Gosselin SJ, Setchell KDR, Harrington GW, Welsh MB, Pylypiw H, Kozeniauskas R, Dollard D, Tarr MJ, Dresser BL. 1989. Nutritional considerations in the pathogenesis of hepatic veno-occlusive disease in captive cheetahs. Zoo Biology 8:339-47.

Keywords: Acinonyx jubatus/captivity/cheetah/diet/disease/liver/plant estrogen/research/veno-occlusive disease/veterinary/VOD/zoo

Abstract: Veno-occlusive disease (VOD) of the liver has been diagnosed in a large number of captive cheetahs. Some ingredients or contaminants present in the diet were suspected as possible causes for this non-infectious disease with high incidence. Eight different diets fed to cheetahs kept in North American zoos were analyzed for vitamin A levels and the presence or absence of plant estrogens, nitrosamines, nitrites, and aflatoxins. Three of the eight diets were considered to contain toxic amounts of vitamin A. In humans and rats, hypervitaminosis A has been associated with hepatic vascular lesions, mainly perisinusoidal fibrosis, which progress eventually to occlusive lesions similar to VOD. Plant estrogens were detected in appreciable amounts only in one of the exotic carnivore diets. The role of plant estrogens in the pathogenesis of VOD in captive cheetahs is not clear at this time and needs further investigation. Based on the liver pathology and diet analyses, nitrosamines or their dietary precursor and aflatoxins can be excluded as possible causes of VOD in cheetahs kept in North American zoos.

Zoo Biology 8:339–347 (1989)

Nutritional Considerations in the Pathogenesis of Hepatic Veno-Occlusive Disease in Captive Cheetahs

Sylvie J. Gosselin, Kenneth D.R. Setchell, George W. Harrington, Mary-Beth B. Welsh, Harry Pylypiw, Raymond Kozeniauskas, Denis Dollard, Melinda J. Tarr, and Betsy L. Dresser

Merrell-Dow Research Institute (S.J.G.), Cincinnati Zoo and Botanical Garden (S.J.G., B.L.D.), and Department of Pediatric Gastroenterology and Nutrition, Children's Hospital Medical Center (K.D.R.S., M.-B.B.W.), Cincinnati; Department of Chemistry, Temple University (G.W.H., H.P., R.K., D.D.), Philadelphia, and Department of Veterinary Pathobiology, The Ohio State University (M.J.T.), Columbus

Veno-occlusive disease (VOD) of the liver has been diagnosed in a large number of captive cheetahs. Some ingredients or contaminants present in the diet were suspected as possible causes for this noninfectious disease with high incidence. Eight different diets fed to cheetahs kept in North American zoos were analyzed for vitamin A levels and the presence or absence of plant estrogens, nitrosaminines, nitrites, and aflatoxins. Three of the eight diets were considered to contain toxic amounts of vitamin A. In humans and rats, hypervitaminosis A has been associated with hepatic vascular lesions, mainly perisinusoidal fibrosis, which progress eventually to occlusive lesions similar to VOD. Plant estrogens were detected in appreciable amounts only in one of the exotic carnivore diets. The role of plant estrogens in the pathogenesis of VOD in captive cheetahs is not clear at this time and needs further investigation. Based on the liver pathology and diet analyses, nitrosamines or their dietary precursors and aflatoxins can be excluded as possible causes of VOD in cheetahs kept in North American zoos.

Key words: liver diseases, diet, vitamin A, plant estrogens

INTRODUCTION

The average life span of cheetahs reaching sexual maturity and kept in North American zoos is 8.8 years, which is shorter than predicted for captive felidae [Marker, 1983–1984, 1985, 1986; Jones, 1980]. Based on a survey of 125 adult cheetahs from 22 North American zoos (Table 1), liver diseases appeared to be the

Received for publication August 19, 1988; revision accepted December 28, 1988.

Address reprint requests to Dr. Sylvie J. Gosselin, Department of Pathology/Toxicology, Merrell-Dow Research Institute, 2110 Galbraith Road, Cincinnati, OH 45215.

