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The Experimental Use of Syrian Hamsters

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INTRODUCTION

The Syrian hamster (*Mesocricetus auratus*) is a widely used experimental animal model. A recent fiscal-year report from the USDA indicates that 172498 hamsters were used in 2007. Although the hamster still makes a significant contribution to research and teaching, the number of hamsters utilized currently is well below their peak usage of over 500000 achieved during the 1980s (Hankenson and Van Hoosier, 2002). Much of this decline is likely attributable to the availability and widespread use of genetically engineered mice. Despite this decline, the hamster still provides key data for a variety of research areas. As such, this chapter will focus primarily on the most current research uses of the hamster. More classical uses will be covered only as they pertain to these current uses.

Hamsters possess unique anatomical and physiological features which make them desirable research models. Unlike other commonly used laboratory rodents, hamsters possess a cheek pouch which can be easily everted and examined in situ at both the gross and microscopic level (Hankenson and Van Hoosier, 2002). The hamster's relative size also allows for better visualization of certain biological systems including the respiratory and reproductive systems when compared to the mouse (Magers et al., 1995). Additionally, hamsters are relatively free of pathogens yet they are naturally susceptible to a wide range of experimental pathogens (Hankenson and Van Hoosier, 2002). Further, laboratory hamsters develop a variety of inherited diseases which display similarities to human conditions. Hamsters possessing some of these inherited traits are commercially available (Biobreeders Inc. Watertown, MA; Table 34.1). In addition to these benefits, hamsters are susceptible to a variety of carcinogens and develop tumors that other research animals less commonly develop. Furthermore, hamsters are susceptible to the induction of a variety of metabolic disorders through the use of dietary manipulations. Finally, the antagonistic nature of hamsters is utilized to study the effect of treatment on male aggressive and defensive behaviors.

TABLE 34.1 Inbred and Spontaneous Mutant Hamsters Currently Available and Their Uses in Research

Name	Research Use
Bio 1.5	Carcinogenicity and dental caries
Bio 14.6	Cardiomyopathy and muscular dystrophy
Bio 15.16	Carcinogenicity studies
Bio F1B	Diabetes and atherosclerosis
Bio HT	Hypertension
Bio To-2	Cardiomyopathy and muscular dystrophy

CANCER RESEARCH

Syrian hamsters display several unique characteristics that make them desired models for carcinogenesis studies. Specifically, they develop tumor types that other models, particularly the mouse, are less apt to develop. Further, they can be reliably infected with oncogenic and oncolytic viruses. This section details the most commonly used hamster models of cancer and carcinogenesis and highlights the key findings discovered in these models.

Pancreatic Adenocarcinoma

Pancreatic tumors of non-endocrine origin are particularly aggressive tumors with a poor prognosis in humans (Uchida et al., 2008). The most common anatomic form of this tumor is ductular adenocarcinoma. The Syrian hamster is used extensively to study this tumor. Most commonly, the tumors are induced by the administration of nitrosamines (particularly *N*-nitrosobis amine) as a single subcutaneous injection. The resulting tumor is both morphologically and biologically similar to human pancreatic ductal adenocarcinoma (Uchida et al., 2008). One of the limitations of this model is the prolonged time-course for tumor induction (as long as 51 weeks). This time-course can be expedited by giving multiple nitrosamine injections (Konishi et al., 1998). Additional limiting factors of the model are the incomplete penetrance of tumor formation even with multiple injections and the low rate of tumor metastasis (Konishi et al., 1998; Mizumoto et al., 1990). Environmental factors, including a choline-deficient diet, given in combination with nitrosamines produce tumors more rapidly and with a greater prevalence in both male and female hamsters (Mizumoto et al. 1988, 1989a, 1989b).

Current studies utilizing the carcinogen injection model focus on treatment and reduction of tumor development. Specifically, chemicals and biologics with the potential to prevent cancer can be given synchronously or shortly after carcinogen administration, and effectiveness in cancer reduction (both tumor size and prevalence) can be assessed phenotypically at specified time points. Utilizing this general scheme several potential anti-cancer compounds were identified, including dimethylamino-parthenolide, celecoxib, iNOS inhibitors, and melatonin (Ruiz-Rabelo et al., 2007; Takahashi et al., 2008; Yip-Schneider et al., 2008). Alternatively, studies can be carried out after induction to determine the efficacy of tumor treatment and metastasis prevention. This approach recently demonstrated that somatostatin analogs are able to decrease metastasis of pancreatic cancers (Kilian et al., 2009).

More recently, a transplantable cell line, PGHAM-1, was isolated from the pancreata of hamsters with

induced pancreatic cancer (Fukuhara et al., 2005). A variety of other biological behaviors can be induced with this transplantable model. Specifically, if the cell line is injected into the pancreas, hamsters develop pancreatic cancer which metastasizes to the liver whereas splenic injection induces direct metastasis to the liver, and intraperitoneal injection induces dissemination to the entire peritoneal cavity (Uchida et al., 2008). Therefore, this model can be used to study the primary disease, metastasis, and dissemination in a rapid fashion. An additional benefit of the transplant model is that it is characterized molecularly and is known to contain mutations of *k-ras*, *Vegf*, and matrix metalloproteinases similar to human pancreatic adenocarcinoma cells (Matsushita et al., 2001).

Respiratory Tract Tumors

Primary Lung Tumors

The two predominant types of lung cancer in humans are small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) (Koletsis et al., 2009; Powell et al., 2009). NSCLC are lung tumors which originate from diverse cell types but behave and are treated in similar fashions. In contrast, SCLC originates primarily from neuroendocrine cells of the respiratory tract (Lee et al., 1992). Both tumor types are associated with tobacco smoking in humans.

In hamsters, lung tumors are induced by carcinogen treatment and typically result in NSCLC. One method to induce lung tumors is to inject the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) subcutaneously (Sunday et al., 1995). Multiple injections must be given over a prolonged (6 months or longer) time course. Modifications to this induction protocol include the use of hyperoxia in conjunction with the carcinogen treatment (Oreffo et al., 1993). Presumably, the addition of hyperoxia increases the potential for free-radical damage to DNA of the lung tissue. The NNK model displays molecular characteristics of human NSCLC including mutations in the *k-ras* gene (Oreffo et al., 1992, 1993). A thorough immunohistochemical characterization of both the chemical model and the chemical plus hyperoxia model indicates that both experimental paradigms induce similar lung lesions that display strong similarity to human NSCLC at the protein level (Sunday et al., 1995).

Upper Airway Tumors

Upper airway tumors occur in the larynx, trachea, or pharynx. The primary risk factors for development of these tumors are smoking and chronic alcohol consumption; however, other environmental and genetic factors may contribute to the disease (Spitz, 1994).

The hamster is susceptible to tumors of the upper airways. These tumors are induced by inhalation or topical application of carcinogens with or without the addition of co-carcinogenic stimuli (Estensen et al., 2007; Homburger et al., 1979; Moon et al., 1992a, 1992b). A reported limitation of topical carcinogen application models is the lack of reproducibility among different labs (Estensen et al., 2007). It is unclear why various labs are unable to faithfully reproduce the cancer phenotype using the same protocols; however, one possibility is that because the hamsters came from different sources, they may be genetically different. To overcome this limitation, a recent publication describes combining the administration of N-methylnitrosourea (MNU) with direct wounding of the tissue (Estensen et al., 2007). The experimental design includes two tracheal wounding procedures done under general anesthesia. The trachea is gently abraded using a curette and this abrasion is coupled with six applications of MNU using a gavage needle. The induction of the wound induces epithelial proliferation which acts epigenetically in conjunction with the genotoxic mutagen to promote carcinogenesis. A benefit of this model is the coinduction of esophageal tumors which mimics the epidemiological linkage of these two tumor types in human smokers (Wattenberg et al., 2004). The model can be altered to incorporate preventative and post-induction treatments. Utilizing this paradigm, difluoromethylornithine (DFMO; a mitosis inhibitor) and 5-fluorouracil (5-FU; a DNA replication inhibitor) treatments were both found to reduce the prevalence of tumor formation in hamsters (Wattenberg et al., 2004).

Oral Carcinogenesis

Oral squamous cell carcinoma (OSCC) is a common cancer of humans and generally carries a poor prognosis (Vairaktaris et al., 2008a, 2008b). Primary risk factors for the development of OSCC include tobacco and alcohol use, but other genetic and environmental factors contribute as well (Williams, 2000). The hamster cheek-pouch carcinogenesis model is one of the most accepted animal models to study oral tumor formation and progression (Vairaktaris et al., 2007, 2008a, 2008b). Carcinogens, most notably 7,12-dimethylbenz(a)anthracene (DMBA), administered by repeated topical application to the buccal pouch, induces carcinomas rapidly (~14 weeks) (Vairaktaris et al., 2008b). The DMBA administration technique is simple and involves anesthetizing the hamsters and brushing the desired carcinogen onto the buccal surface of the cheek pouch. Importantly, oncogenesis can be assayed in vivo or the transformed cells can be grown ex vivo (Wong et al., 1988).

Tumor formation and progression in the hamster cheek pouch occurs in a predictable, reproducible stepwise fashion. First, hyperkeratosis develops followed

rapidly by hyperplasia and dysplasia. Finally, these lesions progress to invasive carcinomas (Vairaktaris et al., 2008b). Cellular and molecular alterations that occur during these predictable stages of tumorigenesis are extensively characterized (Vairaktaris et al., 2007, 2008b). The cellular and molecular alterations in the hamster display many similarities to human OSCC. Early in the disease, tyrosine kinase receptors are highly expressed in hamsters similar to the increase of the ErbB2 tyrosine kinase noted in humans (Werkmeister et al., 2000). Additionally, the oncogenes p53 and c-myc are highly expressed early in hamster tumorigenesis and there is a loss of expression of the p16 tumor suppressor gene during the early dysplastic stage (Papakosta et al., 2006; Vairaktaris et al., 2007). More recently, the microRNA expression profile of the DMBA-treated hamster cheek pouch has been analyzed and compared to normal cells. Treated cells display a unique microRNA profile distinct from normal tissue (Yu et al., 2009). These data imply that microRNA may play a role in the formation and progression of hamster cheek pouch tumors. The similarities of these new data to the human disease are not yet known.

A key advantage of the hamster cheek pouch carcinogenesis model is the predictable nature of tumor progression. Because of this predictability, the hamster model is also utilized to analyze various treatments and preventatives which may be given either concurrently with induction or at specified points during tumorigenesis (Shklar, 1999; Sood et al., 2005). Since the hamster cheek pouch undergoes a predictable pathway of induced oncogenesis, these studies can be accurately timed to the appropriate tumor stage or pre-cancerous lesion. A more recently described advantage of the hamster model is the isolation of buccal pouch stem cells, which can be studied *in vitro* and may provide data on novel treatments (Huang et al., 2009).

SV40 Tumor Induction

Simian vacuolating virus 40 (SV40) is a polyomavirus naturally occurring in macaques that was introduced into humans via contaminated polio vaccines (Pershouse et al., 2006; Rollison et al., 2004). The role of SV40 in human cancers has a long and controversial history. Large epidemiological studies tracking infected humans indicate no link between the agent and cancer (Rollison et al., 2004). Proponents of the link between SV40 and cancer state that the true prevalence of SV40 in the human population is not known, and therefore, an accurate epidemiological assessment cannot be made (Pershouse et al., 2006). Detailing the controversies surrounding the role of the SV40 virus in human tumors is beyond the scope of the current chapter. However, the hamster figures prominently into the data detailing the oncogenic potential of SV40.

Hamsters injected with SV40 develop a variety of different tumors depending on the route of inoculation and the age of hamsters at the time of inoculation. Tumor formation is highest in newborn hamsters and decreases progressively with age (Cicala et al., 1993). Local fibrosarcomas develop with subcutaneous injection of virus, even when given at a low dose in newborn hamsters. In contrast, adults develop fibrosarcomas only when given a high dose of virus (Allison et al., 1967; Cicala et al., 1993). Intravenous inoculation of young hamsters produces a variety of tumors including leukemia, lymphoma, and a variety of sarcomas (Cicala et al., 1993; Diamandopoulos and McLane, 1972). Finally, mesotheliomas develop when hamsters are injected with virus into the heart, peritoneum, or pericardium (Cicala et al., 1993). SV40 viral infection can therefore be utilized to analyze a variety of tumor types using the hamster model.

Recent studies utilizing the hamster lend further evidence to support the hypothesis that SV40 may play a role in human carcinogenesis. Hamsters that are infected with a non-oncogenic SV40 virus strain or a low dose of asbestos, fail to develop tumors. In contrast, when sub-oncogenic doses of the two agents are given together a large percentage of hamsters (90%) develop tumors (Kroczyńska et al., 2006). Additionally, these results are reproducible in *in vitro* cell-culture systems. These data imply that, at least in the hamster, SV40 and asbestos can act as co-carcinogens.

The role of SV40 in human cancers remains highly controversial. However, the hamster model provides an excellent way to prospectively test these hypotheses. Even if SV40 plays no role in human tumorigenesis, much can still be learned from the hamster model regarding how viral agents transform mammalian cells. For example, a recent study demonstrates that differences in the SV40 regulatory region lead to differences in tumor induction in the hamster model (Sroller et al., 2008). These new data provide evidence that various strains of virus possess pro-oncogenic factors and these data argue that epidemiological studies in humans should account not merely for the presence or absence of SV40, but rather for the type of SV40 present.

Estrogen-Dependent Renal Tumors

Exogenous estrogen therapy in post-menopausal women decreases the risk of developing both osteoporosis and coronary artery disease; however, it also increases the risk for development of breast cancer and endometrial adenocarcinoma in this population (Sartwell et al., 1977; Stampfer et al., 1991). The benefits and limitations of the use of estrogen therapy in postmenopausal women remains an active area of research and debate. Animal models of estrogen-induced tumorigenesis

provide valuable mechanistic data to optimize estrogen therapy.

The Syrian hamster is a valuable model to study the effects of exogenous estrogenic compounds on tumor development. The administration of estrogens induces renal tumors in 100% of male hamsters in a predictable fashion (Li and Li, 1996; Liehr, 1997). Most commonly, estrogens are administered to hamsters in the form of slow-release subcutaneous implants which maintain constant levels in the blood (Debauve et al., 2006). In addition to in vivo studies utilizing the estrogen injection or implantation hamster model, HKT-1097 cell-lines generated from this model can be studied in vitro (Laurent et al., 1999).

A wealth of mechanistic data on the tumorigenic potential of estrogenic compounds has been generated utilizing the hamster model. Specifically, administration of a variety of natural and synthetic estrogenic compounds demonstrates that tumorigenesis occurs with some estrogenic compounds but not others (Liehr, 1997; Liehr et al., 1983, 1987a, 1987b). These data led to the hypothesis that tumorigenic estrogens mediate carcinogenicity, at least in part, through their metabolic breakdown products (Liehr, 1997). In particular, estrogen is broken down to 4-hydroxyestrogen, a catecholesterogen, in the hamster kidney (Dwivedy et al., 1992; Liehr, 1997). This intermediate can be further broken down into quinones which cause DNA damage by forming DNA adducts. This pathway, initially characterized in the hamster, was later identified in women with breast cancer. Specifically, the "normal" breast tissue of women with breast cancer displays higher levels of quinones when compared to unaffected controls (Li et al., 1994; Rogan et al., 2003). The estrogen receptor may be actively involved in tumor formation by shuttling quinone directly to nuclear DNA (Bolton and Thatcher, 2008).

Aside from the ability of quinones to directly damage DNA, quinone production results in the formation of reactive oxygen which can also cause DNA damage (Li et al., 1994; Liehr, 1997). Since the breakdown products of estrogen can damage DNA (mutation), and estrogen itself can promote cell growth (proliferation), all of the necessary components of carcinogenesis are present in the estrogen-treated hamster kidney (Liehr, 1997). The administration of some estrogenic compounds does not damage DNA because toxic metabolic byproducts are not generated (Bhat et al., 2003). Cancer induction with these compounds can be rescued by inducing oxidative stress while administering these normally non-oncogenic estrogens. This finding highlights the need for both the proliferative and the DNA-damaging aspects of estrogen to produce tumors. The hamster model may facilitate development of novel, non-DNA-damaging, estrogens which could provide the benefits of estrogenic therapy without the increased risk of cancer.

Oncolytic Viruses

The use of oncolytic adenoviruses holds promise as a future cancer treatment in humans. These adenoviruses kill tumor cells as part of their normal lytic replication cycle (Thomas et al., 2006a). The prospective in vivo study of these viruses is hampered by the lack of animal models that permit the replication of human adenoviruses (Hjorth et al., 1988; Thomas et al., 2006a). However, the hamster can be infected with human adenoviruses via intranasal instillation (Hjorth et al., 1988). In addition, permissive hamster cancer cell lines are available for assessing tumor suppression (Bortolanza et al., 2007; Thomas et al., 2006a). Notably, the Syrian hamster pancreatic carcinoma cell line (SHPC6) is highly permissive for human adenovirus replication (Spencer et al., 2009).

Thomas and colleagues recently developed a step-wise, reproducible hamster model to study the efficacy of adenoviral vectors in tumor therapy (Thomas et al., 2006b). The investigators injected immortalized tumor cells into the flanks of hamsters. After tumors developed, hamsters were inoculated with adenovirus into the respiratory tract. Tumor reduction at both the primary site, and the site of metastasis, was then analyzed. The investigators found that adenovirus inhibits primary tumor growth and metastasis and may promote survival (depending on tumor type injected). The virus is capable of replicating in the liver, lungs, and tumor tissues of the hamster following instillation and distribution in the blood (Thomas et al., 2006b). This experimental paradigm can be expanded to examine the treatment of a variety of tumors in the hamster and potential toxicities associated with the use of these viruses (Dhar et al., 2009; Lichtenstein et al., 2009). A further modification of this method is immunosuppression of hamsters with cyclophosphamide which allows for sustained adenoviral replication and oncolysis (Thomas et al., 2008). The hamster provides a valuable experimental model to evaluate the potential benefits, limitations, and strategies of this novel treatment modality.

METABOLIC DISEASES

Metabolic diseases are an area of great biomedical concern. Although all these diseases may occur independently of one another, they often present with a variety of overlapping clinical signs. Like humans, the hamster is highly susceptible to metabolic diseases and there are similar overlaps in the signs that they develop (Ginsberg, 1996; Gotto, 1992; Laakso, 1996; Lamarche and Lewis, 1998). Therefore, the hamster is an excellent animal model to study metabolic diseases of humans.

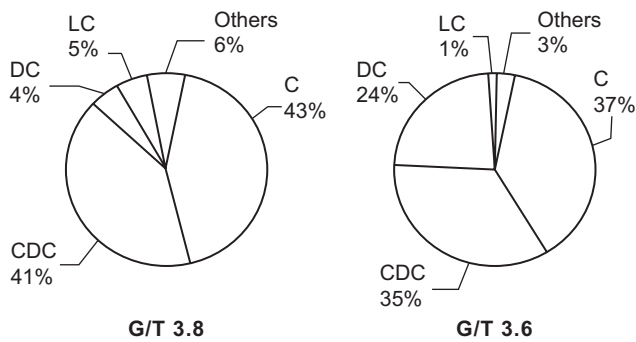


FIGURE 34.1 Distribution of different bile acids in vesicular bile of hamsters (left) and humans (right). The ratio of glyco- and tauro-conjugated bile acids is very similar in both species. C, cholic; CDC, chenodeoxycholic; DC, deoxycholic; LC, lithocholic acid. Modified from Combettes-Souverain et al. 2002, with permission from Elsevier Limited.

Cholesterol Gallstones

Cholesterol cholelithiasis is a significant health problem worldwide. The prevalence of this condition is three times higher in women than in men and increases regularly with age (Capron, 1994). The Syrian hamster is commonly used as a model for this condition which can be induced by excess dietary cholesterol (Cohen et al., 1989; Trautwein et al., 1999) or sucrose (Khallou et al., 1991a). The metabolism of cholesterol in the hamster is similar to humans (Khallou et al., 1991b). The nature and composition of hydrophobic bile salts and the ratio of taurine- and glycine-conjugated bile salts are similar in hamsters and humans (Figure 34.1) (Combettes-Souverain et al., 2002; Hardison, 1983; Singhal et al., 1983). In earlier studies, gallstones were induced in Syrian hamsters by feeding a fat-free glucose-rich diet (Dam, 1971). Diet models have evolved to include elevated levels of butterfat (Cohen et al., 1992; Hayes et al., 1992; Holzbach, 1984). In hamsters, the butterfat-diet induces a high cholesterol/phospholipid ratio in bile which promotes cholesterol cholelithiasis. In contrast, diets rich in safflower oil induce phospholipid secretion and reduce the lithogenicity of bile, thereby inhibiting cholesterol gallstones (Ohshima et al., 1996a).

The Syrian hamster displays significant gender differences in the basal rate of hepatic sterol synthesis which is several-fold higher in females fed a regular chow diet as compared to age-matched males on the same diet (Spady et al., 1983). In contrast to humans, female hamsters are less susceptible to gallstones because they maintain more favorable biliary lipid and bile acid profiles (predominantly glycocholate) characterized by lower molar percentages of cholesterol and chenodeoxycholate (Ayyad et al., 1993; Trautwein et al., 1999). Dietary administration of androgens to female hamsters on a lithogenic diet (0.3% cholesterol) induces

cholesterol gallstones at a comparable rate to induction in males fed a similar diet. In these androgen-treated, cholesterol-fed female hamsters, chenodeoxycholate increases while cholate decreases (Ayyad et al., 1995). Furthermore, castrated male hamsters on the lithogenic diet do not form cholesterol gallstones, and maintain a higher ratio of biliary cholate to chenodeoxycholate as compared to uncastrated males (Ohshima et al., 1996b).

Male LPN hamsters (bred at Laboratoire de Physiologie et de la Nutrition, France) are highly susceptible to cholesterol gallstones (~70%) induced by a low-fat high-sucrose diet, whereas commercial Janvier (JAN) hamsters on a similar diet do not develop gallstones (Boehler et al., 1999; Combettes-Souverain et al., 2002; Ferezou et al., 2000). In LPN hamsters, the sucrose-rich lithogenic diet causes an increase in biliary cholesterol and phospholipid. A cholesterol-enriched diet results in hypercholesterolemia, increased liver cholesterol, and reduced cholesterologenesis along with expression of the LDL receptor in both LPN and JAN hamsters (Souidi et al., 2001). In both strains, the cholesterol-enriched diet increases the cholesterol content in both the LDL and HDL fractions of sera (Souidi et al., 2001; Woollett et al., 1997). Further, excess dietary cholesterol leads to a reduction of CYP7A (the rate-limiting enzyme in the classical pathway of cholesterol breakdown to bile salts) activity and transcription in both LPN and JAN hamsters (Souidi et al., 2001). There is a concurrent stimulation of sterol 27-hydroxylase (CYP27) and oxysterol 7 α -hydroxylase (CYP7B), enzymes involved in the alternative bile-salt pathway of cholesterol conversion to bile salts in both LPN and JAN hamsters. Compared with LPN hamsters, hypercholesterolemia in JAN hamsters is associated with hepatomegaly and fatty liver but only modest hypertriglyceridemia. Interestingly, after cholesterol feeding for 5 weeks, neither LPN nor JAN hamsters develop cholesterol gallstones, perhaps because of the upregulation of the alternative pathway of bile-salt synthesis (Souidi et al., 2001).

Differences in gallstone formation also exist between commercially available hamsters. Charles River Laboratory hamsters display the highest cholesterol saturation of bile on low-cholesterol diets and display a correspondingly high prevalence of stones (64%) when challenged with a high-cholesterol diet (Trautwein et al., 1993). Biobreeder F1 hamsters also commonly form gallstones (58%) when challenged with cholesterol-enriched diets. In contrast, Harlan Sprague-Dawley hamsters display a low prevalence (23%) of gallstones when fed the same diet (Trautwein et al., 1993). These findings highlight the role of genetics in both hamsters and humans in this complex polygenic disease. One drawback of this study is that the sex of these animals was not described and therefore the data are difficult to evaluate thoroughly.

