COMPARATIVE PATHOLOGY OF OAK (*QUERCUS* SPP.) LEAVES IN LABORATORY ANIMALS

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COMPARATIVE PATHOLOGY OF OAK (QUERCUS SPP.)

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF SYMBOLS

BUN - Blood urea nitrogen.

SGPT - Serum glutamic pyruvic transaminase.

SGOT - Serum glutamic oxaloacetic transaminase.

ml - milliliter.

mg/dl - Milligrams per deciliter.

IU/l - International Units per liter.

% - percent.

CHAPTER I

INTRODUCTION

Poisoning of domestic livestock by the ingestion of oak (Quercus spp.) buds, twigs, leaves and acorns is generally an infrequent, yet serious, condition encountered in veterinary medicine. More than 60 different species of oaks have been identified in North America; all of which should be considered potentially toxic to livestock (35). Oak poisoning has been recognized since at least 1662 where it was stated, "Again oak leaves, if sheep eat thereof green, it is evil for them, especially young lambs, which will kill them; and likewise of other cattel." (40, p. 243). Oak poisoning was not mentioned again until 1893 (17). More recently, oak poisoning has been reported as a regionally important, but sometimes widespread, condition of livestock affecting cattle, horses and sheep.

Due to the widespread occurrence of oak poisoning, further study of this condition is warranted. To lessen the cost of investigation of oak poisoning, alternative methods of study have been considered.

The purposes of this investigation were:

1. to develop a model of oak poisoning in one or more laboratory animal species,

2. to compare the effects of ingestion of dried oak leaves on various laboratory animal species.

CHAPTER II

REVIEW OF THE LITERATURE

Introduction

Oak poisoning of livestock has been reported in the United States (2, 10, 16, 25, 26, 27, 34, 36, 37, 41, 42, 43, 45, 49, 50) and in Europe (8, 11, 12, 14, 18, 19, 28, 32, 38, 52, 53, 54, 55, 56). Natural cases of poisoning have been reported in cattle (2, 10, 14, 16, 19, 26, 27, 28, 32, 34, 36, 38, 41, 42, 45, 49, 50, 52, 53, 54), sheep (10) and horses (11, 12, 18, 25, 55). Experimental poisoning by oak or its components has been reported in rabbits (1, 9, 13, 20, 21, 22, 46), goats (4, 5, 6, 7), rats (15, 29, 47, 48), mice (15), cattle (20, 39), sheep (20, 27) and guinea pigs (20). Clinical signs, clinical pathology and gross and histopathologic lesions are similar in all species.

Oak Species Reported as Toxic

Only a small number of oak species have been reported as toxic. Quercus havardi has been reported as toxic in cattle (20, 23, 24, 51) and in rabbits (13, 20, 21, 46). Quercus gambellii is reported to be toxic in cattle (10). Cattle and sheep are reported to be subject to poisoning by Quercus breviloba (10). European literature most commonly mentions Quercus robur as the cause of oak poisoning in cattle (19, 53). Cattle and sheep have been poisoned by Quercus lobata (27). Cattle

have died from ingestion of Quercus incana (24). Other species considered toxic are Quercus stellata (20), Q. marilandica (20), Q. velutina (35), Q. prinus (35), Q. rubra var. borealis (35) and Q. coccinea (35). Most reports do not identify the species of oak suspected in the intoxication.

Common Circumstances in Oak Poisoning

In many outbreaks of oak poisoning several common circumstances are shared. All conditions are not present in all cases but many are frequently noted during outbreaks:

1. Outbreaks tend to occur when less forage is available to livestock. Poisoning by oak leaves and buds tends to occur in the spring (10, 36, 38, 51) whereas poisoning by acorns tends to occur in the fall (12, 14, 19, 27, 34, 38, 50).

2. In years that poisoning occurs due to ingestion of acorns, the acorn crop is unusually heavy (12, 14, 19, 27, 34, 38).

3. Soil conditions may affect the toxicity of the oak plant (36).

4. Mature acorns are usually reported as the toxic agent except where severe weather provides green acorns at ground level (34).

5. Green acorns may be less palatable (15), but more toxic (27) than ripe acorns.

6. Buds and young leaves are more toxic than mature leaves (46), but toxicity due to older leaves has been reported (44).

7. More poisonings occur in younger animals (less than two years old) (16, 34, 41, 42) than occur in older animals (greater than two years old) (27, 45).

8. Certain animals develop a taste for acorns and will eat them preferentially to other food sources (2, 28).

Components of Oak Leaves, Buds and Acorns

Crude extracts of oak buds, leaves and acorns yield a group of chemically similar substances collectively named "tannins". Several distinct chemicals from these tannins have been isolated, identified and tested in animals as described below.

A crude tannin extract was produced by extracting ground oak buds and leaves with 80 C water, followed by alcoholic washing and drying (46). Chemical analysis of the extract identified gallic acid; thus, the extract was designated a gallotannin. In two separate experiments rabbits given this gallotannin via stomach tube developed clinical signs and lesions consistent with natural oak poisoning in other species (13, 46).

Constituents of acorns have been individually tested in laboratory animals (15). It was shown that ellagic acid, gallic acid (3,4,5-trihydroxybenzoic acid), quercitol (cyclohexanepentol), quercitrin and an unidentified alkaloid, were nontoxic when given intraperitoneally to mice. In the same experiment tannic acid was toxic when given intraperitoneally to mice.

Nearly identical gross lesions were produced in rabbits when given gallic acid, pyrogallol, tannic acid or fresh buds and leaves of Quercus havardi. These lesions were consistent with those of oak poisoning in other species (21).

Tannic acid and its constituents, gallic acid and pyrogallic acid,

have a wide variety of effects in herbivorous animals (3). These effects include:

1. Vitamin B12 responsive macrocytic anemia.

2. Lymphocytosis in peripheral blood.

3. Inhibition of the number and the maturation of myeloblasts, promyelocytes and myelocytes which leads to a granulocytopenia.