TABLE 1. Factors contributing to a shortened life span in adult cheetahs kept in North American zoos*

Disease	Percentage
Liver diseases	54.9
Renal failure	38.3
Infectious diseases[a]	20.0
Pneumonia	10.8
Neoplasia	8.3
Diabetes mellitus/pancreatitis	8.3
Miscellaneous	6.6
Unknown	5.0

*The results of the survey are based on pathology reports from 125 adult cheetahs that died between 1945 and 1986. In several animals there was more than one factor and sometimes as many as three and four contributing to their death. The most frequent combination of factors was liver disease and renal failure.
[a]Infectious diseases include bacterial, viral, fungal, and protozoal infections.

most frequent factors contributing to a shortened life span in these animals. Liver diseases of undefined nature have been recognized since the late 1960s to be a major cause of death in captive cheetah [van de Werken, 1967].

Recent studies revealed that the main hepatic lesion responsible for liver disease was a vascular lesion called veno-occlusive disease (VOD) of the liver, which was observed in 60% of the adult cheetah population [Munson and Worley, 1987; Gosselin et al., 1988]. Although this hepatic vascular lesion was seen in cheetahs as young as 1 year of age, the most severe lesions, usually associated with liver failure, were found in cheetahs between 6 and 11 years of age [Gosselin et al., 1988]. The diets are the most obvious common denominator between groups of cheetahs from different zoos and should be suspected in the etiology of a noninfectious disease with high incidence. The purpose of this study was to analyze various diets that have been fed to cheetahs kept in North American zoos for ingredients or contaminants that previously have been shown to be associated with VOD and to assess the extent to which they may play a role in the pathogenesis of the liver lesions in captive cheetahs.

MATERIALS AND METHODS

Cheetah Diets

Seven diets obtained from four different commercial food manufacturers (see Table 2 for ingredients present in the seven commercial diets) and one zoo-prepared diet were analyzed for vitamin A levels and the presence of phytoestrogens, nitrosamines, nitrites, or aflatoxins. Diet 1 was a zoo-prepared diet consisting of 89% ground horsemeat, 4% mineral mix, 2% A&D feeding oil (containing cod liver oil), and 5% beet pulp. Diets 2 through 6 were commercially prepared diets for exotic carnivores; diet 7 was primarily used to feed racing dogs; diet 8 (canned product with liver as the primary component), not specifically formulated for exotic cats, has been used to stimulate the appetite of anorexic felids. Diet 1 has been fed to a group of cheetahs for 3 years, and diets 4, 5, 6, 7, and 8 have been on the market for at least

TABLE 2. Descriptions of diets based on manufacturer's literature

Manufacturer	Diet	Horsemeat	Beef	Meat by-product	Chicken	Liver	Ground bone meal	Dried eggs	Brewer dried yeast	Dried beet pulp	Vit/ Min
A	2	a[a]		b[a]						c[a]	d[a]
	3[b]	a		b		d	c	f	g	e	h
B	4		a	d	c		b				e
C	5	a		b	d	c	e				f
	6[c]		c	a		b	d	e	f		g
	7[d]	a		b			c				d
D	8[e]			b		a			c		d

[a]Ingredients are in the same order as listed by the manufacturers; other ingredients include [b]fish meal and soya meal; [c]dried bakery products, [d]charcoal, and [e]water, ground corn, animal fat, dried skimmed milk, DL-methionine.

5 years; diet 3, for 16 years. Diet 2 is a new commercial diet that has been available since January 1988.

Dietary Analyses: Vitamin A Levels and Contaminants

The levels of vitamin A and the presence or absence of plant estrogens were determined in at least one batch per diet, depending on the availability of the diets (see Table 3 for the number of batches analyzed per diet). Vitamin A analyses of diet samples were done by high-performance liquid chromatography at the Animal Health Diagnostic Laboratory, Michigan State University [Stowe and Goelling, 1981]. A search for estrogenic compounds of plant origin in these diets was carried out with high-pressure liquid chromatography (HPLC) with ultraviolet and electrochemical detection [Setchell et al., 1986]. Definitive chemical identification of these nonsteroidal estrogens was achieved by capillary column gas-liquid chromatography-mass spectrometry (GC-MS) and thermospray ionization liquid chromatography-mass spectrometry-mass spectrometry (LC-MS-MS) [Setchell et al., 1987; Barbuck et al., 1988]. Gas chromatography coupled with a thermal energy analyzer (GC-TEA) was used to detect minimal amounts (few parts per billion) of nitrosamine in diets 1 through 4, horsemeat, and A&D feeding oil (Anderson et al., 1985). In vitro nitrosation consisted of adding hydrochloric acid (20 ml of 0.1 M HCl) with or without sodium nitrite (1 g of $NaNO_2$) to 2 g of frozen powder from diets 1 through 4, horsemeat, and A&D feeding oil. The samples were allowed to react for either 24 or 72 hr and analyzed by GC-TEA. Nitrosation of the samples was confirmed by the photolysis method of Doerr and Fiddler [1977]. One saliva sample was collected from one cheetah after injection with pilocarpine and was analyzed for nitrites and nitrates with previously described methods [Chang et al., 1977; Barsotti et al., 1982]. Aflatoxins (B_1, B_2, G_1, G_2, M_1) were measured in seven diets (one sample each) by high-performance liquid chromatography and nitrites by colorimetry at the Laboratories of Veterinary Diagnostic Medicine, University of Illinois [Qian and Yang, 1984; Ellis, 1984].