Diabetes Mellitus

Diabetes mellitus is a disease of metabolic dysregulation including abnormal glucose metabolism due to derangement of insulin secretion and development of insulin resistance. Diabetes is often accompanied by dyslipidemia (high LDL, VLDL, and chylomicron levels, and a low level of HDL) and elevated risk for the development of atherosclerosis (Ginsberg, 1996; Gotto, 1992; Laakso, 1996; Lamarche and Lewis, 1998).

An animal model of pre-diabetic insulin resistance, the fructose-fed Syrian hamster, is employed to investigate mechanisms mediating overproduction of VLDL in the insulin-resistant state. Feeding fructose for 7 days causes hyperinsulinemia and hyperlipidemia in hamsters with absence of overt hyperglycemia (Taghibiglou et al., 2002). Fructose feeding for a 2-week period induces significant hypertriglyceridemia and hyperinsulinemia (Taghibiglou et al., 2000). Plasma hepatic lipase activity, and hepatocyte hepatic lipase concentration and mRNA levels are increased in these hamsters (Lewis et al., 2004). Activation of farnesoid X receptor (FXR) by the addition of chenodeoxycholic acid in high-fructose-diet-fed hamsters reduces plasma triglyceride and cholesterol concentrations, mainly by decreasing de novo lipogenesis and hepatic secretion of triglyceride-rich lipoproteins (Bilz et al., 2006). These studies provide evidence that stimulation of FXR could decrease the risk of hyperlipidemia in the diabetic state.

Diabetes can be experimentally induced in hamsters by different approaches, such as dietary modifications or use of chemical agents. Chemical agents such as alloxan or streptozotocin (STZ) are commonly used to induce diabetes in animal models. To induce chronic diabetes in hamsters, STZ is more effective and reliable when compared to alloxan (Phares, 1980). STZ depletes nicotinamide adenine dinucleotide (NAD) in pancreatic β -cells leading to necrosis (Ar'Rajab and Ahren, 1993). Furthermore, type 2 diabetes can be induced by administration of STZ to hamsters on a high-fat diet, resulting in an increase in serum lipid profile, fasting blood glucose, and fasting plasma insulin level (Zhu et al., 2007). Another described method to induce type 2 diabetes in hamsters is to inject nicotinamide intraperitoneally 15 minutes before administration of STZ (Fararh et al., 2002). Nicotinamide provides partial protection against the beta-cytotoxic effect of STZ resulting in partial (40%) preservation of pancreatic insulin stores (Masiello et al., 1998). Dietary modifications alone, such as feeding high-fat (15%) diets containing modest cholesterol (0.12%) to hamsters, induce type 2 diabetes as well as obesity, hyperinsulinemia, hyperleptinemia, hypercholesterolemia, and hypertriglyceridemia (van Heek et al., 2001). A combined hyperlipidemia and diabetes hamster model is induced by feeding a fat-rich diet (3% cholesterol and

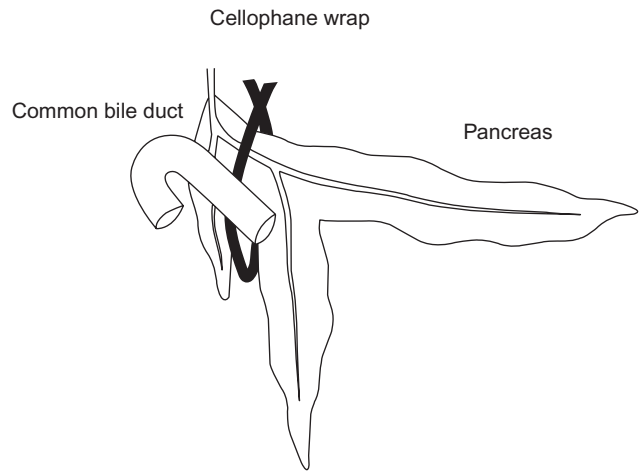


FIGURE 34.2 Displayed is the pancreas and common bile duct. Cellophane (black) is wrapped around the head of the pancreas to induce islet neogenesis. Modified from Rosenberg 1998, with permission from Wiley InterScience.

15% butter fat) and a single IP injection of STZ. These animals exhibit pathobiochemical changes characteristic of both diabetes and hyperlipemia and show an earlier and more severe induction of diabetic and hyperlipidemic changes compared to either STZ or high-fat diet alone (Simionescu et al., 1996).

Albino-panda-albino (APA) hamsters develop diabetes with nephropathy following STZ injections (Inenaga et al., 2002). The STZ-induced diabetic APA hamster is a good model of human diabetic nephropathy because progressive renal lesions are a common component of this model. In addition to renal lesions, the diabetic APA hamster also develops coronary lesions and is an excellent model to investigate the etiology and pathogenesis of aortic dissection accompanying diabetes mellitus in humans (Horiuchi et al., 2005).

Hamsters can be utilized to study islet neogenesis, which is the new formation and differentiation of pancreatic islets. This process is induced in Syrian hamsters by wrapping the head of the pancreas with cellophane tape and is efficient in reversing induced diabetes in hamsters (Figure 34.2) (Rosenberg et al., 1983, 1988). Islet neogenesis-associated protein (INGAP) is involved in the control of islet development and growth (Pittenger et al., 1992). INGAP is identified in both endocrine and exocrine pancreatic cells of normal hamsters, consistent with findings in humans (Flores et al., 2003). The hamster provides a model to understand the potential therapeutic application of islet neogenesis in the treatment of diabetes in humans.

Atherosclerosis

Atherosclerosis is a fibroproliferative disease of the arterial intima caused by the retention of modified

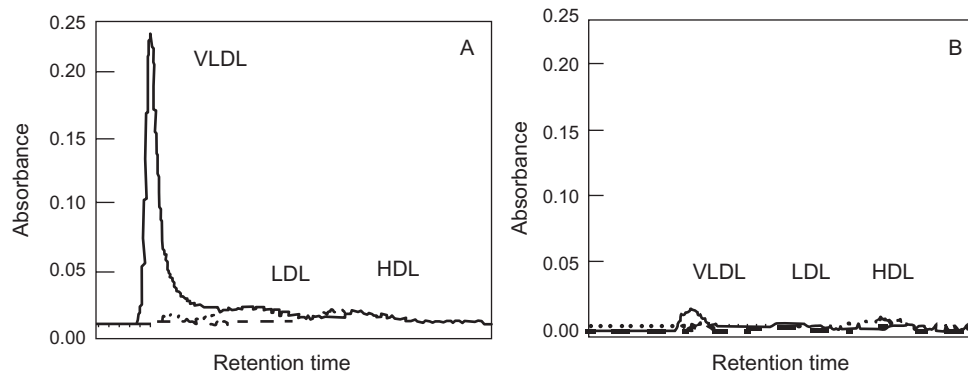


FIGURE 34.3 Distribution of lipoproteins (by FPLC system) in fasting plasma samples from F1B (A) and Syrian (B) hamsters. The low-density fractions of plasma cholesterol in F1B hamsters on a fish oil diet (–) was significantly higher than the Syrian hamsters on a similar diet. Both groups of hamsters had a comparable lipoprotein profile when fed monounsaturated-fatty-acid-rich (–) and N6:N3 fatty acid ratio of ~5 (...) diets. From Cheema and Cornish, 2007, with permission from BioMed Central.

low-density lipoproteins and by hemodynamic and redox stresses (Hayden and Tyagi, 1998, 2000). Hamsters are a good animal model to investigate cholesterol metabolism and atherosclerosis because they possess similar lipid metabolism to humans (Asami et al., 1999; Foxall et al., 1992). As in humans, the main plasma cholesterol carrier in hamsters is LDL (Sullivan et al., 1993). The hamster LDL receptor gene shows strong sequence and structural similarities to the human gene (Bishop, 1992). Unlike mice and rats, which lack cholesterol ester transfer protein, hamsters exhibit all enzymatic pathways in lipoprotein and bile metabolism that are present in humans (Bishop, 1992). The low basal rates of bile acid and cholesterol synthesis, coupled with a lack of CYP7A induction by cholesterol, render the hamster much more sensitive than the rat or mouse to the cholesterolemic effects of excess dietary cholesterol (Horton et al., 1995). In contrast to mice and rats, apolipoprotein (apo) B-48 is exclusively of intestinal origin in hamsters and humans and apoB-100 is exclusively of hepatic origin (Arbeen et al., 1992; Ebara et al., 1994).

Hamsters develop atherosclerosis in a predictive manner in response to dietary manipulation and the vascular changes accompanying the development of atherosclerotic plaques are similar to those encountered in humans (Mitchell and McLeod, 2008; Simionescu et al., 1993; Wissler, 1991). Hypercholesterolemic (0.05% cholesterol and 10% coconut oil) diet-induced atherosclerosis in susceptible hamsters is confined initially to the inner curvature of the aortic arch. Atherogenesis in this region is characterized by the infiltration of monocytes, which become lipid-filled foam cells (Kowala et al., 1991a). Male hamsters on a hyperlipidemic diet (3% cholesterol and 15% butter fat) develop coronary atherosclerotic lesions which are very similar to lesions seen in humans (Sima et al., 1990). Interestingly, hyperglycemia alone in hamsters induces atherosclerotic

lesions in the coronary arteries, aortic arch, and aortic valves, implying that the hyperglycemic hamster could provide a model of diabetes-induced atherosclerosis (Sima et al., 1997).

Albino-panda-albino (APA) hamsters (previously described in the diabetes section of this chapter) develop atheromatous lesions in the aortic arches and show signs of hypercholesterolemia and hypertriglyceridemia with an increased LDL fraction and a decreased HDL fraction following injection of STZ (Han et al., 1992; Kume et al., 1995; O'Brien et al., 1994). The deposition of ApoE and advanced glycation end-products in the atheromatous lesions of these hamsters are similar to humans with atherosclerosis (Kume et al., 1995; O'Brien et al., 1994). The APA hamster, therefore, is a good animal model to study both diabetes and atherosclerosis. Since these conditions are often co-morbidities in humans, this model could provide valuable data to understand the pathogenesis of these diseases and test novel treatments.

The Bio F1B hamster is highly susceptible to diet-induced atherosclerosis. This strain develops aortic atherosclerotic lesions even at low (0.05%) dietary cholesterol concentrations (Kowala et al., 1991b). F1B hamsters on a 20% fish oil diet developed markedly elevated plasma cholesterol and cholesterol ester concentrations compared to wild-type Syrian hamsters (Figure 34.3) (Cheema and Cornish, 2007). Wild-type Syrian hamsters typically display increases in both LDL and HDL cholesterol in response to an atherogenic diet (Hayes et al., 1992). In contrast, F1B hamsters develop highly elevated LDL-cholesterol concentrations without appreciable alterations of HDL-cholesterol (Kowala et al., 1991a).

Ovariectomized hamsters are used to study postmenopausal hypercholesterolemia (Sohn et al., 1999). In humans, there is an association between postmenopausal hormone deficiency and the increased risk for

cardiovascular disease (Sohn et al., 1999). Similar to postmenopausal women, ovariectomized hamsters experience an increase in serum cholesterol and atherosclerosis. This increase occurs even without feeding a high-cholesterol or high-fat diet (Lucas et al., 2003; Sohn et al., 1999).

Hypercholesterolemic hamsters are also a good model of peripheral arterial disease. Angiogenesis in response to femoral artery-induced hindlimb ischemia is reduced in hypercholesterolemic hamsters (Caron et al., 2004). Feeding a cholesterol-rich diet to hamster causes a chronic angiogenic disorder both at the macro- and micro-vascular levels, mimicking the conditions seen in humans with peripheral arterial disease (Caron et al., 2004). This model is also utilized to study the potency of therapeutic gene transfer to overcome revascularization defects in these patients (Caron et al., 2004).

NON-CANCEROUS RESPIRATORY DISEASES

Syrian hamsters possess characteristics that make them ideal models for studying human non-cancerous respiratory diseases. Specifically, researchers can induce respiratory diseases in hamsters that closely resemble similar human diseases. This section outlines common inducible hamster models for human non-cancerous respiratory disease and describes scientific and medical advances made using these models.

Smoke Inhalation

The negative effects of cigarette smoking on the cardiovascular and respiratory systems in humans are well known (Alberg, 2008; Fagerstrom, 2002). Over the past 10 years, an active area of research focuses on the consequences of smoking on the female reproductive tract (Rogers, 2008, 2009). Epidemiological studies demonstrate that women who smoke cigarettes experience increased rates of reproductive problems, including delay to conception, ectopic pregnancies, lower birth weights, and spontaneous abortions (DiCarlantonio and Talbot, 1999; Magers et al., 1995). Syrian hamsters are a prominent rodent used in female reproductive toxicology inhalation studies including mainstream (MS) smoke (active inhalation of a bolus of smoke) and side-stream (SS) smoke (passive inhalation of smoke). Advantages of hamsters in these studies are that they adapt well to smoking machines and they have reproductive tracts that are large enough to allow thorough evaluation (Magers et al., 1995).

To test the effects of smoke inhalation on reproductive parameters, female Syrian hamsters in various stages of estrous or pregnancy are anesthetized, placed in dorsal

recumbency, and exposed through a nose cone to smoke released from the burning end of a cigarette (SS smoke) or to a puff of MS smoke with a puffer box (Magers et al., 1995). A machine of equivalent design that pumps fresh air is used for control animals. Exposure to doses of MS and SS smoke equivalent to those in women who smoke actively or passively (second-hand smoke) is ensured by quantifying serum levels of cotinine, a metabolite of nicotine (DiCarlantonio and Talbot, 1999). The major downfall of this technique is that it exposes females to either MS or SS smoke, but not to both, as would be the case for an active human smoker (Magers et al., 1995). Female hamsters that inhale either MS or SS smoke twice per day for 7 days, starting 1 month prior to mating and ending at day 7 of pregnancy, develop fewer corpus lutea (CL) with accompanying decreases in CL vascularity (Magers et al., 1995). Additional changes in these hamsters include blebbing of ciliated epithelial cells in oviducts, increases in secretory cells of the ampulla, decreases in the ability of the uterus to stretch, and crowding of fetuses. Functionally, the transport of pre-implantation embryos through the oviduct is retarded, and oviduct muscle contraction rate is greatly decreased by smoke inhalation (DiCarlantonio and Talbot, 1999). Transport rate is more significantly retarded in the SS exposure group, suggesting that SS smoke exposure is more detrimental than MS smoke exposure with regard to embryo transport. Inappropriate transport and implantation could explain the increase in ectopic pregnancy in human smokers. Interestingly, when mating is delayed for 1 month following smoke inhalation, all deleterious effects of MS and SS exposure are ablated (Magers et al., 1995). This indicates that the female reproductive tract can quickly recover from the negative effects of smoke inhalation.

COPD and Emphysema

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive airflow obstruction with concurrent inflammation of the small airways and emphysema of lung parenchyma (Cosio Piqueras and Cosio, 2001; Petty, 2006). Emphysema contributes to airflow obstruction by reducing the elasticity of the lung, increasing alveolar size, and increasing airway resistance (Cosio Piqueras and Cosio, 2001). COPD is the fourth most common cause of death in the United States, with a prevalence of approximately 16 million (Petty, 2006). Animal models yield clues to the pathophysiology and therapeutic approaches for COPD (Petty, 2006).

The Syrian hamster is a useful model to study the emphysema component of COPD because hamsters develop severe diffuse emphysema resembling human panacinar emphysema following a single intratracheal dose of porcine pancreatic elastase (Borzone et al., 2007;

Hayes et al., 1977; Snider and Sherter, 1977). Elastase is used as an induction agent because it destroys or impairs the formation of elastin, resulting in emphysema (Soskel et al., 1984). The elastase induction model reproducibly results in alveolar damage and destruction of alveolar septa resulting in airway enlargement, and causes lung hyper-inflation, all of which are seen in humans with COPD (Borzzone et al., 2007; Hayes et al., 1977). Additionally, elastase-treated hamsters do not gain weight at a normal rate, which is analogous to the weight loss seen in humans with emphysema (Snider and Sherter, 1977). Syrian hamsters are also used as a model for emphysema treatment. Intratracheal instillation of hyaluronic acid in hamsters with elastase-induced emphysema reduces emphysema by binding with and protecting elastic fibers from elastase-induced injury, and may be useful in preventing emphysema (Cantor et al., 1997, 2002).

Emphysema can also be induced in hamsters by feeding diets deficient in copper (Soskel et al., 1984). This model requires chronicity (8–10 weeks), thereby resembling the time course of human emphysema development (Soskel et al., 1984). Copper deficiency results in the inhibition of lysyl oxidase-mediated elastin cross-linking, causing impaired elastin formation and emphysema (Soskel et al., 1984). Also, since superoxide dismutase requires copper, copper deficiency leads to free radical accumulation which can cleave elastin bonds and attract inflammatory cells to the lung exacerbating emphysema.

A popular hypothesis regarding the pathogenesis of emphysema is that an imbalance between proteases and antiproteases plays a major role in disease development (Borzzone et al., 2007). When compared to Syrian hamsters, rats develop only mild emphysema when given similar doses of elastin. This could be due to a 60% reduction in serum levels of the antiprotease α 1-antitrypsin in Syrian hamsters compared to rats, which leads to low elastase inhibitory capacity, thereby predisposing hamsters to elastase-induced emphysema.

Pulmonary Fibrosis

Interstitial pulmonary fibrosis (IPF) is a debilitating disease characterized by proliferation of lung fibroblasts, collagen accumulation, loss of alveolar space, reduction in lung volume and compliance, and impairment of gas exchange (Giri et al., 1994, 1997; Lazo et al., 1990; Wang et al., 2002). These changes cause hypoxemia and, if the fibrosis is severe, pulmonary insufficiency and fatal hypoxemia (Lazo et al., 1990). Currently, there are no adequate treatments for IPF and mortality in humans is high (Giri et al., 1994; Iyer et al., 1999; Wang et al., 2002). Bleomycin, a DNA-interactive antineoplastic drug is a known cause of dose-dependent pneumonitis that progresses to IPF in humans (Giri et al., 1994, 1997; Lazo

et al., 1990; Thrall et al., 1979). The prevalence of bleomycin-induced toxicity is reported to be 10%, with many of these cases resulting in death (Lazo et al., 1990).

Bleomycin is one of the most commonly used agents to induce IPF because it causes a similar, reproducible condition in the Syrian hamster (Lazo et al., 1990). A single intratracheal installation of approximately 5mg/kg body weight produces pulmonary fibrosis within 7 days (Lazo et al., 1990). Importantly, other organs are unaffected by this treatment and the treatment induces biochemical, inflammatory, and histological changes similar to those seen in the lungs of humans with IPF (Giri et al., 1994; Thrall et al., 1979; Wang et al., 2002). The bleomycin model of IPF involves an initial injury to the lung, followed by an influx of inflammatory cells that release cytokines (i.e. IL-1, TNF- α , PDGF, and TGF- β), leading to increased collagen synthesis and deposition (Iyer et al., 1999). A drawback of this model is that it produces high mortality in Syrian hamsters (Giri et al., 1994; Lazo et al., 1990). A refinement is the three-dose bleomycin hamster model where IPF is produced by the intratracheal instillation of three lower doses of bleomycin into the lungs of anesthetized hamsters at weekly intervals (Giri et al., 1994; Wang et al., 2002). This model uses repeated insults on the lung to initiate and sustain the fibroproliferative stage of fibrosis, and is the closest model to human IPF because it provides a multi-hit stimulus for lung injury, causing the slow development of IPF (Wang et al., 2002). There is age-selective resistance to bleomycin in young hamsters due to enhanced antioxidant defenses and bleomycin hydrolase activity in neonates (Lazo et al., 1990).

After induction, the hamster model can be used to study antifibrotic compounds (Giri et al., 1994, 1997; Iyer et al., 1999; Wang et al., 2002). Transforming growth factor- β (TGF- β) plays a central role in the pathophysiology of excessive extracellular matrix (i.e. collagen) production resulting in IPF (Iyer et al., 1999; Lazo et al., 1990). TGF- β mRNA and protein levels are increased in fibrotic hamster lungs; therefore, suppressing its production constitutes a rational therapeutic approach (Iyer et al., 1999; Lazo et al., 1990; Wang et al., 2002). Decorin, a proteoglycan component of collagen fibrils, binds and inactivates all isoforms of TGF- β , offering a potential treatment for IPF (Giri et al., 1997). The antifibrotic drug pirfenidone down-regulates the bleomycin-induced overexpression of TGF- β in the lungs, and pirfenidone is now a clinical therapeutic agent for IPF in humans (Antoniou, 2006; Bhatt et al., 2006; Iyer et al., 1999). Further, a TGF- β antagonist, TGF- β chimeric soluble receptor, causes significant reductions in fibrosis in the hamster model (Wang et al., 2002).

Another area of IPF treatment research focuses on the elimination of reactive oxygen species (ROS) and increasing NAD and ATP needed for the repair

of injured pulmonary tissue (Giri et al., 1994). Dietary supplementation with taurine and niacin inhibits lung fibrosis in the bleomycin induced hamster model (Giri et al., 1994). This defense is provided by the ability of taurine to scavenge ROS and the ability of niacin to replenish NAD and ATP levels (Giri et al., 1994).

CARDIOVASCULAR

Syrian hamsters exhibit characteristics that make them desirable models for cardiovascular research. Specifically, spontaneous genetic mutations cause diseases that closely resemble human cardiovascular disease. Further, Syrian hamsters display unique anatomical characteristics, most notably a readily evertible cheek pouch, that facilitate cardiovascular studies.

Cardiomyopathy

Cardiomyopathy is a primary degenerative disease of the myocardium and is characterized as various forms, such as hypertrophic or dilated, based on gross appearance (Sakamoto et al., 1997). Dilated cardiomyopathy (DCM) is characterized by atrial and ventricular dilation with ventricular wall thinning, severe systolic and diastolic left ventricular dysfunction, and heart failure (Ikeda and Ross, 2000). DCM is one of the main causes of congestive heart failure in humans, is the leading cause of hospitalization of older patients in the United States, and is hereditary in 25% of affected patients (Ikeda and Ross, 2000). Hypertrophic cardiomyopathy (HCM) is characterized by increased ventricular wall thickness, generally involving the interventricular septum, and normal or reduced left ventricular volume (Richardson et al., 1996; Rodriguez et al., 2009). HCM is the most common, heritable cardiovascular disease in humans, affecting one in 500 people (Bos et al., 2009; Rodriguez et al., 2009). Approximately 10% of humans with HCM eventually develop left ventricular dilation and DCM (Ikeda and Ross, 2000). The cardiomyopathic Syrian hamster is a naturally occurring, inherited, established animal model for both dilated and hypertrophic cardiomyopathy. In the hamster, both DCM and HCM are caused by a defect in the δ -sarcoglycan gene, a component of the dystrophin complex, which is inherited in an autosomal recessive fashion (Bajusz et al., 1969; Escobales and Crespo, 2006, 2008; Goineau et al., 2001; Ikeda and Ross, 2000; Lipskaia et al., 2007; Ryoke et al., 1999; Sakamoto et al., 1997). The Syrian hamster model shares many features with human DCM and HCM and is used to study the pathophysiology, prevention, and treatment of cardiomyopathy (Escobales and Crespo, 2008; Ryoke et al., 1999).

All cardiomyopathic Syrian hamsters were originally derived from the polymyopathic line 1.50, providing an

example of a single mutation causing different types of cardiomyopathy (Goineau et al., 2001; Sakamoto et al., 1997). Hamster strains Bio 14.6, UM-X7.1, CHF 146, and CHF 147 are characterized by significant hypertrophy of cardiac muscle, while strains 53.58 and Bio TO-2 are characterized by ventricular dilation without hypertrophy (Goineau et al., 2001; Ikeda and Ross, 2000). Some strains, such as the Bio 14.6, exhibit compensatory hypertrophy progressing to left ventricular dilation, thinning and impaired function, while strains such as TO-2 develop dilated cardiomyopathy without an initial hypertrophic response (Goineau et al., 2001; Ikeda and Ross, 2000). These various strains provide diverse models which can be used to study various aspects of pathogenesis.

