

From: Palmer, Lee Anne
To: Jones, Jennifer L
Cc: Rotstein, David; Carey, Lauren
Subject: FW: Zignature Kangaroo Formula: (b) (6) - EON-350158
Date: Tuesday, March 27, 2018 3:25:32 PM
Attachments: 2044632-report.pdf
2044632-attachments.zip

In case of interest – taurine level low?

From: PFR Event [<mailto:pfpreventcreation@fda.hhs.gov>]

Sent: Tuesday, March 27, 2018 3:20 PM

To: Cleary, Michael * <Michael.Cleary@fda.hhs.gov>; HQ Pet Food Report Notification <HQPetFoodReportNotification@fda.hhs.gov>; (b) (6)

Subject: Zignature Kangaroo Formula: (b) (6) - EON-350158

A PFR Report has been received and PFR Event [EON-350158] has been created in the EON System

A "PDF" report by name "2044632-report.pdf" is attached to this email notification for your reference. Please note that all documents received in the report are compressed into a zip file by name "2044632-attachments.zip" and is attached to this email notification.

Below is the summary of the report:

EON Key: EON-350158

ICSR #: 2044632

EON Title: PFR Event created for Zignature Kangaroo Formula; 2044632

AE Date	(b) (6)	Number Fed/Exposed	1
Best By Date		Number Reacted	1
Animal Species	Dog	Outcome to Date	Better/Improved/Recovering
Breed	Retriever - Labrador		
Age	13 Years		
District Involved	PFR- (b) (6) DO		

Product information

Individual Case Safety Report Number: 2044632

Product Group: Pet Food

Product Name: Zignature Kangaroo Formula

Description: At the time of diagnosis (b) (6) (b) (6) was a 13 year old female spayed Labrador retriever who had been maintained on a Zignature Kangaroo formula. She presented with a history of a progressive cough which, prior to presentation, became productive and she coughed up a small volume of pink foam (possible pulmonary edema). On examination she had a 2/6 left apical systolic heart murmur and on echo diagnosed with advanced dilated cardiomyopathy with severe left ventricular dilation, moderate to severe left ventricular systolic dysfunction, and moderate to severe left atrial dilation. Thoracic radiographs were suspicious for early congestive heart failure. A whole blood taurine level was submitted and was low at 168. She was treated with furosemide, benazepril, pimobendan, spironolactone, taurine and L-carnitine and her diet was changed to Royal Canin Early Cardiac. At her recheck in 2/26/18, (b) (6) heart had improved significantly with now mild dilated cardiomyopathy with normalized left atrial dimensions, mild left ventricular dilation and low normal left ventricular systolic function. The furosemide was able to be discontinued at this time.

Submission Type: Initial

Report Type: Adverse Event (a symptom, reaction or disease associated with the product)

Outcome of reaction/event at the time of last observation: Better/Improved/Recovering

Number of Animals Treated With Product: 1

Number of Animals Reacted With Product: 1

Product Name	Lot Number or ID	Best By Date
Zignature Kangaroo Formula		

Sender information

(b) (6)

Owner information

(b) (6)

To view this PFR Event, please click the link below:

<https://eon.fda.gov/eon/browse/EON-350158>

To view the PFR Event Report, please click the link below:

<https://eon.fda.gov> (b) (6)

This email and attached document are being provided to you in your capacity as a Commissioned Official with the U S Department of Health and Human Services as authorized by law You are being provided with this information pursuant to your signed Acceptance of Commission

This email message is intended for the exclusive use of the recipient(s) named above It may contain information that is protected, privileged, or confidential Any dissemination, distribution, or copying is strictly prohibited

The information is provided as part of the Federal-State Integration initiative As a Commissioned Official and state government official, you are reminded of your obligation to protect non-public information, including trade secret and confidential commercial information that you receive from the U S Food and Drug Administration from further disclosure The information in the report is intended for situational awareness and should not be shared or acted upon independently Any and all actions regarding this information should be coordinated through your local district FDA office

Failure to adhere to the above provisions could result in removal from the approved distribution list If you think you received this email in error, please send an email to FDAREportableFoods@fda.hhs.gov immediately