RESULTS

The results of dietary analyses for vitamin A, plant estrogens, nitrosamines, and aflatoxins are given in Table 3. Vitamin A concentrations in diets fed to cheetahs

TABLE 3. Vitamin A levels and contaminants present in diets fed to captive cheetahs

Diet	Vitamin A[a] (IU/kg)	Plant estrogens[b] Daidzein (μg/g)	Plant estrogens[b] Genistein (μg/g)	Nitrosamines (ppb)	In vitro nitrosation w/HCl[c] (ppb)	In vitro nitrosation w/HCl + $NaNO_2$[c] (ppb)	Aflatoxins (ppb)
1	6,091	—[d]	—	<10	<10	20	NA[e]
2	8,855, 7,127, 6782[f]	—,—	—,—	<10,<10,<10	<10,<10	<10, 1,700, 730	—
3	38,550, 33,491	16.4, 25.3, 35.2, 84.6	16.4, 18.1, 21.3, 119.0	<10,<10	<10,<10	144, 5,600	—
4	10,950 6,588	—	—	<10,<10	<10,<10	198, 2,500	—
5	1,055	—	—	NA	NA	NA	—
6	94,121	—	—	NA	NA	NA	—
7	382	—	—	NA	NA	NA	—
8	95,820, 473,918, 321,291	0.64,—	0.06,—	NA	NA	NA	—

[a]Dry weight basis.
[b]Wet weight basis.
[c]Results after 24 hr reaction.
[d]— = undetectable level.
[e]NA = not analyzed.
[f]Results from different batches of the same diet; in this case, the results are from three different batches of diet 2.

ranged from 382 to 473,918 IU/kg, on a dry weight basis. Diets 1, 2, and 4 were within the recommended vitamin A allowance for the domestic cat published by the National Research Council [1978, 1986] (10,000 IU/kg in 1978; 6,000 IU/kg in 1986).

Dietary estrogens of plant origin were identified by GC-MS and LC-MS-MS in only two of the eight diets analyzed. Although the methods employed afforded the detection of a series of isoflavones, including, in addition to coumestrol, daidzein, genistein, formononetin, and biochanin A, daidzein and genistein were the only estrogens detected in these diets. Diet 3 contained variable amounts of these compounds, ranging from 16.4 to 119.0 μg/g of diet, on a wet weight basis. Two batches of soya meal used in the formulation of diet 3 were also analyzed for plant estrogens. Batch 1 contained 214.5 μg/g of daidzein and 166.8 μg/g of genistein, whereas the second batch had four to five times more of these plant estrogens (daidzein, 870.7 μg/g; genistein, 832.9 μg/g). Variable concentrations of plant estrogens in the soya meal added to the feed and uneven mixture of the soya product with the other food ingredients could explain the wide range of plant estrogens found in the different diet 3 batches.

The nitrosamine levels of diets 1 through 4, horsemeat, and A&D feeding oil were all less than 10 ppb. The potential formation of nitrosamines in the stomach of animals was determined by in vitro nitrosation. In vitro nitrosation resulted in the production of minimal, if any, amounts of nitrosamines when HCl was the only compound added to the diet samples. On the other hand, appreciable quantities of nitrosamines were formed when HCl in combination with $NaNO_2$ was allowed to react with the different diet samples. Nitrite levels in the diets ranged from 0.005 to 1.7 ppm. Cheetah saliva had 171 ± 12 ppb of nitrites and 11.45 ± 0.06 ppm of

