Journal of the American Association for Laboratory Animal Science
Copyright 2006
by the American Association for Laboratory Animal Science

Vol 45, No 1
January 2006
Pages 8–24

Historical Special Topic Overview on Rabbit Comparative Biology

Biology of the Rabbit

Nathan R. Brewer

Editor's note: **In recognition of Dr. Nathan Brewer's many years of dedicated service to AALAS and the community of research animal care specialists, the premier issue of *JAALAS* includes the following compilation of Dr. Brewer's essays on rabbit anatomy and physiology. These essays were originally published in the ASLAP newsletter (formerly called *Synapse*), and are reprinted here with the permission and endorsement of that organization. I would like to thank Nina Hahn, Jane Lacher, and Nancy Austin for assistance in compiling these essays.**

Publishing this information in *JAALAS* allows Dr. Brewer's work to become part of the searchable literature for laboratory animal science and medicine and also assures that the literature references and information he compiled will not be lost to posterity. However, readers should note that this material has undergone only minor editing for style, has not been edited for content, and, most importantly, has not undergone peer review. With the agreement of the associate editors and the AALAS leadership, I elected to forego peer review of this work, in contradiction to standard JAALAS policy, based on the status of this material as pre-published information from an affiliate organization that holds the copyright and on the esteem in which we hold for Dr. Brewer as a founding father of our organization.

–Linda A. Toth, Editor in Chief, AALAS Journals

Introduction

The laboratory rabbit (*Orycotolagus cuniculus*) belongs to the family *Leporidae* (rabbits, hares) of the order *Lagomorpha* (leporids, picas). Once classified as a rodent, the rabbit was given a separate order because of dentition differences, chiefly the incisors. Lagomorphs have 2 pairs of upper incisors (they are born with 3 upper pairs but lose the outer pair early). The 2nd pair of upper incisors is smaller and is located immediately behind the 1st. Closer ties exist between lagomorphs and artiodactyls than between lagomorphs and rodents. Other differences, many of which will be presented in this series, justified the suggestion by paleontologists that lagomorphs departed from the main eutherian line early in phylogeny.[174]

The American Rabbit Breeders Association recognizes over 100 breeds of rabbits. Three breeds are commonly used in the laboratory: the Dutch Belted (1.5 to 2 kg); the New Zealand White (5 to 6 kg); and the Flemish Giant (8 to 9 kg).

In the wild, *O. cuniculus* dig burrows, unlike most other rabbits and hares. These burrows can be very extensive, combining with neighboring burrows to form warrens that may occupy 2 or more acres of land. Essentially nocturnal, rabbits may girdle trees and destroy plants at night and retire to their burrows in the daytime. Domesticated rabbits released in the field have been known to develop burrows.

Rabbits can be frightened easily, leading to widely varying responses. Emotional stress can cause a fall in body temperature. The rat can mimic the rabbit in this phenomenon. In most endotherms, including the human, emotional stress tends to cause an increase in body temperature. Fright causes marked stimulation of the autonomic nervous system. Renal ischemia can develop. If the rabbit is then given water by stomach tube, water intoxication, convulsions, and rapid death can result. Compulsive water drinking of pychogenic origin can be brought on by raucous noise (rock music; children playing) and may cause diabetes insipidus.[27] Rabbits made hypoxic have reduced kidney function. Another fright reaction may be splanchnic vasoconstriction, shunting blood to the head and the heart. Emotional stress may cause a leucopenia in rabbits (in cats, it causes a leucocytosis.[158] As in other mammals, stress in rabbits can also cause cardiomyopathy[217] and gastric lesions.[110]

Rabbits must be handled with great care. In picking up a rabbit, obtain a firm grip over the scruff of the neck with 1 hand and support the animal with the other so that the rabbit will not kick. The skeleton of the rabbit is relatively fragile. The rabbit skeleton weighs about one-half that of a cat of the same body weight. Broken backs can occur in rabbits when handlers are not careful.

Originally published in the ASLAP Newsletter 23(3):25–27, 1990

External Features

The body is well endowed with both underfur and guard hairs. The rabbit skin, as in the rat, has blood vessels immediately under the corium layer. It differs from the skin of the rat in that the fascia superficialis in the rabbit is well differentiated because of its elastic fibers and dense collagen content (as it is in mice and guinea pigs). Subcutaneous injections are readily performed in the folds of skin over the back, shoulders, and neck.

Primary external features in the head region include the pinnae (external ears), the laterally located eyes with a broad field of vision, including the rear, and the unique anatomy of the mouth area. The neck has a dewlap that may develop a moist dermatitis due to slobbering.

The female has 4 or 5 pairs of nipples on the ventral surface of the abdomen and thorax. Ducts empty into the nipples independently, unlike the teat structure found in most mammals.[69] The buck has no nipples. In the buck, the penis, surrounded by the prepuce, is posterior to the scrotal sacs, as it is in all lagomorphs, thus differing from most mammals.

The well-developed posterior extremity has 4 fully developed digits. The anterior extremity has 5 digits.

Originally published in the ASLAP Newsletter 25(3):25–26, 1992

Department of Animal Resources, the University of Chicago.

The Eye

The rabbit has laterally positioned eyes, enabling rabbits to visualize a broad field: front, rear, upward and downward. Rabbits are one of the few mammals in which vision is not solely binocular.[23] A 3rd eyelid occupies the anterior portion of the eye. It is a nictitating membrane comparable to the conjunctival fold of the human eye, but is more prominent. It is stiffened by a thin plate of flexible cartilage covered with a layer of glandular tissue and molded to the curvature of the eyeball. A prominent Harderian gland is present. This gland is not present in primates but is found in mammals that have a well developed nictitating membrane. The ciliary body has only a radial muscle, unlike the human eye, which has both a facial and a circular muscle. The rabbit eye has very few cones (the color sensitive receptors), and rabbits are probably color-blind. The retina of the rabbit has a cell type that has not been noted in other animals, the function of which has not been determined.[184]

The control of eye movements is limited in the rabbit, a factor that makes study of the movements less confusing in an animal capable of a greater variety of movements, like the cat. "Look" nystagmus, as differentiated from "stare" nystagmus, is always absent in the rabbit.[44] "Look" nystagmus is found in the human, the monkey, and the dog. It is a movement that is only generated when objects that draw the attention move in the visual field. The accessory optic system of the rabbit is not responsive to vestibular stimuli (pitch or roll).[199]

The rabbit eye is ideal for intracorneal implants. A study of malignant implants demonstrated that the tumor does not generate blood vessels, but rather that "the body feeds the tumor."[72]

Originally published in the ASLAP Newsletter 23(3):25–27, 1990

The Pinnae

In the rabbit, the pinnae (external ears) are large, freely mobile, and can move independently of each other. Parts of the ears are almost hairless. In albino rabbits (New Zealand Whites), exposure to the sun can cause sunburn. Rabbit pinnae have large sebaceous glands, providing easy access for a carcinogen. The sebaceous glands are relatively small in the back of the pinnae.

The pinnae represent a large part of the total body surface (about 12%), are highly vascular, and are the organs in the rabbit having the largest arteriovenous vessels.[85] The rabbit ear has 3 distinct vascular layers.[118] The intermediate vascular layer consists of all of the main arteries, veins, and branches. The frontal and dorsal vascular layers are directly beneath the epithelia and consist of most of the capillary beds. Anteriovenous anastomoses exist in and between all 3 layers. The blood pressure in the central ear artery is about 10 torr less than the pressure in the common carotid artery,[61] and has been the artery of choice in many studies. However, the responses of the pinnae blood vessels to many agents differ from those elicited in other blood vessels of the systemic circulation, a unique genus-specific characteristic. In the common carotid artery of the femoral artery, noradrenaline (NA) and serotonin (5HT) are comparable in potency, but in the external carotid artery of the rabbit, and its branches, including the auricular artery, NA is about 700 times more potent as a vascoconstrictor than is 5HT.[9] Methysergide, a congener of LSD, is a potent antagonist of 5HT in the aorta, yet is a weak 5HT antagonist in the rabbit pinnae. The pinnae of the rabbit may lack in 5HT receptors.[9]

In many species, cold reception from the ear is transmitted through the trigenimnal nucleus, but afferents from the rabbit ear pass primarily through the spinal cord, with little or no representation in the trigeminal nucleus.[84] The ear is an important organ of thermoregulation in the rabbit, aided by a counter-current heat exchange system.[229]

Originally published in the ASLAP Newsletter 23(3):32–33, 1990

The Gastrointestinal Tract

Food and water intake. Rabbits normally comminute their food quite effectively by their molars (except for the fecal pellets, which are swallowed without chewing). However, if food is presented only 2 or 3 times a day, rather than being available at all times, some young rabbits may tend to bolt their food. If the bolted food is coarse, such as dry hay, the stomach may become irritated. For this reason, many husbandmen steam the hay before feeding.

A rabbit deprived of food soon eats its own feces. Rarely can a rabbit deprived of coprophagy survive a fasting period of more than 7 d.[173] In some instances, rabbits, for no known reason, may suddenly decrease or even stop eating for periods of up to 4 wk and then, just as suddenly, resume a normal ingestion pattern.[40] Presumably the rabbits remain alive by the practice of coprophagy.

If rabbits are fed enough fresh green feed, they may drink little water. Like guinea pigs, they have the unusual characteristic of drinking excessively when are fasted, as much 650% of normal on the 3rd day without food. As a result, rabbits that receive water but not food can become sodium depleted.[40] An interesting observation is that rabbits, like guinea pigs and rats, may decrease their water intake during heat stress.[3] An inadequate water intake, particularly under conditions of heat stress, can lead to a withdrawal of water from the cecum, causing cecal impaction.[136]

Oral cavity. The mouth opening is small. The upper lip has a divided groove (hare lip) that is continued by curving right and left to the nostrils. On the inner side of each nostril is a foliated margin covering a sensory pad. Tactile vibrissae, about 20 to 25 on each side of the upper lip, together with the cleft lip, allow rabbits to efficiently locate and eat short grasses. The expansive field of vision of the rabbit does not include the small area beneath the mouth, and the rabbit depends on the sensitivity of the lips and vibrissae for normal ingestion. The relationship between the anatomic arrangement for ingestion and the problem that rabbits have with eating pulverized food is a matter of speculation. When food is pulverized so that drugs can be thoroughly mixed with the food, the food should be re-formed into pellets.[206]

The dental formula of the rabbit is: $\begin{matrix} 2 & 0 & 3 & 2\text{-}3 \\ 1 & 0 & 2 & 3 \end{matrix} \times 2 = 26\text{-}28$

A small pair of incisors is located behind the primary incisors in the upper jaw. The absence of canine teeth allows the lips to be approximated behind the incisors, forming an antechamber in the mouth. The infolding part of the lips brings the fur to the inside of the mouth. As in rodents, the incisors grow continuously, and are normally kept at an optimum size by constant wear. If the teeth do not wear properly, as with a dislocation, the incisors continue to grow and may appear as tusks. The molars have no roots and have deep ridges on the surface that help to comminute the food. The chewing is from side to side and forward and backward at a rate of about 200 cycles per min.[26] When the teeth do not meet properly, an inflammation may result (slobbers), leading to food refusal and starvation.[167]

The tongue is large for the size of the animal. The foliate pa-

pillae, located at the posterior portion of the tongue, are large, much larger than they are on the tongue of the human. Some of the cells in the foliate papillae have unusual lamellar bodies,[210] comparable to those in type II alveolar cells.

Rabbits have 4 pairs of salivary glands: the parotid, the submaxillary, the sublingual, and the zygomatic. The parotid is the largest, extending from the base of the ear to beneath the mandible, and of the 4, is the one most often used in research. Its duct passes forward along the lateral surface of the masseter muscle in close association with branches of the facial nerve and enters the oral cavity opposite the last upper molar. The submaxillary gland is oval shaped and is located at the angle of the mandible. The sublingual gland would be called the minor sublingual gland in many species; the major sublingual gland, which is present in many mammals, is not present in the rabbit. The zygomatic salivary gland is not present in humans and many other species, and lies in the anteroventral angle of the orbit, just ventral to the lacrimal gland that lubricates the upper eyelid.

The enzymes in the salivary glands vary across species. Some animals have no amylase activity (sheep, pig), and others have only a trace of activity (dog). The amylase activity in the rabbit is comparable to that of humans and rats. Young rabbits may suffer from a deficiency of amylase production, and this has been proposed as a contributing factor to the etiology of mucoid enteritis.[147] Galactosidase activity in the salivary glands of the rabbit is comparable to that in the hog, dog, or rat. The parotid or submaxillary salivary glands of the human have no galactosidase activity.[64]

Originally published in the ASLAP Newsletter 23(4):27–31, 1990 and 25(1):23–28, 1992

The Esophagus

The rabbit esophagus has 3 layers of striated muscle.[83] The striated muscle is semi-involuntary and extends into the cardiac part of the stomach.[6] In humans, the skeletal muscle extends only to the upper two-thirds of the esophagus, with the middle 3rd containing some smooth muscle and the lower 3rd consisting of all smooth muscle.[6] Esophageal striated muscle differs from other striated muscle in the body in that it does not atrophy when the nerves are cut.[6] The rabbit is one of those species with no mucous glands in the esophagus.[83]

A characteristic and reproducible electrical potential difference (PD) profile occurs between the esophagus and the stomach of each species, and it is a sensitive and reliable means of evaluating the esophageal integrity. In the rabbit, the gastric PD is low (−12 mv) relative to the esophagus (−26 to −29 mv). In the human, the reverse is true.[151,213]

In most animals, regurgitation from the stomach of chyme containing bile salts and acid is common and of negligible importance. In the rabbit, the contact of bile salts in an acid medium with the esophagus causes a degeneration of the mucosa and the submucosa.[123] Rabbits cannot regurgitate the stomach contents.

Originally published in the ASLAP Newsletter 24(3):32–33, 1991

The Cardia

Control of the cardia (the opening from the esophagus into the stomach) varies widely among species. In most species, including humans, the cardia is not a well-developed sphincter, but it is well developed in lagomorphs and rodents.[28,140] In some species, the muscle surrounding the cardia is prominent and strong (e.g., bat, sloth).[6] In some species, the anatomic arrangement of the cardia prevents the animal from vomiting (e.g., rabbit, rat, horse). Epinephrine relaxes the cardia, but the effect is consistent only in the rabbit.[37] In dogs, cats, and monkeys, epinephrine may constrict the muscles of the cardia, depending on its tonic state.[37] Epinephrine has no effect on the cardia of humans.[37]

Originally published in the ASLAP Newsletter 24(3):32–33, 1991

The Stomach

The rabbit's stomach comprises about 15% of the volume of the gastrointestinal tract. In the New Zealand white rabbit, the moist content of the adult stomach weighs about 90 g or more.

The cardiac portion of the rabbit stomach is large, thin-walled relatively immobile, non-glandular, and lined with stratified squamous epithelium. The epicardial muscle coat is striated, an extension of the muscle tissue of the esophagus. The fundus, which is the major exocrine secretory region of the stomach, has gastic pits lined with parietal (oxyntic) cells that secrete acid and intrinsic factor and with peptic (chief) cells that secrete pepsinogen. The pyloric region is heavily muscled.

