INTRODUCTION

The rabbit is a popular model in laboratory animal medicine due to its relatively large size and docile nature. Though rabbits are sometimes mistakenly thought of as rodents, they are in their own Order Lagomorpha. Among the many breeds of rabbits, by far the most popular in research is the New Zealand White rabbit. Research in these rabbits has contributed to advances in cardiology, orthopedics, dentistry, immunology, and more.

This chapter closely follows the outline presented in the anatomy and physiology chapter of the 1994 edition of The Laboratory Rabbit. In fact, the two chapters by
Cruise and Brewer have been extensively cited owing to the unchanging nature of anatomy.

**EXTERNAL FEATURES**

Rabbits have thin, delicate skin that is generously covered with both underfur and guard hairs (Harcourt-Brown, 2002). The rabbit skin, similar to the rat, has blood vessels immediately under the dermis (Cruise and Brewer, 1994). Unlike the rat, however, the fascia superficialis is well differentiated due to the elastic fibers and dense collagen content (Brewer, 2006). Hair grows in waves starting from the ventrum and grows dorsally and caudally. Thick fur covers the feet in place of footpads. The fragile skin can tear easily and must be handled carefully during any manipulation. Females have a large skin fold on the ventral surface of their neck called the dewlap (Figure 8.1). Breeding females pull hair from this area to create a nest before parturition (Meredith, 2000).

Rabbits have three scent glands: the chin glands, anal glands, and inguinal glands. The chin glands are specialized submandibular glands which open onto the ventral surface of the chin. The inguinal glands are pocket-like perineal glands that lay dorsal to the urogenital opening on either side of the anus. Both males and females have these glands, with males marking more than females and dominant rabbits marking more than submissive rabbits.

**Head and Neck**

Rabbits have pinnae that are large, vascular and able to move independently of one another. They can represent a large part of the total body surface area (up to 12% in New Zealand Whites) (Brewer and Cruise, 1994). When dilated by heat, the rabbit ear shows the presence of large arteriovenous shunts and is thus an important mechanism for thermoregulation (Gordon et al., 1953).

Rabbit ears are fragile and should not be used for restraint. The dorsal skin is thick and contains many hair follicles, while the ventral skin has few hair follicles. The skin on the ventral surface of the ears contains large sebaceous glands that provide a convenient medium for carcinogen study, while those in the dorsum are smaller. The main vessels are the central ear artery and two lateral veins. The central ear artery runs towards the ear tip and bifurcates into two major branches showing a U-turn curve halfway up to the pinnae. Thus in the rabbit, the direction of blood flow in the rostral and caudal edges of the ear is from the pinnae to the base of the ear (Ninomiya, 2000). The central ear artery can be used for blood sampling as well as direct blood pressure measurements, though the pressure is approximately 10 mmHg less than in the common carotid artery. Though the veins and artery in the ear can be used for catheters and blood draws, forceful venipuncture can cause vasculitis, vascular necrosis, and sloughing of the skin.

The rabbit visual field forms almost a complete sphere (Cruise and Brewer, 1994). Eyes are laterally placed, endowing rabbits with a broad field of vision, except for the area under their mouth, which they compensate for with their vibrissae and sensitive lips. The rabbit cornea is large, occupying up to 30% of the globe (Queensberry and Carpenter, 2004). The lens is spherical and large and the ciliary body is small and poorly developed. The fundus of the rabbit is merangiotic, where only part of the inner retina is supplied by retinal vessels. This is in contrast with a holangiotic fundus, seen in dogs, cats, cattle, goats, sheep, pigs, rats, mice, and primates, where the retinal blood supply is from central or cilioretinal arteries (Buyukmihci, 2010). In practical terms, this results in a band of blood vessels and myelinated nerve fibers crossing the retina in a horizontal plane from the optic disc (Williams, 2007) (blood vessels present only laterally and medially to the optic disc) as opposed to a holangiotic fundus that contains blood vessels throughout the retina (Keil, 2010). Because the optic disc lies above the horizontal midline of the eye, it requires the examiner to look upwards during a retinal exam (Harcourt-Brown, 2002).
optic disc has a physiologic cup and the eye does not have a tapetum lucidum, similar to pigs, guinea pigs, primates, and birds (Ollivier et al., 2004).

Rabbits have a third eyelid that moves across the cornea during anesthesia, though it only covers two-thirds of the cornea (Harcourt-Brown, 2002). It also covers a Harderian gland which has a small, white upper lobe and a larger, pink lower lobe. This lower lobe, also known as the deep gland of the nictitating membrane, can prolapse, similar to a “cherry eye” in a dog (Figure 8.2). Because rabbits often freeze on examination, many rabbits fail to exhibit a menace response (Vernau et al., 2007).

Rabbits have an extensive orbital venous plexus, which can make enucleation of the eye complicated. It has been suggested to perform enucleations transconjunctivally, remaining as close to the globe as possible, instead of transpalpebrally, in order to avoid this structure (Williams, 2007). In addition, a large mediastinal mass can cause compression of venous return to the heart, engorging the retrobulbar plexus and resulting in exophthalmos (Wagner et al., 2005). The rectus dorsalis muscle lies several millimeters posterior to the limbus, under the bulbar conjunctiva. Because it is visible through the dorsal conjunctiva, unlike in humans, dogs, or cats (Keil, 2010), it is possible to access this muscle during surgery and use it to stabilize the globe. Other species require dissection to expose the muscle.

The small nasolacrimal duct follows a convoluted path through the lacrimal and frontal bones, ending in a single nasolacrimal punctum on each side. The duct passes close to the molar and incisor tooth roots and can therefore be affected by dental disease (Marini et al., 1996). At the level of the proximal maxillae and the base of the upper incisor, the duct narrows and is a common place for obstruction, resulting in epiphora.

Recent work has detailed the anatomic and structural characteristics of the lacrimal duct system (Ding et al., 2010). Review of published literature has shown that the rabbit lacrimal system more closely resembles that of humans rather than that of rats or mice (Schecter et al., 2010). The smallest branches of the duct system are the intercalated ducts, composed of single-layer cuboidal cells. Several intercalated ducts join to form larger intralobular ducts, which are also cuboidal in shape. Intralobular ducts merge to form interlobular ducts, which drain several lobules and are comprised of simple cuboidal to low columnar cells. From here the interlobular ducts merge into intralobar ducts, which drain individual lobes. The cells here are low to tall columnar cells and range from simple to pseudostratified. Finally, these converge into interlobar ducts, which are of variable size depending on the surrounding tissue. These cells are composed of simple to pseudostratified and stratified columnar cells and the number of cells increases as they approach the main excretory duct (Ding et al., 2010).

**Trunk**

The trunk is composed of the thorax, abdomen, and back. Females have eight to ten nipples while males have similarly placed rudimentary nipples. The anal opening lies distal to the base of the tail and dorsal to the urogenital opening. The anus is surrounded on both sides by hairless inguinal spaces. The male’s urogenital opening continues into a preputial fold which forms a sheath for the penis. In the female, this skin fold forms the vulva, which contains the small clitoris on the ventral wall. In males, the scrotal sacs containing the testes are located on either side of the penis.

**Extremities**

The forelimb is composed of the shoulder, upper arm, forearm, and hand. The hind limb is divided into the thigh, leg, and foot. The front legs have five digits and the rear legs have four, all of which extend into a long, curved claw.

**OSTEOLOGY**

The rabbit’s skeleton is delicate in relation to its size. The skeleton makes up approximately 8% of their body weight in comparison to a cat, whose skeleton represents 12–13% of its body weight (Cruise and Brewer, 1994). Strong epaxial muscles in the presence of a relatively weak lumbar spine predisposes rabbits to fracture of their lumbar spine (Suckow and Douglas, 1997), usually at the seventh lumbar vertebrae (Queensberry and Carpenter, 2004).
Axial Skeleton

**Skull**

The rabbit skull has a number of bones with a spongy texture and wide medullary cavities, in contrast to the smooth, hard skull of the dog (Whitehouse and Grove, 1958). The caudal (nuchal) surface of the skull is composed of the occipital bone, which in turn is formed by the supraoccipital, paired lateral exoccipitals, and the ventral basioccipital. The foramen magnum lies within this space and with its lateral occipital condyles creates the articulation for the atlas. The external occipital protuberance creates a sharp ridge that separates the dorsal surface of the skull from the nuchal surface. The dorsal ligament of the neck and occipital muscles attach to this external occipital protuberance.

The dorsal surface of the skull is formed by the dorsal surface of the occipital, the small interparietal, the paired frontal bones, and the nasal bones. The frontal bones extend ventrally to form part of the orbital wells.