4. Inhibition of thrombocytopoiesis which leads to a thrombocytopenia.

5. Reduction in ruminal bacterial flora with a concurrent decrease in vitamin B12 production.

6. Reduction in responsiveness to acetylcholine and histamine by the stomachs (glandular and nonglandular) and small intestine (tannic acid only).

Ultrastructural Changes Attributable to Tannic Acid

Ultrastructural changes attributable to parenteral administration of tannic acid have been documented in rats and rabbits. Parenteral administration of tannic acid in rats has caused zonation of hepatocytic nucleolar ribonucleoprotein, the significance of which is unknown (47). Rats given tannic acid parenterally also had disaggregation of hepatocytic polyribosomes with a concurrent reduction of incorporation of amino acids into cellular protein (48).

Rabbits given tannic acid parenterally developed both renal and hepatic lesions. Renal lesions included increased cytoplasmic vesicles, swelling of the cytoplasm, accumulation of lipid droplets and death of proximal convoluted tubular epithelia (9). Hepatic lesions include

disorganization of rough endoplasmic reticulum, polyribosomal disaggregation, accumulation of lipid droplets and cellular death (1).

The overall applicability and significance of these results are unknown. The changes in the rabbit were considered to be nonspecific lesions of cell intoxication and death, not specific lesions of tannic acid poisoning (1).

Clinicopathologic Presentations of Oak Poisoning in Various Species

Cattle

Clinical signs and lesions, although somewhat variable from case to case, are generally similar (2, 14, 16, 19, 28, 31, 34, 39, 41, 42, 45, 49, 53).

Typically, affected cattle are depressed, anorexic, afebrile and have a serous-to-mucoid nasal discharge. Rumen motility is decreased or is absent and the rumen contents foul smelling and stratified. Heart and respiration rates are variable. Animals are usually constipated at the onset of signs with the hard fecal balls being covered by large amounts of mucus. The constipation may later change to a mucoid or bloody foul diarrhea. Many affected cattle are polydypsic and polyuric, producing large quantities of dilute urine.

Cattle commonly die within a few days to a month but may occasionally die suddenly. Chronically affected animals become progressively more dehydrated and emaciated and may have signs for several months. Animals which survive the acute condition may return to normal.

Blood urea nitrogen values are generally increased in affected

animals (often over 150 mg/dl) and blood calcium values are low, as are the packed cell volumes. Urinalysis usually reveals a low urine specific gravity (as low as 1.005) an acid pH, and positive urine glucose and protein (between 30 and 100 mg/dl). The SGOT of affected animals may be elevated.

The ratio of total to free cholesterol has been used to monitor liver function in animals poisoned by oak (31). In animals which have developed clinical signs of oak poisoning the level of free cholesterol rises, the esterified cholesterol level drops, but the total cholesterol level remains normal. This indicates a loss of liver function (loss of ability to esterify cholesterol) which is due to the toxic action of oak. Animals which do not have clinically observable effects from oak ingestion have normal cholesterol levels.

Gross lesions in acute cases include a foul rumen content, a catarrhal-hemorrhagic abomasitis and enteritis, hydrothorax, hydropericardium, hydroperitoneum and perirenal and mesenteric edema. The kidneys are usually edematous, pale and have petechial hemorrhages scattered beneath the capsule. Animals which have survived the acute stage have varying degrees of emaciation and subcutaneous edema. The kidneys are often small, pale grey-brown and have a pitted or mottled surface. The abomasum or serosal surfaces may have an ammoniacal odor and oral and esophageal ulceration may be evident.

The most commonly described histologic lesion is that of multifocal nephrosis and necrosis of renal proximal convoluted tubules. Mildly affected tubules have swollen epithelial cells with rarefied, granular cytoplasm and occasional fat vacuoles. More severely affected tubules are lined by dead epithelial cells which have pyknotic or

karyorrhectic nuclei and deeply eosinophilic cytoplasm. Many tubules are dilated and contain pink, smooth to granular protein or cellular casts. Tubules are occasionally separated by interstitial edema. Older renal lesions include tubular regeneration, dilated tubules lined by flattened epithelia, diffuse and multifocal lymphocytic accumulations in the cortex and medulla, and periglomerular fibrosis. Hepatic lesions have not been described in cattle.

Sheep

Poisoning of sheep by oak has been documented and closely resembles the condition in cattle (10).

Clinical signs include listleness, anorexia, decreased rumination and a sticky nasal discharge. Pulse and respiration rates are increased, the animals are normothermic and often have dependent subcutaneous edema. Early in the disease sheep are constipated, having mucus and blood covered fecal balls. Affected sheep often have polyuria and hyposthenuria. Chronic cases often develop a fetid diarrhea. Sheep are more likely to die acutely than are cattle but may be ill for up to one month before death occurs.

Gross lesions in sheep resemble those in cattle and include ascites, hydropericardium, abomasal and small intestinal hemorrhage and edema and an erosive colitis. The kidneys are pale and have petechial hemorrhages scattered throughout.

Histologic description of oak poisoning in sheep is not available.

Horses

Horses have been poisoned by mature green oak leaves (25) and by

acorns (11, 12, 18, 55). Similar signs and lesions are produced by either source of oak.

Affected horses often are depressed, anorexic, have reduced intestinal peristalsis and have abdominal pain. Mucous membranes may have injected vessels and may be icteric. Mildly affected horses may be constipated, whereas severely affected horses may have a fetid diarrhea. Impaction may occur if large numbers of acorns are eaten.

The most striking gross lesion in the horse is severe edema of the large intestine and colon which may be three centimeters thick. The mucosa of both the large and small intestines may be hemorrhagic. No renal lesions are described and the liver lesion is described as "advanced liver damage" in a case of chronic oak poisoning (11).

Histologic description of oak poisoning in horses is not available.