Many features of the TO-2 dilated cardiomyopathy strain closely resemble those of human DCM so this strain is used commonly to characterize the pathophysiology and hemodynamic profiles of DCM in humans (Escobales and Crespo, 2006; Goineau et al., 2001). TO-2 strain cardiomyopathy is progressive, beginning with myolysis, then developing fibrosis followed by hypertrophy and dilation, and culminating in congestive heart failure (Cruz et al., 2007; Escobales and Crespo, 2006). These stages represent the majority of phases seen in humans with cardiomyopathy, including heart dilation, ventricular hypertrophy, fluid congestion, and death (Cruz et al., 2007; Escobales and Crespo, 2006). Acute myocarditis is also observed in humans and hamsters (Escobales and Crespo, 2006). The common hemodynamic features include low cardiac output, elevated left ventricular end-diastolic pressure, delayed left ventricular relaxation rate, increased peripheral resistance, and reduced renal blood flow.

In the TO-2 Syrian hamster, abnormal sarcoplasmic reticulum function results in calcium sequestration and overload, and high ATPase activity results in decreased contractility. These features are partially responsible for decreased cardiac function in this strain, and these abnormalities are hypothesized to be a pathogenic mechanism in human DCM (Goineau et al., 2001). Deficiency of the δ -sarcoglycan gene also affects peripheral and coronary vasculature, ultimately contributing to heart failure in cardiomyopathic hamster models (Escobales and Crespo, 2006, 2008; Lipskaia et al., 2007). Angiotensin II promotes increased oxidative stress and decreased peripheral vasorelaxation, leading to high systemic blood pressure and increased cardiac work load in cardiomyopathic prone TO-2 hamsters (Escobales and Crespo, 2006). Angiotensin-II-dependent oxidative stress influences coronary vasculature by causing endothelial dysfunction which predisposes hamsters to the development of ischemic heart disease and cardiomyopathy (Escobales and Crespo, 2008). Based on the similarities between cardiomyopathic Syrian hamsters and humans,

these results associate angiotensin II with the development of cardiomyopathy in humans with hereditary sarcoglycanopathies (Escobales and Crespo, 2008).

Current medical treatment for human dilated and hypertrophic cardiomyopathy is only palliative (Sakamoto et al., 1997). Syrian hamster cardiomyopathic strains are used in research targeting prevention and treatment of the condition. The treatment of cardiomyopathic hamsters with angiotensin-converting enzyme (ACE) inhibitors improves left ventricular contractility and coronary flow, providing evidence that Syrian hamsters are useful models in studying drug treatment interventions. Coronary vasculature renin-angiotensin system (RAS) plays a role in generating increased coronary reactivity and resistance in young Syrian hamsters that have yet to develop cardiomyopathy. Early RAS blockade may prevent and improve the clinical signs of cardiomyopathy (Escobales and Crespo, 2008). Finally, the administration of carvedilol, a non-selective β -blocker with α_1 -blocker properties, to 6-month-old TO-2 hamsters, improves cardiac function due to decreased peripheral resistance (Cruz et al., 2007).

Microcirculation

The bilateral cheek pouches of the Syrian hamster are invaginations of the oral mucosa which extend to the shoulder region and possess a retractor muscle (Svensjo, 1990). These anatomical structures are highly vascular, thin, easily transilluminated, and can be everted with blood flow intact, making the hamster cheek pouch ideal for intravital microscopy and microcirculation research (Davis and Gore, 1985; Kerger et al., 1995; Klitzman et al., 1983; Svensjo, 1990). Numerous preparations are described in the literature to observe the hamster cheek pouch microscopically. These methods perfuse the tissue with a bicarbonate-buffered saline solution and maintain physiological temperature, oxygen tension, and pH in an anesthetized hamster (Davis and Gore, 1985; Greenblatt et al., 1969; Svensjo, 1990; Yamaki and Kritchman, 1981).

With the everted method, the cheek pouch is grasped with forceps, pulled through the mouth, and pinned over a specialized Lucite support pedestal (Davis and Gore, 1985; Persson et al., 1985). Longitudinal and transverse incisions allow exposure of the pouch in a single-layer preparation with high optical clarity, making this method one of the standards for microcirculation studies (Davis and Gore, 1985; Svensjo, 1990). The disadvantages of the everted preparation are restricted blood flow due to tension on the retractor muscle, and the requirement of pouch incisions. Refined everted techniques eliminate the disadvantage of restricted blood flow. Following a skin incision to expose the pouch the retractor muscle is removed and a thin glass

support plate is positioned in the cheek pouch which allows unrestricted blood flow. The everted pouch can then be observed in a chamber attached over the microscope condenser system. This preparation decreases surgical trauma and preserves the entire cheek pouch vascular supply (Davis and Gore, 1985).

An alternative method is the use of a skin incision in the neck followed by ligation and cutting of the retractor muscle at the point of insertion and retraction of the cheek pouch through the skin incision (Yamaki and Kritchman, 1981). This preparation eliminates tension on the retractor muscle, but requires more surgical manipulation than the everted technique.

A third method, the chamber method, involves incising the skin over the cheek pouch, inserting a translucent chamber through the hamster's mouth into two cheek pouch incisions, and illuminating the chamber with a Lucite rod inserted into the mouth (Greenblatt et al., 1969). This method can be used for acute and chronic experimentation, and does not place excessive tension on the retractor muscle. The primary disadvantage of this method is limited transillumination (Davis and Gore, 1985).

A detailed three-dimensional intravital microscopic view of hamster microcirculation can be visualized using one of the above-described preparations, and intravenous injection of fluorescein-labeled dextran (Endrich et al., 1980; Svensjo, 1990). Intravital microscopy is also used for observation of the microcirculation of non-anesthetized Syrian hamsters using the dorsal skinfold chamber method (Endrich et al., 1980; Lehr et al., 1991; Menger et al., 2002; Nolte et al., 1995). After implantation of two catheters into the jugular vein and carotid artery, two titanium frames are implanted into the dorsal skinfold to extend the double layer of skin. One layer is completely removed and the remaining layer is covered with a cover slip. This preparation allows for chronic studies of microcirculation (Menger et al., 2002).

Ischemia Reperfusion

The hamster cheek pouch is used to study ischemia-reperfusion injury. Ischemia-reperfusion injury is important because it contributes to tissue damage during myocardial and cerebral infarction, and following surgical manipulations that interrupt and then restore blood flow, such as during vascular and organ transplantation and reconstructive surgery (de With et al., 2005; Nolte et al., 1995). Ischemia-reperfusion injury is caused by several factors including the generation of reactive oxygen and nitrogen species and the resulting lipid peroxidation; cytokine production following leukocyte margination, adherence, and infiltration; and activation of the complement system (de Groot and Rauen, 2007; de With et al., 2005; Kaminski et al., 2002;

Yasuhara et al., 1991). The Syrian hamster is extensively used to reveal the pathophysiological mechanisms of ischemia–reperfusion injury, as well as therapeutic options to preserve tissue and vascular viability.

Numerous models of ischemia–reperfusion injury are described using the Syrian hamster cheek pouch. In the model of pressure-induced ischemia a translucent pressure chamber is pressed against the cheek pouch for variable amounts of time and then released to produce reperfusion (Romanus et al., 1977; Yasuhara et al., 1991). The disadvantage of this model is that the results are influenced by the pressure applied to the tissue. In a second model, ischemia is produced by tightening a latex cuff around the neck of an everted cheek pouch for up to an hour followed by cuff release (Persson et al., 1985; Yasuhara et al., 1991). The disadvantage of this model is that tension on the retractor muscle is produced by the everted preparation. Alternatively, ischemia can be induced by compressing the feed arteries and collecting veins of the pouch with a piece of silastic tubing or atraumatic microvascular clips (Bertuglia and Reiter, 2007; de With et al., 2005).

In the incomplete ischemia model, ischemia of the cheek pouch is produced by occluding the ipsilateral common carotid artery, its external branch, and the contralateral external carotid artery (Erlansson et al., 1987; Yasuhara et al., 1991). Partial ischemia better reproduces ischemia as seen in the clinical setting, when compared to models of global ischemia. The disadvantages of this model are that the degree of ischemia is not easily evaluated, and occlusion of the carotid arteries reduces cerebral blood flow (Yasuhara et al., 1991). A further refinement of the incomplete ischemia model is produced by selecting two sections of cheek pouch and placing a triangular chamber made of polyester/plastic film in each area. Ischemia is induced by applying a set amount of pressure to a cover slip over one of the chambers, while the other area acts as a control. Increased pressure is avoided by using a 1.0-mm aperture at one of the chamber corners. Reperfusion is produced when pressure is released after 1 hour (Yasuhara et al., 1991). The advantages of this method include decreased trauma to the pouch microcirculation, the ability to select various sizes of tissue, the maintenance of blood flow in surrounding microvasculature, and the ability to study both ischemic and non-ischemic areas simultaneously. In addition to the cheek pouch, the dorsal skin-fold chamber method can be used in ischemia reperfusion research utilizing an O-shaped silicone ring pressed into the tissue with an adjustable screw clamp, leading to cessation of blood flow into and out of the chamber (Pickelmann et al., 1999).

While Syrian hamster ischemia–reperfusion models are broadly used for elucidating the pathophysiology of the condition, the models are also utilized in the

development of prevention and treatment (Bertuglia and Reiter, 2007; Pickelmann et al., 1999). Melatonin, a potent antioxidant, effectively preserves microcirculation in the hamster cheek pouch during ischemia reperfusion, making melatonin administration a possible preventative measure during situations when ischemia reperfusion injury is a possibility (Bertuglia and Reiter, 2007). Another possible preventative intervention is daflon, a highly purified flavonoid with anti-inflammatory and antioxidative properties. Daflon blocks immigration and accumulation of leukocytes in perivascular tissue during ischemia reperfusion in the Syrian hamster (Pickelmann et al., 1999).

INFECTIOUS DISEASE RESEARCH

Syrian hamsters were introduced as a laboratory animal species in 1930 due to their susceptibility to *Leishmania* spp. and ease of breeding in captivity (Adler, 1948). Prior to the use of Syrian hamsters, Chinese hamsters were the only suitable models for *Leishmania* research but they did not breed well in captivity and had to be imported from the Far East (Adler, 1948). Early on, Syrian hamsters were also found to be useful models for tuberculosis and brucellosis. Syrian hamsters remain a valuable tool for studying many infectious diseases due to their relative lack of spontaneous diseases compared to other rodent models, and their susceptibility to many experimentally induced infectious diseases (Hankenson and Van Hoosier, 2002).

Viruses

Hantavirus

Hantavirus pulmonary syndrome (HPS) is a severe infectious disease caused by numerous members of the *Bunyaviridae* family (Jonsson et al., 2008; Wahl-Jensen et al., 2007). HPS can range from a typical flu-like disease with fever to fatal pneumonia. Unlike other diseases caused by Hantavirus, HPS is transmitted by aerosol and wild rodents in the family *Cricetidae* are the natural hosts of these infectious agents (Hooper et al., 2001). Research conducted on HPS agents must be conducted at ABSL-4 facilities.

The hamster serves as an experimental model to study the pathogenesis of HPS. Specifically, the Syrian hamster is highly susceptible to Andes and Maporal viruses which cause fatal pneumonia and edema in experimentally infected hamsters (McElroy et al., 2004; Milazzo et al., 2002; Wahl-Jensen et al., 2007). In contrast, Sin Nombre virus readily infects the hamster but does not cause disease. Further, Choclo virus is not fatal in the hamster (Eyzaguirre et al., 2008). These varying

results create an understanding of how these agents produce disease. Specifically, Choclo virus damages the endothelium of the lung without significantly inciting inflammation (Eyzaguirre et al., 2008). In contrast, Andes virus targets endothelium and induces a proinflammatory response (Eyzaguirre et al., 2008; Hooper et al., 2001, 2008). This same proinflammatory response is noted in humans with severe HPS. It therefore seems likely that more pathogenic viruses produce disease by both directly damaging lung endothelium and inducing a potent proinflammatory response (Eyzaguirre et al., 2008; Hooper et al., 2001, 2008). Based upon these data a potential treatment of HPS would be the initiation of anti-inflammatory therapy.

Coronavirus (SARS)

In 2003, an outbreak of a previously unknown condition, severe acute respiratory syndrome (SARS), affected more than 8000 people and resulted in 774 deaths across 30 countries (Schaecher et al., 2008). The etiological agent of SARS was identified as a novel coronavirus, SARS-CoV (Drosten et al., 2003). The outbreak was controlled through quarantine of infected individuals and travel advisories (Subbarao and Roberts, 2006). The possibility of future SARS outbreaks has led to the search for an appropriate animal model to study the pathogenesis and potential therapeutics for SARS (Subbarao and Roberts, 2006).

In the hamster model, a high virus titer develops in the respiratory tract following intranasal inoculation of SARS-CoV (Roberts et al., 2005). In the lungs, peak viral replication occurs two days post-infection and is cleared by day 7; however, low levels of virus are present in the nasal turbinates for up to 14 days (Roberts et al., 2005). SARS-CoV elicits a robust neutralizing antibody response in the hamster which can be detected in sera at day 7 post infection and hamsters are protected from re-challenge by 28 days after initial infection (Roberts et al., 2005). In hamsters, viral replication occurs in epithelial cells of the respiratory tract and causes interstitial pneumonia, pulmonary consolidation, and diffuse alveolar damage. A positive correlation exists between pulmonary viral titer and the extent of pneumonia, making the hamster an excellent model for studying the efficacy of potential vaccines and immunotherapy for SARS (Subbarao and Roberts, 2006). Despite the high level of viral replication and associated histopathological lesions, hamsters exhibit no overt clinical signs (Roberts et al., 2005).

Immunotherapy with anti-SARS-CoV monoclonal antibodies (MAbs) has been tested in the hamster model (Roberts et al., 2006). In these studies, the virus is administered intranasally and 24 hours post-infection hamsters are treated with MAbs by intraperitoneal injection. Treatment with MAb 201, a SARS-CoV-specific MAb,

significantly reduces viral replication and the severity of pulmonary lesions in hamsters (Roberts et al., 2006). There is a 1000-fold reduction in viral titer when MAb 201 is given at a dose of 40mg/kg and a 10000-fold reduction when given at a dose of 80mg/kg.

Cyclophosphamide-induced immunosuppression increases the severity of SARS in hamsters when given prior to and during infection (Schaecher et al., 2008). In these studies, hamsters are first given a loading dose of cyclophosphamide (140mg/kg) 2–5 days prior to infection, and then a maintenance dose (100mg/kg) every 3–4 days throughout the course of the study. In treated animals the virus displays a more expansive tissue tropism and high titers are present in the lung, liver, spleen, kidney, and heart and treated animals exhibit weight loss and mortality. This condition is similar to humans with SARS who develop extrapulmonary lesions including splenic atrophy, acute tubular necrosis in the kidneys, neuronal edema and degeneration, heart edema, and myocardial fiber atrophy (Gu and Korteweg, 2007). While the immunosuppressed hamster model does not replicate all of the extrapulmonary lesions in humans it more closely mimics the human disease presentation when compared to the immunocompetent hamster model (Schaecher et al., 2008).

Bacteria

Leptospira spp.

Leptospirosis, caused by organisms in the genus *Leptospira*, is a potentially fatal disease affecting humans and animals worldwide (Guerra, 2009). In humans, clinical signs range from asymptomatic to high fever, severe headache, chills, muscle aches, vomiting, diarrhea, jaundice, abdominal pain, and a rash (Areal, 1962). If the disease is left untreated, kidney damage, meningitis, liver failure, respiratory distress, and death are possible. Leptospirosis is contracted by ingestion or contact with contaminated water, food, or soil (Guerra, 2009).

Two strains of *Leptospira interrogans* (L1–130, Kito) and three strains of *Leptospira noguchii* (Cascata, Hook, and Bonito) produce an acute lethal infection when inoculated intraperitoneally into Syrian hamsters (Silva et al., 2008). Leptospirosis in hamsters is characterized by hepatic and renal complications similar to those seen in acute lethal infection in humans (Silva et al., 2008). Clinical signs that may be observed by the fourth day post-infection include hemorrhage, dehydration, ruffled fur, decreased activity, and isolation from cohorts. Hamsters infected with L1–130 or Kito strains die 7–14 days after inoculation, while hamsters infected with Cascata, Hook, or Bonito die 7–22 days after inoculation. The reproducible lethal nature of these isolates in hamsters, coupled with lesions in target organs that

resemble leptospirosis in humans, provides a useful animal model.

Through the use of this model, new treatment and prophylactic modalities can be tested. For example, azithromycin is an effective treatment for acute leptospirosis in hamsters, with 100% survival, following only two doses initiated 2–4 days post infection (Moon et al., 2007). Azithromycin provides an alternative to the standard doxycycline or penicillin treatment because it lacks contraindications in young children and pregnant women (Jain and Danziger, 2004; Moon et al., 2007).

Clostridium difficile

Clostridium difficile, a Gram-positive spore-forming bacillus, is the leading cause of antibiotic-associated diarrhea in humans (Poutanen and Simor, 2004). Disease occurs when the normal colonic flora is disrupted typically due to clindamycin, ampicillin, or cephalosporin administration and overgrowth of toxin-producing strains of *C. difficile* (Poutanen and Simor, 2004). Pathogenic strains of *C. difficile* produce two toxins, enterotoxin A and cytotoxin B, which are the major virulence factors for *C. difficile* (Razaq et al., 2007). Outbreaks of *C. difficile*, beginning in 2000, are attributed to a newly recognized strain, known as the BI strain (McDonald et al., 2005). In addition to the other toxins mentioned the BI strain of *C. difficile* produces a binary toxin, has an 18-bp deletion in the *tcdC* locus (a negative regulator of toxin A and B), and is resistant to fluoroquinolone antibiotics (McDonald et al., 2005). Patients that acquire *C. difficile* may remain asymptomatic carriers or develop diarrhea, pseudomembranous colitis, or toxic megacolon (Al-Eidan et al., 2000). Treatment consists of stopping the initiating antibiotics and beginning treatment with metronidazole or vancomycin for 10 days. Relapse after completion of treatment occurs in about 20% of cases (Pepin et al., 2005).

The Syrian hamster model for *C. difficile* closely mimics several important aspects of human infection (Kokkotou et al., 2008). Hamsters are orally gavaged with clindamycin followed by gastric inoculation of *C. difficile* 24 hours later (Kokkotou et al., 2008). Hamsters exposed to this experimental paradigm develop hemorrhagic typhlitis, similar to antibiotic-associated pseudomembranous colitis in humans, followed by death within 3 days of infection (Kokkotou et al., 2008). Clinical signs of infection may include diarrhea, weight loss, ataxia, dyspnea, and death (Babcock et al., 2006). Highly virulent strains may cause death without any premonitory signs (Razaq et al., 2007).

Hamsters, like humans, may succumb to a relapse after completing treatment of the primary disease (Kokkotou et al., 2008). Hamsters receiving vancomycin, the historical treatment for human *C. difficile*-associated colitis, display a 75% recurrence rate by 28 days post-initial-infection (Kokkotou et al., 2008).

However, treatment with Rifaximin, a non-absorbable oral antibiotic, results in a 0% recurrence rate, potentially providing refinement to therapy in humans (Kokkotou et al., 2008).

The hamster model of *C. difficile* is also used to test the use of human monoclonal antibodies (HuMAbs) directed against either toxin A (CDA1) or toxin B (MDX-1388) (Babcock et al., 2006). Intraperitoneal administration of CDA1 and MDX1388 daily for 4 days prior to inoculation with *C. difficile* protects against mortality both in the primary disease and in the relapse model of infection (Babcock et al., 2006). The use of HuMAbs may provide a useful therapeutic option either alone or in combination with antibiotics for treatment of humans with *C. difficile* colitis (Babcock et al., 2006).

Mycoplasma pneumoniae

Mycoplasma pneumoniae is the leading cause of pneumonia in children and young adults (Denny et al., 1971). A majority of the cases result in upper respiratory tract infections, with fever, cough, sore throat, headache, and malaise, but some cases may progress to tracheobronchitis or pneumonia (Denny et al., 1971). Antibiotics may reduce the severity of disease, but do not eliminate the infection (Ford et al., 1980). Recovery from *M. pneumoniae* infection protects the individual from reinfection, suggesting that the development of a vaccine is the most promising approach to controlling *M. pneumoniae* infections (Barile et al., 1988).

Syrian hamsters, which do not harbor *Mycoplasma* spp. as part of their indigenous microbiota, provided an early model for studying *Mycoplasma* and potential vaccines and therapeutics (Barile et al., 1988). In this model, *M. pneumoniae* is inoculated into hamsters via either the aerosol, intranasal, or intratracheal routes, and infection results in changes that are consistent with natural human disease (Clyde, 1971). The intratracheal route consistently produces pulmonary disease of greater severity with greater colonization than the other routes of exposure (Barile et al., 1988). In general, peak disease severity occurs 2 weeks post inoculation with hamsters over 6 weeks of age becoming most severely affected (Barile et al., 1988). Assessment of experimental vaccines and other therapeutics can be accomplished by assessment of lung lesion scores. Specifically, lung lesions are scored microscopically by evaluating the degree of leukocyte cell infiltrates, luminal exudate, and parenchymal pneumonia in three cross-sections of the entire lung (Barile et al., 1988). Alternatively, following treatment with a potential chemotherapy agent, viable mycoplasmas in the lung can be quantitated by homogenizing the lungs in mycoplasma liquid medium and plating serial dilutions on agar medium. The use of the hamster in *M. pneumoniae* research has decreased in recent years (2000 and beyond). This reduction

likely stems from the wide availability of mice free of *Mycoplasma* spp.

Treponema pallidum

Two forms of syphilis occur in humans: the venereal form with primary, secondary, and tertiary manifestations and possible congenital transmission, and the endemic form that is usually seen in childhood and is transmitted between children by close contact. In humans, *Treponema pallidum* subsp. *pallidum* is the etiologic agent for venereal syphilis and *T. pallidum* subsp. *endemicum* is the etiologic agent for the endemic form (Kajdacsy-Balla et al., 1993). In the venereal form, primary lesions present as small painless firm raised sores at the site of contact that heal in 3–6 weeks (McAdam and Sharpe, 2010). Secondary lesions occur about 2–10 weeks after the primary lesions and are characterized by widespread cutaneous and mucocutaneous lesions with lymphadenopathy that lasts for several weeks (McAdam and Sharpe, 2010). The tertiary stage occurs in about a third of people that do not receive treatment and appears after a latent period of 5 or more years. Internal organs are the target for the tertiary stage of syphilis, primarily causing cardiovascular or neurologic damage.

When Syrian hamsters are infected with *T. pallidum* subspecies *endemicum*, a disease process similar to

human venereal syphilis develops (Kajdacsy-Balla et al., 1993). Intradermal injection of *T. pallidum* into the inguinal regions of hamsters results in primary lesions at the site of inoculation. The primary lesions form about 3 weeks after inoculation as erythematous papules, which enlarge and become ulcerated by 4 weeks (Figure 34.4A). The lesions continue to expand until the sixth to eighth week post-inoculation when they begin to heal slowly (Kajdacsy-Balla et al., 1993). Around 24 weeks post-infection, secondary lesions develop as perioral ulcers (Figure 34.4B) and an erythematous rash on the paws and cranial trunk (Kajdacsy-Balla et al., 1993). Most infected hamsters die within 28–32 weeks following inoculation due to malnutrition from the presence of severe perioral ulcers. If the hamster survives, the perioral ulcers will resolve. Tertiary lesions in hamsters are not documented; however, this could be due to the rarity of survival past the secondary stage.