The bulla is formed by the tympanic bone and holds the large tympanic cavity and the three ossicles of the middle ear. It continues dorsally into a short wide bony tube with a large opening. This entire tube is the external auditory meatus (Cruise and Brewer, 1994). The rabbit’s tympanic bullae are much larger than most mammals, with a longer and more tubular external auditory meatus (Wingerd and Stein, 1985). The tympanic bullae also appear to be rounder in shape and do not project ventrally beyond the level of the occipital bone as they do in the dog and cat (King et al., 2006).

The squamosal bone, which forms a large portion of the lateral wall of the cranium, lies anteriodorsal to the bulla. A prominent protuberance, the zygomatic process, forms the caudal end of the zygomatic arch. The zygomatic arch is flatter than that of the dog resulting in a narrower skull, which aids the rabbit in burrowing (Osofsky et al., 2007).

The mandibular fossa fits the head of the mandible, and is formed by the hollowed out ventral side of the zygomatic process. The alisphenoid is bordered caudally by the squamosal, and cranially by the orbitosphenoid, which is pierced by the optic foramen. The cephalic wall of the orbit is formed ventrally by the maxilla and dorsally by the lacrimal bone, which extends beyond the orbital rim. The maxilla extends rostrally from the orbit and its lateral zygomatic process, from the rostral end of the zygomatic or jugal bone, forms the main portion of the arch. The bilateral alveolar processes or ventral portion of the maxilla contains the roots of the incisors, and creates the rostral, ventral, and lateral boundaries of the nasal bone.

The ventral portion of the cranium comprises the medially located basioccipital, basisphenoid, and pre-sphenoid bones rostral from the foramen magnum. The basisphenoid is perforated by the round foramen cavernosum which leads into the interior of the bone. The hypophyseal fossa is in the floor of the cranial vault. The ventral aspect of the skull is continued by the palatine bones, where the caudal ends articulate with the two laminae of the pterygoid process of the alisphenoid bone. A thin, dorsal extension of the palatine bone can be visualized from the wall of the orbit. The palatine continues forward medial to the two alveolar processes of the maxilla where it articulates and courses medially to form the caudal portion of the hard palate. The hard palate continues rostrally from the ventral portions of the maxilla and premaxilla.

The nasal cavity is divided into the right and left fossae by the cartilaginous portion of the mesethmoid. It continues caudally with the perpendicular plate of the ethmoid bone which consists of the cribiform plate and paired lateral ethmoidal labyrinth. Caudally, the ventral portion of the cartilaginous septum is supported by the vomer bone. The turbinate bones are located on the lateral walls of the nasal cavity.

The two sides of the mandible join into a fibrous or fibrocartilaginous symphysis. The body, or the horizontal portion, contains the teeth while the caudal vertical portion comprises the ramus.

The hyoid apparatus is comprised of the median hyoid bone and the paired greater and lesser cornua. These are connected laterally by two muscles of the jugular process of the occipital bone. The entire apparatus is enveloped at the base of the tongue and lies between the angles of the mandible.

**Vertebral Column**

The typical vertebral formula is C7T12L7S4C16. However, the number of vertebrae can vary, with 44% of rabbits having 12T/7L, 33% having 13T/6L, and 23% with 13T/7L. The spinal cord ends within S2 in 79% of rabbits, S1 in 19%, and S3 in 2% or rabbits (Greenaway et al., 2001). All of the lumbar vertebrae have prominent mammillary processes of the cranial articular process, where the powerful lumbar muscles attach to the vertebræ (Whitehouse and Grove, 1958). Unlike other domestic animals, the dorsal aspect of the lumbar vertebral mammillary process is level with and slightly ventral to the spinous process. The first three vertebrae of the sacrum are fused, while the fourth sacral vertebra is variably fused (Whitehouse and Grove, 1958) with the third vertebra.

**Ribs and Sternum**

The first seven ribs are true ribs and articulate with the sternum, while the last five ribs (false ribs) do not. The heads of the ribs articulate with the corresponding thoracic vertebra and the caudal part of the body of the vertebræ cranial to it. The costal cartilage of the
seventh, eighth, and ninth ribs are attached to each other. The cartilages of the last three floating ribs are not attached to any others and therefore lie free. The sternum is composed of six sternebrae. The first is the manubrium sterni and the sixth is the xiphoid process with a distinct, thin, broad plate of cartilage protruding from the caudal end.

Appendicular Skeleton

Pectoral Girdle and Limb

The pectoral girdle is made up by the scapula and paired clavicles. The only direct attachment to the axial skeleton is the sternoclavicular ligament (Cruise and Brewer, 1994). The other major attachments are via the musculature. The humerus, radius, and ulna are typical of the mammalian family. The carpus is comprised of two rows of bones. The distal row articulates with the five metacarpal bones and there are five digits. The first digit has two phalanges while the four other digits have three.

Sesamoid bones are located on the palmar and plantar surfaces of the feet and occur in transverse pairs at the metacarpophalangeal junction and in linear pairs at the articulations of the second and third phalanges.

Pelvic Girdle and Limb

The ilium, ischium, and pubis fuse to form the pelvic girdle which is attached to the vertebral column at the iliosacral articulation (Cruise and Brewer, 1994). The os acetabuli, a small accessory bone, together with the ilium and ischium, join to form the acetabulum in the pelvic girdle. The femur attaches only to the tibia while the fibula fuses distally with the tibia for half its length. There are six tarsal bones arranged in three rows. The proximal row has two large bones, the middle row one bone, and the distal row three bones. The first metatarsal is very small, while metatarsals two through five are well-developed. The four digits of the hindlimbs each have three phalanges (Cruise and Brewer, 1994). The sesamoid bones in the pelvic limbs are the patella, the three bones located posterior to the stifle joint, and the small ones on the plantar surface of the foot by the metatarsophalangeal joints and between the second and third phalanges.

Teeth

The dental formula of the rabbit is:

\[
\begin{align*}
1 & \quad 0 & \quad PM^3 & \quad M^2 - 3 \\
12 & \quad 0 & \quad 2 & \quad 3 & \quad 2 \\
& \quad & \quad & \quad & \quad \quad \quad = 26 \text{ or } 28
\end{align*}
\]

Rabbits have hypsodont dentition and there is a long crown in lieu of a true root. The permanent teeth grow in by 3–5 weeks old. The upper and lower incisors grow 10–13 cm a year (Jenkins, 2001). The grinding action against opposing teeth keeps the teeth worn. Dental problems are a common sequellae if there is malocclusion or dislocation. A pair of small incisors, known as peg teeth (Figure 8.3) lies caudal to the larger incisors in the upper arcade. The upper lip has a divided groove (hence the expression “harelip”) that continues curving up right and left of the nostrils. There are 25–30 tactile vibrissae, which together with the cleft lip allow rabbits to locate and eat their food. Rabbits also have a diastema, a space between the incisors and premolars, which together with the “hare-lip” and rostrally positioned incisors help to cut off short pieces of vegetation. Rabbits chew quickly and thoroughly, with jaw movements up to 120 per minute (Cruise and Brewer, 1994).

Tongue

The rabbit’s tongue is large in comparison to the size of the animal. The dorsal surface is covered with small elevations called papillae, which give the tongue its roughened surface. There are four types: vallate, foliate, fungiform, and filiform. All but the last type have associated taste buds. The rabbit’s large tongue and small mouth opening together make visual intubation of the trachea virtually impossible without specialized equipment.

Salivary Glands

Rabbits have four pairs of salivary glands: the parotid, the submaxillary (also called mandibular), the sublingual, and the zygomatic (Cruise and Brewer, 1994).
The larger parotid gland extends below and in front of the ear base between the skin and masseter muscle. The associated duct runs rostrally along the lateral surface of the masseter muscle close to the branches of cranial nerve VII (the facial nerve), and enters the oral cavity opposite the last upper molar. The large size of the parotid gland and the accessibility of the duct make this system a popular research model. The submaxillary gland is oval-shaped and located at the angle of the mandible. The sublingual gland is small in the rabbit. The zygomatic salivary gland, not present in many other animals including humans, lies just below the lacrimal gland in the anteroverentral angle of the orbit.

There is continuous secretion of saliva from the mandibular gland in rabbits, unlike in ruminants where saliva is produced from the parotid glands and in cats and dogs, where it is produced from the sublingual glands (Brewer and Cruise, 1994). Amylase is present in rabbit saliva while lipase and urea are only present in trace amounts (Ruckebusch et al., 1991).

**Esophagus**

The esophagus has three layers of semi-involuntary striated muscles that extend all the way down to the cardia of the stomach, as opposed to in humans, where striated muscle comprises the upper two-thirds of the esophagus, the middle third contains some smooth muscle and the lower third consists of only smooth muscle. There are no mucous glands in the esophagus.