Rabbits

Rabbits with orally administered gallic acid, pyrogallol, tannic acid, leaves of Quercus havardi (21) or crude tannin isolates (13, 46) developed signs and lesions similar to those of cattle. The rabbit has been proposed as a model of oak poisoning in cattle and sheep.

Rabbits given oak leaves or their components become anorexic and lethargic. Diarrhea is often seen before death.

Affected rabbits have an increased packed cell volume, hemoglobin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and blood urea nitrogen (BUN). Serum albumins and globulins, total lipids and cholesterol are unchanged. Beta glucuronidase activity of the liver is increased which is interpreted as a normal detoxification mechanism.

Grossly the liver is mottled and the kidneys are swollen, pale and occasionally hemorrhagic or congested. The stomach is hemorrhagic and frequently has ulcers. The intestines are commonly hemorrhagic.

The liver has severe hepatic necrosis and loss of glycogen histologically. Renal tubular epithelial cells are vacuolated and the tubules occasionally contain dead epithelial cells (13, 21, 46).

Renal Function Tests for Oak Poisoning

In addition to normal blood chemistries and urinalysis, the sodium sulfanilate clearance test has been used to monitor renal filtration during oak poisoning (27). The drug is administered and its clearance through the kidney is measured (normal half life is 20-30 minutes).

Normal Protective Mechanisms Against Oak Poisoning, Prevention and Treatment

Oak poisoning in cattle can be prevented by natural mechanisms in many cases. Oak leaves eaten exclusively are often toxic, whereas oak leaves eaten in addition to relatively small amounts of other feeds, such as hay, are much less toxic or nontoxic (24, 39). Another method of natural protection has been demonstrated in goats (4). The rumenal mucosae of goats has normal tannase activity which varies directly with the content of tannic acid of the rumen. This is thought to be a natural protective mechanism against tannic acid poisoning. Tannase activity has yet to be demonstrated in cattle. No direct relationship between the amount of oak leaves ingested and blood tannic acid levels has been demonstrated (31). This indicates that the critical factor in oak poisoning in cattle is the amount of tannic acid that is

absorbed, not the amount consumed (31). It has been suggested that the absorption of tannic acid is enhanced by the rumen stasis it causes. It was then postulated that the more resistant an animal is to the initial absorption of tannic acid, the less susceptible it is to tannic acid poisoning.

Oak poisoning can be prevented by the use of calcium hydroxide as a feed additive. Rabbits given one part calcium hydroxide to six parts tannic acid were protected from poisoning (22). In separate experiments calves were protected from oak poisoning by being fed a supplemental ration which contained nine and ten percent calcium hydroxide (23, 24). Supplemental feeds which contained less than nine percent calcium hydroxide were less effective in preventing oak poisoning, whereas feeds containing greater than ten percent calcium hydroxide became progressively less palatable.

There is no specific treatment for an animal once it has developed signs of oak poisoning (33). Orally administered mineral oil and fluids have been suggested as mild purgatives. General supportive care to correct dehydration and either the constipation or diarrhea have also been suggested. Beyond these measures very little can be done for the poisoned patient.

CHAPTER III

EXPERIMENTAL PROCEDURES

Goals and Approach

The objective of these experiments was to develop a model of oak poisoning in cattle in an inexpensive laboratory animal.

Dry oak leaves were chosen as a potential toxin because of their abundance, relative ease of harvesting and the ease in which they could be incorporated into a ration. Leaves were harvested in January, 1982, and were taken from a variety of species of oak trees at random.

Experimental animals were fed leaves or leaf/food mixtures free choice. No estimation of the quantity of oak eaten was made, however, animals were observed daily to assure that all were eating. This approach was chosen because it required little technical help and also because it more closely resembles the normal feeding action of animals on range than does some form of force feeding.

Materials and Methods

Ration Preparation

Two types of ration were prepared for the experiments. A low dosage ration was prepared for one group of rats and a 100% oak leaf ration was prepared for all other treatment group animals.

Low Dosage Rations. Low dosage rations were prepared in separate batches as control ration and as five, ten, twenty-five and fifty percent oak leaf rations. The specific quantities of the constituents of each ration are in Table I (Appendix).

Oak leaves were first powdered in an electric blender without the addition of water. This yielded a fine powder composed of all parts of the dried leaf. The oak powder was weighed and aliquoted for each batch of feed. A measured amount of dry laboratory animal feed pellets[1] was soaked in an amount of water suitable to completely break down the pellets. The resulting slurry was completely mixed with the oak leaf powder, gelatin[2] and molasses.[3] This mixture was then spread onto flat metal trays and was allowed to air dry.

Molasses was added to enhance the palatability of the feed. Gelatin was added to minimize wastage of the feed by crumbling. The dried feed was coarsely crumbled and then refrigerated until use to prevent fungal growth.

High Dosage Ration. Dry oak leaves were coarsely crushed by hand. One kilogram of crushed leaves was hand mixed with 64 grams of gelatin, 450 ml of molasses and varying amounts of water. This mixture was packaged while still wet and was frozen until it was used.

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[1]Wayne Lab-Blox, Allied Mills, Inc., Specialty Feeds Dept., Chicago, Ill. 60606.

[2]Knox Unflavored Gelatine, Knox Gelatine, Inc., Englewood Cliffs, N.J. 07632.

[3]Grandma's Unsulphured Molasses, Duffy-Mott Co., Inc., 370 Lexington Avenue, New York, N.Y. 10017.

Randomization of Animals to Groups

Animals were assigned to cages randomly as they were removed from shipping crates. Each cage was given a number. A person uninvolved in this project was asked to pick suitable numbers (cage numbers) which assigned cages to the treatment and control groups.

Feeding Technique

The ration was placed in wire feeders located on the top of the cages. The animals were allowed to feed free choice and water was available at all times. Because the rodents pulled feed down from the feeder for bedding and because relatively small amounts were placed in the feeder at any one time the feed available was always fresh.