Gross pathologic features of hamster syphilis include lymphadenopathy and thymic atrophy (Kajdacsy-Balla et al., 1993). Histologic features include generalized follicular hyperplasia of lymph nodes, hepatic periportal foci of mononuclear cells, and a diffuse increase in mononuclear cells in the sinusoids. The perioral ulcers are characterized by an intense polymorphonuclear infiltrate at their base. Treponemes are visualized in the lymph nodes and perioral ulcers by dark-field

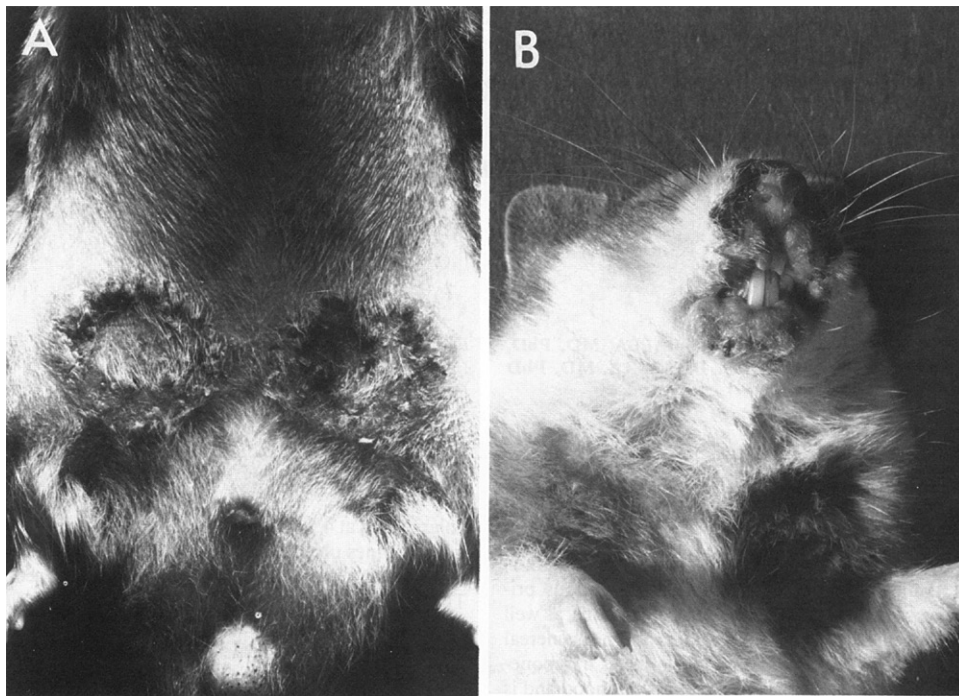


FIGURE 34.4 Hamster with syphilitic lesions. (A) Primary cutaneous lesions form at the site of inoculation as erythematous papules which enlarge and become ulcerated with raised indurated borders. (B) Secondary lesions spontaneously develop approximately 24 weeks after infection in the form of perioral ulceration. From Kajdacsy-Balla et al. 1993 with permission from the American Society for Investigative Pathology.

microscopy. Persistent latent infection is demonstrated in these animals by transfer of lymph node material into naïve hamsters.

Hamsters infected prior to pregnancy transmit syphilis to their offspring congenitally. A majority of the offspring exhibit rhinitis, about a third develop perianal and perigenital lesions, and a quarter are stillborn or die shortly after birth (Kajdacsy-Balla et al., 1993). Human congenital syphilis also results in about 25% of prenatal infections resulting in stillbirth, while 25–30% of newborn infants die shortly after birth and 40% develop syphilis later in life (Crissey and Denenholz, 1984).

Experimental infection of hamsters with *T. pallidum* provides a model to study syphilis infection and drug therapy. Daily clarithromycin given over 7 days successfully eliminates infection in hamsters (Alder et al., 1993). Success is confirmed by failure to infect susceptible hamsters following inoculation with lymph node material from treated hamsters (Alder et al., 1993). These findings may prove useful in establishing alternatives to penicillin treatment, which is the drug of choice for treating human infections.

Hamsters infected with *T. pallidum* for 8 weeks then treated with 4000 IU of penicillin to clear the infection are susceptible to reinfection (Schell et al., 1980). However, hamsters infected with *T. pallidum* for 10–16 weeks and treated with 4000 IU of penicillin are resistant to reinfection (Schell et al., 1980). Following re-inoculation with *T. pallidum*, hamsters do not develop lesions and treponemes are not detectable in the lymph material. The hamster's ability to develop resistance to *T. pallidum* may prove useful in studying human syphilis vaccine development.

While many features of the hamster *T. pallidum* subsp. *endemicum* model make it an excellent model for studying congenital syphilis, it does not utilize *T. pallidum* subsp. *pallidum*, which is the agent that causes congenital syphilis in humans. Hamsters do not develop any lesions in response to *T. pallidum* subsp. *pallidum*. In contrast guinea pigs do develop congenital syphilis in response to *T. pallidum* subsp. *pallidum*, and are therefore more popular current models in the study of congenital syphilis.

Parasites

Toxoplasma gondii

Toxoplasma gondii is an intracellular parasitic protozoan widely distributed in nature. Cats are the definitive host, but all mammals may serve as intermediate hosts. In all hosts, the parasite forms cysts within various tissues (Kean, 1972). Approximately 23% of adolescents and adults in the United States have anti-*T. gondii* antibodies (National Center for Health Statistics, 1994). In some areas of the world, up to 97%

of people are positive for *T. gondii* antibodies (Santos et al., 2009). Infection is usually asymptomatic; however, infection during pregnancy may lead to abortions or to offspring that develop mental retardation, epilepsy, or toxoplasmic retinochoroiditis (Lopez et al., 2000). Ocular disease resolves spontaneously, but reoccurs frequently, and may result in episodic blindness (Pavesio et al., 1995).

The hamster is a reliable model of toxoplasmic retinochoroiditis. Hamsters inoculated intraperitoneally with cysts of *T. gondii* strain ME 49 develop ocular disease without systemic illness (Pavesio et al., 1995). Retinal lesions develop in both eyes by 2–3 weeks after inoculation and cysts form as white pinpoint to optic disc-sized lesions, primarily at the posterior pole of the inner retina. Four weeks post-infection, the lesions enlarge and develop diffuse indistinct edges with vasculitis and occasionally vitritis. Regression typically occurs by 8–9 weeks, but retinal atrophy may persist (Pavesio et al., 1995).

Oral administration of *T. gondii* ME 49 results in a comparable outcome with no systemic signs of illness, and similar but less severe ocular lesions (Gormley et al., 1999). The lesions appear similar in color and position in the retina, however, they are smaller in size, fewer in number, associated with a milder inflammatory reaction, and first appear approximately 1 week later than with the intraperitoneal route.

During the past decade, mice have replaced hamsters as the model of choice for studying ocular toxoplasmosis. Mouse models offer the advantages of a completed genome, the wide availability of knock-out strains, and the ability to reproduce many features of human ocular toxoplasmosis.

Babesia microti

Babesia spp. are protozoal pathogens that infect red blood cells. Many *Babesia* spp. are found in animals, but *Babesia microti* is the main cause of infection in humans and is transmitted by *Ixodes scapularis* ticks (Vannier et al., 2008). Babesiosis in humans can range from asymptomatic to life-threatening. Hemolytic anemia and flu-like symptoms are possible, especially in people without a functional spleen or in people that are otherwise immunocompromised (Vannier et al., 2008).

Syrian hamsters provide a reliable model of babesiosis through intraperitoneal inoculation with *B. microti*-infected red blood cells (Wozniak et al., 1996). Without treatment, infection is patent for 3–5 weeks, and hamsters develop severe anemia and marked parasitemia with low mortality. Parasitemia is evident by day 7 post-inoculation, with a peak parasitemia occurring by day 14. This is followed by a carrier state with low or undetectable levels of parasites.

Because Syrian hamsters are highly susceptible to *B. microti* infection they are commonly utilized to

maintain *B. microti* within the laboratory. *B. microti*-infected hamster blood can be used to infect other animals or they may be used for in vitro studies of *Babesia* during infection of erythrocytes.

The hamster model also provides a valuable tool for assessing new therapeutic options for human babesiosis. Drug treatments are initiated once parasitemia reaches 3–7% of the total red blood cell population (Marley et al., 1997). To determine whether a treatment elicits a complete cure, blood is drawn from a treated hamster 14 days after the last drug dose and administered by intraperitoneal injection into a naïve sentinel hamster. The sentinel hamster is then monitored weekly for 6 weeks for development of parasitemia by examination of thin blood smears (Marley et al., 1997).

Utilizing this experimental approach, clindamycin consistently eradicates *B. microti* in hamsters (Rowin et al., 1982). The combination of quinine and clindamycin results in a more significant and faster therapeutic response and is now the treatment of choice for severely ill human patients with babesiosis (Rowin et al., 1982; Wittner et al., 1996). The combination of atovaquone and azithromycin also eliminates *B. microti* in hamsters and is an alternate therapy for human cases of babesiosis that are resistant to clindamycin and quinine (Falagas and Klemperer, 1996; Wittner et al., 1996).

Leishmania donovani

Visceral leishmaniasis is caused by *Leishmania donovani*, an intracellular protozoan transmitted by sandflies (Chappuis et al., 2007). Visceral leishmaniasis is a progressive disease characterized by prolonged fever, hepatosplenomegaly, anemia, leukopenia, severe weight loss, and ultimately death (McAdam and Sharpe, 2010). Pentavalent antimonial drugs, such as sodium stibogluconate, are the treatment of choice, despite harmful side effects and significant levels of drug resistance (Sundar et al., 2000). Identifying more effective chemotherapeutics is the focus of research for this disease (Wyllie and Fairlamb, 2006).

Hamsters can be experimentally infected with *L. donovani* by intracardiac injection under anesthesia or intraperitoneal injection of amastigotes (Dea-Ayuela et al., 2007; Wyllie and Fairlamb, 2006). Intracardiac injection results in a more rapid infection than the intraperitoneal route; however, the intraperitoneal route results in a greater parasite burden in the spleen (Wyllie and Fairlamb, 2006). Systemic *L. donovani* infection results in clinicopathological features that closely mimic the human disease (Melby et al., 2001). Infection of the hamster results in a persistent increase in parasite burden, progressive cachexia, hepatosplenomegaly, pancytopenia, hypergammaglobulinemia, and ultimately death (Melby et al., 2001).

Early detection of infection can be accomplished using a latex agglutination test developed to diagnose

visceral leishmaniasis in dogs (Wyllie and Fairlamb, 2006). The assay is based on detection of a low-molecular-weight glycoconjugate in the urine. Hamster urine must be diluted 1:10 in phosphate-buffered saline before testing due to its concentrated nature, which creates a vast excess of antigen in the test sample that can result in false-negative results.

Weight loss is the most commonly used antemortem indicator of infection in live hamsters (Wyllie and Fairlamb, 2006). Early detection of infection can be accomplished by comparing body weights between inoculated and control juvenile hamsters where control hamsters gain weight significantly faster than age-matched infected hamsters (Wyllie and Fairlamb, 2006). Weight loss of 25% is used as the end-point for tissue collection and post-mortem analysis and parasite burden can be purified and quantified from a homogenate of the spleen at this endpoint (Dea-Ayuela et al., 2007).

Trypanosoma cruzi

Chagas disease is caused by the flagellate protozoan *Trypanosoma cruzi* (Kirchhoff, 1993). In Chagas-endemic areas of Central and South America, the most common route of infection is from the triatomine insect, which shed *T. cruzi* in their feces. Chagas disease is comprised of two phases, acute and chronic. The acute phase lasts for the first few weeks or months following infection and symptoms include fever, fatigue, body aches, headache, rash, anorexia, diarrhea, and vomiting (Kirchhoff, 1993). Gross lesions may include splenomegaly, hepatomegaly, lymphadenopathy, and local swelling at the site of parasite entry. Rarely, young children or immunocompromised people develop fatal myocarditis or meningoencephalitis (Kirchhoff, 1993). During the chronic phase, infection may remain dormant for decades; however, up to 30% of infected people will develop life-threatening inflammatory cardiomyopathy 15–30 years following infection (Koberle, 1968).

Syrian hamsters, following intraperitoneal injection of *T. cruzi*, develop a *T. cruzi*-induced cardiomyopathy resembling human Chagas cardiomyopathy, and display high levels of anti-*T. cruzi* IgG antibodies (Bilate et al., 2003). *T. cruzi* infection results in the death of some hamsters during the acute phase, within the first 4 months of infection, and during the chronic phase, after 8 months of infection (Bilate et al., 2003). All infected animals develop myocarditis, interstitial fibrosis, and mild-to-severe left ventricular dysfunction (Bilate et al., 2003). In the chronic phase, hamsters also develop ventricular dilation and a decrease in ventricle wall thickness (Bilate et al., 2003). Hamsters do not develop apical or segmental wall hypcontractility, which are additional features of human Chagas cardiomyopathy (Bilate et al., 2003).

The Chagas disease hamster model allows quantitative evaluation of left ventricular function and

myocardial lesions throughout progression of the disease. Novel therapeutics and their effect on the progression of cardiac disease can therefore be evaluated rapidly using the acute and chronic hamster model (Bilate et al., 2003).

Opisthorchis viverrini

Epidemiological studies reveal a high prevalence of cholangiocarcinoma in northeast Thailand (Sriamporn et al., 2004). In this region, the traditional diet exposes the local population to infection with the liver fluke *Opisthorchis viverrini* and nitrosamines through consumption of contaminated water and salt-fermented fish (Pairojkul et al., 1991). The use of a Syrian hamster model established a connection between *O. viverrini* infection, consumption of nitrosamine, and the development of cholangiocarcinoma (Pairojkul et al., 1991).

Syrian hamsters can be readily infected with *O. viverrini* by oral administration of metacercariae. Infection results in inflammation and fibrosis in the periductular region of the liver, similar to human infection (Chaimuangraj et al., 2003; Pairojkul et al., 1991). Feeding *O. viverrini*-infected hamsters subcarcinogenic doses of dimethylnitrosamine results in the development of cholangiocarcinomas in up to 93% of hamsters (Thamavit et al., 1987). In contrast, administration of subcarcinogenic doses of dimethylnitrosamine alone or infection with *O. viverrini* alone does not cause cancer in this animal model, suggesting that these factors interact to produce cholangiocarcinoma (Thamavit et al., 1987, 1996).

After experimental infection with *O. viverrini*, liver procollagen prolyl hydroxylase activity increases, reflecting increased collagen synthesis that is proportional to the intensity of liver fluke infection (Hutadilok et al., 1983). Liver fluke infestation likely acts as an epigenetic promotor of tumor formation, rather than a frank genomic mutagen, by inducing inflammatory and fibrotic changes in the liver (Pairojkul et al., 1991). This is supported by similar studies that utilize complete bile duct ligation in hamsters which results in biliary inflammation and proliferation. If this procedure is performed in hamsters treated with subcarcinogenic doses of dimethylnitrosamine, promotion of cholangiocellular lesions develop similar to the findings in *O. viverrini* infection (Thamavit et al., 1993).

Taenia spp.

Humans are the natural definitive host for *Taenia solium* and *Taenia saginata* (Avila et al., 2002). Human taeniosis is acquired by ingestion of cysticerci in raw or undercooked pork or beef. In the human small intestine, the cysticerci attach to the intestinal wall and develop into adult tapeworms which become gravid approximately 4 months after infection (Avila et al., 2002; McAdam and Sharpe, 2010). Taeniosis is usually

asymptomatic but may result in mild gastrointestinal disturbances (McAdam and Sharpe, 2010). In contrast, when humans ingest embryonated eggs through ingestion of food or water contaminated with human feces, they may serve as intermediate hosts (cysticercosis) (McAdam and Sharpe, 2010). The larvae hatch, penetrate the intestinal wall and disseminate to other organs where they encyst (McAdam and Sharpe, 2010). Cysticerci develop in the central nervous system, heart, eyes, subcutaneous tissue, and skeletal muscle. Clinical manifestations depend on where the cysticerci develop and may include neurologic, cardiac, or ocular deficits, or even death (Avila et al., 2002, 2006).

Hamsters can successfully become infected with adult *Taenia* spp. by being fed cysticerci encysted in rodent muscle (Wang et al., 1999). Oral gavage of cysticerci without muscle encasement results in digestion of the cysticerci and no colonization with adult tapeworms (Wang et al., 1999). Tapeworms grow better in hamsters that are immunosuppressed with steroids; however, it is unclear if this is due to a direct effect of the steroids on the tapeworm or due to depression of the host immune response (Avila, 2006). Tapeworms reach lengths in excess of 30 cm after 30 days, but do not form gravid proglottids in the hamster model (Allan et al., 1991).

Utilizing the hamster model, an ELISA, which detects a *Taenia* spp.-specific fecal antigen, was developed and standardized (Allan et al., 1990). In contrast to identification of eggs in the feces, this test can be used to diagnose infection even during the prepatent period. Additionally, the hamster model can be used to study the morphological and ultrastructural attachment of adult tapeworms to the intestinal wall, the results of which may contribute to a better understanding of the biology of tapeworm infections (Merchant et al., 1998).

Ancylostoma ceylanicum

Hookworm infection affects hundreds of millions of people living in tropical and subtropical climates around the world. Adult hookworms attach to the intestinal mucosa and feed on blood from lacerated capillaries. Chronic hemorrhage from the site of attachment leads to iron-deficiency anemia, serum protein loss, and intestinal inflammation (Held et al., 2006).

Unlike mice, Syrian hamsters are fully permissive hosts for the development of adult *Ancylostoma ceylanicum* hookworms (Bungiro et al., 2003; Carroll et al., 1983). Hamsters can be inoculated with infective *A. ceylanicum* third-stage larvae via oral gavage (Mendez et al., 2005). Hookworm eggs can be detected in the feces 14 days following infection and live adult hookworms can be recovered from the small intestine and colon (Mendez et al., 2005). Infected hamsters experience anemia, weight loss, growth delay, and chronicity of infection, just like children that are infected with

hookworms, making them an excellent model for the study of human hookworm infection (Held et al., 2006; Mendez et al., 2005).

Hamsters can also be orally inoculated with adult *A. ceylanicum* (Bungiro et al., 2003). This method allows for the specific study of host responses to bloodfeeding adult hookworms without the confounding influence of prior larval exposure. This model provides the added benefits of allowing for manipulation of adult hookworms by immunologic, genetic, or pharmacologic methods prior to inoculation into the hamsters and for the study of single-sex infections.

Schistosoma spp.

Schistosomiasis is one of the most prevalent parasitic diseases affecting humans in tropical and subtropical climates, with an estimated 779 million people at risk and over 200 million infected (Steinmann et al., 2006). Following percutaneous invasion flukes mature and lay eggs within hepatic or pelvic blood vessels and eggs migrate to the liver, intestine, or bladder, causing inflammation and scarring possibly leading to hepatic cirrhosis.

Syrian hamsters can be readily infected with *Schistosoma* spp. cercariae via percutaneous or subcutaneous inoculation (Botros et al., 2004). Chemotherapeutic agents can be tested for effectiveness against the juvenile stage of infection by administration at 21 days post inoculation and against adult worms by administration at 49 days post inoculation.

Prion Diseases

Transmissible spongiform encephalopathies (TSE), such as Creutzfeldt-Jakob disease in humans, bovine spongiform encephalopathy in cattle, or scrapie in sheep are fatal neurodegenerative diseases of the central nervous system (Kratzel et al., 2007a, 2007b). A common feature of TSE is that normal host cellular prion protein (PrP^C), which is strongly expressed by cells of the nervous and lymphoreticular systems, converts into an abnormal disease-specific prion protein (e.g. PrP^{Sc} in scrapie) (Kratzel et al., 2007b). This abnormal prion protein is a biochemical marker for TSE and is linked with infectivity.

TSE can be transmitted by oral, intracerebral, intravenous, intraperitoneal, and subcutaneous routes, but the most common route is through ingestion (Kratzel et al., 2007b). To study the course of disease following the oral route of infection, hamsters can be infected with scrapie by housing them with other hamsters that were intracerebrally inoculated with scrapie prions as weanlings (Prusiner et al., 1985). The experimental hamsters cannibalize the infected hamsters when they become terminally ill. Approximately 120 days after

consuming scrapie-infected brain, progressive neurologic signs including ataxia, tremors, and head bobbing develop, and death occurs about 20 days later (Prusiner et al., 1985).

Injection of scrapie-infected brain homogenate into the foot pad using a 27-gauge needle provides an alternative route of experimental infection (Kratzel et al., 2007b). Clinical signs, starting with muscle tremors, begin approximately 78 days following unilateral foot pad injection (Kratzel et al., 2007b). This method of inoculation provides a shorter incubation time than oral inoculation and allows the distribution of scrapie prion protein in nerve tissue to be assessed at various time points. Utilizing this method, scrapie prion protein is detected in the ipsilateral sciatic nerve 60 days post infection and 80 days post infection in the contralateral nerve (Kratzel et al., 2007b). Within the brain, the red nucleus correlating with the ipsilateral sciatic nerve produces stronger prion protein immunoreactivity compared to the contralateral nucleus. These findings suggest centripetal propagation to the CNS and subsequent centrifugal spread to other nerve projections (Kratzel et al., 2007b).

The role of the lymphoreticular system on the pathogenesis of TSE is also studied using the unilateral footpad infection model (Kratzel et al., 2007a). Scrapie prion protein is consistently detected in the ipsilateral popliteal lymph node as early as 2 days post-inoculation. In contrast, the contralateral popliteal lymph node remains negative throughout the study, indicating that systemic spread of scrapie prion protein through the lymphoreticular system does not occur (Kratzel et al., 2007a). Removal of the ipsilateral popliteal lymph node 4 weeks prior to infection with scrapie does not affect the incubation period or mean survival time at high or medium doses; however, at low doses, hamsters remain free of clinical symptoms for 314 days post inoculation (duration of experiment) (Kratzel et al., 2007a). These data suggest that very low doses of scrapie may require replication in the lymphoreticular system prior to invasion of the nervous system (Kratzel et al., 2007a).

OTHER MODELS

Amyloidosis

Amyloidosis is an abnormal deposition of highly ordered proteinaceous material in various organ systems of humans and animals (Coe and Ross, 1990). There are currently 20 clinical syndromes in humans associated with amyloid deposition and each syndrome is classified into primary or secondary amyloidosis based on chemical composition (Hukkanen et al., 2006). Primary amyloidosis is the result of overproduction of immunoglobulin light chains and is principally of

neoplastic or genetic origin. Reactive or secondary amyloidosis is the result of the accumulation of β -pleated fibrils composed of serum amyloid A (SAA), an acute-phase protein associated with inflammation (Hukkanen et al., 2006). In addition to SAA, in reactive amyloidosis, amyloid deposits contain a minor protein component called amyloid P (AP) derived from serum AP (SAP) (Coe and Ross, 1990). Amyloidosis occurs both spontaneously and after induction with amyloid-inducing substances in Syrian hamsters. The spontaneous disease is more prevalent in females compared to males and spontaneous occurrence is promoted by fight wounds, stress, high-protein diets, and various infectious agents (Gruys and Snel, 1994). Syrian hamsters are commonly used as a model of induced amyloidosis, using casein or lipopolysaccharide (LPS) subcutaneous injections (Hol et al., 1986; Niewold et al., 1987). The lag or pre-amyloid phase associated with these amyloid-inducing substances can be accelerated by intraperitoneal or subcutaneous injection with amyloid-enhancing factors (AEF), which are small fragments of amyloid fibrils (Hol et al., 1986; Niewold et al., 1987). AEF injection shortens the pre-amyloid phase for splenic, hepatic, and renal amyloid deposition (Hol et al., 1986).