Report Details - EON-350158

ICSR:	2044632		
Type Of Submission:	Initial		
Report Version:	FPSR.FDA.PETF.V.V1		
Type Of Report:	Adverse Event (a symptom, reaction or disease associated with the product)		
Reporting Type:	Voluntary		
Report Submission Date:	2018-03-27 15:12:36 EDT		
Reported Problem:	Problem Description:	At the time of diagnosis (b) (6), (b) (6) was a 13 year old female spayed Labrador retriever who had been maintained on a Zignature Kangaroo formula. She presented with a history of a progressive cough which, prior to presentation, became productive and she coughed up a small volume of pink foam (possible pulmonary edema). On examination she had a 2/6 left apical systolic heart murmur and on echo diagnosed with advanced dilated cardiomyopathy with severe left ventricular dilation, moderate to severe left ventricular systolic dysfunction, and moderate to severe left atrial dilation. Thoracic radiographs were suspicious for early congestive heart failure. A whole blood taurine level was submitted and was low at 168. She was treatment with furosemide, benazepril, pimobendan, spironolactone, taurine and l-carnitine and her diet was changed to Royal Canin Early Cardiac. At her recheck in 2/26/18, (b) (6) heart had improved significantly with now mild dilated cardiomyopathy with normalized left atrial dimensions, mild left ventricular dilation and low normal left ventricular systolic function. The furosemide was able to be discontinued at this time.	
	Date Problem Started:	(b) (6)	
	Concurrent Medical Problem:	No	
	Outcome to Date:	Better/Improved/Recovering	
Product Information:	Product Name:	Zignature Kangaroo Formula	
	Product Type:	Pet Food	
	Lot Number:		
	Package Type:	BAG	
	Possess Unopened Product:	Unknown	
	Possess Opened Product:	Unknown	
	Product Use Information:	Product Use Stopped After the Onset of the Adverse Event:	Yes
		Adverse Event Abate After Product Stop:	Yes
		Product Use Started Again:	No
		Perceived Relatedness to Adverse Event:	Probably related
		Other Foods or Products Given to the Animal During This Time Period:	Unknown
	Manufacturer /Distributor Information:	Name:	Pets Global - Zignature
		Type(s):	Manufacturer
		Address:	28334 Industry Dr Valencia California 91355 United States

FDACVM-FOIA-2019-1704-000703

		Contact:	Phone: (661) 309-1235
			Web Address: www.zignature.com
		Possess One or More Labels from This Product:	Yes
		Purchase Location Information:	
Animal Information:	Name:	(b) (6)	
	Type Of Species:	Dog	
	Type Of Breed:	Retriever - Labrador	
	Gender:	Female	
	Reproductive Status:	Neutered	
	Weight:	33.18 Kilogram	
	Age:	13 Years	
	Assessment of Prior Health:	Good	
	Number of Animals Given the Product:	1	
	Number of Animals Reacted:	1	
	Owner Information:	Owner Information provided:	Yes
		Contact:	Name: (b) (6)
			Phone: (b) (6)
			Other Phone: (b)(6)
			Email: (b) (6)
		Address:	(b) (6) United States
	Healthcare Professional Information:	Practice Name:	CVCA Cardiac Care for Pets
		Contact:	Name: (b) (6)
			Phone: (b) (6)
			Email: (b)(6)@cvcavets.com
		Address:	(b) (6) United States
		Practice Name:	CVCA Cardiac Care for Pets
		Contact:	Name: (b) (6)
			Phone: (b) (6)
			Email: (b) (6)@cvcavets.com
		Address:	(b) (6) United States
		Type of Veterinarian:	Referred veterinarian
		Permission to Release Records	Yes