Esophageal integrity can be determined by measuring the difference in electrical potential between the esophagus and the stomach. The rabbit has a relatively low gastric potential difference (−12 mV) in comparison to the esophagus (−26 to −29 mV). The opposite is true in humans (Mecheler and Ingelfinger, 1969).

**Gastrointestinal Tract**

The rabbit’s stomach makes up approximately 15% of the volume of the GI tract and is never completely empty (Cruise and Brewer, 1994). In fact, for a rabbit GI tract to become completely empty it would take 9 days. The adult stomach is very acidic, with a pH of 1–2. In contrast, the suckling rabbit has a stomach pH of 5–6.5, which allows bacteria to pass through the GI tract and colonize the hindgut (Harcourt-Brown, 2002). After weaning, the stomach quickly becomes acidic. The cardia is large, thin-walled, non-glandular, and lined with stratified squamous epithelium. The fundus is the major exocrine secretory portion of the stomach. It has gastric pits lined with parietal cells which secrete acid, and intrinsic factor and peptic cells which secrete pepsinogen. The pyloric region is heavily muscled. The duodenum lies at an acute angle and compression of the pyloric valve in response to any increased pressure, such as hepatomegaly, gas, or trichobezoar may occur. The cardia sphincter is well-developed and arranged in such a way that renders the rabbit, like rodents, unable to vomit.

The small intestine is shorter in comparison to other species and comprises about 12% of the GI tract (Suckow and Douglas, 1997). The bile duct and pancreatic duct enter the duodenum separately. The bile duct opens into the duodenum proximally while the pancreatic duct enters distally. The jejunum is less vascularized and its walls are thinner than those of the duodenum.

The ileum ends in the cecum as the rounded sacculus rotundus, which forms the junction between the ileum, cecum, and proximal colon. It is at the ileum that Peyer’s patches first appear. The cecum is the most prominent organ in the abdominal cavity and typically contains 40% of the ingesta. It is a thin-walled organ that folds onto itself three times and has an internal surface made up of a long spiral fold that is continued into the ampulla coli. The distal portion of the cecum ends as a 5-inch, thick-walled, narrow, blind tube known as the vermiform appendix, and contains a large number of lymphoid aggregates. It also secretes bicarbonate ions into the cecum, acting as a buffering agent for the volatile fatty acids formed by cecal fermentation (Cheekem, 1987).

**Ileoceccolic Complex**

This complicated section of the GI tract is challenging to describe due to the three-dimensional, interconnected nature of the area. It acts as the meeting point between the end of the ileum, the cecum, and the proximal colon. Simply put, the end of the ileum, which is the sacculus rotundus and the beginning of the colon, which is the ampulla coli, meet at the cecum to form this intersection (Figures 8.4 and 8.5).

The sacculus rotundus appears to have immunological properties and contains lymph follicles that give it a honeycombed appearance. It is therefore often referred to as the ileocecal tonsil and is a common site for foreign bodies (Jenkins, 2000). The ileum lies nested between the body of the cecum and the upper ascending colon in a C-shaped manner and is attached by peritoneal folds.

The colon is characterized by sacculations (hausstra) and bands (taeniae). The anatomy of the colon has alternatively been described as the proximal and distal colon or as having an ascending, transverse, and descending colon. Both descriptions use the fusus coli, the “pacemaker” of the colon, as a dividing point since
it is a natural anatomic and physiologic demarcation. In this reference the colon will be described as being divided into three sections. The first section, the ascending colon, has five limbs and is separated by flexures (Davies and Davies, 2003). The first limb has three taeniae that form three rows of haustra, which move food along by muscular contractions. Small, wart-like protrusions (about 0.5 cm in diameter), called “warzen” (warts) populate the mucosal surface of this section. They act to increase surface area thereby increasing absorption. The three taeniae gradually taper down to one taenia and one haustrum distally in the second and third limb of the proximal colon. The rest of the colon is devoid of taenia. The transverse and descending colon is separated from the proximal colon by the fusus coli. The fusus coli has mucosa that is 4–5 times thicker than that of the descending colon and contains ganglion aggregates (Harcourt-Brown, 2002). This allows the fusus coli to act as a pacemaker to regulate
peristaltic activity, and controls excretion of the two different types of feces. In New Zealand White rabbits the colon can be a meter long (Cruise and Brewer, 1994). (Table 8.1).

**Gastrointestinal Physiology**

Rabbits are true herbivores. Rabbits are monogastic hindgut fermenters and require a high-fiber diet (between 14–20%). As a prey species, they rely on the rapid transit time of their unique digestive system to keep their body size and weight low, enabling them to be fast-moving and nimble. In this way, a rabbit’s gastrointestinal tract has adapted to the rapid ingestion of large quantities of vegetation (Jenkins, 2001). The transit time of food through the stomach is approximately 3–6 hours and times through the jejunum and ileum are 10–20 and 30–60 minutes, respectively (Carbao and Piquer, 1998). Rabbits mostly eat at dawn and dusk (crepuscular), but eliminate continuously throughout the day. Rabbits chew quickly and thoroughly, preferentially choosing tender, succulent parts of plants as the mainstay of their diets (Queensberry and Carpenter, 2004). High-fiber materials are ingested to stimulate cecolic motility.

Dietary fiber in rabbits is classified as “digestible” and “indigestible”. Indigestible fiber consists of fibers that are larger than 0.5mm and are quickly expelled as undigested hard, dry feces. The ascending colon separates the large indigestible fiber particles from the smaller, digestible fibers. These digestible fibers are less than 0.3mm and are retropulsed back into the cecum where they undergo bacterial fermentation (Harcourt-Brown, 2002). The digestible portion, which ultimately becomes cecotrophs, is moved back and forth in the haustra in the cecum and colon. As the large fibers move into the center of the lumen, the digestible portion moves into the wall of the haustras. When the particles move retrograde back into the cecum, fermentation releases volatile fatty acids and produces vitamins and proteins. The constant back-and-forth movement of the cecum and upper third of the colon causes the food particles to separate. Through this motion the digestible and indigestible fiber parts are simultaneously propelled in opposite directions. This, coupled with the fast digestive time, allows the rabbit to function without having to store large amounts of food in the GI tract.

Coprophagy is an important part of the rabbit physiology. The cecotrophs (also known as “night feces”) are ingested directly from the anus and are softer and lighter in color. They are an important source of nitrogen-containing compounds such as niacin, riboflavin, pantothenic acid, and cyanocobalamin (vitamin B12). The cecotrophs have a mucoid membrane that protects the feces from the low pH of the stomach and are ingested whole (Davies and Davies, 2003). The hard waste feces are produced during the first four hours of food ingestion while the cecotrophs are produced 4–8 hours later. Access to the anus for coprophagy is an important point to keep in mind if placing an Elizabethan-collar or similar such device. The term “night feces” is a misnomer as cecotrophs can be ingested at any time of day as it is influenced by light and feeding patterns (Hornicke et al., 1984).

The GI tract of the rabbit provides an important immunologic function. In rabbits, gut-associated lymphatic tissue (GALT) is distributed along the small intestine, sacculus rotundus, and the vermiform appendix (Lanning et al., 2000). GALT is composed of follicles where diversification of the rabbit primary antibody repertoire occurs. The similarity of the rabbit GALT and chicken bursa has led investigators to hypothesize that the rabbit GALT is the functional equivalent of the bursa (Knight, 1994).

**Liver and Gallbladder**

The liver is comprised of four lobes. The right and left lobes are divided by a deep median cleft. These lobes are then further divided into cranial and caudal lobules (Cruise and Brewer, 1994). The quadrate lobe is a subdivision of the right lobe and lies medial to the gallbladder. The caudate lobe is small, has a narrow attachment to the dorsal hilar region of the liver, and projects dorsally toward the right kidney (Cruise and Brewer, 1994). Torsion of the caudate lobe is possible,
though rare (Queensberry and Carpenter, 2004). The gallbladder is deep within the abdominal cavity in a depression of the caudal surface of the right cranial lobule. The hepatic ducts join to form the common bile duct which receives the cystic duct from the gallbladder and enters the dorsal surface of the duodenum immediately caudal to the pylorus.

The rabbit liver is a typical mammalian liver, consisting of a cribiform sheet of hepatocytes, one cell layer thick (Cruise and Brewer, 1994). Sinusoids drain into a central vein. The perisinusoidal space is formed by the wall of the sinusoids and the wall formed by hepatocytes. In rabbits this space is very narrow so that it is difficult to observe, unlike in humans where it is wider.