Obliteration of the lumen has never been reported, and normally the stomach is never empty in a healthy rabbit. A continuous peristaltic movement originates in the fundic region and progresses to the pylorus.[36] The peristaltic and systolic action of the pylorus propels the partly digested food into the duodenum.

The normally mild peristaltic contractions characteristic in the fundic region increase in intensity with prolonged fasting and become powerful.[164] Unlike the situation in the human, monkey, or dog, in rabbits these hunger contractions are not abated by the sight, smell, taste, chewing, or the sham-swallowing of food.[173] Glucacon given to rats in pharmacologic doses induces a state of satiety.[79] Glucacon does not seem to have this effect in the rabbit.[150]

The combination of the heavily muscled pyloric valve and the acute angle of the duodenum placement contribute to a compression of the pyloric valve that may become serious with slight additional pressure, as from a moderately swollen liver. The rabbit, like the horse and the rat, cannot regurgitate their food, and the closure of the pyloric valve causes even a mild gastritis to be a serious condition. In young rabbits, the extreme discomfort may include rupture of the stomach.

The stomach of the rabbit is very acidic, with a pH of 1 to 2.[197] In the suckling rabbit, the stomach is less acid (pH of 5 to 6.5) and becomes more acidic very rapidly after weaning. The parietal (oxynic) cells secrete hydrogen ions. The parietal cells also secrete intrinsic factor in the rabbit, as in the guinea pig, cat, and primate. In the mouse and rat, intrinsic factor is secreted by the chief cells.[180] In the pig, it is secreted by the mucous cells in the pyloric area of the stomach and in the duodenum.[180]

Originally published in the ASLAP Newsletter 24(1):24–26, 1991

The Small Intestine

The small intestine is relatively short in the rabbit, the total volume being about 12% of that of the entire gastrointestinal (GI) tract. In the dog, pig, or horse, the small intestine represents about 22% of the total GI tract. The duodenum is relatively long in the rabbit. At its origin, the duodenum forms an acute angle with the pylorus, lies close to the liver, and is subject to compression by the liver. The anatomic relationships compound the problems associated with spasms of the pyloric valve. The duodenum forms an irregular loop that subtends the pancreas. Unlike the situation in most mammals, the bile duct and the pancreatic duct enter the duodenum at widely separated points. The bile duct opens into the duodenum near

its origin; the pancreatic duct opens into the duodenum near its terminus. The duodenum shares the duodenal artery and vein with the pancreas.

In the rabbit, the duodenal and jejunal circular folds of the mucous tunic are not as prominent, and the walls are not as thick, as in most mammals. Brunner's glands, found only in mammals, extend over a greater area of the duodenum in rabbits (and in guinea pigs) than they do in most species, although in young humans, some glands of Brunner are found in the jejunum.[45] Brunner's glands open into the crypts of Lieberkuhn in all mammals examined except the opossum.[45] In most mammals, the glands are mucous in type except in the rabbit, horse, and mouse, in which both mucous and serous cells are present.[22,71,76] In the cat, the cells are not typical of either mucous or serous glands, but are of a 3rd cell type.[154,212] In the cat, alkaline phosphatase is present in the glands of Brunner. It is not present in the rabbit.[45]

The jejunum is less vascular and the wall is less thick than in the duodenum. Of 15 species examined from 6 mammalian orders, the rabbit had the least blood supply to the jejunum.[159] The arcuate vessels are relatively distant from the intestine. The vasa recta stemming from the intestinal wall to the arcades do not intercommunicate. Compared to the human, the arcuate system is less complex, although the patterns of the arcuate system and the vasa recta are similar to those in the human. The failure to complete arch formations in certain places, resulting in a hiatus, could make revascularization difficult in a rabbit, if it became necessary.

The coating of fine filaments over the microvilli of the absorptive cells of the intestine, so prominent in many species including the human, is much less prominent in the rabbit.[108,109] Lymph aggregates (Peyer's patches) permeate the epithelial and subepithelial tissue of the intestine, becoming larger and more numerous distally, measuring about 3 by 5 mm at the ileum.

The terminal portion of the ileum empties into an enlarged rounded viscus, the sacculus rotundus (ampulla ilei), which is unique in the rabbit. It contains many lymph follicles that give it a honeycombed appearance. An untested idea is that the sacculus rotundus is to rabbits what the bursa of Fabricius is to birds. In the rabbit, it is sometimes referred to as the "cecal tonsil." A relatively weak valve, the ileo-cecal valve, allows chyme to pass from the ileum to the sacculus rotundus, retarding reverse flow.[97]

Two different contractile mechanisms operate in the small intestine of the rabbit and the guinea pig: 1) a graded slow contraction of the longitudinal muscle that increases with the degree of distention; and 2) a peristaltic, non-graded contraction of the longitudinal muscle that occurs concomitantly with a wave of contraction of the circular muscle. The first mechanism is not present in the rat.[187] Rabbit mesenteric nerve axons are distinctly non-myelinated, and the conduction velocities of the serosal and mesenteric nerve fiber units in the rabbit are comparable to the slowest fibers of the dog or the cat.[48]

The rabbit intestine, like the intestine of humans and guinea pigs, is largely impermeable to macromolecular compounds. Like humans and guinea pigs, the rabbit gets its passive immunity before birth, although some evidence suggests that the neonatal rabbit can absorb some antibodies from its gut for the first few hours after birth.[132] Unlike the situation in carnivores, pigs, insectivores, and ruminants, the ability to absorb immunoglobulins in nursing kits is quite limited.

Rabbits have an important role in the rapidly growing knowledge about peptides in physiology. The production of antibodies to gastroenteropancreatic peptides has been one means of obtaining information on these interesting chemicals. Rabbits have been used often in this development. Over 35 peptides have been identified since the discovery of secretin in 1902 and gastrin in 1905.

Originally published in the ASLAP Newsletter 24(1):24–28, 1991

The Large Intestine

The large intestine of the rabbit is composed of the cecum and the colon. The cecum in the rabbit is large, with a capacity of about 10 times that of the stomach and about 40% of the total digestive tract. The wall of the cecum is thin and relatively smooth. The internal surface is greatly increased by a long spiral fold (also seen in the intestines of sharks and rays), and is continued into the ampulla caecoli. The terminal portion of the cecum, the appendix, is a thick walled narrow blind tube, about 5 in. long and heavily endowed with lymph aggregates.

The pH of the cecum is much higher than is the pH of the stomach. Normally the pH shows wide diurnal variations, being most alkaline in the morning and most acid about midafternoon, after which time the pH gradually increases again.[139] The pH of weanlings differs from that of adults by being more acid. At midafternoon, normal adults have a pH range of 5.9 to 6.8, and weanlings have a range of 5.4 to 6.3. A change in pH causes a change in the type of microorganisms that inhabit the cecum—a transfaunation.[139]

The cecum of the normal rabbit provides an anaerobic environment suitable for the autochtanous microbiota present. An autochthanous microorganism is one that does not cause any detectable immunologic or histologic response and lives symbiotically with its host by playing favorable metabolic roles.[60] A high degree of host specificity helps to control the composition of the microbiota, which are species variable.[16] In the human, the dominant microorganism is *Escherichia coli*. In Muridae, streptococci are dominant. The most abundant microbiote in the rabbit cecum is a 4 to 15 by 2 µm metachromatically staining bacillus.[139] A ciliated protozoan, 15 to 20 by 4 to 6 µm, similar to the *Isotricea* found in ruminants, is also prominent.[139]

The microbiota of the cecum are concomitant to the development of cecotrophs (conglomerates of microorganisms, rich in nitrogen, vitamins, and minerals, and enveloped in a tough mucous coat). The cecotrophs (soft feces) are eliminated on a regular basis once or twice a day, and are ingested directly from the anus (cecotrophagy; coprophagy). The importance of coprophagy to the nutrition of the rabbit is supported by the demonstration that a normal rabbit, stanchioned to prevent coprophagy, will be undernourished and lose weight. Cecotrophs contribute about 83% more niacin, 100% more riboflavin, 165% more pantothenic acid, 42% more cyanocobalamin (vitamin V12),[97,133] and 100% more protein[155] to the diet of a rabbit than is available without coprophagy. The protein content is reinforced by the absorption of urea into the cecum from the blood, followed by the synthesis of ammonic acids from urea by microorganisms.[73]

The cecum of the rabbit does not contribute much to the digestion of crude fiber. Cecotomy in the rabbit does not significantly effect the percentage of crude fiber digested.[56] Compared to other herbivores, the rabbit is not very efficient in its utilization of crude fiber. It uses about half as much as does the guinea pig or the horse.[56]

Studies using germfree animals have contributed much to our knowledge about the cecum. In germfree animals, the number of goblet cells increases throughout the intestinal tract, and the rate of mucin production per goblet cell increases. In conventional animals, microorganisms normally liberate a mucinase that break down high molecular compounds found in mucin. The lack of mucinase in germfree and antibiotic treated animals

leads to a large accumulation of cations that attract and hold water. The accumulation of water in the large intestine causes diarrhea. The feces of germfree animals contain about 65% water. Feces from conventional animals normally contain about 15% water. The hydration of the feces in germfree animals is not influenced by cecotomy.

An increase in the percentage of water in the feces does not necessarily mean that more water is in the feces. Rabbits with diarrhea, as produced by coccidia, have reduced food and water intake, resulting in less total water in the feces than in normal rabbits. The amount of feces is also reduced. In germfree animals, water reabsorption from the cecum and colon is decreased, yet hemoconcentration or tissue dehydration does not occur to any appreciable extent.[141] However, rabbits with diarrhea have a negative potassium balance. The hypokalemia develops due to a combination of reduced food intake and low adrenocorticoid activity that is a unique characteristic of the rabbit.

In rabbits and guinea pigs, an important additional effect of the mucopolysaccarides that accumulate in the ceca of germfree animals is cecal enlargement, even to the point of causing death. The mucopolysaccharides synthesize products that are absorbed and cause certain cardiovascular effects. The active ingredients are found in the supernatant fluid of the cecum and are not found in cecotomized animals or in conventional animals that are not treated with antibiotics.

The colon of the New Zealand white rabbit is about 1 m long and is divided into several parts. The 1st part, the ascending colon, follows the course of the cecum, is composed of 5 parts with 3 limbs extending forward and 2 limbs extending backward, united by flexures. The 1st limb has 3 taeniae forming 3 rows of sacculations (haustra). The taeniae gradually unite distally so that the 3rd limb has only 1 row of haustra. These haustra are not observed in carnivores. The tranverse colon is relatively short, extending from right to left.

Along the great curvature of the junction between the transverse and descending colon is a lightly curved and spindle shaped organ, the fusus coli, an organ that is unique to lagomorphs. About 5 to 8 cm in length, with a thickened circular muscle toward the descending side, and lined with mucosa that is 4 to 5 times as thick as that in the descending colon, it is heavily supplied with ganglion cell aggregates.[15]

The fusus coli is the pacemaker that regulates the passage of hard feces and soft feces (cecotrophs). Regulated by prostaglandins[162], it allows passage of hard feces and, by anti-peristalsis, transports chyme containing less fiber to the cecum. Once or twice a day, at regular periods, it compels the passage of the cecotrophs through the rectum of the anus, where the rabbit ingests them.

The colonic mucosa of the normal rabbit has a grayish white color and an almost transparent appearance. The vascularity is not pronounced, although its appearance varies during the day. The muscularis mucosa is thicker than in the human. The submucosa is very thin. Goblet cells and Paneth cells are not noted in the rectum. Crypts of Lieberkuhm are present, but are not as closely grouped together as in humans.

The rabbit colon resists considerable trauma and manipulation.[121] Moderate hyperemia noted by proctoscopy may be regarded as a positive response to a procedure. Two rectal installations of 1 ml of 1 or 2% formalin in a 24-h period usually produces only a mild hyperemia. Over a 10-d period, such treatment results in varying degrees of hyperemia, but never a severe one.[121] Colitis may be induced in rabbits that are sensitized to egg albumen after mild rectal irritation and then challenged with egg albumen.[121]

Originally published in the ASLAP Newsletter 24(1):29–33, 1991

The Liver

The structure of the mammalian liver is well described.[62,63] The mammalian liver is formed with cribiform sheets of hepatocytes, 1 cell thick, that enclose spaces that communicate with adjacent spaces in which hepatocytes are absent.[32] The spaces are irregular and constitute a continuous labyrinth, which in the human (and the cat) form relatively wide sacs at many sites. In the rabbit (and the horse), the labyrinth is less wide, more cylindrical, and much less variable than it is in most mammals. Variations intermediate between that of the human and the rabbit are found in other mammals.

Sinusoids, contained within the labyrinth formed by the hepatocytes, drain into the central vein. Also draining the liver are the lymph channels, originating from the space of Disse. The space of Disse is located between the wall of the sinusoids and the wall formed by the hepatocytes. Its width varies across species. It is wide in the human, but is so narrow in the rabbit and the mouse that it is difficult to observe. The liver acts as a modest storage organ for body fluids, and mammals with a wide space of Disse have the capacity to store more fluid.

The walls of the sinusoids are formed of cells of the monocyte-phagocyte system (MPS; Kupffer cells; reticuloendotheliocytes). As phagocytes, they are more important in the liver of rabbits, rodents, dogs, and humans than they are in cats, pigs, and ruminants. In the latter species, MPS cells are more prominent in the microvascular endothelial cells of the lungs, where they are termed pulmonary intravascular macrophage (PIMS).[31,224] Differences in the distribution of MPS cells are important in disease processes. The walls of the sinusoids permit the passage of rather large molecules into the space of Disse, and the liver lymph has a relatively high protein content.

The liver, with its anterior surface applied to the diaphragm, presents 4 lobes. A deep median cleft divides it into right and left lobes, which are subdivided into anterior and posterior lobules. Further subdivision of the right posterior lobule occurs in some animals. The quadrate lobe is a subdivision of the right lobe and lies medial to the gallbladder. The caudate lobe is small and circular with a thick extension or stalk.

The liver receives about 70% of its blood at low pressures (usually less than 10 torr) from the portal vein and about 30% of its blood at systemic pressures from the hepatic artery. The venous blood is formed in the siunusoids. The sinusoids, contained within the labyrinth that is formed by the hepatocytes, drain into the central vein at a very low pressure. Also draining the liver are the lymph channels, originating from the space of Disse.

The liver is the seat of a multitude of metabolic activities. It maintains the blood glucose level by converting excess glucose to glycogen or to fatty aids, and by converting glycogen, amino acids, and lactate to glucose. It degrades proteins to amino acids and forms proteins from amino acids. It makes bile acids from cholesterol and bile pigments from heme products. At least 12 of the factors involved in blood clotting are synthesized in the liver. By conjugation, hydrolysis, methylation reduction, or oxidation, many compounds are altered so that they are less toxic, or so that they may be more readily eliminated in the bile or in the kidney.