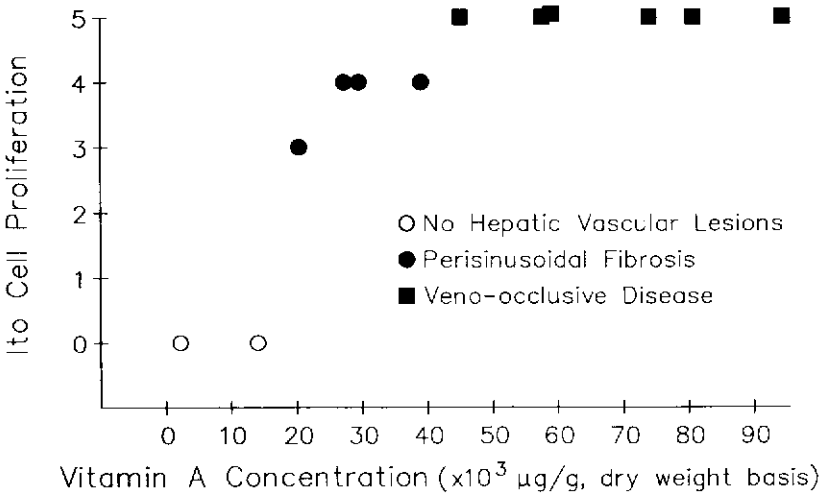

Fig. 1. Vascular lesions, Ito cell proliferation, and vitamin A concentration in the liver of 12 captive cheetahs. Cheetahs with veno-occlusive lesions also have perisinusoidal fibrosis of the liver. Severity code for Ito cell proliferation: 1 = very mild; 2 = mild; 3 = moderate; 4 = moderate to severe; 5 = severe. Liver vitamin A concentrations in 9 of the 12 cheetahs are from Gosselin et al. [1988].

nitrates. Aflatoxins were not detected in any diet and, if present, were below the limit of detection of the method (100 ppb for aflatoxins B_1 and G_1; 50 ppb for aflatoxins B_2 and G_2; 10 ppb for aflatoxin M_1).

DISCUSSION

Veno-occlusive disease of the liver (VOD) in both humans and animals has been shown to have multiple causes, including associations with ingestion of pyrrolizidine alkaloids, aflatoxins, nitrosamines, alcoholic beverages, and excess vitamin A, as well as after oral contraceptive regimens or exposure to irradiation and cancer chemotherapy [Zafrani et al., 1983; Newberne and Butler, 1969; Koppang et al., 1981; McLean et al., 1965; Ungar, 1986; Goodman and Ishak, 1982; Jacques et al., 1979; Kim et al., 1982; Alpert, 1976; Rollins, 1986]. In the cheetah, a number of these known etiologies can be disregarded, including the latter two therapeutic procedures [Gosselin et al., 1988]. A previous study failed to provide any pathological evidence for the presence of pyrrolizidine alkaloids in the diets fed to captive cheetahs [Gosselin et al., 1988]. A genetic basis to explain the high prevalence of VOD in captive cheetahs also can be excluded as a possible cause [Mellis and Bale, 1976; Gosselin et al., 1988].

In this study, the analysis of eight different diets fed to captive cheetahs in the last few years identified only three diets within the recommended vitamin A allowance for the domestic cat [National Research Council, 1978, 1986]. On the basis of these same authorities, diets 3, 6, and 8 were considered to contain toxic amounts of vitamin A, whereas diets 5 and 7 were deficient. In the 12 cheetahs evaluated for liver vitamin A content, an increase in the severity of hepatic lesions, from perisinusoidal fibrosis to VOD, paralleled the increase in concentration of vitamin A (Fig. 1). These

findings suggest that vitamin A excess may play a role in the development of VOD in captive cheetahs. Meal schedules that include raw liver on a regular basis or commercial diets containing liver as a major ingredient probably should be used only for limited periods or as a means of enticing the animal to eat again. Some zoos are feeding whole carcasses or straight horsemeat supplemented with vitamins and minerals to their cheetahs. The majority of companies manufacturing vitamin and mineral supplements quote guaranteed analyses for minimum not for maximum concentrations for most vitamins and minerals in their formulations. Supplementation of the feed could easily result in toxic amounts of vitamin A. When two Cincinnati Zoo cheetahs were fed straight horsemeat or chicken meat with the amount of a vitamin/mineral supplement recommended by the manufacturer for at least 6 months, serum vitamin A levels increased from an average of 256 to 1,929 ng/ml. At these levels, a diagnosis of vitamin A toxicity would be considered in humans [Minuk et al., 1988].