Euthanasia Technique and Schedules

All animals were euthanatized by inhalation of ether. The animal was placed in a jar which contained ether and was deeply anesthetized. It was then removed and blood was collected by cardiac puncture. If more blood was needed it was collected from the thorax at necropsy. Following bleeding, the animal was returned to the ether chamber for euthanasia. A list of scheduled euthanasia times is shown in Table II (Appendix). For sacrifices which required that only part of a treatment group be euthanatized, animals were randomly selected. Animals that died during the study prior to scheduled euthanasia dates were necropsied immediately upon discovery.

Necropsy and Histology Techniques

All animals were examined in dorsal recumbency. All major organs and tissues were examined grossly and were fixed in neutral buffered formalin.

Liver and kidney were processed routinely, embedded in paraffin, sectioned at 6 micrometers and stained with hematoxylin and eosin. Tissues collected but not processed were preserved in formalin. Liver and kidney were chosen for examination because these are the only two tissues in which lesions of oak poisoning have been seen.

Clinical Pathology

Blood was taken terminally from all sacrificed animals. BUN and SGPT were determined on each serum sample. These tests were performed to determine the functional capacity of the kidney and liver, respectively.

Experimental Design

Individual experiments were performed on three different species of laboratory animals. Each experiment had slightly different goals and procedures.

Rats on Low Dosage Rations. Rats were chosen because of their relatively inexpensive cost and upkeep, low genotypic and phenotypic variability and the relative ease with which they can be handled.

Twenty-five Charles River F 344/N white rats were assigned to five separate groups. All rats, except one, were female and all were two months old. The groups of five included rats fed control ration and

rats fed rations containing 5, 10, 25 and 50 percent oak leaves by weight.

The lower dosages of oak leaves were intended to identify toxic dose ranges of oak leaves. The mixture of normal rat feed with oak leaves was intended to increase the palatability and nutritional adequacy of the feed. This additional feed had the potential to be protective however (24,39).

Rats on High Dosage Ration. Rats in this experiment were fed the 100% oak leaf ration. Control ration consisted of normal laboratory animal feed pellets. The high dosage of oak leaves was intended to mimic cattle which have only oak leaves available as a feed source. Two different age groups of rats were used in this experiment. This was intended to investigate whether there is an age susceptibility to oak leaf poisoning.

Group I consisted of 25 Charles River F 344/N white rats, all of which were female and two months old. Ten rats were fed control ration and 15 were fed oak leaves.

Group II consisted of 13 Charles River F 344/N white rats, all of which were female and 11 months old. Four rats were fed control ration and nine were fed oak leaves.

Gerbils. Ten mature Mongolian gerbils were assigned to control and treatment groups based on sex and random assignment of the females. Four females were given normal laboratory animal feed pellets while three females and three male gerbils were given 100% oak leaf ration.

Hamster Study I. Hamsters were chosen as an experimental animal

because of their unique digestive tract. The hamster stomach is divided into two pouches by a muscular sphincter (30). The pregastric pouch is a fermentative stomach which is lined by keratinized stratified squamous epithelium. Volatile fatty acids are found in the pregastric pouch and are primarily composed of acetic acid, though proprionic and butyric acid are also present (30). It is this fermentative ability that made the hamster a potentially good model of oak poisoning in cattle. The gastric stomach is histologically and physiologically similar to that of monogastric animals.

Four mature female Syrian hamsters were divided into two groups. Two control animals were given normal laboratory animal feed pellets while two treatment animals received the 100% oak leaf ration.

Hamster Study II. Sixteen 150 gram female Syrian hamsters were assigned to two groups. Six control animals were fed normal laboratory animal feed pellets while ten treatment animals were fed the 100% oak leaf ration.

CHAPTER IV

RESULTS

Rats on Low Dosage Rations

Rats which consumed control and 5% and 10% oak leaf rations had no gross lesions attributable to oak leaf poisoning. Rats which consumed 25% oak leaf ration had slight-to-moderate depletion of body fat which began at week 3 and continued through week four. Rats which consumed 50% oak leaf ration had moderate-to-severe body fat depletion throughout the duration of the experiment. All animals had food in their gastrointestinal tracts and had no gross kidney or liver lesions. A summary of gross lesions is contained in Table III (Appendix).

Histologic renal lesions were first seen in rats which consumed 50% oak leaf ration after one week on test and were also seen at week two. Similar lesions (though not as severe) were seen at two weeks on test in rats which consumed 25% oak leaf ration. Histologic lesions were confined to the medullary tubules and consisted of dead epithelial cells in tubular walls or lumina. Dead epithelial cells had pyknosis or karyorrhexis and dark pink cytoplasm.

Relatively severe lesions such as these were not evident in any group at week three. All rats killed after four weeks on test (final sacrifice) had occasional dead cells in medullary tubules. Significant hepatic lesions were not seen. A summary of histologic lesions is

contained in Table IV (Appendix).

No difference in BUN was noted between controls and treatment animals. SGPT levels of rats which consumed 50% oak leaf ration were approximately double those of the controls (Table V, Appendix).

Rats on High Dosage Ration

The only gross lesion seen in rats which consumed oak leaves exclusively was depletion of body fat. Body fat depletion in the younger rats (Group I) occurred more quickly and was more severe than in the older rats (Group II). A summary of gross lesions is contained in Table VI (Appendix).

There were no significant differences in the histologic appearances of the liver and kidney between control and treated rats. Some degree of pyknosis or karyorrhexis of medullary tubular epithelial cells was seen in both control and treatment groups. A summary of histologic lesions is contained in Table VII (Appendix).

BUN and SGPT levels did not vary significantly between control rats and treated rats (Table VIII, Appendix).

Gerbils

Depletion of body fat was the only gross lesion seen in gerbils which consumed oak leaves exclusively. A summary of gross lesions is contained in Table IX (Appendix).