The liver contains many enzymes, many of which vary across species.[223] Unlike the situation in most species, mescaline, a hallucinogenic amine found only in plants, is rapidly oxidized in the rabbit liver. Like rats and oxen, rabbits have a higher concentration of rhodanese, the enzyme required for the synthesis of thiocyanate, than is found in all other animals tested. Unlike primates (including humans), rabbits, and all non-primate animals tested, cannot conjugate glutamine as a

detoxication mechanism. The rabbit, like the cat and the rat, has a liver enzyme that is efficient in metabolizing atropine; some rabbits can tolerate large doses of atropine. Some rabbits (about 25%) have a heritable ability to inactivate atropine.[82]

Taurine, a common conjugate with bile acids in most mammals, is not a prominent conjugate in the rabbit. Microsomes of the rabbit liver are severely limited in the ability to synthesize taurine, a deficiency not shared by other mammals tested, even other species of rabbits.[29] Taurine was found in the serum of 3 different strains of rabbits, with a variable transfer defect among the strains.[91] Buphthalmic rabbits (genotype bu/bu) had the lowest concentration of taurine in the aqueous humor of the eye of any rabbits tested.[29]

Over 100 tests have been developed to determine the status of liver function, emphasizing the various functions involved.[131] Because bromsulfophthalein (BSP) is eliminated almost exclusively by the liver, it is widely used, although it has limitations.[47] Indocyanine green (ICG), which is eliminated in unconjugated form in bile, is another popular test of liver function. The rate of clearance of BSP in the rabbit is similar to that in the rat, but faster than in the dog.[125] The rate of clearance of ICG in the rabbit is faster than in the dog or the rat.[126]

Originally published in the ASLAP Newsletter 24(3):34–35, 1991

The Gallbladder

The gallbladder is situated in a deep depression of the caudal surface of the right anterior lobule. The hepatic ducts unite to form the common bile duct, which receives the cystic duct from the gallbladder and enters the dorsal surface of the duodenum immediately poster to the pylorus.

Rabbits produce a large amount of bile. A 2 kg rabbit secretes about 250 ml of bile daily, about 7 times as much as a dog on a weight basis. Secretin, a potent choleretic in other species of mammals, has no effect on bile flow in the rabbit, probably because bile flow is always at a maximum rate in the rabbit.[220] The rabbit is unique in that the kidney can excrete up to 10% of the bile salts that are formed, while in other animals the kidney excretes less than 5% of the bile salts.[24]

All eutherian mammals form varying proportions of cholic acid and chenodeoxychiloic acid as primary bile.[92] Rabbits have a limited ability to make chenodeoxycholic acid[92], and the primary bile acid formed by the hepatocytes is cholic acid. The rabbit is one of those species in which the primary bile acid is not the main component of the bile acid pool. The cholic acid is reduced in the intestine by bacteria to deoxychollic acid, which is recycled and conjugated in the liver with glycine. Glycodeoxycholic acid is the main component of the bile acid pool in the rabbit.

Deoxycholic acid is abundant in rabbits (and humans) but not in rats and mice. The liver in these rodents rapidly reconverts the deoxycholic acid to chollic acid, an ability not shared by the livers of rabbits, humans, or most other mammals.[95]

When a bile duct is obstructed in a portion of the liver, cirrhotic changes and atrophy take place in the affected portion. The remainder of the liver undergoes hypertrophy, a process that usually takes 12 to 15 mo in a dog, cat, or monkey. In a rabbit, the process is complete in 4 to 6 wk.[177] With complete obstruction of the rabbit bile duct, as by flukes, thick white clots appear in the colon.[178]

Originally published in the ASLAP Newsletter 24(3):34–35, 1991

The Pancreas

In the rabbit, the pancreas is a diffused irregular mass in a fold of peritoneum, partly located in a pocket formed roughly by the transverse colon, the stomach, and the duodenum, and partly between the stomach, the inferior pancreatico–duodenal vessels, and the vena cava. The pancreas is intimate with the splenic vessels and with the inferior pancreatico–duodenal vessels, and must be carefully separated from these vessels if the rabbit is to survive pancreatectomy. Pancreatectomized rabbits survive for long periods without insulin, up to 30 d or longer.[87]

The duct of the pancreas enters the duodenum about 35 to 40 cm distal to the entrance of the biliary duct. In most animals, if the vagus nerves are severed, a larger dose of secretin is needed to produce a given response.[143] In the rabbit, cutting the vagi does not affect secretin.[21]

Ligation of the pancreatic duct is considered to cause pancreatic insufficiency because pancreatic enzymes then cannot reach the intestinal tract. In the rabbit, ligation of the duct causes the expected distention of the ductules and fibrosis, but proteolytic enzymes continue to be found in the duodenal lumen; 4 wk after the ligation is performed, chymotrypsin in the intestinal lumen is comparable to the concentration found in non-ligated control animals.[11]

Originally published in the ASLAP Newsletter 24(2):9, 1991

The Heart

The heart of a rabbit does not have a tricuspid valve. The right atrioventricular (A-V) valve consists of a large cusp and a second, much smaller, cusp. There is no 3rd cusp. The cusps are capable of generating spontaneous impulses. Unlike canine valves, which require catecholamines for activity, automaticity occurs in rabbit A-V valves maintained in normal Tyrode solution.[179]

The sinoauricular (S-A) region is complex, with considerable species difference in the location of the atrial ganglionic cells. In the rabbit, the region is well defined. The simplicity of the conductive tissue in the rabbit allowed localization of the exact site of the pacemaker; the rabbit was the 1st mammal in which this localization was accomplished.[101] Only a small group of cells generate the impulses in the rabbit.[25] Nerves enter the region from the atrial septum, the superior vena cava, and the inferior vena cava, and form a rich network of nerve tissue in the region of the node.[172]

The most obvious morphologic difference between cardiac conductive tissue and cardiac muscle is the presence of transverse tubules in the muscle cells. Purkinje cells have no transverse tubules.[198] Most mammals have an admixture of connective tissue with the Purkinje cells, making the conductive tissue readily identifiable yet complicating microelectric recording. Rabbits have little or no connective tissue admixture with the Purkinje fibers; this simplicity of the conductive tissue makes the rabbit the mammal of choice for study of Purkinje fibers.[198]

The Purkinje fibers in the ventricle of the rabbit have other desirable features that make them amenable for study. Of all mammals studied, their shape is closest to a long, cylindrical cell, and they have unusually wide space clefts between them, space clefts that are 25 to 50 times the widths of ungulate preparations. Problems of resistance and of perfusion are greatly reduced in the rabbit preparations.[43]

In the rabbit, the number of gates in the Purkinje fibers is much smaller than in the Purkinje fibers of the dog or the monkey. The action potential duration (APD) increases progressively along the conducting tissue in the dog or the monkey, reaching a maximum within 2 to 3 mm of the junction of the Purkinje fibers and the ventricular myocardium. In the rabbit, the maximum is reached midway in the bundle branches.[78] In rabbit hearts,

a premature excitation causes a prolongation of the APD. The prolongation is not seen in the guinea pig heart.[99]

In the rabbit, the left ventricular branch of the circumflex artery is larger and supplies a much greater portion of the myocardium than does the left anterior descending artery.[70] An interesting difference occurs in the progression of myocardial infarction in rabbits and dogs. Unlike in the dog heart, the infarct in the rabbit heart first appears in the mid-myocardium and then progresses toward both the endocardium and the epicardium.[153]

Xanthine oxidase plays a key role in the generation of cytotoxic oxygen species,[51,146,163] which are implicated in cardiac damage. Xanthine oxidoreductase activity varies among mammals[51], being rather low in rabbits and humans. The human has relatively high uric acid content, which is an excellent inhibitor of xanthine oxidase activity.[163] Although the rabbit heart is relatively free of xanthine oxidase, free radicals contribute to post-ischemic dysfunction,[146] but the rabbit heart is relatively resistant (compared to the dog heart) to oxidative damage.[146]

In rabbits, the slightest irritation of the mucous membrane of the upper respiratory tract as by smoke, chloroform, ammonia, etc., or slight pressure on the laryngeal region, can lead to long lasting heart and respiratory stoppage.[122]

Originally published in the ASLAP Newsletter 24(2):69, 1991

Circulation

The incidence of ossification of cartilage in the carotid ring of the rabbit is much higher than in other mammals.[98] In the rabbit, the ossified cartilage may undergo a metaplastic transformation and develop myeloid tissue.[98]

The aorta of the rabbit has a rhythmic contraction, neurogenic in origin, which is in a precise phasing pattern with the pulse wave. It has not been noted in other mammals.[145]

Species differences occur in the mechanical properties of arteries. The carotid artery of the rabbit is more compliant than in dogs, and has a greater ratio of elastin to collagen than does the dog.[49] It produces a larger maximum diameter response, and has a higher water content and a lower connective tissue content than does the carotid artery of the dog or the rat.[49] The response of the common carotid artery to noradrenaline is essentially the same in the rabbit and the dog, both of which have a greater response than does the rat.[49]

WHHL rabbits have faulty low-density lipoprotein (LDL) receptors and are unable to bind LDL. The resulting great increase in plasma LDL is responsible for rampant atherosclerosis in these animals.[175]

In the rabbit, the aortic nerve has no known chemoreceptors, having baroreceptors only.[116,204] The carotid sinus nerve (v. infra) has both.[30] Originating from the aortic arch, the aortic nerve joins with the afferent fibers from the root of the right subclavian vein to form the depressor nerve that runs alongside, but separate from, the vagosympathetic trunk along the neck. It is only in the rabbit, of all the common laboratory animals, that the depressor nerve is separate from the vagus trunk along the length of the neck. In the dog, cat, and rat, the depressor nerves are separate for only a very short distance below the nodose ganglion.[144] The depressor nerve in the rabbit, being free and having a diameter of 0.1 to 0.2 mm, can easily be implanted with electrodes.[177] The carotid bifurcation and the heart of the rabbit lend themselves handily to enclosure in fluid filled isolated chambers for study.[33,67]

The morphology of the carotid sinus and the carotid body varies widely among species.[2] In rabbits, as in humans, the carotid body is located in the bifurcation of the common carotid and is about 1 by 0.5 mm in size. The carotid sinus is a relatively small swelling at the origin of the internal carotid, and is not nearly as prominent in rabbits as in humans. As in humans, sensory nerve endings are found in the adventitia of the sinus, and are a source of the sinus reflex, fist shown in the rabbit in 1924.[96]

The rabbit is unique in that the external carotid artery and its branches, including the auricular artery, respond differently to serotonin (5HT) than do the arteries in other parts of the systemic circulation.[9] In the aorta, the internal carotid arteries, and the femoral arteries, responses to noradrenaline (NA) and 5HT are comparable. In the external carotid artery and the auricular artery of the rabbit, NA is about 700 times more potent than is 5HT.[41] Receptors for 5HT are absent in the external carotid artery in the rabbit. The rabbit ear is not a suitable model for the study of migraine.

Use of the transparent chamber in the rabbit ear disclosed other differences between the circulation in the rabbit ear and other areas.[41] In the rabbit ear, the arteriovenous circulation opens when the ambient temperature falls to 15 °C. In the human finger, the anastomotic circulation closes down in the response to cold. Intercalated segments composing anastomotic sections in the rabbit ear have thick walls, a rich nerve supply, and faster and more complete contractions than do arteries in most parts of the systemic circulation.[41]

In the rabbit, the internal carotid artery is relatively small, although it is the main source of blood supply to the brain. As in primates and ruminants, the vertebral arteries cannot be relied upon to nourish the rabbit. As in all Leporidae, rabbits have no stapedal artery.

The responses of cerebral vascular flow and cerebral vascular resistance to cerebral sympathetic nerves are much more marked in rabbits (and monkeys) than in dogs and cats.[94] In rabbits, the response is transient, suggesting a vasomotor escape from sympathetic stimulation.[190]

The pulmonary artery and its branches are much more heavily muscled in rabbits (and guinea pigs) than in humans, rats or cats.[68] The muscle thickness is exaggerated by swellings (also found in opossums and dolphins, and in the small arteries of cattle). Muscle swellings have not been found in the pulmonary arteries of primates, muridae, dogs, cats, or bats.[66] The pulmonary artery of the rabbit is extremely sensitive to histamine[226] and acetylcholine[65], which cause marked vasoconstriction. A sensitized rabbit responds to antigen with a severely spastic response of the branches of the pulmonary artery, such that the right ventricle may not be able to force blood through the arterioles.[65]

Originally published in the ASLAP Newsletter 24(4):23–26, 1991

Blood

In rabbits, the dye T-1824 is not a reliable measure of blood volume, as it is in humans or dogs.[233] Radio-iodinated albumen is more reliable.

The ionized fraction of calcium in the serum of rabbits is comparable to that of other mammals.[149] However, rabbits normally have higher total serum calcium concentrations than do other mammals studied (about 14 mg/dl in rabbits vs. about 10 mg/dl in all other mammals studied). In other mammals, the serum calcium content is regulated by parathormone and by calcitriol (the activated metabolite of vitamin D). The absorption of calcium from the gut is regulated by calcitriol in all mammals studied, except in the rabbit. In the rabbit, the absorption from the gut is independent of calcitriol, and the serum calcium level varies directly with the dietary level.[52]

The rabbit differs from the human in its response to the stimulation of degradation products of fibrinogen. In the human, fibrinogen degradation products stimulate the production of

plasma fibrinogen. This response to the low-molecular weight peptides of fibrinolysis does not take place in rabbits.[120]

Deformability is an important characteristic of mammalian red blood cells (RBC), enabling the cells to flow through capillaries that are less than half the diameter of the cells. Deformability varies widely across species. The deformability of the RBC of the rabbit is less than that of humans.[7] In rabbits and humans, oxygen-free radicals have a negative effect on RBC deformability.[100] Alpha-tocopherol tends to obviate the negative role of sepsis on RBC deformability.[168] In rabbits and humans, the plasma fibrinogen concentration affects the deformability of RBC. In other mammals examined (horse, sheep, cattle, goat, camel), the RBC deformability is not influenced by fibrinogen.[7]

The white blood cells (WBC) of the rabbit have features that differ from most mammals.[111] The cell most comparable to the neutrophil in other mammals is the heterophil, a WBC with a nucleus that stains faintly purple, a cytoplasm that stains pink, and 2 types of reddish granules. The larger granules are azurophilic. The smaller granules are called secondary or specific granules.[18]

The eosinophil in the rabbit is distinguished from the heterophil by its larger size and more intensely staining cytoplasmic granules, which are about 3 to 4 times the size of the granules in heterophils.

Basophils, relatively sparse in most other mammals, generally constitute up to 8% to 10% of the total leukocyte count in rabbits.

In most mammals, an increase in the WBC count is a common consequence of acute infections. This is not so in rabbits.[209] Emotional stress causes leukopenia in rabbits[158] but causes leukocytosis in other mammals. In rabbits, the differential distribution of the various WBC populations may give more useful diagnostic information than the total WBC count.