FDA-CVM-FOIA-2019-1704-000704

		to FDA:
Sender Information:	Name:	(b) (6)
	Address:	(b) (6) United States
	Contact:	
	Phone:	(b) (6)
	Email:	(b) (6)@cvcavets.com
	Permission To Contact Sender:	Yes
	Preferred Method Of Contact:	Email
Reported to Other Parties:	Other	
Additional Documents:	Attachment:	(b) (6) Echo Report (b) (6).pdf
	Description:	Echocardiogram (b) (6)
	Type:	Echocardiogram
	Attachment:	(b) (6) Echo Report 2018-02-26.pdf
	Description:	Echocardiogram 2-26-2018
	Type:	Echocardiogram
	Attachment:	(b) (6) Taurine Level 2017-11-03.pdf
	Description:	BW Taurine Level 11-3-2017
	Type:	Laboratory Report

CVCA, Cardiac Care for Pets

(b) (6)

Email: (b) (6)@cvcavets.com
www.cvcavets.com



Client: (b) (6)
Co-owner:
Patient name: (b) (6)
Species: Canine
Breed: Labrador Retriever
Sex: FS
Age: 13 years and 5 months old
Weight: 33.18kg. / 73.15 lbs

Primary Care Veterinarian: (b) (6)
Primary Care Hospital: (b) (6)
Phone: (b) (6) ext: (b) (6)
Fax: (b) (6)
Email:

Cardiac Evaluation Report

Exam Date: 02/26/2018

Diagnosis

- Mild, improved dilated cardiomyopathy - suspect taurine-responsive
- Mild, improved mitral and very mild tricuspid valve regurgitation as cause of heart murmur
- Normal, improved left atrial chamber dilation
- Mild, improved eccentric left ventricular chamber dilation
- Low normal, improved left ventricular contractility/heart muscle function
- Cough - suspect bronchial/primary respiratory disease

Medications

- Decrease Lasix/Furosemide 40 mg tablets - Give 1 and 1/2 tablets twice daily for 1 week then decrease to 1 tablet twice daily for 1 week then decrease to 1/2 tablet twice a day for 1 week then discontinue. Please call if you note an increase respiratory rate while decreasing the Lasix. If there is an increase in cough (but normal respiratory rate), we will consider adding in a bronchodilator.
- Continue Benazapril 10 mg tablets - Give 1 and 1/2 tablets twice daily
- Continue Vetmedin/Pimobendan 7.5 mg EZ tablets - Give 1 tablet twice daily.
- Continue Spironolactone 25 mg tablets - Give 1 tablet twice daily.
- Continue Taurine 1500 mg twice daily.
- Continue L-carnitine 1500 mg three times daily.
- You may purchase the taurine and L-carnitine at any health food or nutrition store or www.puritanspride.com. You may also obtain the L-carnitine in bulk powder form from North Carolina State University by calling 919-513-6325.
- Continue with monthly heartworm and flea/tick control as prescribed by (b) (6).

Please allow 24-48 hours for CVCA to process prescription refill requests.

Refill all medications indefinitely unless directed by CVCA or your primary care veterinarian.

- Please check all medications and dosages on your discharge report against the pharmacy labels.

Please Note

- Please see our website www.cvcavets.com for more information about (b) (6) dilated cardiomyopathy.

Nutrition Recommendations:

- Continue the Royal Canin Early Cardiac diet.
 - Consider fish oil supplements (omega-3 fatty acids). Her dose is approximately EPA 1220 mg and DHA 760 mg total per day. Please start at 1/2 the dose for one week, then increase to the full dose if tolerating well thereafter. Please avoid Cod liver oil and flax seed as well as products with Vit A and/or D.
- For more information about fish oils, please visit -- <http://vet.tufts.edu/heartsmart/diet/important-nutrients-for-pets-with-heart-disease/>
- In addition to the supplements approved by Tuft's Veterinary Nutrition Service, other reputable brands include Welactin and Nordic Naturals. (b) (6) may have additional brand recommendations.

Activity Recommendations:

- Continue normal activity as she wants and is able to do. Please allow (b) (6) to take more breaks and rest during activity.
- Please avoid exercise in the hot/humid weather.