Syrian hamsters are unique when compared to other animal models of secondary amyloidosis because they have an SAP homolog called female protein (FP) which is under estrogenic control (Coe and Ross, 1990). The hamster amyloid model provides the unique opportunity to hormonally manipulate the synthesis of FP and study concurrent amyloid deposition. Female hamsters, when compared to males, possess higher serum concentrations of FP, acquire more amyloid at an earlier age and die at an earlier age due to amyloid accumulation (Coe and Ross, 1990). In the Syrian hamster, FP rather than amyloid fibril, plays a predominant role in the sex-limited expression of amyloidosis (Coe and Ross, 1990). Male Syrian hamsters that are deprived of testosterone by castration or administered diethylstilbestrol (DES) acquire amyloid deposition at an earlier age similar to female hamsters (Coe and Ross, 1990). The amyloidogenic effect of DES in male hamsters is inhibited by testosterone injections, and female hamsters given testosterone are also protected from amyloid deposition (Coe and Ross, 1990). These studies established the importance of FP in this disease and it is hypothesized that FP undergoes calcium-dependent binding of amyloid fibrils which stabilizes and protects the amyloid fibrils after formation (Coe and Ross, 1990).

Sex Behavior and Steroids

Sexual behavior of male humans and most other male mammals is dependent upon gonadal androgen secretion (Meisel and Sachs, 1994). Using a hamster

model, Schulz and colleagues described the two-stage model of sexual behavior development (Schulz and Sisk, 2006). The first stage is the perinatal period when neural circuits become sexually differentiated and the initial programming of adult responses to hormones occurs. The second stage is adolescence, when the structural and functional organization of behavioral circuits are refined and completed, resulting in the expression of sex-typical social behaviors. The presence of testosterone during adolescence results in adults who more readily display male-typical social behaviors compared to adults that matured in the absence of testosterone (Schulz and Sisk, 2006). The testosterone exposure during adolescence defeminizes the brain and behavioral responses to estradiol and progesterone (Schulz and Sisk, 2006).

Castrated male Syrian hamsters that are treated daily with 1000 μ g of dihydrotestosterone (DHT) do not display copulatory behavior or interest in female hamsters in estrus (Arteaga-Silva et al., 2005). In contrast, castrated males treated with 50 μ g of estradiol (E2) show sexual motivation but do not display the ejaculation reflex (Arteaga-Silva et al., 2005). Combined treatment with DHT and E2 restores all components of male sexual behavior in castrated males (Arteaga-Silva et al., 2005). Castrated male Syrian hamsters that receive brief infrequent elevations of testosterone display male sexual behavior (Piekarski et al., 2009). This provides a useful model to assess the neuroendocrine basis of male sexual behavior and raises the possibility that infrequent low-dose androgen replacement may restore sexual behavior in hypogonadal men without inducing negative side-effects.

Flank marking, like reproductive behavior, is activated by testosterone in adulthood (Albers et al., 2002; Johnston, 1981). In contrast, attack behavior toward another male in a resident-intruder paradigm is significantly higher prior to puberty when compared to adulthood, indicating that attack behavior is not under the influence of physiologic testosterone (Romeo et al., 2003). Therefore, exposure to gonadal hormones during adolescence and adulthood facilitates aggression towards an intruder and flank-marking behavior, respectively (Romeo et al., 2003).

Anabolic steroids are abused by humans for their tissue-building potency and performance-enhancing effects. These steroids induce a variety of negative effects including heightened aggression, changes in sexual libido, testicular atrophy, baldness, cancer, and cardiovascular disease (Leshner, 2000). Hamsters are used to study the deleterious behavioral effects of exogenous steroid administration. Specifically adolescent (post-pubertal) male hamsters exposed to anabolic steroids for 2–4 weeks show an increase in aggression (DeLeon et al., 2002; Grimes and Melloni, 2002; Melloni and

Ferris, 1996). In addition, when adolescent hamsters are given exogenous anabolic steroids they do not express submissive behaviors such as defensive posturing, escape dashes, or tail-up walking (Salas-Ramirez et al., 2008). Both adolescent male and adult male hamsters treated with anabolic steroids display increased flank marking. In adolescent hamsters, exposure to anabolic steroids results in levels of sexual behavior comparable to adult hamsters. In contrast, steroid administration in adult hamsters results in decreased sexual behavior compared to untreated controls. These studies suggest that the adolescent brain is more vulnerable than the adult brain to the adverse behavioral consequences of exogenous steroids (DeLeon et al., 2002; Grimes and Melloni, 2002; Melloni and Ferris, 1996; Salas-Ramirez et al., 2008).

The addiction potential of anabolic steroids is evaluated using a classical self-administration paradigm of drug abuse (Madden et al., 1980; Panlilio et al., 2003). Castrated male hamsters that are supplemented with testosterone self-administer additional testosterone at all doses tested (DiMeo and Wood, 2004). In contrast, when testosterone is not exogenously administered, castrated males do not self-administer testosterone (DiMeo and Wood, 2004). These findings indicate that circulating androgens enhance the desire to self-administer testosterone. This study also provides strong evidence that exogenous testosterone administration, particularly in individuals that possess endogenous testosterone, poses a strong potential for addiction.

Nutritional Infertility

Limited food availability diminishes fertility in mammals, particularly in females (Bronson, 1989). The hamster provides a model to evaluate the deleterious effects of inadequate nutrition on fertility. A negative energy balance in hamsters suppresses ovulatory cycles and estrus behavior (Wade et al., 1996). Food deprivation decreases estrogen receptor immunoreactivity in the ventromedial hypothalamus, implying a direct neurological effect of food deprivation in sexual behavior. Treatment with leptin promotes female sexual behavior in ad libitum-fed hamsters; however, in food-deprived hamsters, leptin treatment fails to overcome the loss of estrus behavior associated with poor nutrition. Interestingly, leptin-induced changes in female sexual behavior are not accompanied by changes in estrogen receptor immunoreactivity of the hypothalamus, implying that leptin acts via another mechanism (Wade et al., 1997). Neuropeptide Y (NPY) may play a role in nutritional infertility. Injections of NPY into the central nervous system stimulate robust and long-lasting increases in food intake in hamsters while simultaneously reducing estrus behavior (Corp et al., 2001; Kulkosky et al.,

1988). These studies provide strong evidence that multiple pathways (leptin and NPY) control alterations in female nutrition-associated fertility.

Generalized Dystonia

Dystonia, characterized by involuntary twisting movements and abnormal postures caused by co-contractions of antagonistic muscle groups, is the third most common movement disorder in humans (Raike et al., 2005). The disease is a heterogeneous disorder because patients display clinical signs associated with many different brain regions. Primary dystonia is inherited or arises spontaneously, and secondary dystonia follows brain trauma or insult. These disorders can be further classified, based on affected muscle groups, as focal (involving a small number of muscles) or generalized dystonia (involving all of the muscles throughout the body). The dt^{sz} disorder exhibited in the Bio 86.93 inbred line of Syrian hamsters is an animal model of generalized dystonia (Loscher et al., 1989; Raike et al., 2005). The disorder in hamsters, originally designated sz because of the seizure-like presentation, is inherited in an autosomal recessive fashion (Loscher et al., 1989). The mutation was later renamed dystonic and symbolized as dt^{sz} . In hamsters, dystonic attacks last several hours, vary in severity, progress from the head to the extremities, and are partially age-dependent with signs mostly disappearing after 8 weeks of age (Raike et al., 2005). The dt^{sz} phenotype is modified by hormonal fluctuations and late-term pregnant and nursing dt^{sz} hamsters experience attacks (Raike et al., 2005). Attacks begin with rapid vibrissae twitching, flattening of the ears, and facial contortions, followed by stiffening of the hindlimbs, gait abnormalities, and falling episodes, ending with limb hyperextension, severe truncal torsion, and immobility (Loscher et al., 1989; Raike et al., 2005). The dystonic attacks are stress-induced and initiated by placing the hamsters in a new environment. The motor disturbances can also be pharmacologically initiated with subconvulsant doses of pentylenetetrazol (PTZ), picrotoxin, or inverse benzodiazepine receptor agonists (Gernert et al., 1999; Loscher et al., 1989). The generalized syndrome in humans shares many phenotypic features with hamster dystonia including prolonged attacks lasting up to 4 hours, onset in infancy or childhood, and attacks initiated by stress or excitement (Loscher et al., 1989).

Wound Healing

Traumatic damage to tissue is followed by a complex cascade of tissue-repair events that involve overlapping inflammatory, proliferative, and remodeling phases. Research into understanding the process of tissue repair

focuses on the role of epithelial cells, fibroblasts, endothelial cells, and inflammatory cells (Wong et al., 1993).

Hamsters provide an excellent model for elucidating the role of eosinophils in wound healing (Wong et al., 1993). The induced model involves creating a circular transdermal wound between the shoulder blades and leaving the wound open to heal by secondary intention (Wong et al., 1993). In normal hamster skin, eosinophils are rarely found; however, a prominent eosinophilic infiltrate occurs during cutaneous wound healing. The eosinophils, and other inflammatory cells, provide a cellular source of two cytokines, transforming growth factor- α (TGF- α) and TGF- β_1 , both important regulators of wound healing.

These two cytokines are expressed from eosinophils in a temporal fashion. Eosinophil expression of TGF- α peaks 5 days after cutaneous injury (Wong et al., 1993) followed by a gradual decline. In contrast, expression of TGF- β_1 gradually increases throughout wound healing. The early expression of TGF- α is implicated in epithelial migration, proliferation, and angiogenesis (Barrandon and Green, 1987; Schreiber et al., 1986). Later expression of TGF- β_1 is believed to contribute to the down-regulation of epithelial migration and proliferation, as well as to granulation tissue formation (Quaglino et al., 1990).

Yang et al. (1997) developed an eosinophil-deficient hamster model by treating with anti-interleukin-5 monoclonal antibody (TRFK-5), which inhibits the IL-5-dependent pathway of eosinophil differentiation and maturation. TRFK-5 is injected intraperitoneally 7 and 4 days before and on the same day as wound creation. An absence of eosinophils results in accelerated re-epithelialization of cutaneous wounds, with wound closure occurring 4 days faster than in non-TRFK-5-treated animals. One mechanism which could explain the accelerated wound healing is a reduction in TGF- β_1 , which is antiproliferative for keratinocytes. Eosinophil depletion may be clinically relevant for the treatment of wounds to accelerate wound closure.

Due to the hamster's relatively large oral cavity, an 8-mm circular wound can be created in the oral mucosa overlying the masseter muscle and allowed to heal by secondary intention, providing an excellent model for comparing oral and cutaneous wounds. Similar to cutaneous wounds, eosinophils infiltrate oral wounds and express TGF- β_1 , however, they do not express TGF- α (Yang et al., 1996). The lack of TGF- α expression by eosinophils in oral wounds may reflect the presence of TGF- α and epidermal growth factor (EGF) in hamster saliva. Oral eosinophils can be induced to express TGF- α by first performing sialoadenectomy of the submaxillary and sublingual complex to knock-out the salivary-associated TGF- α and epidermal growth factor (EGF) (Yang et al., 1996). Furthermore, oral eosinophils cease producing TGF- α when EGF is supplemented in

the drinking water. This suggests that EGF and TGF- α in the saliva are responsible for the decreased production of eosinophil-associated TGF- α in oral wounds.

NSAID Gastropathy

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used group of drugs in medicine (Roth, 1988). Although these drugs are extensively utilized, they may result in significant gastrointestinal injury (Tamblyn et al., 1997). The ability of NSAIDs to inhibit prostaglandin synthesis leads to anti-inflammatory and pain reduction, but also compromises the protective properties of the gastric mucosa, potentially leading to gastric mucosal erosions and ulcers (Roth, 1996).

The hamster model of NSAID-induced gastric ulceration is created by subcutaneously injecting indometacin into hamsters (Kolbasa et al., 1988). Indometacin produces gastric antral ulcers in hamsters within 1–5 hours post-administration in a dose-dependent fashion. With repeated administration of indometacin, the gastric lesions become more severe and most hamsters die with perforated antral ulcers after 2–5 days. Indometacin reduces the antral mucosa production of prostaglandin E₂, prostaglandin F_{2 α} , and 6-keto prostaglandin F_{1 α} and increases gastric acid output more than twofold. The ulcers created in this model may be prevented by anti-secretory agents such as cimetidine, methscopolamine bromide, and omeprazole (Kolbasa et al., 1988).

To create a chronic NSAID-induced gastropathy model in hamsters which more closely mimics the disease process in humans, naproxen can be administered twice daily by oral gavage (Fitzpatrick et al., 1999). Gastric ulceration occurs almost exclusively in the antrum and increases in size as a function of dose and time for the first 3 days of naproxen treatment. At a dose of 80 mg/kg given twice a day, naproxen can be used for chronic anti-ulcer drug studies with a low (<5%) mortality rate (Fitzpatrick et al., 1999). Gastric ulcer area decreases in naproxen-treated hamsters by the fourth day of administration, suggesting adaptation of the gastric mucosa. The process of adaptation involves stimulation of gastric mucosal healing and the creation of a gastric mucosa that is more resistant to future injurious agents (Levi and Shaw-Smith, 1994).

The naproxen-induced model provides a useful system to study anti-ulcer drugs. Misoprostol, a prostaglandin analog, when administered in conjunction with naproxen, results in a significant reduction in number and size of gastric ulcers without modifying gastric acid secretion (Fitzpatrick et al., 1999). This same protection is noted in humans (Dajani and Agrawal, 1995). Famotidine, an H₂-receptor antagonist that inhibits stomach acid production, does not reduce the prevalence or number of gastric ulcers in the hamster

(Fitzpatrick et al., 1999). Similarly, H₂-receptor antagonists do not consistently reduce NSAID-induced gastric ulceration in humans (Dajani and Agrawal, 1995). These results suggest that gastric acid secretion is not the primary mechanism of naproxen-induced ulceration in hamsters or humans and that the naproxen hamster model accurately models NSAID-induced antral ulceration in humans (Fitzpatrick et al., 1999).

Gastric ulcer models have also been developed in rats and rabbits using subcutaneous administration of indometacin. Limitations of the rat model include the addition of profound intestinal ulceration and high mortality (Satoh et al., 1981). The rabbit antral ulcer model displays ulcers that are morphologically similar to human ulcers without the high mortality or intestinal injury noted in rats (Wallace and McKnight, 1993); however, the relatively large size of rabbits may make them less desirable when compared to hamsters.

Human Fertility

The hamster zona-free oocyte penetration assay is used to examine human male fertility (Aitken, 2006). This assay was first described in 1980 and involves the incubation of human sperm with hamster eggs that have undergone zona removal (Overstreet et al., 1980). The assay can be utilized both clinically and experimentally to determine human sperm fertility and it analyzes the ability of sperm to capacitate eggs, undergo the acrosome reaction, and fuse with the oocyte. Limitations of the assay are that it is labor-intensive, and difficult to standardize. Despite these limitations, results obtained in the hamster assay correlate well with human in vitro fertilization. Since intracytoplasmic sperm injection (ICSI) is replacing standard IVF in many settings the utility of the zona-free hamster assay from a clinical perspective may be waning.

References

- Adler, S., 1948. Origin of the golden hamster *cricketus auratus* as a laboratory animal. *Nature* 162, 256.
- Aitken, R.J., 2006. Sperm function tests and fertility. *Int. J. Androl.* 29, 69–75, [discussion 105–108](#). [10.1111/j.1365-2605.2005.00630.x](#).
- Alberg, A.J., 2008. Cigarette smoking: health effects and control strategies. *Drugs Today (Barc)*. 44, 895–904. [10.1358/dot.2008.44.12.1308898](#)
- Albers, H.E., Huhman, K.L., Meisel, R.L., 2002. Hormonal basis of social conflict and communication. In: Pfaff, D. (Ed.), *Hormones, Brain and Behavior*. Academic Press, pp. 393–433.
- Alder, J., Jarvis, K., Mitten, M., Shipkowitz, N.L., Gupta, P., Clement, J., 1993. Clarithromycin therapy of experimental *treponema pallidum* infections in hamsters. *Antimicrob. Agents Chemother.* 37, 864–867.
- Al-Eidan, F.A., McElnay, J.C., Scott, M.G., Kearney, M.P., 2000. *Clostridium difficile*-associated diarrhoea in hospitalised patients. *J. Clin. Pharm. Ther.* 25, 101–109.
- Allan, J.C., Avila, G., Garcia Noval, J., Flisser, A., Craig, P.S., 1990. Immunodiagnosis of taeniasis by coproantigen detection. *Parasitology* 101 (Pt 3), 473–477.
- Allan, J.C., Garcia-Dominguez, C., Craig, P.S., Rogan, M.T., Lowe, B.S., Flisser, A., 1991. Sexual development of *taenia solium* in hamsters. *Ann. Trop. Med. Parasitol.* 85, 573–576.
- Allison, A.C., Chesterman, F.C., Baron, S., 1967. Induction of tumors in adult hamsters with simian virus 40. *J. Natl. Cancer Inst.* 38, 567–572.
- Antoniou, S.A., 2006. Pirfenidone for the treatment of idiopathic pulmonary fibrosis. *Expert Opin. Investig. Drugs* 15, 823–828. [10.1517/13543784.15.7.823](#).
- Arbeeny, C.M., Meyers, D.S., Bergquist, K.E., Gregg, R.E., 1992. Inhibition of fatty acid synthesis decreases very low density lipoprotein secretion in the hamster. *J. Lipid Res.* 33, 843–851.
- Arean, V.M., 1962. The pathologic anatomy and pathogenesis of fatal human leptospirosis (weil's disease). *Am. J. Pathol.* 40, 393–423.
- Ar'Rajab, A., Ahren, B., 1993. Long-term diabetogenic effect of streptozotocin in rats. *Pancreas* 8, 50–57.
- Arteaga-Silva, M., Marquez-Villanueva, Y., Martinez-Garcia, R., Hernandez-Gonzalez, M., Bonilla-Jaime, H., Retana-Marquez, S., 2005. Effects of hormonal replacement with androgens and estrogens on male sexual behavior and plasma levels of these steroids in gonadectomized golden hamsters (*mesocricetus auratus*). *Physiol. Behav.* 85, 571–580. [10.1016/j.physbeh.2005.06.004](#).
- Asami, Y., Yamagishi, I., Akiyoshi, K., Tomoike, H., Tsuchida, K., Higuchi, S., 1999. Inhibitory effect of TS-962 on the formation of early atherosclerotic lesions in high fat-fed hyperlipidemic hamsters. *Atherosclerosis* 146, 237–242.
- Avila, G., Aguilar, L., Benitez, S., Yepez-Mulia, L., Lavenat, I., Flisser, A., 2002. Inflammatory responses in the intestinal mucosa of gerbils and hamsters experimentally infected with the adult stage of *taenia solium*. *Int. J. Parasitol.* 32, 1301–1308.
- Avila, G., Teran, N., Aguilar-Vega, L., Maravilla, P., Mata-Miranda, P., Flisser, A., 2006. Laboratory animal models for human *taenia solium*. *Parasitol. Int.* 55 (Suppl.), S99–S103. [10.1016/j.parint.2005.11.015](#).
- Ayyad, N., Cohen, B.I., Mosbach, E.H., Mikami, T., Mikami, Y., Ohshima, A., 1995. Hormonal control of cholesterol cholelithiasis in the female hamster. *J. Lipid Res.* 36, 1483–1488.
- Ayyad, N., Cohen, B.I., Mosbach, E.H., Miki, S., Mikami, T., Mikami, Y., et al. 1993. Age, sex and source of hamster affect experimental cholesterol cholelithiasis. *Lipids* 28, 981–986.
- Babcock, G.J., Broering, T.J., Hernandez, H.J., Mandell, R.B., Donahue, K., Boatright, N., et al. 2006. Human monoclonal antibodies directed against toxins A and B prevent *clostridium difficile*-induced mortality in hamsters. *Infect. Immun.* 74, 6339–6347. [10.1128/IAI.00982-06](#).
- Bajusz, E., Baker, J.R., Nixon, C.W., Homburger, F., 1969. Spontaneous, hereditary myocardial degeneration and congestive heart failure in a strain of syrian hamsters. *Ann. N. Y. Acad. Sci.* 156, 105–129.
- Barile, M.F., Chandler, D.K., Yoshida, H., Grabowski, M.W., Harasawa, R., Razin, S., 1988. Parameters of mycoplasma pneumoniae infection in syrian hamsters. *Infect. Immun.* 56, 2443–2449.
- Barrandon, Y., Green, H., 1987. Cell migration is essential for sustained growth of keratinocyte colonies: The roles of transforming growth factor-alpha and epidermal growth factor. *Cell* 50, 1131–1137.
- Bertuglia, S., Reiter, R.J., 2007. Melatonin reduces ventricular arrhythmias and preserves capillary perfusion during ischemia-reperfusion events in cardiomyopathic hamsters. *J. Pineal Res.* 42, 55–63. [10.1111/j.1600-079X.2006.00383.x](#).
- Bhat, H.K., Calaf, G., Hei, T.K., Loya, T., Vadgama, J.V., 2003. Critical role of oxidative stress in estrogen-induced carcinogenesis. *Proc. Natl. Acad. Sci. U. S. A* 100, 3913–3918. [10.1073/pnas.0437929100](#).
- Bhatt, N., Baran, C.P., Allen, J., Magro, C., Marsh, C.B., 2006. Promising pharmacologic innovations in treating pulmonary fibrosis. *Curr. Opin. Pharmacol.* 6, 284–292. [10.1016/j.coph.2006.03.003](#).

