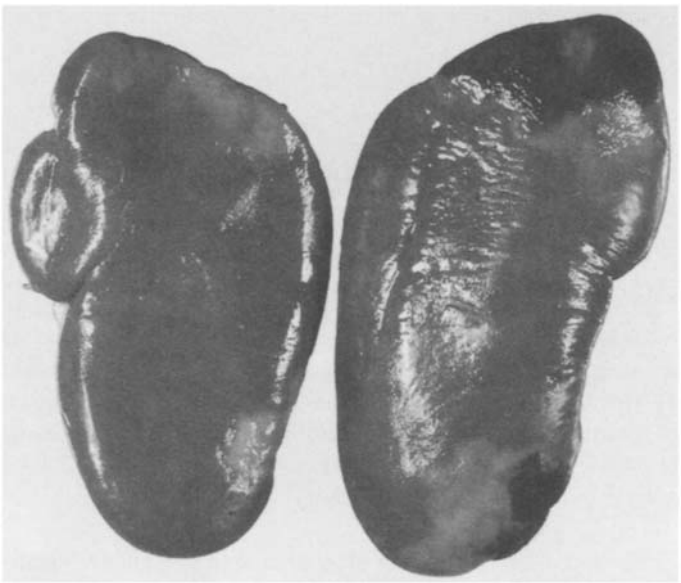

Fig. 13. Renal infarcts in a pig kidney.

Differential diagnosis. The differential diagnosis should include foreign body reactions to the biomaterials.

Prevention and control. Prevention and control consist of strict adherence to sterile technique in flushing and adequate flushing of lines that have high enough concentrations of anticoagulants to prevent thrombus formation.

Treatment. Blood cultures or cultures taken from around the implant may identify the infectious agent responsible, and a sensitivity test should provide information needed to select appropriate antibiotics.

Research complications. Catheter infections are themselves research complications that may result in the animal being terminated from a study or euthanatized due to persistent febrile state or compromised function of one or more organs.

D. Neoplastic Diseases

It has been touted that neoplasms occur with less frequency in pigs than in other domestic animals; however, this commonly held belief may be influenced by the fact that the majority of the pig population is slaughtered before reaching an age when cancer would normally appear with any significant incidence. The tumors that are reported are those seen in young pigs, with the most common tumors being lymphosarcoma, embyronal nephroma, and melanoma.

Lymphosarcomas affect primarily younger animals but can affect mature animals of either sex. Most cases are classified as multicentric; thymic is the next most frequent classification. Infiltration of the liver, spleen, and kidney predominates. Histologically, pigs typically exhibit lymphocytic lymphosarcomas; however, lymphoblastic, histiocytic, and mixed types do occur.

Embryonal nephromas affect pigs under 1 year of age, with a predominance in females. The tumor arises in the kidney parenchyma, is typically unilateral, and may spread to the lungs and liver. Histologically, the classifications that occur most commonly are nephroblastic and epithelial.

Melanomas occur as congenital lesions with exceptionally high frequency in Sinclair miniature swine (85% incidence at 1 year of age) and in Duroc and Hormel breeds. The disease is occasionally seen in other breeds as well. The tumors can be single or multiple and may affect the skin only or may involve metastasis to multiple internal organs. Initially, the skin tumor appears as a flat black spot that becomes a raised nodule. The tumor initiates as a focus of melanocytic hyperplasia within the basal layer. Spontaneous regression, thought to be caused by the cytotoxic effects of infiltrated tumor-specific T lymphocytes, occurs in the vast majority of cases.

E. Miscellaneous

1. Umbilical/Inguinal Hernia

Inguinal and umbilical hernias are two of the most common developmental defects found in swine, with the occurrence of inguinal hernias exceeding that of umbilical. Inguinal hernias occur mainly in male pigs, with increasing presence by 5 weeks of age. It may occur singularly or bilaterally. Incidence is controlled by culling affected animals, as the condition is believed to be inherited polygenically; however, a recent study concluded that umbilical lesions such as omphalitis or umbilical abscesses are associated with herniation (Searcy-Bernal *et al.,* 1994). The occurrence of umbilical hernias varies with breed and sex but can reach 1.2%.

2. Starvation

Starvation is one of the main causes of noninfectious neonatal mortality. In one study, it accounted for 43% of postnatal deaths. Neonatal pigs are deficient in hepatic gluconeogenesis; consequently, they are very susceptible to hypoglycemia with short periods of milk deprivation (36 hr). Factors contributing to this condition include congenital abnormalities, trauma caused by the female, chilling, and female hypogalactia. Infectious hypogalactia (also referred to as MMA for mastitis, metritis, and agalactia) is a condition in which one or more of the mammary glands are inflamed and infected with gram-negative bacteria. Endotoxin release interferes with the release of prolactin and subsequently prevents milk letdown. Oxytocin, antibiotics, and anti-inflammatory drugs are helpful. Tranquilizers such as chlorpromazine have also been shown to have lactogenic effects.

3. Iron Deficiency Anemia

Iron deficiency anemia of the microcytic hypochromic type occurs commonly in suckling pigs that are not supplemented after birth. The pig fetus has minimal capacity for iron storage, and sow's milk contains low concentrations of iron. Unsupplemented piglets will exhibit rough hair coat and elevated respirations. Necropsy findings include a dilated heart and pulmonary edema. It is recommended that piglets receive 100–300 mg of supplemental iron between the time of birth and the time they begin to eat solid food. Injections are preferred over oral supplements, as oral administration of iron may upset the balance of gastrointestinal flora.

4. Behavioral Problems/Fight or Traumatic Injuries (Tail, Ear, and Flank Biting)

Tail, vulva, ear, and flank biting is an inconsistent but widespread problem of group-housed swine. The clinical outcomes are damaged areas of skin that can become infected, leading to abscesses (Huey, 1996), poor performance (Wallgren and Lindahl, 1996), suppurative arthritis (Cowart, 1995), and possible mortality. The basis for this behavior probably stems from the natural tendency of pigs to root and chew to obtain food in their natural environment. In confined group housing, pen mates, for lack of anything better, take the place of natural rooting structures. Iron deficiency anemia has been considered a possible cause for this behavior in piglets. Inadequate ambient temperature control, ventilation, pen and feeder space, and access to water (Rizvi *et al.,* 1998) are also considered contributing factors. However, the most plausible explanation is the lack of sufficient environmental enrichment. Corrective measures should include access to rooting materials, including wood-chip bedding, straw, and "indestructible" polyethylene balls. When groups are formed, the animals should be of similar age and size and of numbers appropriate for the space. Tail docking is also considered a preventive measure since this reduces the incidence of tail biting (Hemsworth, 1999).

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