At Home Monitoring:

- In order to monitor for the development of early congestive heart failure in the out-patient setting, we recommend monitoring your pet's resting respiratory rate several times a week. Normal resting respiratory rates should be less than 30 breaths per minute. Consider using a respiratory rate monitoring application to track (b) (6) respiratory rate - Cardalis or BI Pharma have reliable phone applications. Please contact us if you note a persistent or progressive increase.

Future Anesthesia/Fluid Recommendations:

- We expect (b) (6) to tolerate carefully monitored general anesthesia with normal preoperative bloodwork and a balanced anesthetic regimen. During anesthesia, we recommend careful monitoring of ECG, BP and pulse ox and 1/2 usual surgical fluid rate (ie: 2-4 ml/kg/hr). Carefully monitor for several hours post-operatively for signs of respiratory congestion and consider chest radiographs if these signs occur. There is some risk associated with all anesthetic events.
- Avoid medications with tachycardia as a side effect, such as ketamine, telazol and glycopyrrolate. Cleared for low dose atropine if needed for intraprocedure bradycardia. Avoid medications that significantly alter blood pressure such as acepromazine and Domitor.
- (b) (6) should not receive corticosteroids (prednisone) in the future please contact CVCA for recommendations, if corticosteroids are indicated.

Reevaluation

- Recheck with (b) (6) in the next 2-4 weeks and every 6 months for wellness care as directed, close auscultation, blood pressure and complete lab tests including blood and urine testing (CBC/Chemistry/Urinalysis/Thyroid evaluation). Please forward these results when available.
- Please recheck with CVCA in 6 months for a follow up consultation/examination, blood pressure, and echocardiogram. Please contact us or schedule an earlier appointment if (b) (6) has any problems or symptoms indicative of worsening heart disease or if recommended by (b) (6).

We thank you for trusting in CVCA to care for (b) (6) today. Please do not hesitate to call us with any questions or concerns.

Sincerely,

(b) (6)

Visit Summary

Heart Rate: 130

BP: 155 mmHg

Cuff Size/Location: 6 cuff/LF

History: Recheck DCM, suspected early CHF; doing well; RRR - 16 bpm, increased Lasix in January due to increased cough; cough seems to be intermittent and related to excitement; good appetite; 3 kg weight gain since 10/2017; walks 30-45 minutes per day - slow pace, at times winded but recovers very quickly.

(b) (6) developed a cough last Wednesday (10/25/17). Radiographs and blood work were performed by (b) (6). The lab work (which is unavailable for review) reportedly showed an elevated ALP 440 and GGT 30 and mild lymphopenia. Thoracic radiographs were performed which revealed cardiomegaly. (b) (6) was treated with hydroxyzine 50mg BID, doxycycline 200mg AM and 100mg PM, and hydrocodone 5mg q8-12h. All medications were stopped on Monday as her cough had worsened and she was presented to the (b) (6) for a cardiac evaluation as her coughing had worsened and she had brought up a small volume of pink-tinged foam after a coughing fit. During this time there has been no evidence of lethargy and she continues to eat and drink normally at home.

PPHx: None

Meds: None

Other: UTD on vaccinations, On HW preventative

Diet: changed from Zignature (Kangaroo) to Royal Canin Early Cardiac

Physical Exam Findings: 3/6 pansystolic murmur, PMI - mitral valve, regular rhythm with S3 gallop; LUNGS - clear all fields, panting, normal effort; SI. overweight body condition (BCS - 6/9); Pink mm; PP - SS; PLN - WNL; ABD - hepatomegaly; BAR

Echocardiographic Findings

Mild left ventricular eccentric dilation - significant improvement compared to previous exam; mild, improved centrally located mitral regurgitant jet, normal, improved left atrial dimensions on 2D imaging and on M-mode imaging, mild, low velocity eccentric low velocity tricuspid regurgitation, subjectively normal right ventricular and right atrial dimensions, normal left and right ventricular outflow velocities, low normal, improved indices of systolic function (FS% and EF% by modified Simpson's, normal EPSS, normal transmitral inflow velocities and E:A wave ratio on spectral Doppler tracings, normal TDI E':A' ratio of the lateral mitral annulus, no masses, effusions or heartworms observed.