Blood Cell Values in Rabbits[111]

RBC ($\times 10^6/\mu l$)	6.08 + 0.61
Hematocrit (PCV; Hct) (%)	41.2 + 3.2
Hemoglobin (Hb (g/dl)	12.9 + 1.3
Mean RBC Vol (MCV) (fl)	68.3 + 3.6
Mean RBC Hb Concentration (MCHC)%	31.2 + 1.5
Mean RBC Hb (MCH) (pg)	21.3 + 1.1
Reticulocytes (% of RBC)	3.0 + 1.3
Leukocytes (WBC) ($\times 10^3/\mu l$)	9.79 + 3.21
Heterophils (% of WBC)	45.2 + 13.1
Lymphocytes (% of WBC)	45.3 + 13.0
Eosinophils (% of WBC)	1.9 + 1.5
Monocytes (% of WBC)	2.8 + 3.5
Basophils (% of WBC)	3.0 + 2.3
Platelets ($\times 10^3/\mu l$)	34.3 + 120

Originally published in the ASLAP Newsletter 24(4):27–29, 1991

The Kidney

In this treatise, the nomenclature used is that adopted by the International Union of Physiological Scientists,[130] with modifications.[127]

The kidney of the rabbit is primitive when compared to the kidney of other eutherian mammals[32,113], and differs from them in many ways. The rabbit is the only known mammal in which the tubules can be separated from kidney slices with the basement membrane intact, a factor that has justified its use in many studies involving renal tubule physiology. The rabbit is also used for studies of other body systems, many of which are influenced by metabolic processes involving the kidney. Information about the known differences between the kidney of the rabbit and the kidneys of other animals is thus of special importance.

The right kidney is more craniad than the left. The kidney is unipapillate, and the evaginations of the kidney pelvis fornices are extensive. The epithelium of the fornices in the area of the inner medulla is a single layer of cuboidal cells, comparable to that of the collecting duct epithelium. As the fornices extend to the outer medullary region, the epithelium becomes squamous. Connective tissue is sparse and is closely approximated to the vascular bundles.[166,185]

The arterial system in the cortex of the mammalian kidney is similar in all species. Differences are marked in the medulla (V. infra). Species differences occur in the venous system in the cortex. Anastomoses between arcuate vessels in the venous system are found in all species examined except the seal.[157] The efferent arterioles from the superficial glomeruli do touch the renal surface and are available for injection. Rabbits and rodents (hamster, rat, mouse) have no superficial veins. The blood leaves the cortex by descending to the arcuate veins.[208] In the human, cat, and dog, superficial veins are prominent.[208]

In rabbits, as in most mammals, few, if any, glomeruli touch the renal surface, as they do in amphibians and in the inbred Munich rat. Rabbits have a short neck region of distinct morphology, not noted in rats or humans, connecting the glomerulus to the proximal convoluted tubule (PCT).[188] The PCT has a luminal diameter of about 25 μm[219] and a net fluid absorption rate of about 1 ml/mm/min in adult and as low as 0.3 ml/mm/min in immature rabbits.[137] With bicarbonate in the infusate,[54] parathormone (PTH) depresses the absorption rate in the rabbit PCT.[90]

In many animals, including the rabbit, the PCT can be divided into 3 segments that are less distinguishable in the human. The PCT-S1 segment includes the 1st 2/3 of the PCT, the PCT-S2 includes the last 3rd of the PCT and the 1st part of the straight tubule (pars recta), and the PCT-S3 consists of the terminal part of the pars recta.[227] In rabbits, the S2 segment includes a greater part of the pars recta than it does in rats, and the transition from the S2 to the S3 cells is more gradual.[227] In other mammals (rat, dog), the transition is abrupt.[130] The brush border in the S3 segment is short in the rabbit, tall in the rat, and intermediate in the human.[157]

Peroxisomes, a cellular microbody containing oxidizing enzymes and catalase, are common in the cells of the pars rector and vary in appearance among species. Structures called marginal plates, not prominent in other mammals, are seen in peroxisomes in rabbits and human. The structures are rich in catalase.[161]

In most mammals, PTH increases phosphate excretion by inhibition of phosphate reabsorption in the PCT, and to a lesser extent in the distal convoluted tubule (DCT). The rabbit (and the hamster) are resistant to the phosphaturic effects of PRH.[55,128,202]

Blood flow rates in rabbit kidneys are approximately 195 nl/min in the juxtamedullary and superficial glomeruli and 110 nl/min in the midcortical glomeruli.[203] Some interesting features differentiate glomerular blood flow in rabbits from most other animals. In most mammals, the clearance of inulin (the amount of plasma from which inulin is completely removed each minute) is equal to the glomerular filtration rate (GFR). In contrast, alterations in the blood flow in rabbit glomeruli change the clearance of inulin.[115] Diuresis in rabbits (and seals) is correlated with an increase in the renal plasma flow (RPF) and GFR. The seal responds with a greater intensity of action of the nephrons, whereas the rabbit brings more nephrons into action.[39,115] In most land

mammals, a moderate water load increase has no effect on RPF or GFR.[39] Calcitonin, the 32 amino acid polypeptide produced by the perifollicular cells of the thyroid gland, increases the RPF in rabbits,[183] but does not affect the RPF of dogs or pigs.[181] In rabbits, angiotension II (Ang II) causes vasoconstriction of isolated efferent but not afferent arterioles.[203] In dogs[176] and hamsters,[42] both afferent and efferent arterioles are affected. In rabbits, anoxia causes vasoconstriction of the kidney arterioles and a reduction in kidney function.[39] In dogs and rats, anoxia increases urine flow and electrolyte excretion.[39] When the blood pressure is increased, even doubled, in a rabbit, little or no change occurs in the RPF or the GFR, even in rabbits with denervated kidneys or demedullated adrenals.[211] The site of this auto-regulation is the afferent arteriole. Auto-regulation is present in other mammals, but not to the degree found in the rabbit.[203] Hydration in a rabbit that is not undergoing a fright reaction leads to a marked increase in glomeraluar activity. Up to a 16-fold increase in water diuresis can occur without a significant variation the filtration rate. This has not been seen in other mature mammals.[196] Adult rabbit kidneys react to hydration in an infantile manner.[57]

The number of glomeruli in the rabbit (and the rat) increases after birth.[196] In humans and dogs, all of the glomeruli are present at birth. In humans, ectopic glomeruli are present in neonates, but they disappear as adulthood is reached. Ectopic glomeruli are present in the adult rabbit—about 60 in each kidney.[203] An intermittency occurs in rabbit glomeruli, as in amphibians, and neonatal mammals, but not in most other mature eutherian mammals—a wide variation occurs in the number of glomeruli that are active at any one time.[183] The number of active glomeruli in the rabbit can be increased by caffeine and by salt solution, and can be decreased by vasoconstriction. Thus, with a sympathetic discharge, as may occur with hydration by stomach tube in an animal of unique automatic instability, oliguria, overhydration, convulsions, and even death can result.[211]

The intermediate tubule (the loop of Henle) shows wide variation across species. Most species have both short looped and long looped nephrons. In rabbits, 70% of the loops are long and 40% are short, although only about 7% of the efferent arterioles from the juxtamedullary glomeruli supply blood to the medulla.[113] In other mammals (rat, mouse, *Psammomys*, pig, human), short loops outnumber long loops. In carnivores (cat, dog, fax), all of the loops are long.

The descending limbs of short looped nephrons (SDL) are similar in all species, with epithelium that is relatively simple (type I). The descending thin limbs of the long loops (LDL) show great heterogeneity of the epithelium, especially in the upper part (LDL-U; type II epithelium). The type II cells are deeper, have many mitochondria and intramembranous particles, have deep interdigitations of the basolateral membranes, and have significant levels of Na-K-ATPase activity. Type II epithelium is several times more permeable to sodium than is type I epithelium in the rat and the hamster.[135] In the rabbit, the differences between type I and type II cells are much less marked than they are in most mammals, and the difference in permeability to sodium and chloride between the short limbs and the long limbs in the rabbit are negligible.[106] In addition, the Na-K-ATPase activity along LDL-U cells is present in the hamster, but is absent in the rabbit.[77]

Most mammals, including rabbits and humans, have a medulla in which the blood vessel bundles contain only ascending and descending vasa recta. In contrast, most mammals that have a high urine concentrating ability (rat, mouse, *Psammomys*) have a complex medulla in which the thin descending limbs of the short-looped nephrons cross over and become incorporated into the vascular bundles in the outer medulla.[20,89] The close association of tubules and vascular bundles aids in the recycling of urea.

The distal tubule includes the thick ascending limb (TAL) in the medulla (MTAL) and the cortex (CTAL), the macula densa, and the distal convoluted tubule (DCL). The TAL actively transports NaCl from the lumen to the interstitium, but is almost impermeable to water, contributing to a concentrated urine in the pelvis and a dilute urine in the tubule. Species differences occur in the response of the TAL to various hormones. Vasopressin (ADH) stimulates NaCl reabsorption in the MTAL of the rat and mouse, but has no effect on the MTAL of the rabbit.[156]

In most mammals, most of the calcium and magnesium is reabsorbed in the TAL.[205] In rabbits, the urine is the major route for calcium and magnesium excretion.[119,191] Rabbits fed a 10% $CaCO_3$ diet excrete about 60% in the urine; rats fed a 10% $CaCO_3$ diet excrete less than 2% in the urine.[38] In most mammals, the serum calcium level is regulated by the activated metabolite of vitamin D. In the rabbit, calcium absorption from the gut is independent of this mechanism, the serum calcium level varying with the dietary level.[52] The urinary calcium level varies directly with the serum calcium level. A high level in the diet causes the urine to have a thick, creamy appearance. The rabbit has high levels of total and ultrafilterable calcium in plasma, but the ionized fraction is normal.[149] The high ultrafilterable content is due to the high citrate concentration in the rabbit plasma.

In most mammals, reabsorption of bicarbonate takes place in the TAL. Rabbit TAL does not reabsorb bicarbonate.[50] In many mammals, including the human, bicarbonate produced by catabolism is neutralized by the products of ureagenesis, avoiding an alkalosis.[14] In the rabbit, an animal with a limited nitrogen intake, ureagenesis may be insufficient to titrate the bicarbonate load. The bicarbonate load is increased in the rabbit by the action of microorganisms on organic anions in the gut, producing additional bicarbonate that is absorbed.[169] Rabbit urine often contains bicarbonate gravel.[148]

The enzyme carbonic anhydrase (CA) generates protons and bicarbonate from water and CO_2. A zinc containing enzyme, CA catalyzes the hydration of CO_2 to bicarbonate or the dehydration of bicarbonate to CO_2 and is found in tissues that are involved in the formation of acidic or alkaline fluids. Inhibition of CA activity, as with sulfonamides, causes a drop of about 80% of bicarbonate absorption in the proximal tubule, and an acid disequilibrium develops because protons secreted by apical membranes cannot be buffered by bicarbonate at a fast enough pace. CA is required for the acidification of luminal fluid all along the collecting duct. The TAL of humans, monkeys and rats carry large amounts of CA,[59,142] but no CA is found in the TAL of rabbits, which correlates with an absence of acidification in rabbit TAL.[105]

In most mammals, the luminal fluid of the collecting duct is not in functional contact with CA, except in the inner stripe of the rabbit OMCT.[81,201] The generation of high pCO_2 in alkaline urine, and in the trapping of NH_3 in the lumen, depends on an absence of CA in the luminal fluid. In the inner stripe of the OMCT of the rabbit, the luminal fluid is exposed to CA. The pH is in equilibrium in this segment of the rabbit tubule.

Rabbits are unusually susceptible to low doses of acid administration.[214] In most mammals, the rate of ammonia synthesis and excretion increases markedly when the animal has a chronic metabolic acidosis. The major renal activity in ammonia formation is glutamine deamination, a mechanism stimulated by decreased pH or decreased concentration of bicarbonate. The proximal tubule is the only site of this reaction.[4] In rabbits, a decreased pH does not stimulate the deamination of glutamine. Only a lowered bicarbonate concentration is effective.[195]

If the classical pathway for the formation of ammonia is blocked, as by the administration of 3-mercaptopicolinic acid, the rabbit cannot form ammonia from glutamine in the kidney, whereas other mammals (dogs, rats) are not affected because of the availability of an alternate pathway—use of the malic enzyme, as enzyme not found in the rabbit kidney.[112,182,215,216]

Isolated kidney tubules from the rabbit do not readily use glutamine or glutamate as gluconeogenic substrates, probably because glutamic dehydrogenase is inhibited by ammonia in rabbits.[124] Glucose formation from glutamate is 3 to 4 times greater in rat than in rabbit renal cortex. When glutamine is used as a substrate, glucose production by rat kidney slices is more than 200 times that produced by rabbit kidney slices, and ammonia production is 6 times greater.[124]

Glutamine is synthesized in tissues with the aid of glutamine synthase, an enzyme found in the kidneys of rabbits, guinea pigs, sheep and rats, but not in the kidneys of cats, dog, or pigs. It is found in the brains and livers of all vertebrates. Together with glutaminase, it constitutes a reversible system for the conversion of ammonium glutamate to glutamine and visa versa. The hydrolytic enzyme is increased in both chronic acidosis and chronic alkalosis in the rabbit and the guinea pig, but undergoes no change in the dog.

Arcades, found in many species to different degrees, are ascending tubules in the cortical labyrinth that join deep and mid-cortical nephrons to a collecting tubule. The tubules are comprised of connecting tubule (CNT) cells, collecting duct (CD) cells, and intercalated (IC) cells.[130] The IC cells are mitochondria rich, carbonic anhydrase rich, and have many characteristic rod-shaped particles in the membranes of cytoplasmic vesicles. IC cells are prominent in collecting ducts and other transporting epithelia. Rabbits differ from most other mammals in that the connecting duct does not contain typical CD cells, but only CNT cells interspersed with IC cells.[130] The CNT cells are probably important in potassium secretion, partly controlled by mineralocorticoids.[114] The rabbit differs from most other mammals in that the CNT is a more distinct segment in both structure and function.[127] Adenylate cyclase activity in the CNT is stimulated by both PTH and isproterenol[156]; ADH has no effect on adenylate cyclase activity or on water permeability in this section of the rabbit tubule.[107]

The outer medullary collecting duct (OMCD) of the rat is composed of about 2/3 principal cells and 1/3 intercalated cells. IC cells are darker, have more prominent microvilli, and are important in acid production. In the rabbit, the IC cell population is comparable to that in the rat in the outer strip of the OMCD. In the rabbit, some IC cells are present in the inner stripe of the OMCD, but these are limited to the outer half of the inner stripe, where they represent about 10% to 15% of the call population.[171] In the rat, about 1/3 of the OMCD cells are IC cells.