No significant histologic lesions were seen in liver or kidney. A summary of histologic lesions is contained in Table X (Appendix).

No significant differences in BUN or SGPT were seen between control and treatment animals. A summary of blood chemistries is contained in

Table XI (Appendix).

Hamster Study I

Severe depletion of body fat was seen in both treatment animals. No other gross lesions were seen. A summary of gross lesions is contained in Table XII (Appendix).

Similar histologic renal changes were seen in one control and two treatment animals. Most renal medullary tubular epithelial cells were pyknotic. Occasional medullary tubular epithelial cells were dead as determined by the presence of pyknosis or karyorrhexis and had deeply eosinophilic cytoplasm. Small numbers of cortical tubules contained dead epithelial cells as determined by the presence of pyknosis. The centrilobular hepatocytes of control animals had rarefied, granular cytoplasm (glycogen) whereas those of treated animals did not. The treated animals had multifocal areas of hepatocellular necrosis characterized by loss of hepatocytes and accumulation of cellular debris and neutrophils. Infectious agents were not seen. A summary of histologic lesions is contained in Table XIII (Appendix).

Blood samples were available only from control animals so that no comparison between control and treatment animals could be made. Blood chemistry values are contained in Table XIV (Appendix).

Hamster Study II

Moderate to severe depletion of body fat was seen in all treatment animals. No specific gross lesions attributable to oak poisoning were seen. A summary of gross lesions is contained in Table XV (Appendix).

Similar histologic renal changes were seen in all animals except one. The changes consisted of severe nuclear pyknosis of medullary tubular epithelial cells. The extent of this change ranged from a narrow band at the corticomedullary junction to involvement of the entire medulla and isolated tubules in the cortex. Hepatic changes seen in treated animals consisted of loss of glycogen from centrilobular hepatocytes. A summary of histologic lesions is contained in Table XVI (Appendix).

No significant differences were seen in BUN and SGPT of control and treatment animals. A summary of blood chemistries is contained in Table XVIII (Appendix).

CHAPTER V

DISCUSSION AND CONCLUSIONS

Discussion

The only consistent gross lesion seen in any group of animals was loss of body fat. Nearly all animals eating a diet composed partly or entirely of dried oak leaves had slight-to-severe depletion of body fat. This indicates that either the oak diet is not a complete diet or that the animals did not eat a sufficient quantity to maintain their body weight. In actuality, both factors probably contributed to the loss of condition in these animals. Toxic effects of the oak leaves may also have caused loss of body fat.

Varying degrees of renal medullary tubular epithelial pyknosis and karyorrhexis were seen in all groups of animals, but not in all animals of a group. These changes occurred in both control and treatment animals. This indicates that the lesions were not due to poisoning by oak leaves, but to some other cause. Other causes might have included poor nutrition, effects of the ether used for euthanasia or slow fixation of the tissues by formalin. The precise cause of the changes could not be determined based on the available data.

Hepatocytic glycogen loss in Hamster Group II treatment animals suggests an energy deficit. Causes of this deficit have already been discussed.

With the exception of rats on low dose rations, no group of animals had significant changes in BUN or SGPT. Rats which consumed 50% oak leaf ration had SGPT levels which were consistently two times those of the control group. This difference possibly represented altered liver function due to lack of energy. A several fold increase of SGPT would have been indicative of an oak induced liver lesion.

The lack of lesions from ingestion of dried oak leaves may have been due to one of two causes. First, the species of animals used in this study may not have been susceptible to poisoning by dry oak leaves. Another possibility was that the dried leaves may have been nontoxic or weakly toxic. Thus, if the animals did not eat a sufficient quantity of the leaves, no lesions would be seen. The design and intent of this experiment did not allow interpretation of these possibilities.

Additional work could be performed to further investigate the toxic potential of oak leaves in laboratory animals. Dried leaves could be fed to a species such as the rabbit, which is known to be susceptible to some forms of oak leaves. Another alternative would be to feed oak buds and young leaves to the species used in the experiments reported herein.

Conclusions

Dried oak leaves fed to rats, gerbils and hamsters failed to create liver or kidney lesions. This lack of effect may be due to lack of susceptibility of the animals or lack of toxicity of the dried oak leaves.

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APPENDIX

TABLE I

COMPONENTS OF LOW DOSAGE RATIONS FOR RATS

Feed	Laboratory Animal Feed Pellets (grams)	Ground Oak Leaves (grams)	Gelatin (grams)	Molasses (ml)
Control	400	0	8	20
5% Oak Leaf	665	35	12	40
10%	450	50	8	20
25%	412.5	137.5	8	20
50%	200	200	8	20

TABLE II

SCHEDULES OF EUTHANASIA FOR VARIOUS TREATMENT GROUPS AND CONTROLS

Treatment Group and Controls	Euthanasia Interval (weeks on study)
Rats on Low Dosage Rations	1, 2, 3, 4
Rats on High Dosage Ration	
Young Rats (Group I)	1, 2, 3, 4
Older Rats (Group II)	1, 2, 3, 4
Gerbils	2, 3
Hamsters (Study I)	2
Hamsters (Study II)	1, 2

TABLE III

GROSS LESIONS OF RATS ON LOW DOSAGE RATIONS

Animal	Sacrifice Interval (Weeks of Study)	Gross Lesions
C-1[1]	1	NGL[2]
C-2	2	NGL
C-3	3	NGL
C-4	4	NGL
C-5	4	NGL
5-1	1	NGL
5-2	2	NGL
5-3	3	NGL
5-4	4	NGL
5-5	4	NGL
10-1	1	NGL - male
10-2	2	NGL
10-3	3	Pregnant - 11 pups
10-4	4	Body fat depletion, nursing 13 pups
10-5	4	Body fat depletion, nursing 10 pups
25-1	1	NGL
25-2	2	NGL
25-3	3	Slight body fat depletion
25-4	4	Moderate body fat depletion
25-5	4	Moderate body fat depletion
50-1	1	Severe body fat depletion
50-2	2	Severe body fat depletion
50-3	3	Severe body fat depletion
50-4	4	Moderate body fat depletion
50-5	4	Moderate body fat depletion

[1]C=Control, 5=5% oak leaf ration, etc.; the following number is the animal identification.