- Bilate, A.M., Salemi, V.M., Ramires, F.J., de Brito, T., Silva, A.M., Umezawa, E.S., et al. 2003. The syrian hamster as a model for the dilated cardiomyopathy of chagas' disease: a quantitative echocardiographical and histopathological analysis. *Microbes Infect.* 5, 1116–1124.
- Bilz, S., Samuel, V., Morino, K., Savage, D., Choi, C.S., Shulman, G.I., 2006. Activation of the farnesoid X receptor improves lipid metabolism in combined hyperlipidemic hamsters. *Am. J. Physiol. Endocrinol. Metab.* 290, E716–22. [10.1152/ajpendo.00355.2005](https://doi.org/10.1152/ajpendo.00355.2005).
- Bishop, R.W., 1992. Structure of the hamster low density lipoprotein receptor gene. *J. Lipid Res.* 33, 549–557.
- Boehler, N., Riottot, M., Ferezou, J., Souidi, M., Milliat, F., Serougne, C., et al. 1999. Antilithiasic effect of beta-cyclodextrin in LPN hamster: Comparison with cholestyramine. *J. Lipid Res.* 40, 726–734.
- Bolton, J.L., Thatcher, G.R., 2008. Potential mechanisms of estrogen quinone carcinogenesis. *Chem. Res. Toxicol.* 21, 93–101. [10.1021/tx700191p](https://doi.org/10.1021/tx700191p).
- Bortolanza, S., Alzuguren, P., Bunuales, M., Qian, C., Prieto, J., Hernandez-Alcoceba, R., 2007. Human adenovirus replicates in immunocompetent models of pancreatic cancer in syrian hamsters. *Hum. Gene Ther.* 18, 681–690. [10.1089/hum.2007.017](https://doi.org/10.1089/hum.2007.017).
- Borzzone, G., Liberona, L., Olmos, P., Saez, C., Meneses, M., Reyes, T., et al. 2007. Rat and hamster species differences in susceptibility to elastase-induced pulmonary emphysema relate to differences in elastase inhibitory capacity. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 293, R1342–R1349. [10.1152/ajpregu.00343.2007](https://doi.org/10.1152/ajpregu.00343.2007).
- Bos, J.M., Towbin, J.A., Ackerman, M.J., 2009. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* 54, 201–211. [10.1016/j.jacc.2009.02.075](https://doi.org/10.1016/j.jacc.2009.02.075).
- Botros, S., William, S., Ebeid, F., Cioli, D., Katz, N., Day, T.A., et al. 2004. Lack of evidence for an antischistosomal activity of myrrh in experimental animals. *Am. J. Trop. Med. Hyg.* 7, 206–210.
- Bronson, F.H., 1989. *Mammalian Reproductive Biology*. University of Chicago Press, Chicago, IL.
- Bungiro, R.D., Anderson, B.R., Cappello, M., 2003. Oral transfer of adult *Ancylostoma ceylanicum* hookworms into permissive and nonpermissive host species. *Infect. Immun.* 7, 1880–1886.
- Cantor, J.O., Cerreta, J.M., Armand, G., Turino, G.M., 1997. Further investigation of the use of intratracheally administered hyaluronic acid to ameliorate elastase-induced emphysema. *Exp. Lung Res.* 23, 229–244.
- Cantor, J.O., Shteyngart, B., Cerreta, J.M., Turino, G.M., 2002. The effect of lysozyme on elastase-mediated injury. *Exp. Biol. Med.* (Maywood) 227, 108–113.
- Capron, J.P., 1994. What are the characteristics of patients in whom cholesterol calculi are formed? *Gastroenterol. Clin. Biol.* 18, 988–995.
- Caron, A., Michelet, S., Caron, A., Sordello, S., Ivanov, M.A., Delaere, P., et al. 2004. Human FGF-1 gene transfer promotes the formation of collateral vessels and arterioles in ischemic muscles of hypercholesterolemic hamsters. *J. Gene Med.* 6, 1033–1045. [10.1002/jgm.594](https://doi.org/10.1002/jgm.594).
- Carroll, S.M., Grove, D.I., Dawkins, H.J., Mitchell, G.F., Whitten, L.K., 1983. Infections with a Malaysian dog strain of *Ancylostoma ceylanicum* in outbred, inbred and immunocompromised mice. *Parasitology* 87 (Pt 2), 229–238.
- Chaimuangraj, S., Thamavit, W., Tsuda, H., Moore, M.A., 2003. Experimental investigation of opisthorchiasis-associated cholangiocarcinoma induction in the syrian hamster - pointers for control of the human disease. *Asian Pac. J. Cancer. Prev.* 4, 87–93.
- Chappuis, F., Sundar, S., Hailu, A., Ghalib, H., Rijal, S., Peeling, R.W., et al. 2007. Visceral leishmaniasis: What are the needs for diagnosis, treatment and control?. *Nat. Rev. Microbiol.* 5, 873–882. [10.1038/nrmicro1748](https://doi.org/10.1038/nrmicro1748).
- Cheema, S.K., Cornish, M.L., 2007. Bio F1B hamster: A unique animal model with reduced lipoprotein lipase activity to investigate nutrient mediated regulation of lipoprotein metabolism. *Nutr. Metab. (Lond.)* 4, 27. [10.1186/1743-7075-4-27](https://doi.org/10.1186/1743-7075-4-27).
- Cicala, C., Pompetti, F., Carbone, M., 1993. SV40 induces mesotheliomas in hamsters. *Am. J. Pathol.* 142, 1524–1533.
- Clyde Jr., W.A., 1971. Immunopathology of experimental mycoplasma pneumoniae disease. *Infect. Immun.* 4, 757–763.
- Coe, J.E., Ross, M.J., 1990. Amyloidosis and female protein in the syrian hamster. concurrent regulation by sex hormones. *J. Exp. Med.* 171, 1257–1267.
- Cohen, B.I., Matoba, N., Mosbach, E.H., McSherry, C.K., 1989. Dietary induction of cholesterol gallstones in hamsters from three different sources. *Lipids* 24, 151–156.
- Cohen, B.I., Mosbach, E.H., Ayyad, N., Miki, S., McSherry, C.K., 1992. Dietary fat and fatty acids modulate cholesterol cholelithiasis in the hamster. *Lipids* 27, 526–532.
- Combettes-Souverain, M.M., Souidi, M., Parquet, M.A., Ferezou, J.M., Riottot, M.J., Serougne, C.J., et al. 2002. The syrian golden hamster strain LPN: a useful animal model for human cholelithiasis. *J. Nutr. Biochem.* 13, 226–236.
- Corp, E.S., Greco, B., Powers, J.B., Marin Bivens, C.L., Wade, G.N., 2001. Neuropeptide Y inhibits estrous behavior and stimulates feeding via separate receptors in syrian hamsters. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 280, R1061–R1068.
- Cosio Piqueras, M.G., Cosio, M.G., 2001. Disease of the airways in chronic obstructive pulmonary disease. *Eur. Respir. J. Suppl.* 34, 41s–49s.
- Crissey, J.T., Denenholz, D.A., 1984. Syphilis. *Clin. Dermatol.* 2, 1–166.
- Cruz, N., Arocho, L., Rosario, L., Crespo, M.J., 2007. Chronic administration of carvedilol improves cardiac function in 6-month-old syrian cardiomyopathic hamsters. *Pharmacology* 80, 144–150. [10.1159/000103254](https://doi.org/10.1159/000103254).
- Dajani, E.Z., Agrawal, N.M., 1995. Prevention of nonsteroidal anti-inflammatory drug-induced gastroduodenal ulcers: role of mucosal protective and gastric antisecretory drugs. *Dig. Dis.* 13 (Suppl. 1), 48–61.
- Dam, H., 1971. Determinants of cholesterol cholelithiasis in man and animals. *Am. J. Med.* 51, 596–613.
- Davis, M.J., Gore, R.W., 1985. A new preparation for microcirculatory studies of the hamster cheek pouch. *Am. J. Physiol.* 248, H143–H146.
- de Groot, H., Rauen, U., 2007. Ischemia-reperfusion injury: processes in pathogenetic networks: a review. *Transplant. Proc.* 39, 481–484. [10.1016/j.transproceed.2006.12.012](https://doi.org/10.1016/j.transproceed.2006.12.012).
- de With, M.C., Haug, S.J., Brigitte van der Heijden, E.P., Segal, S.S., 2005. Ischemia-reperfusion impairs ascending vasodilation in feed arteries of hamster skeletal muscle. *Microcirculation* 12, 551–561. [10.1080/10739680500253451](https://doi.org/10.1080/10739680500253451).
- Dea-Ayuela, M.A., Rama-Iniguez, S., Alunda, J.M., Bolas-Fernandez, F., 2007. Setting new immunobiological parameters in the hamster model of visceral leishmaniasis for in vivo testing of antileishmanial compounds. *Vet. Res. Commun.* 31, 703–717. [10.1007/s11259-007-0040-5](https://doi.org/10.1007/s11259-007-0040-5).
- Debauxe, G., Nonclercq, D., Ribaucour, F., Wiedig, M., Gerbaux, C., Leo, O., et al. 2006. Early expression of the helicase-like transcription factor (HLTF/SMARCA3) in an experimental model of estrogen-induced renal carcinogenesis. *Mol. Cancer* 5, 23. [10.1186/1476-4598-5-23](https://doi.org/10.1186/1476-4598-5-23).
- DeLeon, K.R., Grimes, J.M., Melloni Jr., R.H., 2002. Repeated anabolic-androgenic steroid treatment during adolescence increases vasopressin V(1A) receptor binding in syrian hamsters: Correlation with offensive aggression. *Horm. Behav.* 42, 182–191.
- Denny, F.W., Clyde Jr, W.A., Glezen, W.P., 1971. Mycoplasma pneumoniae disease: Clinical spectrum, pathophysiology, epidemiology, and control. *J. Infect. Dis.* 123, 74–92.
- Dhar, D., Spencer, J.F., Toth, K., Wold, W.S., 2009. Pre-existing immunity and passive immunity to adenovirus 5 prevents toxicity caused by an oncolytic adenovirus vector in the Syrian hamster model. *Mol. Ther.* 17, 1724–1732. [10.1038/mt.2009.156](https://doi.org/10.1038/mt.2009.156).

- Diamandopoulos, G.T., McLane, M.F., 1972. The tumor imprint technique for demonstrating SV40 T antigen by immunofluorescence. *Proc. Soc. Exp. Biol. Med.* 141, 62–66.
- DiCarlantonio, G., Talbot, P., 1999. Inhalation of mainstream and sidestream cigarette smoke retards embryo transport and slows muscle contraction in oviducts of hamsters (*Mesocricetus auratus*). *Biol. Reprod.* 61, 651–656.
- DiMeo, A.N., Wood, R.I., 2004. Circulating androgens enhance sensitivity to testosterone self-administration in male hamsters. *Pharmacol. Biochem. Behav.* 79, 383–389. [10.1016/j.pbb.2004.08.015](https://doi.org/10.1016/j.pbb.2004.08.015).
- Drosten, C., Gunther, S., Preiser, W., van der Werf, S., Brodt, H.R., Becker, S., et al. 2003. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N. Engl. J. Med.* 348, 1967–1976. [10.1056/NEJMoa030747](https://doi.org/10.1056/NEJMoa030747).
- Dwivedy, I., Devanesan, P., Cremonesi, P., Rogan, E., Cavalieri, E., 1992. Synthesis and characterization of estrogen 2,3- and 3,4-quinones. comparison of DNA adducts formed by the quinones versus horseradish peroxidase-activated catechol estrogens. *Chem. Res. Toxicol.* 5, 828–833.
- Ebara, T., Hirano, T., Mamo, J.C., Sakamaki, R., Furukawa, S., Nagano, S., et al. 1994. Hyperlipidemia in streptozocin-diabetic hamsters as a model for human insulin-deficient diabetes: comparison to streptozocin-diabetic rats. *Metabolism* 43, 299–305.
- Endrich, B., Asaishi, K., Gotz, A., Messmer, K., 1980. Technical report—a new chamber technique for microvascular studies in unanesthetized hamsters. *Res. Exp. Med. (Berl)*. 177, 125–134.
- Erlansson, M., Persson, N.H., Svensjo, E., Bergqvist, D., 1987. Macromolecular permeability increase following incomplete ischemia in the hamster cheek pouch and its inhibition by terbutaline. *Int. J. Microcirc. Clin. Exp.* 6, 265–271.
- Escobales, N., Crespo, M.J., 2008. Early pathophysiological alterations in experimental cardiomyopathy: the syrian cardiomyopathic hamster. *P. R. Health Sci. J.* 27, 307–314.
- Escobales, N., Crespo, M.J., 2006. Angiotensin II-dependent vascular alterations in young cardiomyopathic hamsters: role for oxidative stress. *Vascul. Pharmacol.* 44, 22–28. [10.1016/j.vph.2005.09.008](https://doi.org/10.1016/j.vph.2005.09.008).
- Estensen, R.D., Anderson, W.R., Galbraith, A.R., Hartle, D.E., Jordan, M.M., Ondrey, F.G., et al. 2007. A method of producing carcinoma in upper aerodigestive tree and esophagus of the syrian golden hamster using wounding and instillation of N-methylnitrosourea. *Cancer Epidemiol. Biomarkers Prev.* 16, 1644–1650. [10.1158/1055-9965.EPI-06-1075](https://doi.org/10.1158/1055-9965.EPI-06-1075).
- Eyzaguirre, E.J., Milazzo, M.L., Koster, F.T., Fulhorst, C.F., 2008. Choclo virus infection in the syrian golden hamster. *Am. J. Trop. Med. Hyg.* 78, 669–674.
- Fagerstrom, K., 2002. The epidemiology of smoking: health consequences and benefits of cessation. *Drugs* 62 (Suppl. 2), 1–9.
- Falagas, M.E., Klempner, M.S., 1996. Babesiosis in patients with AIDS: a chronic infection presenting as fever of unknown origin. *Clin. Infect. Dis.* 22, 809–812.
- Fararh, K.M., Atoji, Y., Shimizu, Y., Takewaki, T., 2002. Isulintropic properties of nigella sativa oil in streptozotocin plus nicotinamide diabetic hamster. *Res. Vet. Sci.* 73, 279–282.
- Ferezou, J., Combettes-Souverain, M., Souidi, M., Smith, J.L., Boehler, N., Milliat, F., et al. 2000. Cholesterol, bile acid, and lipoprotein metabolism in two strains of hamster, one resistant, the other sensitive (LPN) to sucrose-induced cholelithiasis. *J. Lipid Res.* 41, 2042–2054.
- Fitzpatrick, L.R., Sakurai, K., Le, T., 1999. Effect of naproxen on the hamster gastric antrum: ulceration, adaptation and efficacy of anti-ulcer drugs. *Aliment Pharmacol. Ther.* 13, 1553–1562.
- Flores, L.E., Garcia, M.E., Borelli, M.I., Del Zotto, H., Alzugaray, M.E., Maiztegui, B., et al. 2003. Expression of islet neogenesis-associated protein in islets of normal hamsters. *J. Endocrinol.* 177, 243–248.
- Ford, M.J., Telfer Brunton, W.A., Millar, J., Stewart, C., Critchley, J.A., 1980. Mycoplasma pneumonia: failure of erythromycin therapy. *Scott. Med. J.* 25, 126–128.
- Foxall, T.L., Shwaery, G.T., Stucchi, A.F., Nicolosi, R.J., Wong, S.S., 1992. Dose-related effects of doxazosin on plasma lipids and aortic fatty streak formation in the hypercholesterolemic hamster model. *Am. J. Pathol.* 140, 1357–1363.
- Fukuhara, M., Uchida, E., Tajiri, T., Aimoto, T., Naito, Z., Ishiwata, T., 2005. Re-expression of reduced VEGF activity in liver metastases of experimental pancreatic cancer. *J. Nippon Med. Sch.* 72, 155–164.
- Gernert, M., Richter, A., Loscher, W., 1999. In vivo extracellular electrophysiology of pallidal neurons in dystonic and nondystonic hamsters. *J. Neurosci. Res.* 57, 894–905.
- Ginsberg, H.N., 1996. Diabetic dyslipidemia: Basic mechanisms underlying the common hypertriglyceridemia and low HDL cholesterol levels. *Diabetes* 45 (Suppl. 3), S27–30.
- Giri, S.N., Blaisdell, R., Rucker, R.B., Wang, Q., Hyde, D.M., 1994. Amelioration of bleomycin-induced lung fibrosis in hamsters by dietary supplementation with taurine and niacin: Biochemical mechanisms. *Environ. Health Perspect.* 102 (Suppl. 10), 137–147.
- Giri, S.N., Hyde, D.M., Braun, R.K., Gaarde, W., Harper, J.R., Pierschbacher, M.D., 1997. Antifibrotic effect of decorin in a bleomycin hamster model of lung fibrosis. *Biochem. Pharmacol.* 54, 1205–1216.
- Goineau, S., Pape, D., Guillo, P., Ramee, M.P., Bellissant, E., 2001. Hemodynamic and histomorphometric characteristics of dilated cardiomyopathy of syrian hamsters (bio TO-2 strain). *Can. J. Physiol. Pharmacol.* 79, 329–337.
- Gormley, P.D., Pavesio, C.E., Luthert, P., Lightman, S., 1999. Retinochoroiditis is induced by oral administration of toxoplasma gondii cysts in the hamster model. *Exp. Eye Res.* 68, 657–661. [10.1006/exer.1998.0655](https://doi.org/10.1006/exer.1998.0655).
- Gotto Jr, A.M., 1992. Hypertriglyceridemia: risks and perspectives. *Am. J. Cardiol.* 70, 19F–25F.
- Greenblatt, M., Choudari, K.V., Sanders, A.G., Shubik, P., 1969. Mammalian microcirculation in the living animal: methodologic considerations. *Microvasc. Res.* 1, 420–432.
- Grimes, J.M., Melloni Jr, R.H., 2002. Serotonin modulates offensive attack in adolescent anabolic steroid-treated hamsters. *Pharmacol. Biochem. Behav.* 73, 713–721.
- Gruys, E., Snel, F.W., 1994. Animal models for reactive amyloidosis. *Baillieres Clin. Rheumatol.* 8, 599–611.
- Gu, J., Korteweg, C., 2007. Pathology and pathogenesis of severe acute respiratory syndrome. *Am. J. Pathol.* 170, 1136–1147. [10.2353/ajpath.2007.061088](https://doi.org/10.2353/ajpath.2007.061088).
- Guerra, M.A., 2009. Leptospirosis. *J. Am. Vet. Med. Assoc.* 234 (472-8), 430. [10.2460/javma.234.4.472](https://doi.org/10.2460/javma.234.4.472)
- Han, J.S., Sugawara, Y., Doi, K., 1992. Rapid induction of glomerular lipidosis in APA hamsters by streptozotocin. *Int. J. Exp. Pathol.* 73, 75–84.
- Hankenson, F.C., Van Hoosier, G.L., 2002. Biology and diseases of hamsters. In: Fox, J.G., Anderson, L.C., Loew, F.L., Quimby, F.W. (Eds.), *Laboratory Animal Medicine*. Academic Press, San Diego, CA, pp. 167–202.
- Hardison, W.G., 1983. Relation of hepatic taurine pool size to bile-acid conjugation in man and animals. *Prog. Clin. Biol. Res.* 125, 407–417.
- Hayden, M.R., Tyagi, S.C., 2000. Arteriogenesis: angiogenesis within unstable atherosclerotic plaque—interactions with extracellular matrix. *Curr. Interv. Cardiol. Rep.* 2, 218–227.
- Hayden, M.R., Tyagi, S.C., 1998. Arterial vascular remodeling: the endothelial cell's central role. *Mo. Med.* 95, 213–217.
- Hayes, J.A., Christensen, T.G., Snider, G.L., 1977. The hamster as a model of chronic bronchitis and emphysema in man. *Lab. Anim. Sci.* 27, 762–770.

- Hayes, K.C., Khosla, P., Kaiser, A., Yeghiazarians, V., Pronczuk, A., 1992. Dietary fat and cholesterol modulate the plasma lipoprotein distribution and production of pigment or cholesterol gallstones in hamsters. *J. Nutr.* 122, 374–384.
- Held, M.R., Bungiro, R.D., Harrison, L.M., Hamza, I., Cappello, M., 2006. Dietary iron content mediates hookworm pathogenesis in vivo. *Infect. Immun.* 74, 289–295.
- Hjorth, R.N., Bonde, G.M., Pierzchala, W.A., Vernon, S.K., Wiener, F.P., Levner, M.H., et al. 1988. A new hamster model for adenoviral vaccination. *Arch. Virol.* 100, 279–283.
- Hol, P.R., Snel, F.W., Niewold, T.A., Gruys, E., 1986. Amyloid-enhancing factor (AEF) in the pathogenesis of AA-amyloidosis in the hamster. *Virchows Arch. B. Cell. Pathol. Incl Mol. Pathol.* 52, 273–281.
- Holzbach, R.T., 1984. Animal models of cholesterol gallstone disease. *Hepatology* 4, 191S–198S.
- Homburger, F., Soto, H., Althoff, J., Dalquen, P., Heitz, P., 1979. Carcinoma of the larynx in hamsters exposed to cigarette smoke. animal model: susceptible inbred line of syrian hamsters (BIO 15.16). *Am. J. Pathol.* 95, 845–848.
- Hooper, J.W., Larsen, T., Custer, D.M., Schmaljohn, C.S., 2001. A lethal disease model for hantavirus pulmonary syndrome. *Virology* 289, 6–14. [10.1006/viro.2001.1133](https://doi.org/10.1006/viro.2001.1133).
- Hooper, J.W., Ferro, A.M., Wahl-Jensen, V., 2008. Immune serum produced by DNA vaccination protects hamsters against lethal respiratory challenge with andes virus. *J. Virol.* 82, 1332–1338. [10.1128/JVI.01822-07](https://doi.org/10.1128/JVI.01822-07).
- Horiuchi, K., Takatori, A., Inenaga, T., Ohta, E., Ishii, Y., Kyuwa, S., et al. 2005. Histopathological studies of aortic dissection in streptozotocin-induced diabetic APA hamsters. *Exp. Anim.* 54, 363–367.
- Horton, J.D., Cuthbert, J.A., Spady, D.K., 1995. Regulation of hepatic 7 alpha-hydroxylase expression and response to dietary cholesterol in the rat and hamster. *J. Biol. Chem.* 270, 5381–5387.
- Huang, A.H., Chen, Y.K., Chan, A.W., Shieh, T.Y., Lin, L.M., 2009. Isolation and characterization of normal hamster buccal pouch stem/stromal cells - A potential oral cancer stem/stem-like cell model. *Oral Oncol.* [10.1016/j.oraloncology.2009.07.003](https://doi.org/10.1016/j.oraloncology.2009.07.003).
- Hukkanen, R.R., Liggitt, H.D., Anderson, D.M., Kelley, S.T., 2006. Detection of systemic amyloidosis in the pig-tailed macaque (*macaca nemestrina*). *Comp. Med.* 56, 119–127.
- Hutadilok, N., Thamavit, W., Upatham, E.S., Ruenwongsa, P., 1983. Liver procollagen prolyl hydroxylase in opisthorchis viverrini infected hamsters after praziquantel administration. *Mol. Biochem. Parasitol.* 9, 289–295.
- Ikeda, Y., Ross Jr., J., 2000. Models of dilated cardiomyopathy in the mouse and the hamster. *Curr. Opin. Cardiol.* 15, 197–201.
- Inenaga, T., Nishida, E., Kawamura, S., Yoshikawa, Y., 2002. Renal function tests on diabetes-induced and non-induced APA hamsters. *Exp. Anim.* 51, 437–445.
- Iyer, S.N., Gurujeyalakshmi, G., Giri, S.N., 1999. Effects of pirfenidone on transforming growth factor-beta gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. *J. Pharmacol. Exp. Ther.* 291, 367–373.
- Jain, R., Danziger, L.H., 2004. The macrolide antibiotics: a pharmacokinetic and pharmacodynamic overview. *Curr. Pharm. Des.* 10, 3045–3053.
- Johnston, R.E., 1981. Testosterone dependence of scent marking by male hamsters (*mesocricetus auratus*). *Behav. Neural Biol.* 31, 96–99.
- Jonsson, C.B., Hooper, J., Mertz, G., 2008. Treatment of hantavirus pulmonary syndrome. *Antiviral Res.* 78, 162–169. [10.1016/j.antiviral.2007.10.012](https://doi.org/10.1016/j.antiviral.2007.10.012).
- Kajdacsy-Balla, A., Howeedy, A., Bagasra, O., 1993. Experimental model of congenital syphilis. *Infect. Immun.* 61, 3559–3561.
- Kaminski, K.A., Bonda, T.A., Korecki, J., Musial, W.J., 2002. Oxidative stress and neutrophil activation—the two keystones of ischemia/reperfusion injury. *Int. J. Cardiol.* 86, 41–59.
- Kean, B.H., 1972. Clinical toxoplasmosis—50 years. *Trans. R. Soc. Trop. Med. Hyg.* 66, 549–571.
- Kerger, H., Torres Filho, I.P., Rivas, M., Winslow, R.M., Intaglietta, M., 1995. Systemic and subcutaneous microvascular oxygen tension in conscious syrian golden hamsters. *Am. J. Physiol.* 268, H802–H810.
- Khallou, J., Riottot, M., Parquet, M., Verneau, C., Lutton, C., 1991a. Biodynamics of cholesterol and bile acids in the lithiasic hamster. *Br. J. Nutr.* 66, 479–492.
- Khallou, J., Riottot, M., Parquet, M., Verneau, C., Lutton, C., 1991b. Biodynamics of cholesterol and bile acids in the lithiasic hamster. *Br. J. Nutr.* 66, 479–492.
- Kilian, M., Gregor, J.I., Heukamp, I., Helmecke, K., Hanel, M., Wassersleben, B., et al. 2009. Impact of octreotide and SOM-230 on liver metastasis and hepatic lipidperoxidation in ductal pancreatic adenocarcinoma in syrian hamster. *Clin. Exp. Metastasis.* [10.1007/s10585-009-9271-x](https://doi.org/10.1007/s10585-009-9271-x).
- Kirchhoff, L.V., 1993. Chagas disease. american trypanosomiasis. *Infect. Dis. Clin. North Am.* 7, 487–502.
- Klitzman, B., Popel, A.S., Duling, B.R., 1983. Oxygen transport in resting and contracting hamster cremaster muscles: Experimental and theoretical microvascular studies. *Microvasc. Res.* 25, 108–131.
- Koberle, F., 1968. Chagas' disease and chagas' syndromes: the pathology of american trypanosomiasis. *Adv. Parasitol.* 6, 63–116.
- Kokkotou, E., Moss, A.C., Michos, A., Espinoza, D., Cloud, J.W., Mustafa, N., et al. 2008. Comparative efficacies of rifaximin and vancomycin for treatment of clostridium difficile-associated diarrhea and prevention of disease recurrence in hamsters. *Antimicrob. Agents Chemother.* 52, 1121–1126. [10.1128/AAC.01143-07](https://doi.org/10.1128/AAC.01143-07).
- Kolbasa, K.P., Lancaster, C., Olafsson, A.S., Gilbertson, S.K., Robert, A., 1988. Indomethacin-induced gastric antral ulcers in hamsters. *Gastroenterology* 95, 932–944.
- Koletsis, E.N., Prokakis, C., Karanikolas, M., Apostolakis, E., Dougenis, D., 2009. Current role of surgery in small cell lung carcinoma. *J. Cardiothorac. Surg.* 4, 30. [10.1186/1749-8090-4-30](https://doi.org/10.1186/1749-8090-4-30).
- Konishi, Y., Tsutsumi, M., Tsujiuchi, T., 1998. Mechanistic analysis of pancreatic ductal carcinogenesis in hamsters. *Pancreas* 16, 300–306.
- Kowala, M.C., Nunnari, J.J., Durham, S.K., Nicolosi, R.J., 1991a. Doxazosin and cholestyramine similarly decrease fatty streak formation in the aortic arch of hyperlipidemic hamsters. *Atherosclerosis* 91, 35–49.
- Kowala, M.C., Nunnari, J.J., Durham, S.K., Nicolosi, R.J., 1991b. Doxazosin and cholestyramine similarly decrease fatty streak formation in the aortic arch of hyperlipidemic hamsters. *Atherosclerosis* 91, 35–49.
- Kratzel, C., Kruger, D., Beekes, M., 2007a. Relevance of the regional lymph node in scrapie pathogenesis after peripheral infection of hamsters. *BMC Vet. Res.* 3, 22. [10.1186/1746-6148-3-22](https://doi.org/10.1186/1746-6148-3-22).
- Kratzel, C., Mai, J., Madela, K., Beekes, M., Kruger, D., 2007b. Propagation of scrapie in peripheral nerves after footpad infection in normal and neurotoxin exposed hamsters. *Vet. Res.* 38, 127–139. [10.1051/vetres:2006047](https://doi.org/10.1051/vetres:2006047).
- Kroczyńska, B., Cutrone, R., Bocchetta, M., Yang, H., Elmishad, A.G., Vacek, P., et al. 2006. Crocidolite asbestos and SV40 are cocarcinogens in human mesothelial cells and in causing mesothelioma in hamsters. *Proc. Natl. Acad. Sci. U. S. A.* 103, 14128–14133. [10.1073/pnas.0604544103](https://doi.org/10.1073/pnas.0604544103).
- Kulkosky, P.J., Glazner, G.W., Moore, H.D., Low, C.A., Woods, S.C., 1988. Neuropeptide Y: behavioral effects in the golden hamster. *Peptides* 9, 1389–1393.
- Kume, S., Takeya, M., Mori, T., Araki, N., Suzuki, H., Horiuchi, S., et al. 1995. Immunohistochemical and ultrastructural detection of advanced glycation end products in atherosclerotic lesions of human aorta with a novel specific monoclonal antibody. *Am. J. Pathol.* 147, 654–667.