Analysis of eight diets using GC-MS and LC-MS-MS led to the identification of two plant estrogens, daidzein and genistein, that belong to the class of nonsteroidal estrogens, the isoflavones. They were found in relatively high concentrations in only one diet (diet 3, which has been fed to more than 60% of the captive cheetah population) and were shown to originate from the added soyprotein products. Soybeans contain naturally large amounts of these compounds [Axelson et al., 1984; Eldridge and Kwolek, 1983; Murphy, 1982; Seo and Morr, 1984]. The estrogenic activity of these isoflavones has been confirmed with a standard bioassay using immature mice and by repeatedly inducing signs of estrus in domestic cats [Setchell et al., 1987; Setchell et al., in preparation]. VOD in captive cheetahs could be the result of the direct effect of these plant estrogens on the vascular wall or changes in blood coagulation with secondary liver involvement, as has been suggested for other estrogens [Almen et al., 1975; Friederici, 1967; Irey and Norris, 1973; Widmann and Fahimi, 1976; Alpert, 1976; Dugdale and Masi, 1971]. The earliest vascular lesion observed in cheetahs with VOD was intimal thickening of the central vein as a result of the proliferation of smooth muscle–like cells and the presence of excessive amounts of fine fibers [Gosselin et al., 1988]. These vascular changes share many similarities with the intimal vascular proliferation described in women taking oral contraceptives, in pregnant animals, and in animals treated with estrogens [Irey et al., 1970; Irey and Norris, 1973; Albert, 1967; Albert and Bhussry, 1967; Friederici, 1967; Gammal, 1976]. It is interesting to note that veno-occlusive lesions are also seen in alcoholic cirrhosis and have been suggested to be caused by contaminants, which would include plant estrogens but not ethanol [Goodman and Ishak, 1982; Gavaler et al., 1987]. Further studies are needed to clarify the possible role of plant estrogens in the pathogenesis of VOD in captive cheetahs.

Nitrosamine intoxication has been associated with vascular lesions resembling VOD of the liver in several animal species, with pigs and poultry requiring tenfold more nitrosamines (100 ppm) than do cattle, sheep, and mink [Koppang et al., 1981; McLean et al., 1965; Ungar, 1986; Koppang, 1974a,b,c]. Accidental poisonings have been described in animals eating fish meal containing sodium nitrite as a preservative [Koppang, 1964, 1966; Koppang and Helgebostad, 1966]. Nitrosamines are formed by a reaction between nitrite and trimethylamine or lower amines from the fish [Koppang, 1966]. The production of fish meal from fresh and from formaldehyde- and sodium benzoate–preserved catches also results in the formation

of considerable nitrosamines [Koppang, 1974b]. At the Cincinnati Zoo, a 10-year-old California sea lion that was basically fed a diet of fresh frozen fish was diagnosed as having severe hepatic VOD. Nitrosamine levels in the zoo-prepared diet and the three commercial diets were less than 10 ppb, which is at least 10^3 to 10^4 times lower than the amounts required to induce VOD in other animal species. Nitrosating agents, such as nitrites, present in the various feeds were considered to be at insignificant levels because very little, if any, in vitro nitrosation occurred when only HCl was added to the diet samples. On the other hand, HCl with $NaNO_2$ resulted in the formation of appreciable amounts of nitrosamines. The source of nitrites in cheetahs would be their saliva, where 171 ppb of nitrites was found. Nitrates (11.45 ppm), also in cheetah saliva, may play a role since a proportion of nitrates could be reduced endogenously to nitrites [Spiegelhalder et al., 1976]. It should be noted, however, that the histologic sequence of events in the hepatic damage observed in cheetahs with VOD does not parallel the sequence following nitrosamine intoxication [Gosselin et al., 1988; Koppang, 1966, 1974a,c; Koppang et al., 1981; McLean et al., 1965]. Nitrosamines are also known for their carcinogenic potential, and the United States Department of Agriculture has set 10 ppb as the concern level and 17 ppb as the action level for cured meats such as bacon [Federal Register, 1978]. Although tumors originating from the liver should be expected after long-term exposure, in a study of 104 adult cheetahs only one cholangiocellular carcinoma was diagnosed in the liver of a 9-year-old male [Gosselin et al., 1988]. On the basis of these pathological observations, nitrosamines as a possible cause of VOD in cheetahs was considered to be questionable. Aflatoxins, another food contaminant, have occasionally been associated with occlusion of the central veins and could be excluded as a possible cause of VOD in captive cheetahs, based on liver pathology and chemical analysis of seven diets fed to these animals [Newberne and Butler, 1969; Gosselin et al., 1988].