[2]NGL=No Gross Lesions.

TABLE IV

HISTOLOGIC LESIONS OF RATS ON
LOW DOSAGE RATIONS

Animal	Sacrifice Interval (weeks on study)	Liver	Kidney
C-1[1]	1	NSL[2]	NSL
C-2	2	NSL	NSL
C-3	3	NSL	NSL
C-4	4	NSL	Slight medullary epithelial necrosis
C-5	4	NSL	Slight medullary epithelial necrosis
5-1	1	NSL	NSL
5-2	2	NSL	slight medullary epithelial necrosis
5-3	3	NSL	NSL
5-4	4	NSL	slight medullary epithelial necrosis
5-5	4	NSL	slight medullary epithelial necrosis
10-1	1	NSL	NSL
10-2	2	NSL	NSL
10-3	3	NSL	NSL
10-4	4	NSL	slight medullary epithelial necrosis
10-5	4	NSL	slight medullary epithelial necrosis
25-1	1	NSL	NSL
25-2	2	NSL	slight medullary epithelial necrosis
25-3	3	NSL	NSL
25-4	4	NSL	slight medullary epithelial necrosis
25-5	4	NSL	slight medullary epithelial necrosis
50-1	1	NSL	severe medullary epithelial necrosis
50-2	2	NSL	severe medullary epithelial necrosis
50-3	3	NSL	NSL
50-4	4	NSL	slight medullary epithelial necrosis
50-5	4	NSL	slight medullary epithelial necrosis

[1] C=Control, 5=5% oak leaf ration, etc.; the following number is the animal identification.

[2] NSL=No Significant Lesions.

TABLE V

BLOOD CHEMISTRIES OF RATS ON
LOW DOSAGE RATIONS

Animal	Sacrifice Interval (weeks on study)	BUN (mg/dl)	SGPT (IU/l)
C-1[1]	1	ND[2]	ND
C-2	2	14	28
C-3	3	18	27
C-4	4	19	33
C-5	4	20	27
5-1	1	ND	ND
5-2	2	17	27
5-3	3	19	47
5-4	4	23	30
5-5	4	17	34
10-1	1	ND	ND
10-2	2	12	29
10-3	3	19	47
10-4	4	24	38
10-5	4	21	39
25-1	1	ND	ND
25-2	2	15	42
25-3	3	11	34
25-4	4	19	65
25-5	4	20	60
50-1	1	ND	ND
50-2	2	6	80
50-3	3	10	70
50-4	4	21	70
50-5	4	16	69

[1]C=Control, 5=5% oak leaf ration, etc.; the following number is the animal identification.

[2]ND=No Data.

TABLE VI

GROSS LESIONS OF RATS ON HIGH DOSAGE RATION

Animal	Sacrifice Interval (weeks on study)	Gross Lesions
Group I		
C-100[1]	1	NGL[3]
C-200	1	NGL
C-300	2	NGL
C-400	2	NGL
C-500	3	NGL
C-600	3	Hydrometra
C-700	4	NGL
C-800	4	NGL
C-900	4	NGL
C-1000	4	Ovarian cyst
100-1[2]	1	Severe body fat depletion
100-2	1	Severe body fat depletion
100-3	1	Severe body fat depletion
100-4	2	Severe body fat depletion
100-5	2	Severe body fat depletion
100-6	2	Severe body fat depletion
100-7	3	Severe body fat depletion
100-8	3	Severe body fat depletion
100-9	3	Severe body fat depletion
100-10	4	Severe body fat depletion
100-11	4	Severe body fat depletion
100-12	4	Severe body fat depletion
100-13	4	Severe body fat depletion
100-14	4	Severe body fat depletion
100-15	4	Severe body fat depletion

TABLE VI (Continued)

Animal	Sacrifice Interval (weeks on study)	Gross Lesions
Group II		
C-A	1	NGL
C-B	2	NGL
C-C	3	Hydrometra
C-D	4	Ovarian cyst, mesenteric fat necrosis
200-1[4]	1	NGL
200-2	1	NGL
200-3	2	Slight depletion of body fat
200-4	2	Slight depletion of body fat
200-5	3	Slight depletion of body fat
200-6	3	NGL
200-7	4	Slight depletion of body fat
200-8	4	Slight depletion of body fat
200-9	4	Mesenteric fat necrosis

[1] C=Control; the following number is the animal identification.

[2] 100=100% oak leaf ration Group I; the following number is the animal identification.

[3] NGL=No Gross Lesions.

[4] 200=100% oak leaf ration Group II; the following number is the animal identification.

TABLE VII

HISTOLOGIC LESIONS OF RATS ON
HIGH DOSAGE RATION

Animal	Sacrifice Interval (weeks on study)	Liver	Kidney
Group I			
C-100[1]	1	NSL[3]	NSL
C-200	1	NSL	NSL
C-300	2	NSL	NSL
C-400	2	NSL	NSL
C-500	3	NSL	Slight medullary epithelial necrosis
C-600	3	NSL	Slight medullary epithelial necrosis
C-700	4	NSL	Slight medullary epithelial necrosis
C-800	4	NSL	Slight medullary epithelial necrosis
C-900	4	NSL	Slight medullary epithelial necrosis
C-1000	4	NSL	Slight medullary epithelial necrosis
100-1[2]	1	NSL	Slight medullary epithelial necrosis
100-2	1	NSL	NSL
100-3	1	NSL	NSL
100-4	2	Multifocal necrosis	Slight medullary epithelial necrosis
100-5	2	NSL	Slight medullary epithelial necrosis
100-6	2	NSL	Slight medullary epithelial necrosis
100-7	3	Locally extensive fatty change	Very slight medullary epithelial necrosis
100-8	3	NSL	Very slight medullary epithelial necrosis