In the rabbit, IC cells are not present in the initial part of the inner medullary collecting duct (IMCD). In the rat, the IMCD has about 90% of principal cells, with about 10% IC cells interspersed among them.[171] The inner collecting duct (ICD) normally reabsorbs about 2% of the glomerular filtrate. Active reabsorption of sodium takes place in the IMCD, and, in most mammals, is stimulated by aldosterone and inhibited by diuretics (amiloride, thiazide, furosamide). Rabbit IMCD cells are not sensitive to any of the loop diuretics.[171]

The cells in the inner medulla are the only cells in the mammalian body that are normally exposed to high concentrations of NaCl and urea, an environment that would be lethal to most mammalian cells. Renal medullary cells adapt to such exposure by accumulating high concentrations of organic solutes. Species differ in the solutes carried. In the rabbit, the betaine content is much higher,[225] and the glycerolphosphorylcholine (GPC) content is much lower than in the rat.[17,89]

Uric acid is the final product of purine metabolism in the human, and is handled in a widely variable manner in the kidneys of different species of mammals. The human has one of the lowest excretion ratios. Out of about 9000 mg of urate filtered daily, only about 700 mg are excreted in the human. The rabbit has one of the highest excretion ratios. As much as 160% of the filtered load is excreted, indicating that much of the secreted load is also excreted. An anion exchange mechanism located in the luminal plasma membrane of the dog and the rat affects the reabsorption in the proximal tubule. Rabbits do not have the urate-anion exchange mechanism.[86]

Originally published in the ASLAP Newsletter 24(3):36–39, 1991 and 25(1):28–33, 1992

The Skeleton

The skeleton of the rabbit is relatively fragile, representing about 8% of the body weight. In comparison, the skeleton of a cat of about the same body weight represents about 13% of the body weight. The bones of the rabbit skull are spongier than in most mammals and contain wide spaces. The immovable sutures between the skull bones are more distinctive than in most mammals and become less distinct with age.

Skull. The posterior (nuchal) surface of the skull is formed by the composite occipital bone, which is formed by developmental fusion of the supraoccipital, the paired lateral exoccipitals, and the ventral basioccipital. It is pierced by the foramen magnum, which at each side bears the occipital condyles for articulation with the altas. The nuchal surface of the skull is separated from the dorsal surface by a sharp ridge having a median projection, the external occipital protuberance. The dorsal ligament of the neck and occipital muscles attach to the latter.

The dorsal surface of the skull is formed by the dorsal surface of the occipital (supraoccipital) bone, the small interparietal bone (which separates the supraoccipital from the pair of parietal bones), the paired frontal bones, and the nasal bones, which roof the nasal cavities. The frontal bones have anterior and posterior dorsolaterally situated supraorbital processes and also extend ventrally to form part of the orbital wells.

The inverted cone-shaped mastoid portion of the periotic or petramastoid bone with its pitted surface is visible at the posteriolateral aspect of the cranium. Enclosed in it and its petrous portion is the inner ear. The mastoid portion and the prominent, round tympanic bulla conceal the petroid portion. The bulla is formed by the tympanic bone and contains the large tympanic cavity, encloses the 3 ossicles of the middle ear, and continues dorsally into a short wide bony tub with a large opening, which in the natural state would be continued into the aperture of the external ear. The whole tube is the external acoustic meatus.

Anterodorsal to the preceding bones is the squamosal bone, which forms a large portion of the lateral wall of the cranium. It has a prominent projection, the zygomatic process, which forms the caudal end of the zygomatic arch. The hollowed out ventral side of the zygomatic process forms mandibular fossa, which holds the head of the mandible. Anterior to the squamosal bone is the alisphenoid, and anterior to it is 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 orbit rim. The maxilla extends forward from the orbit. Its lateral zygomatic process forms the anterior aspect of the zygomatic arch and is fused with the anterior end of the zygomatic or jugal bone, which forms the main portion of the arch. The alveolar process or ventral portion of the maxilla

contains the roots of the cheek teeth. Anterior to the maxilla is the premaxilla, in which are inserted the roots of the incisors. It joins medially with its opposite member and bounds the anterior ventral and lateral part of the nasal cavity. Its frontal process extends dorsocaudally along the lateral aspect of the nasal bone.

The medially situated basioccipital, basisphenoid, and presphenoid bones proceeding cephalad from the foramen magnum form the ventral aspect of the cranium. The basisphenoid is perforated by the round foramen cavernosum, which leads into the interior of the bone. The hypophyseal fossa is located on its dorsal surface (the floor of the cranial vault).

The ventral aspect of the skull continues into the paired palatine bone. The caudal ends of this bone are notched and articulate with the 2 lamine of the pterygoid process of the alisphenoid bone. Part of the thin dorsal extension of the palatine bone can be seen in the wall of the orbit. The palatine continues forward medial to the alveolar process of the maxilla with which it articulates and spreads medially to join its opposite member and thus forms the caudal portion of the hard palate. The hard palate continues anteriorly as the ventral portions of the maxilla and premaxilla. These are pierced by the long and narrow paired incisive foramina, which are continuous across the median line in their caudal third.

In the bisected skull, the structure of the nasal cavity can be observed. The cavity is divided into right and left fossae by the median, vertical cartilaginous nasal septum (cartilaginous portion of the mesethmoid). This is continuous caudally with the perpendicular plate of the ethmoid bone, which consists also of the cribiform plate exposed to the anterior cranial fossa and the paired lateral ethmodial labyrinths. Posteriorly, the ventral portion of the cartilaginous septum is supported by the vomer-bone. The scroll-like turbinate bones are situated on the lateral walls of the nasal cavity. The maxilloturbinalor concha inferior are rigid masses of bone that occupy the anterior portion of the lateral wall of the nasal fossa. The other paired turbinates are represented by the nasoturbinals and the ethmoturbinals.

The mandible is composed of paired members united by a fibrous or fibrocatilaginous sumphysis. The horizontal portion, which bears the teeth, comprises the body and the posterior vertical portion extending from the angle, comprises the ramus.

For convenience, the hyoid apparatus is mentioned with the skull even though it is derived from embryonic visceral arches. It is comprised of a median hyoid bone and the paired greater and lesser cornua, which articulate medially with the former and are connected laterally by 2 muscles to the jugular process of the occipital bone. The apparatus is embedded in the base of the tongue for which it functions as a support and lies between the angles of the mandible.

Vertebral column. The usual vertebral formula is $C_7T_{12}L_7S_4C_{16}$. Thirteen thoracic vertebrae are present in some animals. The first 2 cervical vertebrae are modified as in other species, the spinous processes are enlarged in the thoracic region, the sacral vertebrae are fused to form the sacrum, and the last 9 coccygeal vertebrae are devoid or arches and thus solid.

Ribs. Normally, the 12 pairs of ribs each consist of a dorsal bony portion and a shorter, ventral cartilaginous portion. The head of the rib articulates with the corresponding thoracic vertebra and with the posterior part of the body of the vertebra cephalad to it. The costal cartilages of the first 7 ribs (the true ribs) articulate with the sternum, while the cartilages of the last 5 ribs (the false ribs) do not. The costal cartilage of the 8th rib is attached to that of the 7th and that of the 9th to the 8th. The cartilages of the last 3 ribs (floating ribs) lie free as they are not attached to any others.

Sternum. The sternum is composed of 6 distinct sternebrae. The 1st is the manubrium sterni and the 6th is the xiphoid process, which has a thin, but broad plate of cartilage at its caudal end.

Originally published in the ASLAP Newsletter 26(1):5–8, 1993[129,221]

Appendicular Skeleton

Pectoral girdle and limb. The pectoral girdle consists of the scapula and the small clavicle. Its only direct attachment to the axial skeleton is through the sternoclavicular ligament, with the major attachments being provided by muscles. The humerus, radius, and ulna are as in other species. The carpus consists of 2 rows; bones of the distal row articulate with the 5 metacarpal bones. The 5 digits are each comprised of 3 phalanges, with the exception of the 1st digit (pollex), which has 2. Sesamoid bones are located on the volar surface of the foot, occurring in transverse pairs at the metacapophalangeal articulations and in linear pairs at the articulations of the 2nd and 3rd phalanges. The pisiform carpal bone (1 of the 9) is also a sesamoid bone.

Pelvic girdle and limb. The pelvic girdle is made up of the paired coxal or innominate bones formed by the fusion of the ilium, ischium, and pubis and is firmly attached to the vertebral column at the iliosacral articulation. The coxal bones are ventrally united via the pelvic symphysis, involving both the pubis and ischium. A small accessory bone, the os acetabuli, is present in the rabbit, thus excluding the pubis from the acetabulum, which is formed by the former bone plus the ilium and ischium.

The femur articulates distally with the tibia alone. The fibula is represented as a thin, bladelike bone along the lateral side of the tibia. The fibula is fused with the tibia distally for somewhat more than half their length. It attaches proximally to the lateral condyle of the tibia, and its only free portion is joined to the tibia by the interosseous ligament.

The 6 tarsal bones are arranged in 3 rows, with the proximal row containing 2 large bones, the middle row 1 bone, and the distal row 3 bones. Metatarsals 2 through 5 are well developed, while the 1st metatarsal is reduced to an inconspicuous splinter. The 4 digits of the hind limb each have 3 phalanges.

Originally published in the ASLAP Newsletter 26(1):5–8, 1993[129,221]

Metabolism

The metabolic rate (MR) varies widely among different species of endotherms, being roughly related to the surface area of the mammal. The fasting MR of a 2 kg rabbit is about 120 kcal/d and about 750 kcal/m^2.

The neonatal rabbit is an ectotherm until day 7.[80] The neonatal rabbit has a much higher fat content than the rat[102] and is more comparable to normal human infants at term (16% of the body weight).[46] The gluconeogenic precursors are low in the liver of the rabbit. Rabbit pups maintain normogycemia, even without suckling, until their glycogen reserves are exhausted, which occurs about 6 h post-partum.[192] The neonatal rabbit has all of the enzymes necessary for gluconeogenesis[34], which starts 30 min after parturition, with lactate, alanine, and glycerol as precursors.[152] In a fasting neonatal rabbit, hypoglycemia develops concomitantly with a marked ketosis.[34] The hypoglycemia is due to limited gluconeogenic precursors.

The mammalian hexokinases, the enzymes involved in the phosphorylation of glucose, are found in various tissues. Glucokinase, a specific hexokinase, is found in liver only. The phosphorylation of glucose by glucokinase is species specific, with the rabbit, guinea pig, rat, mouse, pig and dog having high rates of glucose incorporation into glycogen. In man, cat, ruminants and ruminant-like marsupials, glucokinase activity is low or absent, and the rates of conversion of glucose to glycogen are

relatively low. The rate of formation of fatty acids from glucose in adipose tissue is relatively high in rabbits (and in rats, guinea pigs, and hamsters) compared with the rate in humans. In the rabbit, at glucose concentrations of about 250 mg/dl, glucose uptake is about 2.5 to 5 μM/g/h. In the human, with glucose at concentrations of about 200 mg/dl, uptake into neutral lipids is only 0.2 to 0.5 μM/g/h.[193]

Isolated hepatocytes from rabbit and rat differ in the response of both gluconeogenesis and glycogenolysis to stimulation by catecholamines. Young rats are sensitive to both alpha- and beta-adrenergic stimulation; old rats are primarily alpha-adrenergic sensitive.[230]

Species show marked differences in the rate of glucose transport into red blood cells (RBCs). About 26 mg of glucose can enter 1 ml of packed human RBCs per min. The maximum rate at which glucose can enter rabbit RBCs is 0.1 mg/ minute.[193] Other species differences also occur. Glucose is a potent inhibitor of fructose transport in RBCs of humans but not in those of rabbits.[193]

Rabbit adipose tissue is relatively unresponsive to the adipokinetic effect of catecholamines, while rat, mouse, or human adipose tissue is strongly responsive to the lipolytic action of catecholamines.[134]

Differences also occur in the metabolic response of various species to diabetes. Alloxan-diabetic rabbits show no increase in the gluconeogenic rate from lactate, pyruvate, propionate, or fructose.[231] However, alloxan-diabetic rats and diabetic humans show an increase in gluconeogenesis from lactate or pyruvate.[53] With alanine or glutamine, gluconeogenesis increases in rabbits, rats, and humans.[232] Mannose stimulates the production of insulin by beta cells of the pancreas in the rabbit, but not in the dog.[19]

Amidinotranferase, the enzyme that mediates the initial step in the formation of creatine by combining arginine and glycine to form guanidioacetic acid, is found in the liver, kidney, and pancreas of the human. The enzyme has no activity in the liver of the rabbit, rat, or dog.

Some rabbits are subject to a hereditary dysfunction in the handling of intracellular calcium. White muscle fibers are particularly rich in myosin ATPase. In species that may have a heritable excess of calcium, the excess calcium may overstimulate the ATPase, causing an untoward increase in muscle activity and body temperature.[180]

The rabbit is a steroid sensitive species, in common with the mouse, rat, and hamster. Primates have a low sensitivity to steroids, as do ferrets and guinea pigs. The most dramatic response to steroids is a rapid decrease in weight of the thymus, spleen, and lymph nodes, and a lymphopenia.

Metoclopromide, a dopamine antagonist, does not stimulate aldosterone secretion in rabbits as it does in the rhesus monkey or the human.[200]

Amrinone, a synthetic cardiac inotrope, varies in potency across species. Pretreatment with a beta-adrenoceptor antagonist inhibits part of an amrinone-induced response in rabbit papillary muscle, but not in the cat papillary muscle or the guinea pig atrial muscle.[194]

Originally published in the ASLAP Newsletter 26(2):5–9, 1993

Water Metabolism

Individuals and species have no single or fixed requirements for water. The intake depends on availability, ambient temperature, humidity, diet, housing conditions, and stress. Under normal conditions, a 3 kg rabbit is about 58% exchangeable water, with a half time turnover of about 3.9 d and a loss of about 340 ml daily.[170] About half of the imbibed water that is not immediately excreted is stored in the skin.

Rabbits show a linear relationship between water and food intake.[40] When hyperphagia occurs, as when food is diluted with sawdust, water intake is proportionally increased. With water deprivation, food intake is gradually reduced. After 3 d without water, the food intake is less than 2% of normal. Finally, a complete cessation occurs.[40]

In the wild, *O. cuniculus* can survive for 2 mo on dry pastures in summer without drinking water. During this period, on a diet of foliage containing only 7% to 10% water, the rabbit undergoes a water loss equal to 48% of its body weight,[93] displaying an extreme tolerance of dehydration. Even camels cannot withstand a water loss greater than 40% of the body weight.[186] A dog undergoes circulatory failure when water loss reaches 11% to14% of its body weight.[3]

Rabbits (and guinea pigs) are unusual in that they drink excessively when fasted. After 3 d without food, a rabbit may drink up to 650% of its normal amount.[39] Fasting rabbits do not conserve sodium, and polydipsia may result in sodium depletion.[40]

Rabbits drink relatively little during heat dehydration, and may require up to 30 d for full recovery.[74] The slow recovery involves periods of excessive fluctuations in body weight.

In rabbits, panting is not efficient, and when sufficiently dehydrated, the rabbit does not pant. The conservation of water is more important than is the dissipation of heat. Rabbits salivate with an increase in ambient temperature, but are not efficient at this means of reducing body temperature.