Comments

Dear (b) (6),

Thank you for sending (b) (6) to see us with (b) (6) today. I am quite pleased with (b) (6) exam today. She has had remarkable improvement in her echocardiogram with the cardiac medications, change in diet and supplementation with Taurine and L-carnitine. Her risk for congestive heart failure at this point is very low so we will be weaning (b) (6) off the Lasix/furosemide while (b) (6) monitors (b) (6) respiratory rate. Her current cough is likely due to respiratory disease and if the cough progresses/worsens, we will consider adding in a bronchodilator, such as Theophylline. Right now, with the marked improvement, (b) (6) long-term prognosis has improved considerably. I suspect we will be able to further discontinue cardiac medications if her heart remains stable. We will continue to closely monitor (b) (6) heart disease via serial echocardiography and institute further therapy when progression is noted. While on this course of medication, it is important to monitor the chemistry profiles and blood pressures. Hopefully, (b) (6) will continue to do so well - she's a sweetie!

We appreciate your continued referrals and the trust you place in CVCA to co-manage your cardiac patients. We look forward to working with you on this case and others. In an effort to continue to improve CVCA's service to both you and your clients, please visit our website at www.cvcavets.com and complete our online referring veterinarian survey.

Sincerely,

(b) (6) - Cardiology

11/10/17 09:05:38

(b) (6)

->

(b) (6) Page 001

(b) (6)

(b) (6)

Owner:
Patient:
Species:
Breed:
Age:
Gender:

(b) (6)

CANINE
LABRADOR_RETRIE
11Y
FS

(b) (6)

Account: 21467

Requisition #: (b) (6)
Accession #: (b) (6)
Order rec'd: 11/03/2017
Ordered by: (b) (6)
Reported: 11/10/2017

TAURINE (WHOLE BLOOD)				
Test		Result		
TAURINE		168	(200 - 350)	L
Testing performed at University of California, Davis				

(b) (6)

11/10/2017

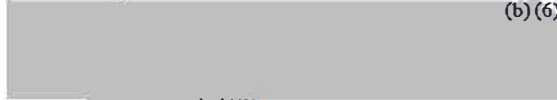
FINAL REPORT

PAGE 1 OF 1

(b) (6)

CVCA, Cardiac Care for Pets

(b) (6)



www.cvcavets.com



Client: (b) (6)
Co-owner: (b) (6)
Patient name: (b) (6)
Species: Canine
Breed: Labrador Retriever
Sex: FS
Age: 13 years and 5 months old
Weight: 33.18kg. / 73.15 lbs

Primary Care Veterinarian: (b) (6)
Primary Care Hospital: (b) (6)
Phone: (b) (6) ext (b) (6)
Fax: (b) (6)
Email: (b) (6)

Cardiac Evaluation Report

Exam Date: (b) (6)

Diagnosis

- Advanced dilated cardiomyopathy - ruleout idiopathic vs. taurine-responsive
- Mild to moderate mitral valve regurgitation as cause of heart murmur
- Trace tricuspid valve regurgitation
- Moderate to severe left atrial chamber dilation
- Severe eccentric left ventricular chamber dilation
- Moderate to severe decrease in contractility/heart muscle function
- Mild left ventricular wall thinning
- Mild right atrial and right ventricular chamber dilation
- Progressive cough - rule out: early left sided congestive heart failure vs. mainstem bronchial compression

Medications

- Begin Lasix/Furosemide 40 mg tablets - Give 1 tablet twice daily.
 - > For mild increases in respiratory rate/effort, you may give an additional dose of Lasix.
 - > If you are consistently giving an additional dose of Lasix, please contact our office so we may help adjust medications long-term.
 - > We may increase this dose in the future based on at home monitoring of breathing and recheck blood work.
- Begin Benazapril 10 mg tablets - Give 1 tablet twice daily for 4 days then increase to 1 and 1/2 tablet twice daily thereafter.
- Begin Vetmedin/Pimobendan 5mg tablets - Give 1 and 1/2 tablets twice daily. Will switch to 7.5 mg EZ tablets at 1 tablet twice daily. The 7.5mg tablet will be compounded through (b) (6) pharmacy, please call them to set up shipping and billing (b) (6)
- Please call if you notice a decrease in appetite, vomiting, lethargy, weakness or any other signs of illness while beginning/adjusting the medications.
- Continue with monthly heartworm and flea/tick control as prescribed by (b) (6).