TABLE VII (Continued)

Animal	Sacrifice Interval (weeks on study)	Liver	Kidney
100-9	3	NSL	NSL
100-10	4	NSL	NSL
100-11	4	NSL	NSL
100-12	4	NSL	Very slight medullary epithelial necrosis
100-13	4	Moderate centrilobular fatty change	Slight medullary epithelial necrosis
100-14	4	Slight centrilobular cytoplasmic rarification	Very slight medullary epithelial necrosis
100-15	4	NSL	Slight medullary epithelial necrosis
Group II			
C-A	1	NSL	NSL
C-B	2	NSL	Slight medullary epithelial necrosis
C-C	3	NSL	Slight medullary epithelial necrosis
C-D	4	NSL	Very slight medullary epithelial necrosis
200-1[4]	1	NSL	NSL
200-2	1	NSL	NSL
200-3	2	NSL	Slight medullary epithelial necrosis
200-4	2	Moderate centrilobular fatty change	Slight medullary epithelial necrosis
200-5	3	NSL	Slight medullary epithelial necrosis
200-6	3	Focal fatty change	Slight medullary epithelial necrosis
200-7	4	Moderate centrilobular fatty change	NSL

TABLE VII (Continued)

Animal	Sacrifice Interval (weeks on study)	Liver	Kidney
200-8	4	Slight centrilobular fatty change	Slight medullary epithelial necrosis
200-9	4	Slight centrilobular fatty change	Slight medullary epithelial necrosis

[1]C=Control; the following number is the animal identification.

[2]100=100% oak leaf ration Group I; the following number is the animal identification.

[3]NSL=No Significant Lesions.

[4]200=100% oak leaf ration Group II; the following number is the animal identification.

TABLE VIII

BLOOD CHEMISTRIES OF RATS ON
HIGH DOSAGE RATION

Animal	Sacrifice Interval (weeks on study)	BUN (mg/dl)	SGPT (IU/l)
Group I			
C-100[1]	1	16	28
C-200	1	16	50
C-300	2	16	55
C-400	2	17	127
C-500	3	17	42
C-600	3	19	47
C-700	4	17	28
C-800	4	16	50
C-900	4	14	44
C-1000	4	15	80
100-1[2]	1	16	80
100-2	1	13	45
100-3	1	13	35
100-4	2	11	91
100-5	2	16	146
100-6	2	12	73
100-7	3	11	58
100-8	3	15	48
100-9	3	10	49
100-10	4	16	45
100-11	4	18	90
100-12	4	16	42
100-13	4	16	45
100-14	4	17	58
100-15	4	16	100

TABLE VIII (Continued)

Animal	Sacrifice Interval (weeks on study)	BUN (mg/dl)	SGPT (IU/l)
Group II			
C-A	1	12	60
C-B	2	13	109
C-C	3	12	52
C-D	4	15	50
200-1[3]	1	13	50
200-2	1	14	40
200-3	2	10	100
200-4	2	10	173
200-5	3	8	45
200-6	3	12	62
200-7	4	12	70
200-8	4	13	43
200-9	4	11	43

[1]C=Control; the following number is the animal identification.

[2]100=100% oak leaf ration Group I, the following number is the animal identification.

[3]200=100% oak leaf ration Group II; the following number is the animal identification.

TABLE IX

GROSS LESIONS OF GERBILS ON 100%
OAK LEAF RATION

Animals	Sacrifice Interval (weeks on study)	Gross Lesions
GC-1[1]	2	NGL[3]
GC-2	2	NGL
GC-3	3	NGL
GC-4	3	NGL
G100-1[2]	2	Severe body fat depletion <u>Dentostomella</u> sp. in small intestine
G100-2	2	Severe body fat depletion <u>Dentostomella</u> sp. in small intestine
G100-3	2	Severe body fat depletion Purulent otitis media and interna and meningitis
G100-4	3	Severe body fat depletion
G100-5	3	Severe body fat depletion
G100-6	3	Severe body fat depletion

[1]GC=Gerbil Control; the following number is the animal identification.

[2]G100=Gerbil 100% oak leaf ration; the following number is the animal identication.

[3]NGL=No Gross Lesions.

TABLE X

HISTOLOGIC LESIONS OF GERBILS ON 100% OAK LEAF RATION

Animals	Sacrifice Interval (weeks on study)	Liver	Kidney
GC-1[1]	2	NSL[3]	NSL
GC-2	2	NSL	NSL
GC-3	3	NSL	NSL
GC-4	3	Centrilobular cytoplasmic rarefication	NSL
G100-1[2]	2	NSL	NSL
G100-2	2	NSL	NSL
G100-3	2	NSL	slight medullary epithelial necrosis
G100-4	3	NSL	NSL
G100-5	3	NSL	NSL
G100-6	3	NSL	NSL

[1]GC=Gerbil Control; the following number is the animal identication.

[2]G100=Gerbil 100% oak leaf ration; the following number is the animal identication.

[3]NSL=No Significant Lesions.

TABLE XI

BLOOD CHEMISTRIES OF GERBILS ON
100% OAK LEAF RATION

Animals	Sacrifice Interval (weeks on study)	BUN (mg/dl)	SGPT (IU/l)
GC-1[1]	2	29	125
CG-2	2	23	76
CG-3	3	21	80
CG-4	3	16	110
G100-1[2]	2	8	98
G100-2	2	9	ND[3]
G100-3	2	11	89
G100-4	3	14	170
G100-5	3	15	110
G100-6	3	17	100

[1]GC=Gerbil Control; the following number is the animal identication.

[2]G100=Gerbil 100% oak leaf ration; the following number is the animal identication.