Rabbits mainly secrete biliverdin rather than bilirubin in their bile, similar to most non-mammalian species; 25–50% of rabbits also produce atropinase, which can inactivate atropine, and thus it is a poor choice as an anti-cholinergic.

Rabbits secrete a large amount of bile in relation to their size. A 2-kg rabbit can secrete up to 250 ml of bile a day, in contrast to the dog, which secretes seven times less on a weight basis (Brewer and Cruise, 1994). Although secretin is a potent choleretic in other mammalian species, it has no effect on bile flow in the rabbit (Wheeler, 1968).

**Pancreas**

The rabbit pancreas is a diffuse organ that is often hidden in the surrounding mesentery. It is also close to the splenic and caudal pancreatico-duodenal vessels. The pancreatic duct empties into the duodenum approximately 35–40 cm distal to the entrance of the biliary duct and appears to be the only laboratory animal with a single, separate pancreatic duct (Brachet, 1935). This duct is actually the accessory duct, as the terminal portion of the main pancreatic duct regresses during embryonic development (Harcourt-Brown, 2002). Pancreatic surgery can be challenging in rabbits and thus must be performed with great care.

Ligation of the pancreatic duct induces atrophy and fibrotic replacement of the pancreatic acini in the rabbit (Catala et al., 1987), similar to other mammalian species. However, unlike many other species, where ligation of the pancreatic duct causes pancreatic insufficiency, rabbits continue to populate the duodenum with proteolytic enzymes. It has been hypothesized that smaller pancreatic ducts communicate directly with the duodenum to supply these enzymes (Arvanitakis and Folscroft, 1978). In fact, it appears that pancreatic duct ligation does not induce long-term visible pathologic signs except for a chronic and progressive diabetogenic state leading to irreversible pathology (Catala et al., 2001).

**Spleen**

The spleen lies on the left dorsolateral surface of the greater curvature of the stomach and is small compared to that of other species. The rabbit’s relatively small spleen has been attributed to the fact that the gut-associated tissue contains about 50% of the total lymphoid tissue mass. At birth, the rabbit spleen lacks follicles and germinal centers and only begins to develop lymphatic follicles at 2 weeks of age (Jeklova et al., 2007).

Rabbits have been a popular model for polyclonal antibody production due to their large body size, good responsiveness to immuno-stimulation, and ease of blood collection. The most popular sites for antigen injection include the skin of the dorsum, biceps femoris, quadriceps, and popliteal lymph node. Intraperitoneal injections are generally not performed in rabbits.

**Adrenals**

The adrenal glands lie cranial and medial to the kidneys. The left adrenal gland is caudolateral to the origin of the superior mesenteric artery and the right adrenal gland lies close to the caudal vena cava.

**Kidney**

Unlike most other mammals, which have multipapillate kidneys, rabbits have a unipapillate kidney, similar to rodents. The anatomy of a unipapillate kidney, where one papilla and one calyx enter the ureter directly, makes the renal pelvis a direct extension of the ureter (Dwyer and Schmidt-Nielsen, 2003). As is typical in mammals, the right kidney lies more cranial than the left kidney.

The rabbit medulla has narrow ends curled around at the lower and upper poles of the kidney, similar to an orange segment (Sheehan and Davis, 1959). The structures of the medulla, which contain the loops of Henle, collecting ducts, and vasa recta, merge toward the papilla, which projects out from the center of the medulla. The medulla is divided into an outer zone, which is further divided into an outer and an inner stripe, and an inner zone, which forms the papillae (Kaiissling and Kriz, 1979). The transition from the inner stripe to the outer stripe occurs at the level of the fornices. All the vascular bundles in the rabbit kidney are of uniform size and have a regular distribution throughout the inner stripe. They do not fuse to form secondary bundles, as they do in the rat and mouse (Kaiissling and Kriz, 1979). The total venous system in the medulla is also simpler than in other species (Kaiissling and
Kriz, 1979), where the venous vasa recta ascend with the bundles as opposed to ascending independently of the bundles. The simple structure of the rabbit medulla is considered to be a primitive one compared to other species, such as the rat and mouse, which have a more complex medullary architecture and concomitant higher functional efficiency (Kaislining and Kriz, 1979).

The pelvic tissues form two septa that surround the medullary pyramid. The pelvic cavity extends between the septa and the pyramid to the fornix. It then extends outwards to form a series of secondary pouches on the outer surface of the pelvic septa (Sheehan and Davis, 1959). The typical unipapillate pelvis is generally a simple, funnel-shaped space (Dwyer and Schmidt-Nielsen, 2003), but can, as in the rabbit kidney, have elaborate, extensive evaginations. The epithelia of the fornices, at the level of the inner medulla, are composed of a single layer of cuboidal cells, whereas in the outer medullary region the epithelium is squamous. There are two distinct layers of smooth muscle fibers found in the walls of the renal pelvis. The inner layer contains fibers that insert near where the pelvic wall joins the base of the papilla, and are continuous with the ureteral smooth muscle. The outer layer is highly innervated, more diffuse and covers only the renal pelvis. It connects with the inner layers but ends abruptly at the junction of the ureter (Dwyer and Schmidt-Nielsen, 2003). The rabbit kidney is unique in that the tubules can be separated from kidney slices with the basement membrane intact. This makes the rabbit a useful model for renal tubule physiology studies (Brewer, 2006).

Each adult kidney contains approximately 200,000 nephrons (Rytand, 1938). Unlike dogs and humans, the number of glomeruli in rabbits increases after birth (Smith, 1951), similar to rats. Ectopic glomeruli are normal in adult rabbits, about 60 in each kidney (Steinhausen et al., 1990). These ectopic glomeruli often produce small cysts in the pelvic septum and can sometimes be seen with the naked eye (Moffat and Fourman, 1964).

Differences in definition and nomenclature have resulted in a variety of terminology of renal anatomy. This text will refer heavily to the previous work done by Cruise and Brewer as stated above. As in many animals, the rabbit proximal convoluted tubule (PCT) is divided into three segments: the PCT-S1 (first two-thirds of the PCT), the PCT-S2 (last third of the PCT and first part of the parts recta), and the PCT-S3 (the terminal part of the pars recta) (Woodhall et al., 1978). Transitions between segments are gradual compared to other mammals such as the dog and rat (Kaislining and Kriz, 1979). The proximal tubule plays an important role in water reabsorption as it reabsorbs two-thirds of the glomerular filtrate. The epithelium of the proximal tubule is made up of a single layer of cells supported by a basement membrane (Quigley et al., 2003). The proximal convoluted tubule has a net fluid absorption rate of 1 ml/mm/kg in the adult and around 0.3 ml/mm/min in juvenile rabbits (Quigley and Baum, 1990).

The rabbit loops of Henle are composed of 66% long and 34% short loops, with only 7% of the efferent arterioles from the juxtaposed glomeruli supplying blood to the medulla (Kaislining and Kriz, 1979). In contrast, other mammals such as the rat, mouse, pig, and human have more short loops than long, while carnivores such as the cat, fox, and dog have only long loops (Cruise and Brewer, 1994). The thin descending limb of Henle’s loop is different in short- and long-looped nephrons (Kaislining and Kriz, 1979). In long-looped nephrons it descends through the outer medullary zone into the inner medulla. In short loops, as well as in the thin ascending limbs of long loops, they pass over into the distal tubule. The thin descending limbs also exhibit great differences in luminal diameter and cellular thickness. The larger limbs (outer diameter up to 40µm) are thought to give rise to the longest loops, the limbs of intermediate size (diameter range from 30µm to 20µm) to the intermediate-length loops, and the small thin limbs (outer diameter 20µm) to the short loops (Kaislining and Kriz, 1979).