Originally published in the ASLAP Newsletter 26(2):5–9, 1993

Reproduction

Rabbit reproduction has been studied intensely.[10,12,13,218] In this presentation, only the major morphophysiologic differences exhibited by *O. cuniculus* will be discussed. The rabbit, like the cat and the ferret,[75] is an induced ovulator and does not exhibit an estrous cycle as do most mammals. The doe will usually accept the buck at any time. Paired mating is recommended, with the doe being taken to the buck's cage, observed until mating takes place, and then returned to her own cage. Sexual excitement causes the release of follicle stimulating hormone (FSH), which induces ovulation about 10 h after coitus. In *O. cuniculus*, the timing of ovulation can be predicted with greater accuracy than is possible in any other species.

Rabbit eggs are larger (approximately 160 μm diameter) and more rapid in development than those of any other mammalian species.[1] Passage of the eggs through the oviduct and the tubo-uterine junction into the uterus occurs about 4 d after mating. The oviduct of the rabbit is usually abundant in albumen secreting cells. The tubo-uterine junction is surrounded by villi that project into the uterine lumen. The rabbit is a species in which the zygote (the developing embryo) lies in the uterine cavity and fills up the lumen (central implantation).[8] In women, the embryo penetrates the endometrial epithelium (interstitial implantation). In lagomorphs, the placenta is of the hemoendothelial type (Grosser classification).[88] In this type, maternal blood bathes the looped fetal capillaries. Maternal globulins pass into the fetus, providing passive systemic immunity, as in the human. At birth, the intestines of the neonatal rabbit are relatively impermeable to macromolecules, unlike the situation in ruminants and pigs. Two complete uteri are present in the rabbit, as in primitive vertebrates and in monotremes. Two complete utero-vaginal canals are present, with no corpus uteri. The rabbit (and the chinchilla) has 2 cervices. Most mammals only have 1. The cervices are never plugged with mucus.

The changes that occur in the vaginal epithelium of rodents during the estrous cycle are not seen in the rabbit, and are not a

reliable means of determining the physiologic state of the reproductive cycle in the rabbit. No amount of estrogen will induce any degree of cornification in the rabbit vagina.[13] When primed with estrogen, immature rabbits produce a specific anhydrase activity that is used for the bioassay of progesterone, an effect not found in mice.[160]

Pseudopregnancy can occur if coitus does not cause pregnancy, if does in the same cage mount one another, or if the rabbit is injected with luteinizing hormone (LH). In psudopregnancy, corpora lutea form, lactating glands develop, fur is plucked from the breast for nest building, and glandular development of the uterine mucosa occurs. Pseudopregnancy lasts about 15 to 16 d.

The gestation period is usually 31 to 32 d. During delivery, the doe assumes a position in which she can use her mouth to assist in the delivery and to clean fetal membranes from the young. She usually eats the placenta. The pups are born naked, blind and helpless. New Zealand white rabbits weigh about 65 g at birth. They double their weight in about a week and develop rapidly. The eyes open on about the 10th d, and rabbits begin eating dry food at about 3 wk of age. The pups are nursed only once a day. The doe usually weans the pups at about 8 wk of age, but some practices force weaning as early as 4 wk of age.

In lagomorphs and marsupials, the scrotum and testes are located in front of the penis. In all other placental mammals, the scrotum is located behind the penis. An unusual feature of rabbits is the comparative absence of a glans on the penis. The gubernaculum, a cord of smooth muscle and connective tissue, is retained in the adult buck as a band attaching the testes to the end of the scrotal sac. In humans, it is present only in the developing fetus. Rabbits have open communication between the sac of the testes and the abdominal cavity. The association of the vasa deferentia with the spermatic vessels to form a spermatic cord, as in man, is imperfectly expressed.

Originally published in the ASLAP Newsletter 26(3):1719, 1993

Lactation

Rabbit kits are born naked, blind, and helpless, and have a total dependence on milk up to day 10. A small amount of solid food (approximately 5%) is ingested at day 15. Solid food and cecotrophy begin on day 20. Cecotrophy at the adult level takes place between day 25 and day 30.[5]

The rabbit suckles its kits once a day, at a regular 24-h interval. At 3 d of age, the kit's stomach holds milk weighing 25% of its weight.[222] The curd is released into the duodenum in small quantities over the 24-h period.

The mammary gland of the doe has 8 nipples, each with ducts that empty independently, unlike the teat structure that is found in most mammals.[69] The buck has no nipples. The tight junctions between the secretory cells leak a bit throughout lactation[165], which is another departure from the situation in most mammals. In the doe, the milk is stored mainly in the secretory alveoli. The milk accumulates in the mammary gland in linear progression for 24 h, then, if not suckled or milked, it rapidly decreases in the rate of accumulation. In the New Zealand White rabbit, the 24-h accumulation is about 200 ml.[10]

Rabbit milk differs in composition from that of other eutherian species and changes markedly during the short period of lactation. The lactose content is low and gets lower during the lactation period.[165] The protein and fat contents are high.[138] Rabbit milk contains other saccharides along with galactose[35] and is higher in niacin[228], methionine, and glycine.[103,104] Rabbit milk, like cow's milk, is low in iron, but rabbits have a large iron reserve at birth so the kits are not dependent on milk for iron.[207]

Composition of Rabbit Milk[138]

Days Post Partum	Water	Protein	Lactose	Fat
Colostrum	68	13.5	1.6	14.7
4 Days	74	13.4	1.0	9.0
30 Days	63	16.9	0.2	17.5

Percentage Composition of Milk of the Cow and Human[58]

	Water	Protein	Lactose	Fat
Cow	87	3.5	4.8	4.0
Human	87	1.7	6.4	4.6

The amount of immunity transferred to the neonate by colostrum differs across species. In the rabbit, as in the human, the neonatal intestine is relatively impermeable to macromolecules. Immunity is transferred to the fetus, a condition made possible because of the hemoendothelial placenta. In many other mammals (e.g., ruminants, pigs), multi-layered placentae prevent passage of immune globulins in the fetus. In these species, colostrums, rich in antibodies, are absorbed through the intestine of the neonate. In muridae, part of the immunity is extended to the fetus and part to the neonate. Closure to macromolecules takes place in the muridae intestine about day 20 post-partum, at weaning time.[222]

Originally published in the ASLAP Newsletter 23(4):27–31, 1990

References

1. **Adams CE.** 1970. The development of rabbit eggs after culture in vitro for 1-4 days. J Embryol Exp Morph **23:**21–34.
2. **Adams WE.** 1958. The comparative morphology of the carotid body and carotid sinus. Springfield (IL): CC Thomas.
3. **Adolph EF.** 1947. Tolerance to heat and dehydration in several species of animals. Am J Physiol **151:** 564–575.
4. **Alpern RJ, Stone DK, Rector FC.** 1991. Renal acidification. In: Brenner BM, Rector FC, editors. The kidney. Philadelphia: Saunders. p 318–379.
5. **Alus G, Edwards NA.** 1977. Development of the digestive tract of the rabbit from birth to weaning. Proc Nutr Soc **36:**3a.
6. **Alwarez WC.** 1941. An introduction to gastroenterology. New York: Hoeber.
7. **Amin TM, Sirs JA.** 1985. The blood rheology of man and various animal species. Quart J Exp Physiol **70:**37–49.
8. **Amoroso EC.** 1952. Placentation. In: Parkes AS, editor. Marshall's physiology of reproduction. London: Longman-Green. p 127–311.
9. **Apperly E, Humphrey PP, Levy GP.** 1976. Receptors for 5-hydroxytryptamine and noradrenaline in rabbit isolated ear artery and aorta. Br J Pharmacol **58:**211–221.
10. **Arrington LR, Kelley KC.** 1976. Domestic rabbit biology and production. Gainesville: University of Florida Press.
11. **Arvanitakis C, Folscroft J.** 1978. Effect of pancreatic duct ligation and structure in the rabbit. Experientia **34:**77–79.
12. **Asdell SA.** 1964. Patterns of mammalian reproduction. 2nd ed. Ithaca: Comstock.
13. **Asdell SA.** 1965. Reproduction and development. Physiological Mammalogy **2:**1–14.
14. **Atkinson DE, Bourke E.** 1987. Metabolic aspects of the regulation of systemic pH. Am J Physiol **252:**F947–F956.
15. **Auer J.** 1925. Further notes on the fusis coli of the rabbit. Proc Soc Exp Med Biol **22:**301–303
16. **Baba E, Kusanagi M, Fukata T, Arakaua A.** 1987. Establishment of specific pathogen-free rabbits by inoculation of hysterectomy-derived rabbits with fecal suspension and anaerobic bacteria. Lab Anim Sci **37:**765–768.
17. **Bagnasco S, Balaban R, Fales H, Yang YM, Burg M.** 1986. Predominant active organic solutes in rat and rabbit enal medullas. J Biol Chem **261:**5872–5877.
18. **Bainton DF, Farquhar MG.** 1966. Origin of granules in polymorphonuclear leukocytes. J Cell Biol **28:**27–30.

19. **Ball EG, Cooper O.** 1960. Studies on the metabolism of adipose tissue: III. The response to insulin by different types of adipose tissue and in the presence of metabolites. J Biol Chem **235:**584–588.
20. **Bankir L, de Rouffignac C.** 1985. Urinary concentrating ability: insights from comparative anatomy. Am J Physiol **249:** R643–668.
21. **Baxter SG.** 1931. Nervous control of pancreatic secretion in the rabbit. Am J Physiol **96:**349–355.
22. **Bensley BA.** 1903. The structure of the glands of Brunner. Dicennial Publ Univ Chicago **10:** 279–329.
23. **Bensley BA.** 1948. Practical anatomy of the rabbit. Philadelphia: Blakiston.
24. **Bergstrom S, Danielsson H.** 1967. Metabolism of bile salts. Hand Physiol Sect. 6 **5:** 2391–2407.
25. **Bleeker WK, Mackaay AJ, Masson-Pevet M, Bouman, LN, Becker AE.** 1980. Functional and morphological organization of the rabbit sinus node. Circ Res **46:**11–22.
26. **Blount WP.** 1945. Rabbit ailments. London: Watmoughs Ltd.
27. **Boorman GA, Bree MI.** 1969. Diabetes insipidus syndrome in a rabbit. J Am Vet Med Assoc **155:**1218–1220.
28. **Botha GSM.** 1958. Histological observations on the gastroesophageal junction in the rabbit. J Anat **92:**441–446.
29. **Bremer J.** 1956. Species difference in the conjugation of bile acids with taurine and glycine. Biochem J **63:**507–513.
30. **Brewer NR.** 1937. Blood pressure responses to carbon monoxide poisoning. Am J Physiol **120:**91–95.
31. **Brewer NR.** 1990. Morphophysiology of the mammalian lung, IV. The pulmonary circulation. Synapse **23:**33–39.
32. **Brewer NR.** 1991. The morphophysiology of the rabbit kidney. Proc Inst Med Chic.
33. **Brody DA, Mirvis DM, Ideker RE, Cox JW Jr, Keller FW, Larsen RA, Bandura JP.** 1977. Relative dipolar behavior of the equivalent T-wave generator: quantitative comparison with ventricular excitation in the rabbit heart. Circ Res **40:**263–268.
34. **Callikan S, Ferre P, Pegorier JP, Girard JR, Marliss EB, Assan R.** 1979. Fuel metabolism in fasted newborn rabbits. J Dev Physiol **1:**267–281.
35. **Calvert DT, Knight CH, Peaker M.** 1985. Milk accumulation and secretion in the rabbit. Quart J Exp Physiol **70:**357–363.
36. **Cannon WB.** 1911. The importance of tonus for the movements of the alimentary canal. Arch Int Med **8:**417–426.
37. **Carlson AJ, Boyd TE, Pearcy JF.** 1922. Studies on the visceral sensory nervous system. XIII. The innervation of the cardia and lower end of the esophagus in animals. Am J Physiol **62:**14–41.
38. **Cheeke PR, Amberg JW.** 1973. Comparative calcium excretion by rats and rabbits. J Anim Sci **37:**450–454.
39. **Chew RM.** 1965. Water metabolism of mammals. Physiol Mammal **2:**43–178.
40. **Cizek LJ.** 1961. Relationship between food and water ingestion in the rabbit. Am J Physiol **201:**557–566.
41. **Clark ER, Clark EL.** 1934. Observations on living arteriovenous anastomosis as seen in transparent chambers introduced in the rabbit ear. Am J Anat **54:**229.
42. **Click RL, Joyner WL.** 1979. Reactivity of glomerular afferent and efferent arterioles in renal hypertension. Kidney Int **15:**109–115.
43. **Colatsky TJ, Tsein RW.** 1979. Electrical properties associated with wide intercellular clefts in rabbit Purkinje fibers. J Physiol **290:**227–252.
44. **Collewijn H.** 1981. The oculomotor system of the rabbit and its plasticity. Berlin: Springer-Verlag.
45. **Cooke AR.** 1967. The glands of Brunner. Hand Physiol **2:**1087–1095.
46. **Cornblath M, Schwartz R.** 1976. Disorders of carbohydrate metabolism in infancy. Philadelphia: Saunders.
47. **Cornelius CE.** 1980. Clinical biochemistry of domestic animals. New York: Academic Press.
48. **Cottrell DF.** 1984. Mechanoreceptors of the rabbit duodenum. Am J Ecp Physiol **69:**677–684.
49. **Cox RH.** 1978. Comparison of carotid artery mechanics in the rat, rabbit, and dog. Am J Physiol **234:**H280–H288.
50. **de Rouffignac C.** 1990. The urinary concentrating mechanism. In: Kinne RKH, editor. Urinary concentrating mechanism (comparative physiology). Basel: Karger. p 31–102.
51. **DeJong W, Van Der Meer P, Nieukoop AS, Huizer T, Stroeve RJ, Bos E.** 1990. Xanthine oxidoreductase activity in perfused hearts of various species, indcluding humans. Circ Res **67:**770–773.
52. **DeLuca HF.** 1974. Vitamin D: the vitamin and the hormone. Fed Proc **33:**2211–2219.
53. **Demuetter RC, Shreeve WW.** 1963. Conversion of DL-2^{14}C or -3^{14}C or pyruvate-2^{14}C to blood glucose in humans: effects of diabetes, insulin, tolbutamide and glucose load. J Clin Invest **42:**525–533.
54. **Dennis VW.** 1976. Influence of bicarbonate on parathyroid hormone induced changes in fluid absorption by the proximal tubiles. Kidney Int **10:**373–380.
55. **Dennis VW, Bello-Reus E, Robinson RR.** 1977. Response of phosphate transport to parathyroid hormone in segments of the rabbit nephron. Am J Physiol **233:**F29–F38.
56. **DeOme GC, Leffel EC.** 1972. Effect of cecotomy on digestive processes in the rabbit. J Anim Sci **35:**215.
57. **Dicker SE, Heller H.** 1945. The mechanism of water diuresis in normal rats and rabbits as analyzed by inulin and diodone clearances. J Physiol **103:**449.
58. **Dittmer DS.** 1961. Blood and other body fluids biological handbooks. Washington DC: FASEB Press.
59. **Dobyan DC, Magill LS, Friedman PA, Herbert SC, Bulger RE.** 1982. Carbonic anhydrase in the human kidney: a histochemical and immunocytochemical study. Anat Rec **204:**185–197.
60. **Dubos R.** 1968. The gastrointestinal microbiota of the so-called normal mouse. Carworth Europe Collected Papers **2:**11–17.
61. **Edwards AWT, Korner PI, Thornburn GD.** 1959. The cardiac output of the unanesthetized rabbit, and the effects of preliminary anesthesia, environmental temperature, and carotid occlusion. Quart J Exp Physiol **44:**309–321.
62. **Elias H.** 1959. A re-examination of the mammalian liver, II. The hepatic lobule and its relation to the vascular and biliary systems. Am J Anat **84:**379–456.
63. **Elias H.** 1959. A re-examination of the mammalian liver. I. Parenchymal architecture. Am J Anat **84:**311–333.
64. **Ellison SA.** 1967. Proteins and glycoproteins in saliva. Hand Physiol 2:531–559.
65. **Essex H.** 1965. Anaphylaxis and anaphylactoid reactions. In: Hamilton WF, editor. Handbook of physiology: circulation. Washington DC: American Physiological Society.
66. **Ettinger GH.** 1931. An investigation of the conditions in the pulmonary circulation of the guinea pig. Quart J Exp Physiol **21:**59.
67. **Faris IB, Iannos J, Jamieson GG, Ludbrook J.** 1980. The carotid sinus baroreceptor reflex in conscious rabbits. J Physiol **298:**321-331.
68. **Fishman AP.** 1963. Dynamics of the pulmonary circulation. In: Hamilton WF, editor. Handbook of physiology: circulation. Washington DC: American Physiological Society. p 1667–1743.
69. **Fleet IR, Peaker M.** 1978. Mammary function and its control at the cessation of lactation in the goat. J Physiol **279:**491–507.
70. **Flores NA, Davies RL, Sheridan DJ.** 1989. Microangiographic investigation of the effects of radiographic contrast media and hyperkalemia on coronary artery calibre in the rabbit. Quart J Exp Physiol **74:**181–195.
71. **Florey HW, Harding HE.** 1933. The functions of Brunner's glands and the pyloric end of the stomach. J Pathol Bacteriol **37:**431–453.
72. **Folkman J, Merler E, Abernathy C, Williams G.** 1971. Isolation of a tumor factor responsible for angiogenesis. J Exp Med **133:**275–288.
73. **Forsythe SJ, Parker DS.** 1985. Urea turnover and transfer to the digestive tract in the rabbit. Br J Nutr **53:**183–190.
74. **Fowler R.** 1955. An unexpected slow phase in the equilibration of body water content. Australas Ann Med **4:**128–134.
75. **Fox JG.** 1988. Biology and diseases of the ferret. Philadelphia: Lea and Fibiger.
76. **Friend DS.** 1964. The fine structure of Brunner's gland in the mouse. J Cell Biol **23:**32A–33A.
77. **Garg LC, Knepper MA, and Burg MB.** 1981. Mineralocorticoid effects on Na-K-ATPase in individual nephron segments. Am J Physiol **240:**F536-F544.
78. **Gautier P, Caroboeuf E.** 1980. The site gating in the ventricular conducting system of rabbit, dog, and monkey hearts. Experientia **36:**431–433.