In 2 weeks, if (b) (6) is eating and feeling well:

- Begin Spironolactone 25 mg tablets - Give 1 tablet once daily for 4 days then increase to 1 tablet twice daily thereafter.

- Begin Taurine 1500 mg twice daily.
- Begin L-carnitine 1500 mg three times daily.
- You may purchase the taurine and L-carnitine at any health food or nutrition store or www.puritanspride.com. You may also obtain the L-carnitine in bulk powder form from North Carolina State University by calling 919-513-6325.

Please allow 24-48 hours for CVCA to process prescription refill requests.

Refill all medications indefinitely unless directed by CVCA or your primary care veterinarian.

- **Please check all medications and dosages on your discharge report against the pharmacy labels.**

Please Note

- Please see our website www.cvcavets.com for more information about (b) (6) dilated cardiomyopathy.

Nutrition Recommendations:

- (b) (6) is on a specialized diet which could be contributing to taurine deficiency. Please change her to a new diet, as her housemate is on a novel protein diet - consider prescription diets such as Royal Canin or Science Diet. Please discuss diet options with (b) (6)
 - In patients with early/mild heart failure, CVCA recommends feeding a diet with less than 80 mg of sodium per 100 kCal of food (50-80 mg/100 kCal). In patients with refractory heart failure signs, further sodium restriction may be beneficial.
 - For more information about sodium content of various foods, please visit:
 - Dog: http://vet.tufts.edu/wp-content/uploads/reduced_sodium_diet_for_dogs.pdf
 - Treats: http://vet.tufts.edu/wp-content/uploads/treats_for_dogs_with_heart_disease.pdf
 - CVCA recommends avoiding kidney diets unless (b) (6) has kidney disease that warrants protein restriction.
 - Diet changes should be done gradually (ie. over ~1 month) to avoid GI upset and avoided until (b) (6) is stable and eating well on the cardiac medications, usually about 2 weeks after starting or adjusting therapy.
 - If you are interested in a consultation with a veterinary nutritionist, please visit --<http://vetnutrition.tufts.edu/make-an-appointment/>
 - CVCA recommends fish oil supplements (omega-3 fatty acids) in many dogs with cardiac disease. Her dose should be approximately EPA 1220 mg and DHA 760 mg total per day. Please start at 1/2 the dose for one week, then increase to the full dose if tolerating well thereafter. Please avoid Cod liver oil and flax seed as well as products with Vit A and/or D.
- For more information about fish oils, please visit --<http://vet.tufts.edu/heartsmart/diet/important-nutrients-for-pets-with-heart-disease/>
- In addition to the supplements approved by Tuft's Veterinary Nutrition Service, other reputable brands include Welactin and Nordic Naturals. (b) (6) may have additional brand recommendations.

Activity Recommendations:

- Keep (b) (6) very quiet for the next 3-4 days with only brief leash walks to eliminate.
- Once her coughing has resolved, (b) (6) may gradually resume activity as she wants and is able to do. Please allow (b) (6) to take more breaks and rest during activity.
- Please try avoid burst type activity, as this increases the arrhythmia risk and avoid exercise in the hot/humid weather.
- Please try to warm (b) (6) up for 5-10 minutes with walking prior to moderate activity and take more rests during more vigorous activity.