Superficial nephrons and upper midcortical nephrons drain separately via a connecting tubule to a cortical collecting duct (Kaislining and Kriz, 1979). Arcades are ascending tubules in the cortical labyrinth that join deep and midcortical nephrons to a collecting tube. These tubules are composed of connecting tubule cells (CNT), collecting duct (CD) cells, and intercalated (IC) cells (Kriz and Bankir, 1988). On average, six nephrons drain into one cortical collecting duct (Kaislining and Kriz, 1979). The IC cells are rich in mitochondria and have many rod-shaped particles in the membranes of cytoplasmic vesicles. The IC cells are prominent in collecting ducts and other transporting epithelia. Unlike most mammals, the rabbit’s connecting ducts do not contain typical CD cells, but only CNT cells interspersed with IC cells (Kriz and Bankir, 1988). The rabbit is also unique in that the CNT has a more distinct segment in structure and in function (Kneeper and Rector, 1991). The cells of the CNT appear “lighter” on light and electron microscopy and have numerous infoldings of the basal cell membrane (Kaislining and Kriz, 1979). There are IC cells in the inner stripe of the outer medullary collecting duct (OMCD), but these only occur in the outer half of the inner stripe, where they comprise 10–15% of the cell population (Ridderstale et al., 1988). The simple, clear-cut structural and functional organization of the rabbit distal nephron makes it a useful tool to understand more complex systems in rats, mice, and humans (Loffing, 2002).
Similar to amphibians and neonatal mammals, rabbits have a wide range in the number of active glomeruli at any one time (Salako et al., 1971). Up to a 16-fold increase in water diuresis is possible without a significant change in glomerular filtration rate (Smith, 1951). Even a blood pressure increase of up to 100% will result in little or no change to the glomerular filtration rate (Smith, 1951). This autoregulation, found to some degree in other mammals, but not to the extent found in rabbits, occurs at the level of the afferent arteriole (Steinhausen et al., 1990).

The rabbit only has a limited capacity to concentrate urea, so when the urea load increases, so does the amount of urine production (Kneiper and Rector, 1991). In most mammals inulin clearance is equal to the glomerular filtration rate. In rabbits, however, inulin clearance can be changed by altering blood flow of the rabbit glomeruli, specifically at the afferent arterioles (Brewer, 2006). Since the creatinine clearance and inulin clearance are equal in the rabbit, it can therefore be used to measure glomerular filtration rate (Kaplan and Smith, 1935). Rabbits are also not sensitive to the actions of loop diuretics (Ridderstrale et al., 1988), such as furosemide.

Rabbits are especially susceptible to low doses of acid administration. Unlike most mammals, a decreased plasma pH does not stimulate the deamination of glutamine, which is the major mechanism in ammonia synthesis. Only lowered bicarbonate (HCO$_3^-$) concentration is effective in stimulating this system (Simpson and Sharrard, 1969). The rabbit is also not as efficient in HCO$_3^-$ reabsorption as other mammals. Most mammals avoid alkalosis by neutralizing HCO$_3^-$ catabolism with ureagensis. If rabbits are fed a diet low in nitrogen, they are unable to titrate enough HCO$_3^-$ through ureagensis. HCO$_3^-$ is also absorbed through the gut. These two conditions make the rabbit susceptible to a greater HCO$_3^-$ load that other mammals. In addition, carbonic anhydrase, an enzyme that catalyzes hydration of CO$_2$ to HCO$_3^-$ is absent in the rabbit’s thick ascending limbs of the renal tubules unlike other mammals (Ernst, 1975; Iino, 1981). In the rabbit, the collecting duct is an important site for acid secretion, bicarbonate reabsorption, and active secretion of bicarbonate (Hamm, 1990). The transition between the convoluted part of the distal tubule to the connecting tubule is marked and clear. Here, the heterogeneous epithelium of the distal tubule changes into the heterogeneous epithelium of the connecting tubule (Kaissling and Kriz, 1979). In concordance with this change in anatomy is a change in physiology, namely the absorption of NaCl. In this and all subsequent segments the sodium–potassium ATPase activity is significantly lower.

The final degradation product of purine metabolism in the human is uric acid. Different species of mammals handle this differently. Whereas humans, with 700 out of 9000 mg of urate filtered daily, have one of the lowest excretion ratios, the rabbit has one of the highest (Brewer and Cruise, 1994). Since as much as 160% of the filtered load is excreted, it is likely that much of the secreted load is also excreted. In the dog and rat less than 40% is excreted (Brewer and Cruise, 1994). The anion-exchange mechanism, located in the luminal plasma membrane in the dog and rat that affects reabsorption in the proximal tubule does not exist in the rabbit.

Rabbit urine is generally cloudy due to the high concentration of ammonium magnesium phosphate and calcium carbonate monohydrate precipitates (Suckow and Douglas, 1997). Rabbit urine can also vary in color from orange and brown to red, depending on the diet, and can be mistaken for hematuria (Harcourt-Brown, 2002). Though most mammals regulate their calcium levels through the activated metabolite of vitamin D, rabbits’ absorption of calcium from the gut makes their calcium levels independent of this mechanism (DeLuca, 1974). Unlike most mammals, urine is the major route of excretion for calcium in the rabbit (Kennedy, 1965). Because of this, rabbits are unusual in that serum calcium levels vary with their diet. Rabbits fed a 10% calcium carbonate diet can excrete almost 60% of the calcium in their urine (Cheeke and Amberg, 1973). A high-calcium diet can result in thick, creamy urine, and prolonged feeding of a high-calcium diet can result in calcification of the aorta and kidney.

Urine color can vary from yellow to red due to porphyrin pigments. Though thought to be derived from the diet, the source of porphyrin has not yet been identified. Urine pH is typically around 8.2 and the rabbit produces 50–75 ml/kg of urine a day (Gillett, 1994).

**Male Genital Organs**

Male rabbits have two hairless scrotal sacs cranial to the penis. The testis has an elongated oval shape with a blunt cranial pole and a pointed caudal pole. The testes descend at 12 weeks and the inguinal rings do not close. Males have open inguinal canals and can retract their testicles abdominally, which they do during sexual inactivity or periods of inadequate food. Care must be taken to close the inguinal rings during castration.

The nomenclature of the accessory sex glands of the rabbit has been a source of historical confusion due to the use of terminology for other mammalian species as well as poor consensus among anatomists (Holtz and Foote, 1978). For example, in humans the terms seminal vesicle and vesicular gland are used interchangeably. In rabbits, however, they have been described as...
two distinct glands. In addition, different rabbit sources name the glands differently. Most references include the prostate, seminal vesicles, and bulbourethral glands. Other sources include the terms propocrine and paraprostatic gland. For the sake of continuity the accessory glands here are listed (roughly cranial to caudal) as: seminal vesicles, vesicular glands, prostate, paraprostatic glands, and bulbourethral glands (Cruise and Brewer, 1994) (Figure 8.6).

The seminal vesicles are the most cranial glands located at the neck of the bladder. Depending on the amount of fluid it contains, the size of the seminal vesicles can vary greatly. The ductus deferens enters the ventral wall of the seminal vesicle dorsal to the bladder (Cruise and Brewer, 1994). The vesicular glands are cranial to the seminal vesicles, cranial to the prostate and separated by a very thin connective tissue septum (Kurtul et al., 2001). The vesicular gland ducts enter the urethra at the seminal colliculus. The prostate overlaps the caudal part of the vesicular glands and can be distinguished anatomically by its lighter color (Kurtul et al., 2001). Four to six small prostatic ducts enter the urethra on both sides and posterior to the seminal colliculus (Cruise and Brewer, 1994). The bulbourethral glands lie caudal to the prostate and are separated from it by a distinct groove. The paraprostatic glands are small, club-shaped glands that are at the ventrolateral aspect of the prostate (Holtz and Foote, 1978).

These glands cannot be visualized dorsally and are very small. All glands are bilobed, except the bulbourethral glands, which are paired.

The penis does not have an os penis, but instead has a free extremity called the pars libera. Dorsolateral to the body of the penis are the white inguinal glands and the associated brown inguinal glands, which empty their secretions into the hairless inguinal spaces. Though some references cite males as not having nipples, it appears that males have very small, rudimentary nipples under their fur.

Female Genital Organs

The female reproductive tract has a bicornuate uterus with two cervices that open independently into the vagina. The mesometrium can be a major site of fat deposition, making ovario-hysterectomies of overweight does challenging. The urethra enters the vagina at a vestibulum known as the urogenital sinus (Cruise and Brewer, 1994), which extends out into the vulva. The bulbourethral gland, similar to that of the male, lies on the dorsal wall of the vestibulum. The clitoris is located along the ventral surface of the urogenital sinus with the glands clitoris projecting into the urogenital aperature.

Though sexual maturity depends on the breed, in general body weight is more important than age (Suckow and Douglas, 1997). Small breeds can reach sexual maturity at 4–5 months, medium breeds at 4–6 months and large breeds at 5–8 months. New Zealand White rabbit females reach maturity at around 5 months while males reach maturity at 6–7 months. Does mature earlier than bucks, with the bucks producing sperm 40–70 days after reaching puberty (Queensberry and Carpenter, 2004).

Rabbits are induced ovulators and do not have a defined estrous cycle. Ovulation occurs approximately 10 hours after copulation. Pseudopregnancy can occur if coitus does not result in pregnancy, if a doe mounts another doe, or if the rabbit is injected with luteinizing hormone (Kennelly and Foote, 1965) or human chorionic gonadotropin. Pseudopregnancy can last 15–16 days. Does are generally receptive for 14–16 days followed by 1–2 days of non-receptivity.