CONCLUSIONS

Vitamin A excess is associated with perisinusoidal fibrosis and probably 26% of the VOD cases diagnosed in a captive adult cheetah population [Gosselin et al., 1988]. The deleterious effect of hypervitaminosis A is not limited to the liver; it has been associated in the domestic cat with skeletal abnormalities and reproductive disorders [Seawright et al., 1970]. Therefore, vitamin A levels in commercially prepared diets for exotic carnivores should probably be corrected to match the daily vitamin A allowance for the domestic cat, with a range between 6,000 and 10,000 IU/kg [National Research Council 1978, 1986]. These levels should satisfy the needs encountered during pregnancy, lactation and growth of young animals based on studies done in the domestic cat. Long-term nutritional studies, starting with young cheetahs, would establish if the recommended range for dietary vitamin A is appropriate for these captive animals.

The role of plant estrogens in the pathogenesis of VOD in captive cheetahs is not clear at this time and needs further investigation. Currently, there is no available evidence that nitrosamines or their dietary precursors and aflatoxins cause any problem in these captive animals.

ACKNOWLEDGMENTS

This research was supported in part by the Cooperative Research Program of The Columbus Zoo and The Ohio State University (grant 718621), the Deramus

Foundation, Inc., Kansas City, Missouri, and the National Cancer Institute (PHS grant CA43342). The authors thank the following zoological institutions for their contributions to this project: Cleveland, Columbus, Fort Wayne, Philadelphia, and St. Louis.

REFERENCE

Albert, E.N. The effect of pregnancy on the elastic membranes of mesometrial arteries in the guinea pig. AMERICAN JOURNAL OF ANATOMY 120:611–625, 1967.

Albert, E.N.; Bhussry, B.R. The effects of multiple pregnancies and age on the elastic tissue of uterine arteries in the guinea pig. AMERICAN JOURNAL OF ANATOMY 121:259–269, 1967.

Almen, T.; Hartel, M.; Nylander, G.; Olivecrona, H. The effect of estrogen on the vascular endothelium and its possible relation to thrombosis. SURGERY, GYNECOLOGY AND OBSTETRICS 140:938–940, 1975.

Alpert, L.I. Veno-occlusive disease of the liver associated with oral contraceptives: Case report and review of literature. HUMAN PATHOLOGY 7:709–718, 1976.

Anderson, L.; Zimmerman, F.; Pylypiw, H.; Harrington, G.W. An apparatus for the trace determination of N-nitrosamines in small samples. ANALYTICAL CHEMISTRY 57:2996–2997, 1985.

Axelson, M.; Sjovall, J.; Gustafsson, B.E.; Setchell, K.D.R. Soya—a dietary source of the non-steroidal oestrogen equol in humans and animals. JOURNAL OF ENDOCRINOLOGY 102:49–56, 1984.

Barbuck, R.J.,; Coutant, J.E.; Setchell K.D.R.,; Welch, M.B. The use of thermospray LC/MS/MS for the class identification and structural verification of phytoestrogens in soy protein preparation. PROCEEDINGS OF THE AMERICAN SOCIETY OF MASS SPECTROMETRY, 1988.

Barsotti, D.; Pylypiw, H.; Harrington, G.W. Determination of nitrite and nitrate by differential pulse polarography. ANALYTICAL LETTERS 15(A17):1411–1422, 1982.

Chang, S.K.; Kozeniauskas, R.; Harrington, G.W. Determination of nitrite ion using differential pulse polarography. ANALYTICAL CHEMISTRY 49:2272–2275, 1977.

Doerr, R.C.; Fiddler, W. Photolysis of volatile nitrosamines at the picrogram level as an aid to confirmation. JOURNAL OF CHROMATOGRAPHY 140:284–286, 1977.

Dugdale, M.; Masi, A.T. Hormonal contraception and thromboembolic disease: Effects of the oral contraceptives on hemostatic mechanisms. JOURNAL OF CHRONIC DISEASES 23:775–790, 1971.

Eldridge, A.C.; Kwolek, W.F.J. Soya-bean isoflavones: Effect of environment and variety on composition. JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY 31:394–396, 1983.