[3]ND=No Data.

TABLE XII

GROSS LESIONS OF HAMSTERS ON 100% OAK LEAF RATION (STUDY I)

Animal	Sacrifice Interval (days on study)	Death	Lesions
HC-1[1]	14	Euthanatized	NGL[3]
HC-2	14	Euthanatized	NGL
H100-1[2]	7	Died	Slight body fat depletion
H100-2	14	Euthanatized	Severe body fat depletion

[1]HC=Hamster control; the following number is the animal identification.

[2]H100=Hamster 100% oak leaf ration (Study I); the following number is the animal identification.

[3]NGL=No Gross Lesions.

TABLE XIII

HISTOLOGIC LESIONS OF HAMSTERS ON 100% OAK LEAF RATION (STUDY I)

Animal	Sacrifice Interval (days on study)	Liver	Kidney
HC-1[1]	14	NSL[3]	Multiple areas of chronic ischemia
HC-2	14	NSL	Severe medullary epithelial necrosis
H100-1[2]	7	Multifocal necrosis glycogen depletion	Severe medullary and slight cortical epithelial necrosis; multiple areas of chronic ischemia
H100-2	14	Multifocal necrosis glycogen depletion	Severe medullary and slight cortical epithelial necrosis

[1]HC=Hamster control; the following number is the animal identification.

[2]H100=Hamster 100% oak leaf ration (Study I); the following number is the animal identification.

[3]NSL=No Significant Lesions.

TABLE XIV

BLOOD CHEMISTRIES OF HAMSTERS ON 100% OAK LEAF RATION (STUDY I)

Animal	Sacrifice Interval (days on study)	BUN (mg/dl)	SGPT (IU/l)
HC-1[1]	14	21	46
HC-2	14	19	100
H100-1[2]	7	ND[3]	ND
H100-2	14	ND	ND

[1]HC=Hamster control; the following number is the animal identification.

[2]H100=Hamster 100% oak leaf ration (Study I); the following number is the animal identification.

[3]ND=No Data.

TABLE XV

GROSS LESIONS OF HAMSTERS ON 100% OAK LEAF RATION (STUDY II)

Animal	Sacrifice Interval (days on study)	Death	Lesions
HC-A[1]	7	Euthanatized	NGL[3]
HC-B	7	Euthanatized	NGL
HC-C	7	Euthanatized	NGL
HC-D	14	Euthanatized	Hydrometra
HC-E	14	Euthanatized	Hydrometra
HC-F	14	Euthanatized	NGL
H200-1[2]	7	Euthanatized	Moderate body fat depletion
H200-2	7	Euthanatized	Moderate body fat depletion
H200-3	7	Euthanatized	Moderate body fat depletion
H200-3	7	Euthanatized	Moderate body fat depletion
H200-4	7	Euthanatized	Moderate body fat depletion
H200-5	7	Euthanatized	Moderate body fat depletion
H200-6	12	Died	Severe body fat depletion
H200-7	12	Died	Severe body fat depletion
H200-8	13	Euthanatized moribund	Severe body fat depletion
H200-9	14	Euthanatized	Severe body fat depletion
H200-10	14	Euthanatized	Severe body fat depletion

[1]HC=Hamster control; the following letter is the animal identification.

[2]H200=Hamster 100% oak leaf ration (Study II); the following number is the animal identification.

[3]NGL=No Gross Lesions.

TABLE XVI

HISTOLOGIC LESIONS OF HAMSTERS ON 100% OAK LEAF RATION (STUDY II)

Animal	Sacrifice Interval (days on study)	Liver	Kidney
HC-A[1]	7	NSL[3]	Severe Medullary epithelial pyknosis
HC-B	7	NSL	Severe medullary epithelial pyknosis
HC-C	7	NSL	Severe medullary epithelial pyknosis
HC-D	14	NSL	Slight medullary epithelial pyknosis
HC-E	14	NSL	Moderate medullary epithelial pyknosis
HC-F	14	NSL	Severe medullary epithelial pyknosis
H200-1[2]	7	Glycogen depletion	Severe medullary epithelial pyknosis
H200-2	7	Glycogen depletion	Severe medullary epithelial pyknosis
H200-3	7	Glycogen depletion	Severe medullary epithelial pyknosis
H200-4	7	Glycogen depletion	Severe medullary epithelial pyknosis
H200-5	7	Glycogen depletion	Severe medullary epithelial pyknosis
H200-6	12	Glycogen depletion	Severe medullary epithelial pyknosis
H200-7	12	Glycogen depletion	Severe medullary epithelial pyknosis
H200-8	13	Glycogen depletion	NSL
H200-9	14	Glycogen depletion	Severe medullary and cortical epithelial pyknosis
H200-10	14	Glycogen depletion	Severe medullary and cortical epithelial pyknosis

[1]HC=Hamster control; the following letter is the animal identification.

[2]H200=Hamster 100% oak leaf ration (Study II); the following number is the animal identification.

[3]NSL=No Significant Lesions.

TABLE XVII

BLOOD CHEMISTRIES OF HAMSTERS ON 100% OAK LEAF RATION (STUDY II)

Animal	Sacrifice Interval (days on study)	BUN (mg/dl)	SGPT (IU/l)
HC-A[1]	7	25	91
HC-B	7	25	118
HC-C	7	23	91
HC-D	14	22	58
HC-E	14	20	43
HC-F	14	17	96
H200-1[2]	7	12	100
H200-2	7	13	82
H200-3	7	17	91
H200-4	7	14	73
H200-5	7	17	64
H200-6	12	ND[3]	ND
H200-7	12	ND	ND
H200-8	13	35	73
H200-9	14	ND	ND
H200-10	14	ND	ND

[1]HC=Hamster control; the following letter is the animal identification.

[2]H200=Hamster 100% oak leaf ration (Study II); the following number is the animal identification.

[3]ND=No Data.

VITA

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