- Laakso, M., 1996. Lipids and lipoproteins as risk factors for coronary heart disease in non-insulin-dependent diabetes mellitus. *Ann. Med.* 28, 341–345.
- Lamarque, B., Lewis, G.F., 1998. Atherosclerosis prevention for the next decade: risk assessment beyond low density lipoprotein cholesterol. *Can. J. Cardiol.* 14, 841–851.
- Laurent, G., Nonclercq, D., Journe, F., Brohee, R., Toubeau, G., Falmagne, P., et al. 1999. Characterization of a cell line established from diethylstilbestrol-induced renal tumors in syrian hamsters. *In Vitro Cell. Dev. Biol. Anim.* 35, 339–345. [10.1007/s11626-999-0084-7](https://doi.org/10.1007/s11626-999-0084-7).
- Lazo, J.S., Hoyt, D.G., Sebti, S.M., Pitt, B.R., 1990. Bleomycin: a pharmacologic tool in the study of the pathogenesis of interstitial pulmonary fibrosis. *Pharmacol. Ther.* 47, 347–358.
- Lee, T.K., Eshinart, J.D., Blackburn, L.D., Silverman, J.F., 1992. The size of small cell lung carcinoma cells. ratio to lymphocytes and correlation with specimen size and crush artifact. *Anal. Quant. Cytol. Histol.* 14, 32–34.
- Lehr, H.A., Guhlmann, A., Nolte, D., Keppler, D., Messmer, K., 1991. Leukotrienes as mediators in ischemia-reperfusion injury in a microcirculation model in the hamster. *J. Clin. Invest.* 87, 2036–2041. [10.1172/JCI115233](https://doi.org/10.1172/JCI115233).
- Leshner, A.I., 2000. Anabolic steroid abuse. NIH#00-3721, 1–8.
- Levi, S., Shaw-Smith, C., 1994. Non-steroidal anti-inflammatory drugs: how do they damage the gut? *Br. J. Rheumatol.* 33, 605–612.
- Lewis, G.F., Murdoch, S., Uffelman, K., Naples, M., Szeto, L., Albers, A., et al. 2004. Hepatic lipase mRNA, protein, and plasma enzyme activity is increased in the insulin-resistant, fructose-fed syrian golden hamster and is partially normalized by the insulin sensitizer rosiglitazone. *Diabetes* 53, 2893–2900.
- Li, J.J., Li, S.A., 1996. Estrogen carcinogenesis in the hamster kidney: a hormone-driven multistep process. *Prog. Clin. Biol. Res.* 394, 255–267.
- Li, Y., Trush, M.A., Yager, J.D., 1994. DNA damage caused by reactive oxygen species originating from a copper-dependent oxidation of the 2-hydroxy catechol of estradiol. *Carcinogenesis* 15, 1421–1427.
- Lichtenstein, D.L., Spencer, J.F., Doronin, K., Patra, D., Meyer, J.M., Shashkova, E.V., et al. 2009. An acute toxicology study with INGN 007, an oncolytic adenovirus vector, in mice and permissive syrian hamsters; comparisons with wild-type Ad5 and a replication-defective adenovirus vector. *Cancer Gene Ther.* 16, 644–654. [10.1038/cgt.2009.5](https://doi.org/10.1038/cgt.2009.5).
- Liehr, J.G., 1997. Hormone-associated cancer: mechanistic similarities between human breast cancer and estrogen-induced kidney carcinogenesis in hamsters. *Environ. Health Perspect.* 105 (Suppl 3), 565–569.
- Liehr, J.G., Ballatore, A.M., McLachlan, J.A., Sirbasku, D.A., 1983. Mechanism of diethylstilbestrol carcinogenicity as studied with the fluorinated analogue E-3',3'',5',5''-tetrafluorodiethylstilbestrol. *Cancer Res.* 43, 2678–2682.
- Liehr, J.G., Hall, E.R., Avitts, T.A., Randerath, E., Randerath, K., 1987a. Localization of estrogen-induced DNA adducts and cytochrome P-450 activity at the site of renal carcinogenesis in the hamster kidney. *Cancer Res.* 47, 2156–2159.
- Liehr, J.G., Purdy, R.H., Baran, J.S., Nutting, E.F., Colton, F., Randerath, E., et al. 1987b. Correlation of aromatic hydroxylation of 11 beta-substituted estrogens with morphological transformation in vitro but not with in vivo tumor induction by these hormones. *Cancer Res.* 47, 2583–2588.
- Lipskaia, L., Pinet, C., Fromes, Y., Hatem, S., Cantaloube, I., Coulombe, A., et al. 2007. Mutation of delta-sarcoglycan is associated with ca(2+) -dependent vascular remodeling in the syrian hamster. *Am. J. Pathol.* 171, 162–171.
- Lopez, A., Dietz, V.J., Wilson, M., Navin, T.R., Jones, J.L., 2000. Preventing congenital toxoplasmosis. *MMWR Recomm Rep.* 49, 59–68.
- Loscher, W., Fisher Jr, J.E., Schmidt, D., Fredow, G., Honack, D., Iturrian, W.B., 1989. The sz mutant hamster: a genetic model of epilepsy or of paroxysmal dystonia?. *Mov. Disord.* 4, 219–232. [10.1002/mds.870040304](https://doi.org/10.1002/mds.870040304).
- Lucas, E.A., Lightfoot, S.A., Hammond, L.J., Devareddy, L., Khalil, D.A., Daggy, B.P., et al. 2003. Soy isoflavones prevent ovariectomy-induced atherosclerotic lesions in golden syrian hamster model of postmenopausal hyperlipidemia. *Menopause* 10, 314–321. [10.1097/01.GME.0000051509.84118.FD](https://doi.org/10.1097/01.GME.0000051509.84118.FD).
- Madden, C., Oei, T.P., Singer, G., 1980. The effect of schedule removal on the maintenance of heroin self-injection. *Pharmacol. Biochem. Behav.* 12, 983–986.
- Magers, T., Talbot, P., DiCarlantonio, G., Knoll, M., Demers, D., Tsai, I., et al. 1995. Cigarette smoke inhalation affects the reproductive system of female hamsters. *Reprod. Toxicol.* 9, 513–525.
- Marley, S.E., Eberhard, M.L., Steurer, F.J., Ellis, W.L., McGreevy, P.B., Ruebush II, T.K., 1997. Evaluation of selected antiprotozoal drugs in the babesia microti-hamster model. *Antimicrob. Agents Chemother.* 41, 91–94.
- Masiello, P., Broca, C., Gross, R., Roye, M., Manteghetti, M., Hillaire-Buys, D., et al. 1998. Experimental NIDDM: development of a new model in adult rats administered streptozotocin and nicotinamide. *Diabetes* 47, 224–229.
- Matsushita, A., Onda, M., Uchida, E., Maekawa, R., Yoshioka, T., 2001. Antitumor effect of a new selective matrix metalloproteinase inhibitor, MMI-166, on experimental pancreatic cancer. *Int. J. Cancer* 92, 434–440.
- McAdam, A.J., Sharpe, A.H., 2010. Infectious diseases. In: Kumar, V., Abbas, A., Fausto, N., Aster, J.C. (Eds.), *Robbins and Cotran Pathologic Basis of Disease*. Saunders, Philadelphia, PA, pp. 331–398.
- McDonald, L.C., Killgore, G.E., Thompson, A., Owens Jr, R.C., Kazakova, S.V., Sambol, S.P., et al. 2005. An epidemic, toxin gene-variant strain of clostridium difficile. *N. Engl. J. Med.* 353, 2433–2441. [10.1056/NEJMoa051590](https://doi.org/10.1056/NEJMoa051590).
- McElroy, A.K., Smith, J.M., Hooper, J.W., Schmaljohn, C.S., 2004. Andes virus M genome segment is not sufficient to confer the virulence associated with andes virus in syrian hamsters. *Virology* 326, 130–139. [10.1016/j.virol.2004.05.018](https://doi.org/10.1016/j.virol.2004.05.018).
- Meisel, R.L., Sachs, B.D., 1994. The physiology of male sexual behavior. In: Knobil, E., Neill, J. (Eds.), *The Physiology of Reproduction*. Raven Press, New York, NY, pp. 3–105.
- Melby, P.C., Chandrasekar, B., Zhao, W., Coe, J.E., 2001. The hamster as a model of human visceral leishmaniasis: progressive disease and impaired generation of nitric oxide in the face of a prominent Th1-like cytokine response. *J. Immunol.* 166, 1912–1920.
- Melloni Jr, R.H., Ferris, C.F., 1996. Adolescent anabolic steroid use and aggressive behavior in golden hamsters. *Ann. N. Y. Acad. Sci.* 794, 372–375.
- Mendez, S., Valenzuela, J.G., Wu, W., Hotez, P.J., 2005. Host cytokine production, lymphoproliferation, and antibody responses during the course of *Ancylostoma ceylanicum* infection in the Golden Syrian hamster. *Infect. Immun.* 73, 3402–3407.
- Menger, M.D., Laschke, M.W., Vollmar, B., 2002. Viewing the microcirculation through the window: some twenty years experience with the hamster dorsal skinfold chamber. *Eur. Surg. Res.* 34, 83–91.
- Merchant, M.T., Aguilar, L., Avila, G., Robert, L., Flisser, A., Willms, K., 1998. *Taenia solium*: description of the intestinal implantation sites in experimental hamster infections. *J. Parasitol.* 84, 681–685.
- Milazzo, M.L., Eyzaguirre, E.J., Molina, C.P., Fulhorst, C.F., 2002. Maporal viral infection in the syrian golden hamster: a model of hantavirus pulmonary syndrome. *J. Infect. Dis.* 186, 1390–1395. [10.1086/344735](https://doi.org/10.1086/344735).
- Mitchell, P.L., McLeod, R.S., 2008. Conjugated linoleic acid and atherosclerosis: studies in animal models. *Biochem. Cell Biol.* 86, 293–301. [10.1139/o08-070](https://doi.org/10.1139/o08-070).

- Mizumoto, K., Ito, S., Kitazawa, S., Tsutsumi, M., Denda, A., Konishi, Y., 1989a. Inhibitory effect of butylated hydroxyanisole administration on pancreatic carcinogenesis in syrian hamsters initiated with N-nitrosobis(2-oxopropyl)amine. *Carcinogenesis* 10, 1491–1494.
- Mizumoto, K., Kitazawa, S., Ito, S., Takashima, Y., Tsutsumi, M., Denda, A., et al. 1989b. Cycles of repeated augmentation pressure in rapid production of pancreatic and cholangiocellular carcinomas in hamsters initiated with N-nitrosobis(2-oxopropyl)amine. *Carcinogenesis* 10, 1457–1459.
- Mizumoto, K., Tsutsumi, M., Denda, A., Konishi, Y., 1988. Rapid production of pancreatic carcinoma by initiation with N-nitrosobis(2-oxopropyl)amine and repeated augmentation pressure in hamsters. *J. Natl. Cancer Inst.* 80, 1564–1567.
- Mizumoto, K., Tsutsumi, M., Kitazawa, S., Denda, A., Konishi, Y., 1990. Usefulness of rapid production model for pancreatic carcinoma in male hamsters. *Cancer Lett.* 49, 211–215.
- Moon, J.E., Rivard, R.G., Griffith, M.E., Ressler, R.A., McCall, S., Reitstetter, R.E., et al. 2007. Effect of timing and duration of azithromycin therapy of leptospirosis in a hamster model. *J. Antimicrob. Chemother.* 59, 148–151. [10.1093/jac/dkl453](https://doi.org/10.1093/jac/dkl453).
- Moon, R.C., Rao, K.V., Detrisac, C.J., Kelloff, G.J., 1992a. Animal models for chemoprevention of respiratory cancer. *J. Natl. Cancer Inst. Monogr.* 13, 45–49.
- Moon, R.C., Rao, K.V., Detrisac, C.J., Kelloff, G.J., 1992b. Hamster lung cancer model of carcinogenesis and chemoprevention. *Adv. Exp. Med. Biol.* 320, 55–61.
- National Center for Health Statistics, 1994. Plan and operation of the third national health and nutrition examination survey, 1988–94. Hyattsville, MD: US Department of Health and Human Services, Public Health Service.
- Niewold, T.A., Hol, P.R., van Andel, A.C., Lutz, E.T., Gruys, E., 1987. Enhancement of amyloid induction by amyloid fibril fragments in hamster. *Lab. Invest.* 56, 544–549.
- Nolte, D., Menger, M.D., Messmer, K., 1995. Microcirculatory models of ischaemia-reperfusion in skin and striated muscle. *Int. J. Microcirc. Clin. Exp.* 15 (Suppl 1), 9–16.
- O'Brien, K.D., Deeb, S.S., Ferguson, M., McDonald, T.O., Allen, M.D., Alpers, C.E., et al. 1994. Apolipoprotein E localization in human coronary atherosclerotic plaques by in situ hybridization and immunohistochemistry and comparison with lipoprotein lipase. *Am. J. Pathol.* 144, 538–548.
- Ohshima, A., Cohen, B.I., Ayyad, N., Mosbach, E.H., 1996a. Dietary fat alters biliary lipid secretion in the hamster. *Lipids* 31, 949–954.
- Ohshima, A., Cohen, B.I., Ayyad, N., Mosbach, E.H., 1996b. Effect of castration and hormonal supplementation on cholesterol cholelithiasis in the male hamster. *Lipids* 31, 945–948.
- Oreffo, V.I., Lin, H.W., Gumerlock, P.H., Kraegel, S.A., Witschi, H., 1992. Mutational analysis of a dominant oncogene (c-ki-ras-2) and a tumor suppressor gene (p53) in hamster lung tumorigenesis. *Mol. Carcinog.* 6, 199–202.
- Oreffo, V.I., Lin, H.W., Padmanabhan, R., Witschi, H., 1993. K-ras and p53 point mutations in 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced hamster lung tumors. *Carcinogenesis* 14, 451–455.
- Overstreet, J.W., Yanagimachi, R., Katz, D.F., Hayashi, K., Hanson, F.W., 1980. Penetration of human spermatozoa into the human zona pellucida and the zona-free hamster egg: a study of fertile donors and infertile patients. *Fertil. Steril.* 33, 534–542.
- Pairojkul, C., Shirai, T., Hirohashi, S., Thamavit, W., Bhudhisawat, W., Uttaravicien, T., et al. 1991. Multistage carcinogenesis of liver-fluke-associated cholangiocarcinoma in thailand. *Princess Takamatsu Symp.* 22, 77–86.
- Panlilio, L.V., Katz, J.L., Pickens, R.W., Schindler, C.W., 2003. Variability of drug self-administration in rats. *Psychopharmacol. (Berl.)* 167, 9–19. [10.1007/s00213-002-1366-x](https://doi.org/10.1007/s00213-002-1366-x).
- Papakosta, V., Vairaktaris, E., Vylliotis, A., Derka, S., Nkenke, E., Vassiliou, S., et al. 2006. The co-expression of c-myc and p53 increases and reaches a plateau early in oral oncogenesis. *Anticancer Res.* 26, 2957–2962.
- Pavesio, C.E., Chiappino, M.L., Gormley, P., Setzer, P.Y., Nichols, B.A., 1995. Acquired retinochoroiditis in hamsters inoculated with ME 49 strain toxoplasma. *Invest. Ophthalmol. Vis. Sci.* 36, 2166–2175.
- Pepin, J., Valiquette, L., Cossette, B., 2005. Mortality attributable to nosocomial clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in quebec. *CMAJ* 173, 1037–1042. [10.1503/cmaj.050978](https://doi.org/10.1503/cmaj.050978).
- Pershouse, M.A., Heivly, S., Girtsman, T., 2006. The role of SV40 in malignant mesothelioma and other human malignancies. *Inhal. Toxicol.* 18, 995–1000. [10.1080/08958370600835377](https://doi.org/10.1080/08958370600835377).
- Persson, N.H., Erlansson, M., Svensjo, E., Takolander, R., Bergqvist, D., 1985. The hamster cheek pouch—an experimental model to study postischemic macromolecular permeability. *Int. J. Microcirc. Clin. Exp.* 4, 257–263.
- Petty, T.L., 2006. The history of COPD. *Int. J. Chron. Obstruct Pulmon Dis.* 1, 3–14.
- Phares, C.K., 1980. Streptozotocin-induced diabetes in syrian hamsters: new model of diabetes mellitus. *Experientia* 36, 681–682.
- Pickelmann, S., Nolte, D., Leiderer, R., Mollmann, M., Schutze, E., Messmer, K., 1999. Effects of the phlebotropic drug daflon 500 mg on postischemic reperfusion injury in striated skin muscle: a histomorphologic study in the hamster. *J. Lab. Clin. Med.* 134, 536–545.
- Piekarski, D.J., Routman, D.M., Schoomer, E.E., Driscoll, J.R., Park, J.H., Butler, M.P., et al. 2009. Infrequent low dose testosterone treatment maintains male sexual behavior in syrian hamsters. *Horm. Behav.* 55, 182–189. [10.1016/j.yhbeh.2008.10.003](https://doi.org/10.1016/j.yhbeh.2008.10.003).
- Pittenger, G.L., Vinik, A.I., Rosenberg, L., 1992. The partial isolation and characterization of ilotropin, a novel islet-specific growth factor. *Adv. Exp. Med. Biol.* 321, 123–130, discussion 131–2.
- Poutanen, S.M., Simor, A.E., 2004. Clostridium difficile-associated diarrhea in adults. *CMAJ* 171, 51–58.
- Powell, J.W., Dexter, E., Scalzetti, E.M., Bogart, J.A., 2009. Treatment advances for medically inoperable non-small-cell lung cancer: Emphasis on prospective trials. *Lancet Oncol.* 10, 885–894. [10.1016/S1470-2045\(09\)70103-2](https://doi.org/10.1016/S1470-2045(09)70103-2).
- Prusiner, S.B., Cochran, S.P., Alpers, M.P., 1985. Transmission of scrapie in hamsters. *J. Infect. Dis.* 152, 971–978.
- Quaglino Jr, D., Nanney, L.B., Kennedy, R., Davidson, J.M., 1990. Transforming growth factor-beta stimulates wound healing and modulates extracellular matrix gene expression in pig skin. I. excisional wound model. *Lab. Invest.* 63, 307–319.
- Raika, R.S., Jinnah, H.A., Hess, E.J., 2005. Animal models of generalized dystonia. *NeuroRx* 2, 504–512.
- Razaq, N., Sambol, S., Nagaro, K., Zukowski, W., Cheknis, A., Johnson, S., et al. 2007. Infection of hamsters with historical and epidemic BI types of clostridium difficile. *J. Infect. Dis.* 196, 1813–1819. [10.1086/523106](https://doi.org/10.1086/523106).
- Richardson, P., McKenna, W., Bristow, M., Maisch, B., Mautner, B., O'Connell, J., et al. 1996. Report of the 1995 world health Organization/International society and federation of cardiology task force on the definition and classification of cardiomyopathies. *Circulation* 93, 841–842.
- Roberts, A., Thomas, W.D., Guarner, J., Lamirande, E.W., Babcock, G.J., Greenough, T.C., et al. 2006. Therapy with a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody reduces disease severity and viral burden in golden syrian hamsters. *J. Infect. Dis.* 193, 685–692. [10.1086/500143](https://doi.org/10.1086/500143).
- Roberts, A., Vogel, L., Guarner, J., Hayes, N., Murphy, B., Zaki, S., et al. 2005. Severe acute respiratory syndrome coronavirus infection of golden syrian hamsters. *J. Virol.* 79, 503–511. [10.1128/JVI.79.1.503-511.2005](https://doi.org/10.1128/JVI.79.1.503-511.2005).