Ellis, R.L. Meat and meat products. Pp. 431–443, in OFFICIAL METHODS OF ANALYSIS OF THE ASSOCIATION OF OFFICIAL ANALYTICAL CHEMISTS (Method #24.044). S. Williams, ed. Arlington, VA, Association of Official Analytical Chemists, Inc., 1984.

FEDERAL REGISTER 43(143):32136, 1978.

Friederici, H.H.R. The early response of uterine capillaries to estrogen stimulation. LABORATORY INVESTIGATION 17:322–333, 1967.

Gammal, E.G. Intimal thickening in arteries of rats treated with synthetic sex hormones. BRITISH JOURNAL OF EXPERIMENTAL PATHOLOGY 57:248–254, 1976.

Gavaler, J.S.; Rosenblum, E.R.; Van Thiel, D.H.; Eagan, P.K.; Pohl, C.R.; Campbell, I.M.; Gavaler, J. Biologically active phytoestrogens are present in bourbon. ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH 11: 399–406, 1987.

Goodman, Z.D.; Ishak, K.G. Occlusive venous lesions in alcoholic liver disease. GASTROENTEROLOGY 83:786–796, 1982.

Gosselin, S.J., Loudy, D.L.; Tarr, M.J.; Balistreri, W.F.; Setchell, K.D.R.; Johnston, J.O.; Kramer, L.W.; Dresser, B.L. Veno-occlusive disease of the liver in captive cheetah. VETERINARY PATHOLOGY 25:48–57, 1988.

Irey, N.S.; Marion, W.C.; Taylor, H.B. Vascular lesions in women taking oral contraceptives. ARCHIVES OF PATHOLOGY 89:1–8, 1970.

Irey, N.S.; Norris, H.J. Intimal vascular lesions associated with female reproductive steroids. ARCHIVES OF PATHOLOGY 96:227–234, 1973.

Jacques, E.A.; Buschmann, R.J.; Layden, T.J. The histopathologic progression of vitamin A-induced hepatic injury. GASTROENTEROLOGY 76:599–602, 1979.

Jones, M.L. Lifespan in mammals. Pp. 495–509 in THE COMPARATIVE PATHOLOGY OF ZOO ANIMALS. R.J. Montali, G. Migaki, eds. Washington, D.C., Smithsonian Institution Press, 1980.

Kim, C.J., Park, C.I.; Kim, C.S.; Lee, Y.B. Histochemical and ultrastructural studies of hepatic fibrogenesis; its initiation and the effect of dexamethasone in rats. YONSEI MEDICAL JOURNAL 23:89–97, 1982.

Koppang, N. An outbreak of toxic liver injury in ruminants. NORDISK VETERINAERMEDICIN 16:305–322, 1964.

Koppang, N. A severe progressive liver disease in fur animals. I. Symptoms and organ changes. NORDISK VETERINAERMEDICIN 18:205–209, 1966.

Koppang, N. Toxic effect of dimethylnitrosamine in cows. JOURNAL OF THE NATIONAL CANCER INSTITUTE 52:523–528, 1974a.

Koppang, N. Dimethylnitrosamine—formation in fish meal and toxic effects in pigs. AMERICAN JOURNAL OF PATHOLOGY 74:95–108, 1974b.

Koppang, N. The toxic effects of dimethylnitrosamine in sheep. ACTA VETERINARIA SCANDINAVIA 15:533–543, 1974c.

Koppang, N.; Helgebostad, A. Toxic hepatosis in fur animals. II. The etiology elucidated by feeding experiments. III. Conditions affecting the formation of the toxic factor in herring meal. NORDISK VETERINAERMEDICIN 18:210–225, 1966.

Koppang, N.; Helgebostad, A.; Armstrong, D.; Rimeslatten, H. Toxic and carcinogenic effects of dimethylnitrosamine (DMNA) in the blue fox *(Alopex lagopus)*. ACTA VETERINARIA SCANDINAVIA 22:501–516, 1981.

Marker, L. NORTH AMERICAN REGIONAL STUDBOOK. Winston, OR, Wildlife Safari, 1983–1984.

Marker, L. NORTH AMERICAN REGIONAL STUDBOOK. Winston, OR, Wildlife Safari, 1985.

Marker, L. NORTH AMERICAN REGIONAL STUDBOOK. Winston, OR, Wildlife Safari, 1986.