The placenta is hemochorial and passive immunity is endowed to the young through the yolk sac instead of through colostrum or placenta (Suckow and Douglas, 1997). Breeding life for a doe can be up to 3 years while that of a buck is around 5–6 years. Gestation is usually 31–32 days. Pregnancy can be confirmed at day 14 with palpation, day 11 with radiography and day 7 with ultrasonography.

Semen is deposited into the anterior vagina, where the sperm individually pass through the cervical mucus. During an active corpus luteal phase, such as early...
pregnancy or pseudopregnancy, the cervical secretions are thick and mucoid, thereby inhibiting sperm transport.

Reproductive Behavior

Receptivity in a female is denoted by a swollen, moist dark pink to red vulva. Does do not have a defined estrous cycle, but a certain rhythm can be determined. Vaginal cytology is generally not useful. Due to territorial behavior, the doe should always be introduced to the buck’s cage. Fifteen to 20 minutes (often much less than that) is usually sufficient to determine if the doe will accept the buck. Receptive females will exhibit lordosis and present the perineum to the buck. Non-receptive behavior includes running away, biting, vocalizing, or cornering. If the doe refuses the buck, the doe should be taken away. This prevents physical trauma to either animal as well as psychological trauma to the buck.

Bucks initiate copulation by sniffing, grooming, nuzzling, tail-flagging (elevation of the hindquarters with a stiff-legged gait and tail flat across the back), and enurinat (urine spraying) at the female (Queensbury and Carpenter, 2004). Experienced males often initiate mating within minutes of being introduced to a receptive female. Copulation is quick, generally over after a few thrusts. The male, whose hindquarters are off the ground, falls off and emits a characteristic cry after ejaculation. Robust males will attempt to copulate almost immediately.

Parturition in rabbits is known as “kindling” and typically happens in the early morning hours. This is characterized by the rabbit pulling off fur for nest building and a decreased appetite for 2–3 days beforehand. Both anterior and breech presentations are normal. Kits are born altricial, nurse only once a day, and open their eyes around day 10. Kits can ingest up to 35% of their body weight in milk in less than 5 minutes (Hudson and Distel, 1983). Kits begin eating dry food at 21 days and are usually weaned at 8 weeks. Litter size depends on parity, with primaparous does producing smaller litters. Though textbooks describe eight mammary glands, this can be variable. A kit has total dependence on milk until day 10. Does can become pregnant during the post-partum period and can be lactating and pregnant at the same time.

Cardiovascular System

Rabbits have a relatively small heart. In fact, it represents only 0.2% of the rabbit’s total body weight in contrast to 0.76% in dogs (Hew and Keller, 2003). The rabbit conduction system is similar to that of other mammals and includes the sinoatrial node, intermodal pathways, AV node, His bundle, and bundle branches.

The sinoatrial (SA) node is well-defined, less complex than that of other mammals, and relatively long considering its total heart size (James, 1967). The rabbit’s SA node has a very large percentage of P cells, which are not distinctly organized about a central artery (Hew and Keller, 2003). This simplicity allows the exact location of the pacemaker to be delineated, and in fact the rabbit is the first mammal in which the SA node was localized (Bleeker et al., 1980).

Though the rabbit has a right and left coronary artery, most of the heart is supplied by the left coronary artery and its branches (James, 1967). The AV node and the His bundle are relatively small in the rabbit, and their only arterial circulation is supplied by the septal artery (James, 1967). Branches from the septal artery are perpendicular to its long axis and ascend across the right ventricular septal endocardium to the His bundle and the AV node. This sequence is opposite from that of humans.

Rabbits have a left and right cranial vena cava (Pariaut, 2009). The presence of a left cranial vena cava results in an extremely large coronary sinus, which in turn disrupts most of the atrial septal structures cranially. The internal carotid artery is relatively small despite being the main blood supply source to the brain. The pulmonary artery is heavily muscled compared to other species (Cruise and Brewer, 1994).

The primary return of venous blood from the head is the external jugular vein, unlike in humans, where it is the internal jugular vein. Unlike other species, there are few anastomoses between the branches of the internal and external jugular veins. Therefore, ligation of the external jugular vein can cause swelling and protrusion of the eyeball (Hoyt et al., 1994). This usually resolves itself in 24 hours. Ligation of the external carotid artery causes ipsilateral ocular necrosis.

Rabbit heart rates can range from 180–300 beats/min, with higher heart rates often seen due to the increased sympathetic tone secondary to stress (Pariaut, 2009). The right atrio-ventricular valve has two bicuspid leaflets rather than three and the aorta has a rhythmic contraction that is neurogenic in origin.

Most mammal hearts have a mixed population of connective tissue and Purkinje cells. Though this makes the conductive tissue readily distinguishable, this mixture also complicates microelectric recordings (Brewer and Cruise, 1994). Rabbits have little or no connective tissue admixture with the Purkinje cell, which makes the rabbit the species of choice for Purkinje fiber studies (Sommer and Johnson, 1968). In addition, these cells have a long cylindrical shape with wide clefts between them. These clefts, 25–50 times the width found in other species, reduce the problems with resistance and perfusion encountered in other species (Colatsky and Tsien, 1979).
The aortic nerve subserves no chemoreceptors, only baroreceptors (Kardon et al., 1974). The nerve to the carotid sinus subserves both. This nerve joins the afferent fibers from the root of the right subclavian vein to form the depressor nerve. Unlike other laboratory animals where the depressor nerve is free for only a short distance, the depressor nerve in the rabbit runs separately from the vagosympathetic trunk, making it easily accessible for electrode implantation (Cruise and Brewer, 1994). The carotid artery is more compliant than that of the dog and has a greater ratio of elastin to collagen (Cox, 1978).

Due to the fact that rabbits exhibit hypercholesterolemia within a few days of being fed a high-cholesterol diet, they are the most widely used animal in atherosclerosis research (Yanni, 2004). The Watanabe rabbit is a classic model for heritable hypercholesterolemia (Aliev and Burnstock, 1998) and plays an important role in atherosclerosis research. Rabbit lipoprotein metabolism correlates to human lipoprotein metabolism more closely than mice. Rabbit and human lipoprotein profiles are rich in low-density lipoproteins (LDL), while the mouse is rich in high-density lipoproteins (HDL) (Zhang et al., 2009). Rabbits and humans also have abundant plasma cholesteryl ester protein (CETP), whereas mice do not. Rabbits do not develop tissue plaques as humans do (Kolodgie et al., 1996). Instead, early lesions come in the form of foam cells originating from macrophages. In addition, the massive inflammation exhibited by rabbits does not reflect human physiology. Long-term studies of rabbits on a high-cholesterol diet are difficult since the high hepatotoxicity makes long-term survival in rabbits rare (Yanni, 2004). Advanced lesions can be induced in the thoracic and abdominal aorta by combining a high-cholesterol diet with a single or double balloon injury (Abela et al., 1995). These balloon lesions create plaques with lipid cores covered by a fibrous cap and a high density of smooth muscle cells (Yanni, 2004) and are more similar to human atherosclerotic lesions than those produced by solely feeding a high-cholesterol diet (Aikawa et al., 2001). Interestingly, female rabbits accumulate less cholesterol in the aorta than male rabbits when fed a high-cholesterol diet, but this protective effect is not present when the aorta is subject to balloon injury (Holm et al., 1998).

Recently, high-cholesterol-diet-fed rabbits have been used as a model for Alzheimer disease. Amyloid-β (Aβ), a peptide fragment of the larger membrane spanning β-APP protein containing senile plaques (SP), is found in excessive amounts in the brains of patients with Alzheimer disease (Sparks, 2008). Rabbits fed a high-cholesterol diet exhibited a high accumulation of neuronal Aβ compared to control rabbits (Sparks et al., 1994). The finding that increased circulating blood cholesterol levels also increases cholesterol levels in the brain (Sparks et al., 1994) has contributed to the more frequent use of the cholesterol-fed rabbit model.

Blood pressure measurements can be obtained with the Doppler method. Blood pressure and heart rate in the rabbit tend to increase during the night (Pariaut, 2009), with the most common systolic blood pressure measurement between 120 and 180 mmHg.

Respiratory System

Larynx and Pharynx

The rabbit epiglottis is a relatively large structure that lies dorsal to the soft palate, thereby allowing air directly from the nasopharynx to the larynx and trachea without entering the oral cavity. It is this anatomy that makes the rabbit an obligate nose-breather and is important to remember when attempting intubation of the trachea (Figures 8.7 and 8.8). The glottis of the rabbit is small and with the relatively large tongue, the glottis remains well covered.