- Rodriguez, J.E., McCudden, C.R., Willis, M.S., 2009. Familial hypertrophic cardiomyopathy: basic concepts and future molecular diagnostics. *Clin. Biochem.* 42, 755–765. [10.1016/j.clinbiochem.2009.01.020](https://doi.org/10.1016/j.clinbiochem.2009.01.020).
- Rogan, E.G., Badawi, A.F., Devanesan, P.D., Meza, J.L., Edney, J.A., West, W.W., et al. 2003. Relative imbalances in estrogen metabolism and conjugation in breast tissue of women with carcinoma: potential biomarkers of susceptibility to cancer. *Carcinogenesis* 24, 697–702.
- Rogers, J.M., 2009. Tobacco and pregnancy. *Reprod. Toxicol.* 28, 152–160. [10.1016/j.reprotox.2009.03.012](https://doi.org/10.1016/j.reprotox.2009.03.012).
- Rogers, J.M., 2008. Tobacco and pregnancy: overview of exposures and effects. *Birth Defects Res. C. Embryo. Today* 84, 1–15. [10.1002/bdrc.20119](https://doi.org/10.1002/bdrc.20119).
- Rollison, D.E., Page, W.F., Crawford, H., Gridley, G., Wacholder, S., Martin, J., et al. 2004. Case-control study of cancer among US army veterans exposed to simian virus 40-contaminated adenovirus vaccine. *Am. J. Epidemiol.* 160, 317–324. [10.1093/aje/kwh212](https://doi.org/10.1093/aje/kwh212).
- Romanus, M., Stenqvist, O., Haljamae, H., Seifert, F., 1977. Pressure-induced ischemia. I. an experimental model for intravital microscopic studies in hamster cheek pouch. *Eur. Surg. Res.* 9, 444–459.
- Romeo, R.D., Schulz, K.M., Nelson, A.L., Menard, T.A., Sisk, C.L., 2003. Testosterone, puberty, and the pattern of male aggression in syrian hamsters. *Dev. Psychobiol.* 43, 102–108. [10.1002/dev.10125](https://doi.org/10.1002/dev.10125).
- Rosenberg, L., Brown, R.A., Duguid, W.P., 1983. A new approach to the induction of duct epithelial hyperplasia and nesidioblastosis by cellophane wrapping of the hamster pancreas. *J. Surg. Res.* 35, 63–72.
- Rosenberg, L., Duguid, W.P., Brown, R.A., Vinik, A.I., 1988. Induction of nesidioblastosis will reverse diabetes in syrian golden hamster. *Diabetes* 37, 334–341.
- Roth, S.H., 1996. NSAID gastropathy. A new understanding. *Arch. Intern. Med.* 156, 1623–1628.
- Roth, S.H., 1988. Salicylates revisited. are they still the hallmark of anti-inflammatory therapy? *Drugs* 36, 1–6.
- Rowin, K.S., Tanowitz, H.B., Wittner, M., 1982. Therapy of experimental babesiosis. *Ann. Intern. Med.* 97, 556–558.
- Ruiz-Rabelo, J.F., Vazquez, R., Perea, M.D., Cruz, A., Gonzalez, R., Romero, A., et al. 2007. Beneficial properties of melatonin in an experimental model of pancreatic cancer. *J. Pineal Res.* 43, 270–275. [10.1111/j.1600-079X.2007.00472.x](https://doi.org/10.1111/j.1600-079X.2007.00472.x).
- Ryoke, T., Gu, Y., Mao, L., Hongo, M., Clark, R.G., Peterson, K.L., et al. 1999. Progressive cardiac dysfunction and fibrosis in the cardiomyopathic hamster and effects of growth hormone and angiotensin-converting enzyme inhibition. *Circulation* 100, 1734–1743.
- Sakamoto, A., Ono, K., Abe, M., Jasmin, G., Eki, T., Murakami, Y., et al. 1997. Both hypertrophic and dilated cardiomyopathies are caused by mutation of the same gene, delta-sarcoglycan, in hamster: An animal model of disrupted dystrophin-associated glycoprotein complex. *Proc. Natl. Acad. Sci. U. S. A.* 94, 13873–13878.
- Salas-Ramirez, K.Y., Montalto, P.R., Sisk, C.L., 2008. Anabolic androgenic steroids differentially affect social behaviors in adolescent and adult male syrian hamsters. *Horm. Behav.* 53, 378–385. [10.1016/j.yhbeh.2007.11.004](https://doi.org/10.1016/j.yhbeh.2007.11.004).
- Santos, T.R., Costa, A.J., Toniollo, G.H., Luvizotto, M.C., Benetti, A.H., Santos, R.R., et al. 2009. Prevalence of anti-toxoplasma gondii antibodies in dairy cattle, dogs, and humans from the jauru micro-region, mato grosso state, brazil. *Vet. Parasitol.* 161, 324–326. [10.1016/j.vetpar.2009.01.017](https://doi.org/10.1016/j.vetpar.2009.01.017).
- Sartwell, P.E., Arthes, F.G., Tonascia, J.A., 1977. Exogenous hormones, reproductive history, and breast cancer. *J. Natl. Cancer Inst.* 59, 1589–1592.
- Satoh, H., Inada, I., Irada, T., Maki, Y., 1981. Indomethacin produces gastric antral ulcers in the re-fed rat. *Gastroenterology* 81, 719–725.
- Schaecher, S.R., Stabenow, J., Oberle, C., Schriewer, J., Buller, R.M., Sagartz, J.E., et al. 2008. An immunosuppressed syrian golden hamster model for SARS-CoV infection. *Virology* 380, 312–321. [10.1016/j.virol.2008.07.026](https://doi.org/10.1016/j.virol.2008.07.026).
- Schell, R.F., LeFrock, J.L., Chan, J.K., Bagasra, O., 1980. LSH hamster model of syphilitic infection. *Infect. Immun.* 28, 909–913.
- Schreiber, A.B., Winkler, M.E., Derynck, R., 1986. Transforming growth factor-alpha: a more potent angiogenic mediator than epidermal growth factor. *Science* 232, 1250–1253.
- Schulz, K.M., Sisk, C.L., 2006. Pubertal hormones, the adolescent brain, and the maturation of social behaviors: lessons from the syrian hamster. *Mol. Cell. Endocrinol.* 254–255, 120–126. [10.1016/j.mce.2006.04.025](https://doi.org/10.1016/j.mce.2006.04.025).
- Shklar, G., 1999. Development of experimental oral carcinogenesis and its impact on current oral cancer research. *J. Dent. Res.* 78, 1768–1772.
- Silva, E.F., Santos, C.S., Athanzio, D.A., Seyffert, N., Seixas, F.K., Cerqueira, G.M., et al. 2008. Characterization of virulence of leptospira isolates in a hamster model. *Vaccine* 26, 3892–3896. [10.1016/j.vaccine.2008.04.085](https://doi.org/10.1016/j.vaccine.2008.04.085).
- Sima, A., Bulla, A., Simionescu, N., 1990. Experimental obstructive coronary atherosclerosis in the hyperlipidemic hamster. *J. Submicrosc. Cytol. Pathol.* 22, 1–16.
- Sima, A., Popov, D., Starodub, O., Stancu, C., Cristea, C., Stern, D., et al. 1997. Pathobiology of the heart in experimental diabetes: Immunolocalization of lipoproteins, immunoglobulin G, and advanced glycation endproducts proteins in diabetic and/or hyperlipidemic hamster. *Lab. Invest.* 77, 3–18.
- Simionescu, M., Popov, D., Sima, A., Hasu, M., Costache, G., Faitar, S., et al. 1996. Pathobiochemistry of combined diabetes and atherosclerosis studied on a novel animal model. the hyperlipemic-hyperglycemic hamster. *Am. J. Pathol.* 148, 997–1014.
- Simionescu, N., Sima, A., Dobrian, A., Tirziu, D., Simionescu, M., 1993. Pathobiochemical changes of the arterial wall at the inception of atherosclerosis. *Curr. Top. Pathol.* 87, 1–45.
- Singhal, A.K., Finver-Sadowsky, J., McSherry, C.K., Mosbach, E.H., 1983. Effect of cholesterol and bile acids on the regulation of cholesterol metabolism in hamster. *Biochim. Biophys. Acta* 752, 214–222.
- Snider, G.L., Sherter, C.B., 1977. A one-year study of the evolution of elastase-induced emphysema in hamsters. *J. Appl. Physiol.* 43, 721–729.
- Sohn, E., Daggy, B.P., Arjmandi, B.H., 1999. Ovariectomized hamster: a potential model of postmenopausal hypercholesterolemia. *J. Nutr. Biochem.* 10, 660–663.
- Sood, S., Shiff, S.J., Yang, C.S., Chen, X., 2005. Selection of topically applied non-steroidal anti-inflammatory drugs for oral cancer chemoprevention. *Oral Oncol.* 41, 562–567. [10.1016/j.oraloncology.2005.01.003](https://doi.org/10.1016/j.oraloncology.2005.01.003).
- Soskel, N.T., Watanabe, S., Sandberg, L.B., 1984. Mechanisms of lung injury in the copper-deficient hamster model of emphysema. *Chest* 85, 70S–73S.
- Souidi, M., Combettes-Souverain, M., Milliat, F., Eckhardt, E.R., Audas, O., Dubrac, S., et al. 2001. Hamsters predisposed to sucrose-induced cholesterol gallstones (LPN strain) are more resistant to excess dietary cholesterol than hamsters that are not sensitive to cholelithiasis induction. *J. Nutr.* 131, 1803–1811.
- Spady, D.K., Turley, S.D., Dietschy, J.M., 1983. Dissociation of hepatic cholesterol synthesis from hepatic low-density lipoprotein uptake and biliary cholesterol saturation in female and male hamsters of different ages. *Biochim. Biophys. Acta* 753, 381–392.
- Spencer, J.F., Sagartz, J.E., Wold, W.S., Toth, K., 2009. New pancreatic carcinoma model for studying oncolytic adenoviruses in the permissive syrian hamster. *Cancer Gene Ther.* [10.1038/cgt.2009.36](https://doi.org/10.1038/cgt.2009.36).
- Spitz, M.R., 1994. Epidemiology and risk factors for head and neck cancer. *Semin. Oncol.* 21, 281–288.
- Sriamporn, S., Pisani, P., Pipitgool, V., Suwanrungruang, K., Kamsa-ard, S., Parkin, D.M., 2004. Prevalence of opisthorchis

- viverrini infection and incidence of cholangiocarcinoma in khon kaen, northeast thailand. *Trop. Med. Int. Health* 9, 588–594. [10.1111/j.1365-3156.2004.01234.x](https://doi.org/10.1111/j.1365-3156.2004.01234.x).
- Scroller, V., Vilchez, R.A., Stewart, A.R., Wong, C., Butel, J.S., 2008. Influence of the viral regulatory region on tumor induction by simian virus 40 in hamsters. *J. Virol.* 82, 871–879. [10.1128/JVI.01626-07](https://doi.org/10.1128/JVI.01626-07).
- Stampfer, M.J., Colditz, G.A., Willett, W.C., Manson, J.E., Rosner, B., Speizer, F.E., et al. 1991. Postmenopausal estrogen therapy and cardiovascular disease. ten-year follow-up from the nurses' health study. *N. Engl. J. Med.* 325, 756–762.
- Steinmann, P., Keiser, J., Bos, R., Tanner, M., Utzinger, J., 2006. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect. Dis.* 6, 411–425.
- Subbarao, K., Roberts, A., 2006. Is there an ideal animal model for SARS? *Trends Microbiol.* 14, 299–303. [10.1016/j.tim.2006.05.007](https://doi.org/10.1016/j.tim.2006.05.007).
- Sullivan, M.P., Cerda, J.J., Robbins, F.L., Burgin, C.W., Beatty, R.J., 1993. The gerbil, hamster, and guinea pig as rodent models for hyperlipidemia. *Lab. Anim. Sci.* 43, 575–578.
- Sundar, S., More, D.K., Singh, M.K., Singh, V.P., Sharma, S., Makharia, A., et al. 2000. Failure of pentavalent antimony in visceral leishmaniasis in India: Report from the Center of the Indian epidemic. *Clin. Infect. Dis.* 31, 1104–1107. [10.1086/318121](https://doi.org/10.1086/318121).
- Sunday, M.E., Willett, C.G., Graham, S.A., Oreffo, V.I., Linnoila, R.I., Witschi, H., 1995. Histochemical characterization of non-neuroendocrine tumors and neuroendocrine cell hyperplasia induced in hamster lung by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone with or without hyperoxia. *Am. J. Pathol.* 147, 740–752.
- Svensjo, E., 1990. The hamster cheek pouch as a model in microcirculation research. *Eur. Respir. J. (Suppl. 12)*, 595s–600s, discussion 600s–601s.
- Taghibiglou, C., Carpentier, A., Van Iderstine, S.C., Chen, B., Rudy, D., Aiton, A., et al. 2000. Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance. evidence for enhanced lipoprotein assembly, reduced intracellular ApoB degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model. *J. Biol. Chem.* 275, 8416–8425.
- Taghibiglou, C., Rashid-Kolvear, F., Van Iderstine, S.C., Le-Tien, H., Fantus, I.G., Lewis, G.F., et al. 2002. Hepatic very low density lipoprotein-ApoB overproduction is associated with attenuated hepatic insulin signaling and overexpression of protein-tyrosine phosphatase 1B in a fructose-fed hamster model of insulin resistance. *J. Biol. Chem.* 277, 793–803. [10.1074/jbc.M106737200](https://doi.org/10.1074/jbc.M106737200).
- Takahashi, M., Kitahashi, T., Ishigamori, R., Mutoh, M., Komiya, M., Sato, H., et al. 2008. Increased expression of inducible nitric oxide synthase (iNOS) in N-nitrosobis(2-oxopropyl)amine-induced hamster pancreatic carcinogenesis and prevention of cancer development by ONO-1714, an iNOS inhibitor. *Carcinogenesis* 29, 1608–1613. [10.1093/carcin/bgn152](https://doi.org/10.1093/carcin/bgn152).
- Tamblyn, R., Berkson, L., Dauphinee, W.D., Gayton, D., Grad, R., Huang, A., et al. 1997. Unnecessary prescribing of NSAIDs and the management of NSAID-related gastropathy in medical practice. *Ann. Intern. Med.* 127, 429–438.
- Thamavit, W., Kongkanuntn, R., Tiwawech, D., Moore, M.A., 1987. Level of opisthorchis infestation and carcinogen dose-dependence of cholangiocarcinoma induction in Syrian golden hamsters. *Virchows Arch. B. Cell. Pathol. Incl. Mol. Pathol.* 54, 52–58.
- Thamavit, W., Pairojkul, C., Tiwawech, D., Itoh, M., Shirai, T., Ito, N., 1993. Promotion of cholangiocarcinogenesis in the hamster liver by bile duct ligation after dimethylnitrosamine initiation. *Carcinogenesis* 14, 2415–2417.
- Thamavit, W., Tiwawech, D., Moore, M.A., Ito, N., Shirai, T., 1996. Equivocal evidence of complete carcinogenicity after repeated infection of syrian hamsters with opisthorchis viverrini. *Toxicol. Pathol.* 24, 493–497.
- Thomas, M.A., Spencer, J.F., La Regina, M.C., Dhar, D., Tollefson, A.E., Toth, K., et al. 2006a. Syrian hamster as a permissive immunocompetent animal model for the study of oncolytic adenovirus vectors. *Cancer Res.* 66, 1270–1276. [10.1158/0008-5472.CAN-05-3497](https://doi.org/10.1158/0008-5472.CAN-05-3497).
- Thomas, M.A., Spencer, J.F., La Regina, M.C., Dhar, D., Tollefson, A.E., Toth, K., et al. 2006b. Syrian hamster as a permissive immunocompetent animal model for the study of oncolytic adenovirus vectors. *Cancer Res.* 66, 1270–1276. [10.1158/0008-5472.CAN-05-3497](https://doi.org/10.1158/0008-5472.CAN-05-3497).
- Thomas, M.A., Spencer, J.F., Toth, K., Sagartz, J.E., Phillips, N.J., Wold, W.S., 2008. Immunosuppression enhances oncolytic adenovirus replication and antitumor efficacy in the Syrian hamster model. *Mol. Ther.* 16, 1665–1673. [10.1038/mt.2008.162](https://doi.org/10.1038/mt.2008.162).
- Thrall, R.S., McCormick, J.R., Jack, R.M., McReynolds, R.A., Ward, P.A., 1979. Bleomycin-induced pulmonary fibrosis in the rat: Inhibition by indomethacin. *Am. J. Pathol.* 95, 117–130.
- Trautwein, E.A., Liang, J., Hayes, K.C., 1993. Cholesterol gallstone induction in hamsters reflects strain differences in plasma lipoproteins and bile acid profiles. *Lipids* 28, 305–312.
- Trautwein, E.A., Siddiqui, A., Hayes, K.C., 1999. Characterization of the bile acid profile in developing male and female hamsters in response to dietary cholesterol challenge. *Comp. Biochem. Physiol. A. Mol. Integr. Physiol.* 124, 93–103.
- Uchida, E., Matsushita, A., Yanagi, K., Hiroi, M., Aimoto, T., Nakamura, Y., et al. 2008. Experimental pancreatic cancer model using PGHAM-1 cells: Characteristics and experimental therapeutic trials. *J. Nippon Med. Sch.* 75, 325–331.
- Vairaktaris, E., Papageorgiou, G., Derka, S., Moulavassili, P., Nkenke, E., Kessler, P., et al. 2007. Expression of ets-1 is not affected by N-ras or H-ras during oral oncogenesis. *J. Cancer Res. Clin. Oncol.* 133, 227–233. [10.1007/s00432-006-0161-1](https://doi.org/10.1007/s00432-006-0161-1).
- Vairaktaris, E., Papakosta, V., Derka, S., Vassiliou, S., Nkenke, E., Spyridonidou, S., et al. 2008a. H-ras and c-fos exhibit similar expression patterns during most stages of oral oncogenesis. *In Vivo* 22, 621–628.
- Vairaktaris, E., Spyridonidou, S., Papakosta, V., Vylliotis, A., Lazaris, A., Perrea, D., et al. 2008b. The hamster model of sequential oral oncogenesis. *Oral Oncol.* 44, 315–324. [10.1016/j.oraloncology.2007.08.015](https://doi.org/10.1016/j.oraloncology.2007.08.015).
- van Heek, M., Austin, T.M., Farley, C., Cook, J.A., Tetzloff, G.G., Davis, H.R., 2001. Ezetimibe, a potent cholesterol absorption inhibitor, normalizes combined dyslipidemia in obese hyperinsulinemic hamsters. *Diabetes* 50, 1330–1335.
- Vannier, E., Gewurz, B.E., Krause, P.J., 2008. Human babesiosis. *Infect. Dis. Clin. North Am.* 22, 469–488 viii–ix. [10.1016/j.idc.2008.03.010](https://doi.org/10.1016/j.idc.2008.03.010).
- Wade, G.N., Lempicki, R.L., Panicker, A.K., Frisbee, R.M., Blaustein, J.D., 1997. Leptin facilitates and inhibits sexual behavior in female hamsters. *Am. J. Physiol.* 272, R1354–8.
- Wade, G.N., Schneider, J.E., Li, H.Y., 1996. Control of fertility by metabolic cues. *Am. J. Physiol.* 270, E1–19.
- Wahl-Jensen, V., Chapman, J., Asher, L., Fisher, R., Zimmerman, M., Larsen, T., et al. 2007. Temporal analysis of andes virus and sin nombre virus infections of syrian hamsters. *J. Virol.* 81, 7449–7462. [10.1128/JVI.00238-07](https://doi.org/10.1128/JVI.00238-07).
- Wallace, J.L., McKnight, G.W., 1993. Characterization of a simple animal model for nonsteroidal anti-inflammatory drug induced antral ulcer. *Can. J. Physiol. Pharmacol.* 71, 447–452.
- Wang, I.C., Guo, J.X., Ma, Y.X., Chung, W.C., Lu, S.C., Fan, P.C., 1999. Sexual development of taenia solium in hamsters from rodent-derived cysticerci. *J. Helminthol.* 73, 347–350.
- Wang, Q., Hyde, D.M., Gotwals, P.J., Giri, S.N., 2002. Effects of delayed treatment with transforming growth factor-beta soluble receptor in a three-dose bleomycin model of lung fibrosis in hamsters. *Exp. Lung Res.* 28, 405–417. [10.1080/01902140290096700](https://doi.org/10.1080/01902140290096700).
- Wattenberg, L.W., Wiedmann, T.S., Estensen, R.D., 2004. Chemoprevention of cancer of the upper respiratory tract of the

- syrian golden hamster by aerosol administration of difluoromethylornithine and 5-fluorouracil. *Cancer Res.* 64, 2347–2349.
- Werkmeister, R., Brandt, B., Joos, U., 2000. Clinical relevance of erbB-1 and -2 oncogenes in oral carcinomas. *Oral Oncol.* 36, 100–105.
- Williams, H.K., 2000. Molecular pathogenesis of oral squamous carcinoma. *Mol. Pathol.* 53, 165–172.
- Wissler, R.W., 1991. Update on the pathogenesis of atherosclerosis. *Am. J. Med.* 91, 3S–9S.
- Wittner, M., Lederman, J., Tanowitz, H.B., Rosenbaum, G.S., Weiss, L.M., 1996. Atovaquone in the treatment of babesia microti infections in hamsters. *Am. J. Trop. Med. Hyg.* 55, 219–222.
- Wong, D.T., Donoff, R.B., Yang, J., Song, B.Z., Matossian, K., Nagura, N., et al. 1993. Sequential expression of transforming growth factors alpha and beta 1 by eosinophils during cutaneous wound healing in the hamster. *Am. J. Pathol.* 143, 130–142.
- Wong, D.T., Gallagher, G.T., Gertz, R., Chang, A.L., Shklar, G., 1988. Transforming growth factor alpha in chemically transformed hamster oral keratinocytes. *Cancer Res.* 48, 3130–3134.
- Woollett, L.A., Kearney, D.M., Spady, D.K., 1997. Diet modification alters plasma HDL cholesterol concentrations but not the transport of HDL cholesteryl esters to the liver in the hamster. *J. Lipid Res.* 38, 2289–2302.
- Wozniak, E.J., Lowenstine, L.J., Hemmer, R., Robinson, T., Conrad, P.A., 1996. Comparative pathogenesis of human WA1 and babesia microti isolates in a syrian hamster model. *Lab. Anim. Sci.* 46, 507–515.
- Wyllie, S., Fairlamb, A.H., 2006. Refinement of techniques for the propagation of leishmania donovani in hamsters. *Acta Trop.* 97, 364–369. [10.1016/j.actatropica.2006.01.004](https://doi.org/10.1016/j.actatropica.2006.01.004).
- Yamaki, T., Kritchman, M., 1981. Technical report. hamster cheek pouch preparation for biomicroscopy: a new approach. *Microvasc. Res.* 21, 299–301.
- Yang, J., Torio, A., Donoff, R.B., Gallagher, G.T., Egan, R., Weller, P.F., et al. 1997. Depletion of eosinophil infiltration by anti-IL-5 monoclonal antibody (TRFK-5) accelerates open skin wound epithelial closure. *Am. J. Pathol.* 151, 813–819.
- Yang, J., Tyler, L.W., Donoff, R.B., Song, B., Torio, A.J., Gallagher, G.T., et al. 1996. Salivary EGF regulates eosinophil-derived TGF-alpha expression in hamster oral wounds. *Am. J. Physiol.* 270, G191–202.
- Yasuhara, H., Hobson II, R.W., Dillon, P.K., Duran, W.N., 1991. A new model for studying ischemia-reperfusion injury in hamster cheek pouch. *Am. J. Physiol.* 261, H1626–9.
- Yip-Schneider, M.T., Wu, H., Njoku, V., Ralstin, M., Holcomb, B., Crooks, P.A., et al. 2008. Effect of celecoxib and the novel anti-cancer agent, dimethylamino-parthenolide, in a developmental model of pancreatic cancer. *Pancreas* 37, e45–53. [10.1097/MPA.0b013e318172b4dd](https://doi.org/10.1097/MPA.0b013e318172b4dd).
- Yu, T., Wang, X.Y., Gong, R.G., Li, A., Yang, S., Cao, Y.T., et al. 2009. The expression profile of microRNAs in a model of 7,12-dimethylbenz[a]anthracene-induced oral carcinogenesis in Syrian hamster. *J. Exp. Clin. Cancer Res.* 28, 64. [10.1186/1756-9966-28-64](https://doi.org/10.1186/1756-9966-28-64).
- Zhu, Y., Wang, H.J., Chen, L.F., Fang, Q., Yan, X.W., 2007. Study of ATP-binding cassette transporter A1 (ABCA1)-mediated cellular cholesterol efflux in diabetic golden hamsters. *J. Int. Med. Res.* 35, 508–516.