79. **Gearz H, Smith GP.** 1982. Pancreatic glucacon and postprandial satiety in the rat. Physiol Behav **28:**312–322.
80. **Gelineo S.** 1964. Organ systems in adaptation: the temperature regulating system. Hand Physiol Sect **4:**259–282.
81. **Giamarco RA, Goldstein MB, Halperin JS, Hammeke MD, Richardson RM, Robson WL, Stinebaugh BJ, Halperin ML.** 1978. Collecting duct hydrogen ion secretion in the rabbit: role of potassium. J Lab Clin Med **91:**948–959.
82. **Godeaux J, Tonneson M.** 1949. Investigations into atropine metabolism in animal organisms. Acta Pharmacol Toxicol **5:**95–109.
83. **Goetsch E.** 1910. The structure of the mammalian esophagus. Am J Anat **10:**40.
84. **Gordon CJ, Heath JE.** 1986. Integration and central processing in temperature regulation. Ann Rev Physiol **48:**595–612.
85. **Gordon DR, Flasher S, Drury DR.** 1953. Size of the largest arteriovenous vessels in various organs. Am J Physiol **173:**270–281.
86. **Grantham JJ, Chonko AM.** 1991. Renal handling of organic anion and cations: excretion of uric acid. In: Brenner BM, Rector FC. The kidney. Philadelphia: Saunders. p 483–501.
87. **Greeley PO.** 1937. Pancreatectomy in rabbits. Proc Soc Exp Med Biol **37:**309.
88. **Grosser O.** 1927. Fruhentwicklung, eihautbildung, und placentation des menschen und des saugetiere. Munchen: JF Bergman.
89. **Gullans SR, Blumenfeld JD, Balaschi JA, Kaleta M, Brenner RM, Heilig CW, Herbert SC.** 1988. Accumulation of major organic osmolytes in rat renal inner medulla in dehydration. Am J Physiol **255(4 Pt 2):**F626-F634.
90. **Hamburger RJ, Lawson NL, Schwarz JH.** 1976. Response to parathyroid hormones in defined segments of proximal tubule. Am J Physiol **230:**286–290.
91. **Harris TM, Nance CS, Sheppart LB, Fox RR.** 1983. Evidence for an hereditary defect in taurine transport in the ciliary epithelium of an inbred strain of rabbits. J Inherit Metabolic Dis **6:**163–166.
92. **Haslewood GAD.** 1968. Evolution and bile salts. In: Handbook of physiology. Alimentary Canal. Sect 6, Vol 5. Washington (DC): American Physiological Society. p 2375–2390.
93. **Hayward JS.** 1961. The ability of the wild rabbit to survive conditions of water restriction. CSIRO Wildlife Res **6:**160–175.
94. **Heistad DD, Marcus ML, Gross PM.** 1978. Effect of sympathetic nerves on cerebral vessels in dog, cat, and monkey. Am J Physiol **235:**H544–H552.
95. **Hellstrom K, Sjovall J.** 1962. Turnover of deoxycholic acid in the rabbit. J Lipid Res **3:**297–404.
96. **Hering HE.** 1924. Sinus caroticus an der Ursprungstelle der carotis interna als ausgangsort eines hemmenden herzeflexes und einer depressorischen gefassreflexes. Munch Med Wsche **71:**701–704.
97. **Herndon JF, Hare EL.** 1953. Surgical removal of the cecum and its effect on digestion and growth in rabbits. J Nutr **57:**387–397.
98. **Heuper WC.** 1945. Ossified cartilage with ossified fat marrow in the aortic ring of the rabbit. Arch Pathol **39:**89–90.
99. **Hiraoka M, Kawano S.** 1987. Mechanisms of increased amplitude and duration of the plateua with sudden shortening of diasytolic intervals in rabbit ventricular cells. Circ Res **60:**14–26.
100. **Hirayama T, Folmerez P, Hanson R, Jonsson O, Pettersson S, Roberts D, Schersten T.** 1986. Effect of oxygen-free radicals on rabbits and human erythrocytes. Scand J Thorac Cardiovasc Surg **20:**247–252.
101. **Hoffman BF.** 1965. Arioventricular conduction in mammalian hearts. Ann N Y Acad Sci **127:**105–112.
102. **Hudson DG, Hull D.** 1975. Growth of adipose tissue in the fetal rabbit. Biol Neonate **27:**71–79.
103. **Hunt CE, Carlton WW.** 1965. Cardiovascular lesions associated with copper deficiency in rabbits. J Nutr **87:**385–393.
104. **Hunt CE, Carlton WW, Newberne PM.** 1970. Interrelationships between copper deficiency and dietary ascorbic acid in the rabbit. Br J Nutr **22:**565–573.
105. **Iino Y, Burg MB.** 1981. Effect of acid base status in vivo on bicarbonate transport by rabbit renal tubules in vitro. Jpn J Physiol **31:**99–107.
106. **Imai M.** 1984. Functional heterogeneity of the descending limbs of Henle's loop. II. Interspecies differences among rabbits, rats and hamster. Pfluger's Arch **402:**393–401.
107. **Inai M.** 1979. The connecting tubule: a functional division of the rabbit distal nephron segments. Kidney Int **15:**655–670.
108. **Ito S.** 1964. The surface coating of enteric micorvilli. Anat Rec **148:**294.
109. **Ito S.** 1965. The enteric surface coat on cat intestinal microvilli. J Cell Biol **27:**475–491.
110. **Iversen JO, Hoff GL, Yuill TM, Hanson RP.** 1972. Gastric lesions in the snowshoe hare. J Wildlife Dis **8:**7–9.
111. **Jain NC.** 1986. Schalm's veterinary hematology. Philadephia: Lee and Fibiger.
112. **Jomain-Baum M, Shcramm VL, Hanson RW.** 1976. Mechanism of 3-mercaptopicolinic acid inhibition of hepatic phosphoenolpyruvate carboxykinase (GTP). J Biol Chem **251:**37–44.
113. **Kaissling B, Kriz W.** 1979. Structural analysis of the rabbit kidney. Adv Anat Embryol Cell Biol **56:**1–121.
114. **Kaissling B, LeHir M.** 1982. Distal tubular segments of the rabbit kidney after adaptation to altered Na- and K-intake. Cell Tissue Res **224:**469–492.
115. **Kaplan BI, Smith HW.** 1935. Excretion of inulin, creatinine, xylose and urea in the normal rabbit. Am J Physiol **113:**354–360.
116. **Kardon MB, Peterson DF, Bishop VS.** 1974. Beat-to-beat regulation of heart rate by afferent stimulation of the aortic nerve. Am J Physiol **227:**598–600.
117. **Karemaker JM, Borst C, Schreurs AW.** 1980. Implantable stimulating electrode for baroreceptor afferent nerves in rabbits. Am J Physiol **239:**307–317.
118. **Kawato F, Kouno T, Harada Y, Makizumi S, Tsumuraya Y, Kishi Y, Takahashi K.** 1989. A scanning electron microscopic study on the arteriovenous anastomoses of the rabbit ear using corrosive resin casts. Kaibogaku Zasshi [Eng Abstr Jpn] **63:**185–195.
119. **Kennedy A.** 1965. The urinary excretion of calcium by normal rabbits. J Comp Pathol **75:**69–74.
120. **Kessler M, Bell WR.** 1980. Stimulation of fibrinogen biosynthesis: a possible functional role of fibrinogen. Blood **55:**40–47.
121. **Kirsner JB, Elchlepp JG, Goldgraber MB, Ablaza J, Ford H.** 1959. Production of an experimental ulcerative "colitis" in rabbits. Arch Pathol **68:**392–408.
122. **Kisch B.** 1953. The heart rate and ECG of small animals. Exp Med Surg **11:**117–130.
123. **Kivilaakso E, Fromm D, Silen W.** 1981. Effect of bile salts and related compounds on esophageal mucosa. Scand J Gastroenterol **67:**119–121.
124. **Klahr S.** 1971. Relation of renal gluconeogenesis to ammonia production in the rabbit. Am J Physiol **221:**69–74.
125. **Klassen CD, Plaa GL.** 1967. Species variation in metabolism, storage, and excretion of sulfobromophtlein. Am J Physiol **213:**1322–1326.
126. **Klassen CD, Plaa GL.** 1969. Plasma disappearance and biliary excretion of indocyanine green in rats, rabbits, and dogs. Tox Appl Pharmacol **15:**374–384.
127. **Knepper MA, Rector FC.** 1991. Urinary concentration and dilution. In: Brenner BM, Rector FC, editors. The kidney. Philadelpha: Saunders. p 445–482.
128. **Knox FG, Preiss J, Kim JK, Dousa TP.** 1977. Mechanism of resistance to the phosphaturic effect of parathyroid hormone in the hamster. J Clin Invest **59:**675–683.
129. **Kozma C, Macklin W, Cummins LM, Mauer R.** 1974. In: Weisbroth SH, Flatt RE, Kraus AL, editors. The biology of the laboratory rabbit. New York: Academic Press. p 5072.
130. **Kriz W, Bankir L.** 1988. A standard nomenclature for structures of the kidney. Am J Physiol **254:**F1–F8.
131. **Kruckenberg S, Kidd R.** 1989. Liver function test. In: Loeb WF, Quimby FW, editors. The clinical chemistry of laboratory animals. New York: Pergamon. p 309–319.
132. **Kulangara AC, Schechman AM.** 1962. Passage of heterologous serum proteins from mother into fetalc ompartments in the rabbit. Am J Physiol **203:**1071–1080.
133. **Kulwich R, Struglia L, Pearson PB.** 1953. The effects of coprophagy on the excretion of B-vitamins in the rabbit. J Nutr **49:**639–645.
134. **Lafontan M.** 1979. Inhibition of epinephrine-induced lipolysis in isolated white adipocytes of aging rabbits by increased alpha-adrenergic responsiveness. J Lipid Res **20:**208–216.