Lungs

Lungs are divided into cranial, middle, and caudal lobes with the right caudal lung lobe additionally divided into the lateral and medial lobes. The thymus does not regress with age and lies in the cranial ventral thoracic cavity. The right cranial lung lobe is larger than the left cranial lung lobe due to the presence of the heart in the left pleural cavity.

The sole blood supply to the pleura is the pulmonary artery. Extensive anastomosis with the pulmonary artery occurs at the level of the hilus in the rabbit, unlike in the dog, cat, or monkey (Cruise and Brewer, 1994). In rabbits the bronchial artery extends to the third division of the bronchi. There is a lack of collateral blood supply beyond this area, which places the rabbit at serious risk if an obstruction to the pulmonary artery occurs.

The rabbit lung does not contain respiratory bronchioles, but instead terminates in vestibules which contain alveoli (Cruise and Brewer, 1994). The air flow volume of the left lung is higher than that of the right due to the lower resistance of the proximal airways per unit volume (Yokoyama, 1979).

BRAIN AND SPINAL CORD

The brain is anatomically similar to other mammals. It is enclosed by the meninges: the outer dura mater, the arachnoid, and the inner pia mater (Wingerd and Stein, 1985). The dura mater adheres to the periosteum of the skull and extends down between the cerebral hemispheres as the falx cerebri. It becomes the tentorium cerebelli (Kozma et al., 1974) at the level of the cerebellum and cerebrum.

The forebrain consists of the telencephalon and the diencephalon. The telencephalon is comprised of the
cerebrum (cerebral cortices and basal nuclei), and is the largest portion of the brain. The diencephalon is comprised of the metathalamus, thalamus, hypothalamus, pineal gland, and pituitary gland. The optic chiasm lies within the diencephalon (Wingerd and Stein, 1985). The rabbit’s cerebral cortex is lissencephalic, or smooth, due to the lack of gyri. The two hemispheres are divided by a longitudinal cerebral fissure (sagittal fissure) and are connected at the bottom by a white matter tract, the corpus callosum. All sensory pathways must travel through the thalamus to reach the cerebral cortex, with the exception of olfaction (Oliver Jr and Lorenz, 1993). The olfactory bulbs are positioned at the rostral and ventral ends of the cerebral hemispheres, receive the sensory endings of the olfactory nerve, and are relatively large (Osofsky et al., 2007; Wingerd and Stein, 1985). The dorsally located pineal body originates from the corpus callosum and courses caudodorsally, nearly into the caudal end of the cerebral hemispheres.

The midbrain (mesencephalon) lies caudal to the diencephalon and is comprised of the dorsal tectum...
(Latin = roof) and ventral tegmentum (Latin = covering) (Osofsky et al., 2007). The tectum consists of the rostral and caudal colliculi, which, unlike dogs and cats, are clearly visible in the rabbit (Craigie, 1951). The rostral colliculi, which are larger than the caudal colliculi (Craigie, 1951), are involved in the visual reflex while the caudal colliculi are important in the auditory reflex. Important structures in the tegmentum include the mesencephalic aqueduct, the red nucleus, and the reticular activating system (Wingerd and Stein, 1985).

The hindbrain (rhombencephalon) consists of the cerebellum, pons, and medulla. The cerebellum and pons form the metencephalon and the medulla forms the myelencephalon, the most caudal part of the brain (Wingerd and Stein, 1985). The thalamus, hypothalamus, midbrain, pons, and medulla make up the brainstem.

Similar to other mammals, the cerebellum consists of the central vermis and the right and left cerebellar hemispheres. Rabbits have prominent paraflocculi, which are ventrolateral extensions of the cerebellar hemispheres (Cruise and Brewer, 1994). The paraflocculus is often damaged when removed due to its being almost completely enclosed by the dorsal portion of the petrosal bone (Cruise and Brewer, 1994). The paraflocculus is separate from the flocculus but has connections at the pyramids and uvula. The flocculus has been extensively studied in rabbits due to its importance in the mechanism of the vestibulo-ocular reflex and in the sensory and sensorimotor integration for retinal image stabilization (Voogd and Wylie, 2004). In the midsagittal plane, the cerebellum is triangular in shape, instead of the round shape seen in other domestic animals such as the dog, cat, horse, and sheep (Osofsky et al., 2007).

The pons lies caudal to the cerebral peduncles. The ventral part of the pons contains the transverse pontine fibers that transverse across the ventral aspect of the brain into the cerebral peduncles (Osofsky et al., 2007). These thick, paired ridges, which are separated by the median interpeduncular fossa, lie just behind the mammillary body. The third cranial nerve emerges from the brain by removing the dorsal portion of the petrosal bone (Cruise and Brewer, 1994). The paraflocculus is separate from the flocculus but has connections at the pyramids and uvula. The flocculus has been extensively studied in rabbits due to its importance in the mechanism of the vestibulo-ocular reflex and in the sensory and sensorimotor integration for retinal image stabilization (Voogd and Wylie, 2004). In the midsagittal plane, the cerebellum is triangular in shape, instead of the round shape seen in other domestic animals such as the dog, cat, horse, and sheep (Osofsky et al., 2007).

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The sensory and motor roots of CN V lie at the lateral border of the pons. The small abducens nerve arises along the lateral margin of the anterior end of the pyramid via several delicate rootlets (Cruise and Brewer, 1994). CN VII and VIII arise from the lateral margin of the trapezoid body. CN IX (glossopharyngeal nerve), X (vagus nerve), and XI (accessory nerve) arise from the lateral margin of the medulla by several linearly arranged roots. CN XII (hypoglossal nerve) arises through several roots from the ventral surface of the caudal medulla at the lateral margin of the pyramid.

The cerebellum is visualized by removing the fourth ventricle and consists of the central vermis and the laterally located right and left cerebellar hemispheres (Wingerd and Stein, 1985). The posterior medullary velum supports a choroid plexus. The fourth and third ventricles are connected by the aqueduct of Silvius. The dorsal aspect of the third ventricle can be seen by spreading the caudal tips of the cerebral hemispheres and pulling away the pineal body. At the roof of the third ventricle is another choroid plexus. Small, spindle-shaped masses called habenulae form the lateral margins of the aperture. The two habenulae are united caudally by the habenular commissure. The thalami are thick masses of nervous tissue that form the lateral walls of the ventricle. The dorsal portion of the thalamus forms an oval projection, the lateral thalamic tubercle, lateral to the habenula, and the anterior tubercle of the thalamus, a small elevation in the angle between the lateral tubercle and the cranial portion of the opening of the third ventricle. The lateral geniculate bodies lie at the most lateral parts of the dorsal surface at each side of the lateral tubercle. The medial geniculate bodies are less pronounced and lie caudomedial to the lateral bodies.

Dividing the cerebrum along the sagittal fissure exposes the midline structures. The lateral ventricle is exposed by removing the dorsal wall of one cerebral hemisphere. The corpus callosum ends rostrally in a club-shaped form and bends downward caudally, forming the splenium, which is attached to the body of the fornix. A pair of curved bands form the fornix, which fuses for a short distance in the midline until it forms the body of the fornix.

Similar to the brain, the spinal cord is enclosed by the meninges. The dura mater, the outermost layer, is a thick fibrous layer that is not firmly attached to the bone, and thereby creates an epidural space. The pia mater, the innermost layer, is a very thick membrane that is continuous with the dura mater. Fine connecting tissue resembling a spider web extends from the arachnoid mater to the pia mater (Osofsky et al., 2007).
The space between the arachnoid and the pia mater is known as the subarachnoid space, which contains the cerebrospinal fluid (King, 1987). Because the spinal cord and vertebral column have different growth rates, spinal cord segments and nerve roots are not necessarily housed in the corresponding vertebrae (Craigie, 1951). There are two enlargements of the spinal cord: the brachial and lumbar intumescences, or enlargements (Kozma et al., 1974). The brachial enlargement is located in the caudal cervical region and contains the spinal cord segments of cervical nerves 4 through 8 and thoracic nerve 1 (Osofsky et al., 2007). These nerves contribute to the brachial plexus. The lumbar enlargement contains the ventral rami of lumbar nerves 4 to 7 and sacral nerves 1 to 3 and contributes to the lumbosacral plexus. These areas contain a large number of neurons and cell bodies that innervate the muscles of the thoracic and pelvic limbs. Due to the fact that the spinal cord continues into the sacral vertebrae, it is important to remember that the chance of accidental puncture of the dura and arachnoid membranes during epidural injection is higher than in other animals (Johnston, 2005).