McLean, E.; Bros, G.; McLean, A.E.M. Venous occlusions in the liver following dimethylnitrosamine. BRITISH JOURNAL OF EXPERIMENTAL PATHOLOGY 46:367–369, 1965.

Mellis, C.; Bale, P.M. Familial veno-occlusive disease with probable immune deficiency. JOURNAL OF PEDIATRICS 88:236–242, 1976.

Minuk, G.Y.; Kelly, J.K.; Hwang, W.S. Vitamin A hepatotoxicity in multiple family members. HEPATOLOGY 8:272–275, 1988.

Munson, L.; Worley, M.B. Comparative hepatic histopathology in snow leopards and cheetahs. PROCEEDINGS OF THE AMERICAN ASSOCIATION OF ZOO VETERINARIANS, 1987.

Murphy, P.A. Phytoestrogen content of processed soybean products. FOOD TECHNOLOGY (Champaign) 34:60–64, 1982.

National Research Council: NUTRIENT REQUIREMENTS OF CATS. Washington, D.C., National Academy Press, 1978.

National Research Council: NUTRIENT REQUIREMENTS OF CATS. Washington, D.C., National Academy Press, 1986.

Newberne, P.M.; Butler, W.H. Acute and chronic effects of aflatoxin on the liver of domestic and laboratory animals: A review. CANCER RESEARCH 29:236–250, 1969.

Qian, G.-S.; Yang, G.C. Rapid extraction and detection of aflatoxins B_1 and M_1 in beef liver. JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY 32:1071–1073, 1984.

Rollins, B.J. Hepatic veno-occlusive disease. AMERICAN JOURNAL OF MEDICINE 81: 297–306, 1986.

Seawright, A.A.; English, P.B.; Gartner, R.J.W. Hypervitaminosis A of the cat. Pp. 1–27 in ADVANCES IN VETERINARY SCIENCE AND COMPARATIVE MEDICINE. C.A. Brandly, C.E. Cornelius, eds. New York, Academic Press, 1970.

Seo, A.; Morr, C.V. Improved high-performance liquid chromatographic analysis of phenolic acids and isoflavonoids from soybean protein products. JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY 32:530–533, 1984.

Setchell, K.D.R.; Welsh, M.B.; Lim, C.K. HPLC analysis of phytoestrogens in soy protein preparations with ultraviolet, electrochemical, and thermospray mass spectrometric detection. JOURNAL OF CHROMATOLOGY 385:267–274, 1986.

Setchell, K.D.R.; Gosselin, S.J.; Welsh, M.B.; Johnston, J.O.; Balistreri, W.F.; Kramer, L.W.; Dresser, B.L.; Tarr, M.J. Dietary estrogens—a probable cause of infertility and liver disease in captive cheetahs. GASTROENTEROLOGY 93: 225–233, 1987.

Setchell, K.D.R.; Gosselin, S.J.; Gates, J.; Johnston, J.O.; Tarr, M.J.; Dresser, B.L. Metabolism of plant estrogens in cheetahs and other felidae, including the domestic cat. (In preparation.)

Spiegelhalder, B.; Eisenbrand, G.; Preussman, R. Influence of dietary nitrite on nitrite content of human saliva. FOOD AND COSMETIC TOXICOLOGY 14:545–548, 1976.

Stowe, H.D.; Goelling, B. Experience with HPLC for diagnostic serum and tissue vitamin A assays. Pp. 385–395 in PROCEEDINGS OF THE AMERICAN ASSOCIATION OF VETERINARY LABORATORY DIAGNOSTICIANS, 1981.

Ungar, H. Venoocclusive disease of the liver and phlebectatic peliosis in the golden hamster exposed to dimethylnitrosamine. PATHOLOGY, RESEARCH AND PRACTICE 181:180–187, 1986.

van de Werken, H. PRELIMINARY REPORT ON CHEETAHS IN ZOOS AND IN AFRICA. Amsterdam, Royal Zoological Society, 1967.

Widmann, J.-J.; Fahimi, H.D. Proliferation of endothelial cells in estrogen-stimulated rat liver. LABORATORY INVESTIGATION 34:141–149, 1976.

Zafrani, E.S.; Pinaudeau, Y.; Dhumeaux, D. Drug-induced vascular lesions of the liver. ARCHIVES OF INTERNAL MEDICINE 143:495–502, 1983.