135. **Lamiere NH, Lifschitz MD, Stein JH.** 1977. Heterogeneity of nephron function. Ann Rev Physiol **39:**184.
136. **Land J.** 1981. The nutrition of the commercial rabbit. I. Physiology, digestibility, and nutrient requirements. Nutr Abstr Rev **51:**197–225.
137. **Larsson L, Horster M.** 1976. Ultrastructure and net fluid transport in isolated perfused developing proximal tubules. J Ultrastruct Res **54:**276–285.
138. **Lebus F.** 1971. Composition chimique du lait de lapine evolution au cours de la traite at el fontion du state de lactation. Ann Zootech **21:**185–191.
139. **Lelkes L, Chang CL.** 1987. Microbial dysbiosis in rabbit mucoid enteropathy. Lab Anim Sci **37:**757–763.
140. **Lendrum EC.** 1947. Anatomic features of the cardiac orifice of the stomach with special reference to cardiospasm. Arch Int Med **59:**474–511.
141. **Licois D, Mongin P.** 1980. An hypothesis on the pathogenesis of diarrhea in the rabbit based on the study of intestinal contents. Reprod Nutr Dev **20:**1209–1216.
142. **Lonnerholm G, Wistrand PJ.** 1948. Carbonic anhydrase in the human kidney: a histochemical and immunocytochemical study. Kidney Int **25:**886–898.
143. **Magee DF, Fragola LA, White TT.** 1965. Influence of parasympathetic innervation on the volume of pancreatic juice. Ann Surg **161:**605–607.
144. **Mancia G, Lorenz RR, Shepherd JT.** 1976. Reflex control of circulation by heart and lungs. Intern Rev Physiol **9:**111–144.
145. **Mangel A, Fahim M, van Breemen C.** 1981. Rhythmic contractile activity of the in vivo rabbit aorta. Nature **289:**892–894.
146. **Matsuki T, Cohen MV, Downey JM.** 1990. Free radical scavengers will preserve wall motion in the xanthin oxidase-deficient rabbit heart. Coronary Artery Dis **1:**383–390.
147. **McCuistion WR.** 1964. Rabbit mucoid enteritis. Vet Med **59:**815–818.
148. **McKinney JD, Burg B.** 1977. Bicarbonate transport by rabbit cortical collecting tubules. Effect of acid and alkali loads in vivo on transport in vitro. J Clin Invest **60:**766–768.
149. **McLean FC, Hastins AB.** 1935. The state of calcium in the fluids of the body. I. The conditions affecting the ionization of calcium. J Biol Chem **108:**322.
150. **Means GD, Burns JM.** 1988. Glucacon auto-immunization fails to stimulate food intake of growth in young rabbits. Comp Biochem Physiol A **91:**621–625.
151. **Mecheler KJH, Ingelfinger FJ.** 1969. Correlation of electrical surface potentials, intraluminal pressures, and nature of tissue in the gastroesophageal junction of man. Gastroenterology **52:**966–971.
152. **Mims LC.** 1979. Adaptive neogenesis in preterm and term rabbits. Pediatr Res **13:**241–245.
153. **Miura T, Downey JM, Ooiwa H, Ogawa S, Adachi T, Noto T, Shizukuda Y, Iimura O.** 1989. Progression of a myocardial infarction in a collateral flow deficient species. Jpn Heart J **30:**695–708.
154. **Moe R.** 1960. The ultrastructure of Brunner's glands of the cat. J Ultrastr Res **4:**58–92.
155. **Moir RJ.** 1968. Ruminant digestion and evolution. Hand Physiol **6:**2673–694.
156. **Morel F.** 1981. Sites of hormone action in the mammalian nephron. Am J Physiol **240:**F164.
157. **Munkacsi IM, Newstead JD.** 1985. The intrarenal and pericapsular venous system of kidneys of the ringed seal. Phoca hiopida J Morphol **184:**361–373.
158. **Nice LB, Katz HL.** 1936. Emotional leucopenia in rabbits. Am J Physiol **117:**575.
159. **Noer RJ.** 1943. The blood vessels of the jejunum and ileum: a comparative study of man and certain laboratory animals. Am J Anat **73:**293–333.
160. **Ogawa Y, Pincus G.** 1961. Further studies of progestin bioassay using the endometrial response in the rabbit. Endocrinology **68:**680–686.
161. **Ohno S.** 1985. Peroxisomes of the kidney. Int Rev Cytol **95:**131–162.
162. **Pairet M, Boutssou T, Ruckebusch Y.** 1986. Colonic formation of soft feces in rabbits: a role for endogenous prostaglandins. Am J Physiol **250:**G302–G308.
163. **Parks DA, Tan S, Evans RA, et al.** 1990. Uric acids: a physiologic inhibitor of xanthine oxidase [abstract] In: In search of physiological principles: the use of animal diversity and novel technology; 1990 Oct 6–10; Orlando (FL). Bethesda (MD): APS. Physiologist **33(4):**Abstract nr 64.5.
164. **Patterson TL.** 1933. Comparative physiology of the gastric hunger mechanism. Ann NY Acad Sci **34:**55–72.
165. **Peaker M, Taylor JC.** 1975. Milk secretion in the rabbit: changes during lactation and the mechanism of ion support. J Physiol **279:**491–507.
166. **Pfeiffer EW.** 1968. Comparative anatomic observations of the mammalian renal pelvis and medulla. J Anat **102:**321–331.
167. **Pollock S.** 1951. Slobbers in the rabbit. J Am Vet Med Assoc **190:**443–444.
168. **Powell RJ, Machiedo GW, Rush BF Jr, Dikdan G.** 1989. Effect of alpha-tocopherol on red cell deformability and survival in sepsis. Curr Surg **46:**380–382.
169. **Richardson RM, Goldstein MB, Stinebaugh BJ, Halperin ML.** 1979. Influence of diet and metabolism on urinary acid excretion in the rat and rabbit. J Lab Clin Med **94:**510–518.
170. **Richmond CR, Langhan WH, Trujillo TT.** 1962. Comparative metabolism of tritiated water by mammals. J Cell Comp Physiol **59:**4–53.
171. **Ridderstrale Y, Kashgarian M, Koeppen B, Giebisch G, Stetson D, Ardito T, Stanton B.** 1988. Morphological heterogeneity of the rabbit collecting duct. Kidney Int **34:**655–670.
172. **Roberts LA, Slocum GR, Riley DA.** 1989. Morphoplgical study of the innervation pattern of the rabbit sinoatrial node. Am J Anat **185:**74–88.
173. **Rogers PT.** 1915. Contributions of the physiology of the stomach. XX. The contractions of the rabbit's stomach during hunger. Am J Physiol **36:**183–190.
174. **Romer AS.** 1960. Vertebrate paleontology. Chicago: University of Chicago Press.
175. **Rosenfeld ME, Faggiotto A, Ross R.** 1985. The role of mononuclear phagocytes in primate and rabbit models of atherosclerosis. In: Proc. 4th Leiden Conference on Mononuclear Phagocytes. The Hague: Martinus Nijhoff. p 795–802.
176. **Rosival L, Navar LG.** 1983. Effects on renal hemodynamics of inra-arterial infusions of angiotensin I and II. Am J Physiol **245:** F181–F187.
177. **Rous P, Larimore LD.** 1920. The biliary factor in liver lesions. J Exp Med **19:**249–272.
178. **Rous P, McMaster PE.** 1919. A) Viscous activity of the gall bladder during biliary stasis. B) The determining factor in the causation of white stasis bile. Proc Soc Exp Med Biol **18:**159.
179. **Rozanski GD, Jalife J.** 1986. Automaticity in atrioventricular valve leaflets of rabbit hearts. Am J Physiol **250:**H397–H406.
180. **Ruckebusch Y, Phaneuf L-P, Dunlop R.** 1990. Physiology of small and large animals. Philadelphia: B.C. Decker. p 254-275.
181. **Russell RGG, Fleisch H.** 1968. The renal effects of thyrocalcitonin in the pig and in the dog. In: Taylor S, editor. Thyrocalcitonin and the C cell. London: Heineman.
182. **Saggerson ED, Evans CJ.** 1975. The activities and intracellular distribution of nicotinamide-adenine dinucleotide phosphate-malate dehydrogenase, phosphophenolpyruvate carboxykinase and pyruvate carboxylase. Biochem J **146:**329–332.
183. **Salako LA, Smith AJ, Smith RN.** 1971. The effect of porcine calcitonin on renal function in the rabbit. J Endocrinol **50:**485–491.
184. **Sandell JH, Masland RH.** 1989. Shape and distribution of an unusual retinal neuron. J Comp Neurol **280:**489–497.
185. **Schmidt-Nielsen B.** 1977. Role of the renal pelvis in the modification of the urinary concentration and composition. Fed Proc **36:**2493–503.
186. **Schmidt-Nielsen B, Schmidt-Nielsen K, Houpt TR, Jarnum SA.** 1956. Water balance in the camel. Am J Physiol **185:**185–194.
187. **Schneider R.** 1966. The longitudinal muscle component of the peristaltic reflex in the guinea pig isolated ileum. Br J Pharmacol **27:**387–397.

188. **Schonheyder HC, Maunsbach AR.** 1975. Ultrastructure of a specialized neck region in the rabbit nephron. Kidney Int **7:**145–153.
189. **Schwartz MM, Venkatachalam MA.** 1974. Structural differences in thin loops of Henle. Kidney Int **6:**193–208.
190. **Sercombe R, Lacombe P, Aubineau P, Mamo H, Pinard E, Reynier-Rebuffel AM, Seylaz J.** 1978. Is there an active mechanism limiting the influence of the sympathetic system on the cerebral vascular bed? Evidence for vasomotor escape from sympathetic stimulation in the rabbit. Brain Res **164:**81–102.
191. **Sharegh GR, Agus ZS.** 1982. Magnesium transport in the cortical thick ascending limb of Henle's loop of the rabbit. J Clin Invest **69:**759–769.
192. **Shelley MJ.** 1961. Gycogen reserves and their changes at birth. Br Med Bull **17:**137–143.
193. **Shreeve WW.** 1974. Physiological chemistry of carbohydrates in mammals. Philadelphia: Saunders.
194. **Siegl PKS, Morgan G, Sweat GS.** 1984. Response to amrinone in isolated cardiac muscles from cat, rabbit, and guinea pig. J Cardiovasc Pharmacol **6:**281–287.
195. **Simpson DP, Sherrard DJ.** 1969. Regulation of glutamine metabolism in vitro by bicarbonate ion and pH. J Clin Invest **48:**1088–1096.
196. **Smith HW.** 1951. The Kidney. New York: Oxford. p 535.
197. **Smith HW.** 1965. Observations in the flora of the alimentary tract of animals and factors affecting its composition. J Pathol Bacteriol **89:**95–102.
198. **Sommer JR, Johnson EA.** 1968. Cardiac muscle, a comparative study in Purkinje fibers and ventricular fibers. J Cell Biol **36:**497–526.
199. **Soodak RE, Simpson JL.** 1988. The accessory optin system of the rabbit. I. Basic visual response properties. J Neurophysiol **60:**2037–2054.
200. **Sowers JR, Sharp B, Levin ER, Golub MS, Eggena P.** 1981. Metaclopramide, a dopamine antagonist, stimulates aldosterone secretion in rhesus monkeys but not in dogs or rabbits. Life Sci **29:**2171–2176.
201. **Star RA, Burg MB, Knepper MA.** 1987. Luminal disequilibrium pH and ammonia transport in outer medullary collecting duct. Am J Physiol **252:**F1148–F1157.
202. **Steele TH.** 1976. Renal resistance to parathyroid hormone during phosphrus deprivation. J Clin Invest **58:**1461–1464.
203. **Steinhausen M, Endlich K, Wiegman DL.** 1990. Glomerular blood flow. Kidney Int **38:**769–784.
204. **Stinnett HO, Sepe FJ.** 1979. Rabbit cardiovascular responses during PEEP before and after vagotomy. Proc Soc Exp Med Biol **162:**485–494.
205. **Suki WN, Rouse D, Ng RCK, Kokko JP.** 1980. Calcium transport in the thick ascending limb of Henle: heterogeneity of junction in the medullary and cortical segments. J Clin Invest **66:**1004–1009.
206. **Szabo S, Kouraunakis P, Kovacs K, Tuchweber B, Garg BD.** 1974. Prevention of organomercurial intoxication by thyroid deficiency in the rat. Toxicol Appl Pharmacol **30:**175–184.
207. **Tarvydas H, Jordan SM, Morgan EH.** 1968. Iron metabolism during lactation in the rabbit. Br J Nutr **22:**565–573.
208. **Tisher CC, Madsen KM.** 1991. Anatomy of the kidney. In: Brenner BM, Rector FC, editors. The kidney. Philadelphia: Saunders. p 3–75.
209. **Toth LA, Krueger JM.** 1989. Hematologic effects of exposure to three infective agents in rabbits. J Am Vet Med Assoc **195:**981–986.
210. **Toyoshima K, Tandler B.** 1989. Dense-cured vesicles and unusual lamellar bodies in type III gustatory cells in taste buds of rabbit foliate papillae. Acta Anat (Basel) **135:**365–369.
211. **Trueta J, Barclay AE, Daniel PM.** 1947. Studies on the renal circulation. New York: Blackwell.
212. **Tschassownikow N.** 1926. Uber die struktur der Brunner's chen und pylorus-drusen und ihre beziehung zu einander. Anat Anz **61:**417–431.
213. **Turner KS, Powell DW, Carney CN, Orlando RC, Bozymski EM.** 1978. Intramural electrical potential difference in the mammalian esophagus in vivo. Gastroenterology **75:**286–291.
214. **Walter F.** 1877. Untersuchungen uber die wirkung der sauren auf den tiershen organisms. Arch Exp Pathol Pharmakol **7:**148–178.
215. **Watford M, Vinay P, Lemieux G, Gougoux A.** 1980. Inhibition of renal gluconeogenesis and phosphoenolpyruvate carboxykinase activity by 3-mercaptopicolinic acid. Can J Biochem **58:**440–445.
216. **Watford M, Vinay P, Lemieux G, Gougoux A.** 1980. The regulation of glucose and pyruvate formation from glutamate and citric acid-cycle itnermediates in the kidney cortex of rats, dogs, rabbits, and guinea pigs. Biochem J **188:**741–748.
217. **Weber WH, Vanderwatt JJ.** 1973. Cardiomyopathy in crowded rabbits. S Afr Med J **47:**1591–1595.
218. **Weisbroth SH, Flatt RE, Kraus AL.** 1974. The biology of the laboratory rabbit. New York: Academic Press.
219. **Welling LW, Welling DJ.** 1976. Shape of the epithelial cells and intercellular channels in the rabbit proximal nephron. Kidney Int **9:**385–394.
220. **Wheeler HO.** 1968. Water and electrolytes in bile. In: Handbook of physiology. Alimentary Canal. Sect 6, Vol 5. Washington (DC): American Physiological Society. p 2409–2431.
221. **Whitehouse RH, Grove JA.** 1956. Dissection of the rabbit. London: Unversity Tutorial Press.
222. **Widdowson EM.** 1985. Development of the digestive system. Am J Clin Nutr **41:**384–390.
223. **Williams RT.** 1967. The biosynthesis of conjugation and detoxication products. In: Bernfeld P, editor. Biogenesis of natural compounds. 2nd ed. New York: Pergamon Press. p 589–639.
224. **Winker GC.** 1988. Pulmonary intravascular macrophages in domestic animal species. Am J Anat **181:**217–234.
225. **Wolff SD, Balaban RS.** 1990. Regulation of the predominant renal medullary organic solids in vivo. Ann Rev Physiol **52:**727–746.
226. **Woodbury RA, Hamilton WF.** 1941. The effect of histamine on the pulmonary blood pressure of various animals with and without anesthesia. J Pharmacol Exp Therap **71:**293.
227. **Woodhall PR, Tisher CC, Simonton CA, Robinson RR.** 1978. Relationship between para-aminohippurate secretion and cellular morphology in rabbit proximal tubules. J Clin Invest **61:** 1320–1329.
228. **Wooley JG, Sebrell WH.** 1945. Niacin, an essential growth factor for rabbits fed a purified diet. J Nutr **29:**191–199.
229. **Yokoi Y.** 1964. Function of vascular counter current heat exchanger in pyrogen induced fever. Proc Soc Exp Med Biol **115:**1014–1017.
230. **York MA, Rufo GA, Ray PD.** 1980. Gluconeogenesis in rabbit liver: III. The influences of glucagon, epinephrine, and alpha and beta adrenergic agents on gluconeogenesis in isolated hepatozytes. Biochem Biophys Acta **632:**517–526.
231. **Zaleski J, Bryta J.** 1978. Effect of alloxan diabetes on gluconeogenesis and oreogenesis in isolated rabbit liver cells. Biochem J **176:**153–158.
232. **Zaleski J, Zeblocki K, Bryta J.** 1981. The stimulatory effect of alloxan diabetes on the gluconeogenesis from alanine and glutamine in rabbit hepatocytes. Int J Biochem **13:**713–720.
233. **Zizza F, Reeve EB.** 1958. Erroneous measurement of plasma volume in the rabbit by T-1824. Am J Physiol **194:**522–526.