The formula for spinal nerves is C6T1L5S4C6. The spinal cord contracts to a thin filament at the middle sacrum, where it is called the filum terminale, and continues caudally to the base of the tail. The dorsal spinal nerves originate cranial to their exit from the vertebral column, thereby forming the cauda equina which continues down with the filum terminale caudally (Cruise, 1994). Because the spinal cord extends more caudally in the rabbit, the cauda equina is less pronounced than it is in humans (Craigie, 1951).

**METABOLISM**

The fasting metabolic rate of a rabbit is approximately 44–55 kcal/kg/day (Gillett, 1994). The fat content of the neonate is about 16% of body weight, similar to a human infant (Cornblath and Schwartz, 1976). Neonates have a low reserve of gluconeo- genic precursors in the liver. However, kits are able to remain normoglycemic without suckling until the glycogen reserves are depleted, about 6 hours postpartum (Shelley, 1961). Kits only nurse once a day during the dark phase (Jilge, 1993), and are a good model for nursing-anticipatory behavior as they show a clear locomotor anticipatory behavior in response to a nursing mother (Caba and Gonzalez-Mariscal, 2009).

Rabbits have a high intake of water compared to body size, approximately 50–150 ml/kg. Rabbits fed fresh greens ad libitum will often not drink water (Cheeke and Amberg, 1972), while high-protein diets increase water needs. When deprived of water rabbits will decrease food intake and gradually become anorectic. Fasted rabbits also will become polydipsic, eventually ingesting almost 650% of the normal water intake by day three (Brewer and Cruise, 1994). The water source and ability of the rabbit to reach the water source should be ascertained.

**Thermoregulation**

The normal body temperature of an adult New Zealand White rabbit at rest is between 38.5–39.5°C (101.3–103.1°F) (Ruckebusch et al., 1991). Rabbits are uncomfortable in temperatures over 20°C (68°F) and can be significantly stressed by temperatures over 28°C (82°F). The recommended ambient temperatures (16°C–21°C/60.8–69.8°F), as outlined by the Guide for the Care and Use of Laboratory Animals, is significantly lower than that for other laboratory species (Jenkins, 2001).

As mentioned previously, the ears play an important role in thermoregulation due to the countercurrent heat-exchange system present there (Kawato et al., 1989). It has been shown that there is adrenergic and cholinergic innervation of the arteriovenous anastomoses (AVAs) and that the constriction of the AVA walls controls microcirculation (Iijima and Tagawa, 1976). Other examples of AVAs in nature include the pampiniform plexus, nasal mucosa, and counter-current mechanisms in the various appendages of birds, whales, and seals (Ninomiya, 2000). While these heat-exchange networks consist of arteries and corresponding veins, the rabbit ear network is composed of a major artery and a number of capillaries surrounding the vessel (Ninomiya, 2000). This anatomy allows venous blood to drain more slowly, which enhances heat exchange within the narrow skin space.

Rabbits are unable to sweat, and salivation and panting are usually insufficient to dissipate heat. Moderately heat-stressed rabbits can exhibit decreased food consumption and impaired gastrointestinal function (Jenkins, 2001). They will also lie down in a stretched or prone posture versus a resting one (Finzi et al., 1992). Unlike most mammals, the rabbit shows little increase in heart rate in response to heat. Similar to the rat, the rabbit does not have a carotid rete (Daniel et al., 1952), which normally plays an important role in blood cooling in the brain. Blood from the head drains into the external jugular vein without a pathway to keep the brain cool (Ninomiya, 2000). This unique anatomy makes rabbits highly susceptible to high temperatures (Morimoto, 2009), which can ultimately result in death.

**BEHAVIOR**

Rabbits are social, nocturnal animals that, despite over 2000 years of domestication, still have a highly developed prey instinct. As with most prey species,
rabbits will become immobile when scared or stressed, making them difficult to assess or examine. This defense, sometimes called “tonic immobility”, has been directly related to the proximity of the predator. When tested during the immobility phase, rabbits that are closer to a predator will right themselves more slowly, while those closer to a home cage will right themselves more quickly (Ewell and Cullen, 1981). Another defense adaptation is to run quickly towards a hiding place such as a burrow or hide box (Gunn-Dore, 1997). Rabbits that are handled in the first week of life showed less fear as adults. In fact, simply being exposed to human scent during this time period decreases fear among rabbits (Ducs et al., 2009).

Rabbits are very territorial and will use their scent glands as well as feces to mark their territory. They can also mark with urine and by “chinning” people and their environment. Rabbits can have very complex social structures. They will show dominance by mounting, barbering, and scent-marking (Baysm et al., 2006). Females are aggressive, if not lethal, towards kits not their own. Despite being timid and shy, rabbits are intelligent and cognizant of their surroundings (Jenkins, 2001). They apparently recognize not only other rabbits, but are able to identify individual humans as well (Davis, 2000).

Laboratory animal housing should take into consideration natural behaviors and preferences of the species being housed. The following recommendations do not take into account experimental, space, and budget issues that all facilities face, but rather is a summary of recommendations for optimal laboratory housing collected from the literature.

Whenever possible, rabbits should be socially housed, with compatible pairs or trios being the most effective. Group housing of immature rabbits is possible without risk to injury. Ideally however, groups should be formed soon after weaning (Gunn-Dore, 1997). Rabbits that have been single-housed for more than 6 months should not be group-housed; they may be very fearful and lack motor skills due to prolonged inactivity. Adult male rabbits should not be housed together as they will fight and can sustain serious injury.

When choosing housing it is important that vertical distance is taken into account as well as horizontal space in order to ensure that rabbits can assume a typical lookout posture (Gunn-Dore, 1997). Housing should attempt to mimic a burrow with an open front and closed top bottom and sides (Jenkins, 2001). Though wire bottom cages are common in laboratory rabbit housing, rabbits should be given an area of solid flooring. In addition, rabbits should be given a hide box, which affords them an escape route when stressed. Toys and other types of enrichment, including being fed hay, should also be provided.

Similar to other species of social animals that are frequently housed singly in the laboratory environment, stereotypical behaviors can sometimes be observed in these rabbits. These include chewing/licking/biting of the bars, the floor, the walls, and the water bottles, hair-pulling and eating, nose-sliding, head-swaying and pawing the cage walls, rearing, and self-mutilation (Gunn-Dore, 1997). Some animals will simply become lethargic and will either exhibit poor appetite or, conversely, excessive appetite. Singly housed rabbits should be in visual contact with other rabbits and extra enrichment should be provided.

Rabbits are obligate nose breathers and thus do not like to have their noses touched. This is important to keep in mind when performing oral exams or attempting to medicate or force feed. Grunts, growls, and snorts indicate anger or annoyance. They can also “thump” their back feet when upset. It is best to approach these rabbits carefully as they will scratch and bite their handlers. Fear or pain is exhibited by a high-pitched scream, as well as an extended head, flattened ears, and bulging eyes. A rabbit in pain can be inactive, dull, become hunched, attempt to hide, or excessively scratch and lick. They can also become aggressive and bite.

The most common response to pain is anorexia. Often this is the first clinical sign to be noted. Rabbits will also grind their teeth, especially in response to visceral and dental pain (Johnston, 2005). Most rabbits will sit quietly in the back of the cage with minimal movement when painful. However, some rabbits will go through periods of rapid and uncontrolled movement and will struggle when handled. Some rabbits will breathe slowly with an obvious nasal flare and deep breathing pattern, in contrast to their usual rapid, shallow respiration (Johnston, 2005). A painful rabbit will also stop grooming itself and other cagemates.

Grooming is a normal behavior and healthy rabbits will spend a lot of time grooming themselves and other rabbits. If a rabbit grooms after being handled, this usually indicates that the rabbit has recovered from the interaction. Rabbits exhibit a behavior called “tooth purring”, which is exhibited by fast, light grinding of teeth and quivering whiskers. This is usually a sign of contentment and can be distinguished from bruxism, which indicates GI pain, by the slower, louder sounds produced (Baysm et al., 2006). Rabbits can lick a person to show affection, as well as nip at them to get their attention or solicit petting.

Rabbits tend to urinate and defecate in the same location, thereby making it possible to litter-train them. However, it is best to train them when still juveniles, as adults, especially males, will defecate to mark territory.

It is possible to “hypnotize” a rabbit by placing the animal on its back with its neck stretched out and the belly gently rubbed. The breathing should decrease and
the pupils constrict (Baysm et al., 2006). However, this method appears to be dependent on the individual handler and rabbit and should never be used in place of sedatives or anesthesia.

In general, rabbits are gentle, docile animals that make them an ideal species for the research environment. Proper and careful training of laboratory workers can make the interaction calm and less stressful for both the animal and handler.

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References


II. RABBITS


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