At Home Monitoring:

- Monitor for signs of cough, respiratory difficulty, exercise intolerance, abdominal swelling, weakness, lethargy, etc. If you note any of these symptoms, please notify CVCA or (b) (6) as these symptoms may indicate recurrent congestive heart failure. If you note an increase in cough, respiratory rate or effort, please feel free to give an additional dose of Lasix/Furosemide, while contacting CVCA.
- In order to monitor for the development of early congestive heart failure in the out-patient setting, we recommend monitoring your pet's resting respiratory rate several times a week. Normal resting respiratory rates should be less than 30 breaths per minute. Consider using a respiratory rate monitoring application to track (b) (6) respiratory rate - Cardalis or BI Pharma have reliable phone applications. Please contact us if you note a persistent or progressive increase.
- In addition, (b) (6) is sadly at increased risk for sudden cardiac death due to her cardiac disease. Dobermans are particularly at risk for development of severe, sudden malignant arrhythmias that sadly may result in sudden death. However, we hope to minimize these risks with our treatment plan.

Future Anesthesia/Fluid Recommendations

- Avoid intravenous or subcutaneous fluid therapy in the future, if possible. If fluid therapy is indicated, please contact CVCA.
- (b) (6) should not receive corticosteroids (prednisone) in the future please contact CVCA for recommendations, if corticosteroids are indicated.
- Avoid elective anesthesia, as (b) (6) is at high risk for complications due to the degree of cardiac disease. If anesthesia is necessary in the future, please contact CVCA for recommendations for monitoring and anesthetics.

Reevaluation

- Please recheck with (b) (6) in the next day or two to obtain taurine levels. Please forward these results when available.
- Please recheck with (b) (6) in 2 weeks for a follow up examination and blood chemistry profile with electrolytes and as recommended by (b) (6). Please forward these results when available.
- Please recheck with (b) (6) every 4-6 months for a follow up examination and blood chemistry profile with electrolytes and as recommended by (b) (6). Please forward these results when available.
- Please recheck with CVCA in 5 months for a follow up consultation/examination, blood pressure, and echocardiogram. Please contact us or schedule an earlier appointment if (b) (6) has any problems or symptoms indicative of worsening heart disease or if recommended by (b) (6).

Visit Summary

Heart Rate: 132 bpm

BP: 100mmHg (based on MR gradient)

History:

(b) (6) developed a cough last Wednesday (10/25/17). Radiographs and blood work were performed by (b) (6). The lab work (which is unavailable for review) reportedly showed an elevated ALP 440 and GGT 30 and mild lymphopenia. Thoracic radiographs were performed which revealed cardiomegaly. (b) (6) was treated with hydroxyzine 50mg BID, doxycycline 200mg AM and 100mg PM, and hydrocodone 5mg q8-12h. All medications were stopped on Monday as her cough had worsened and she was presented to the (b) (6) for a cardiac evaluation as her coughing had worsened and she had brought up a small volume of pink-tinged foam after a coughing fit. During this time there has been no evidence of lethargy and she continues to eat and drink normally at home.

PPHx: None

Meds: None

Other: UTD on vaccinations, On HW preventative

Diet: Zignature (Kangaroo)

Physical Exam Findings:

BAR, sweet but nervous

OP/EENT: Pink, moist mucous membranes, CRT <2s, mild periodontal disease, LS OU, clear AU, No nasal or ocular discharge, no cough on tracheal palpation

PLN: WNL

H/L: Grade 2/6 left apical protosystolic heart murmur, regular rhythm, strong synchronous femoral pulses, RR: 36 breaths/min, questionable mild increase in bronchovesicular sounds bilaterally, no crackles or wheezes ausculted, eupneic

Abd: Soft non-painful abdominal palpation, no palpable masses or fluid wave

MS/Neuro: BCS 5/9, Amb x 4, Mentally alert and appropriate

Integ: Normal turgor, subcutaneous mass left ventrum

Other Diagnostics:

10/27/17 pDVM CXR: Generalized cardiomegaly characterized by widening of the cardiac silhouette and loss of the caudal cardiac waist consistent with left atrial enlargement. Slight left auricular bulge. Increased sternal contact and rounding of the right heart on the VD radiograph. Dorsal deviation of the trachea. Prominent pulmonary vasculature with a questionable mild increase in interstitial opacity in the caudodorsal lung fields which may suggest early congestive heart failure/pulmonary edema.

Echocardiographic Findings

Severe left ventricular eccentric hypertrophy with apical rounding and increased sphericity, mild-moderate centrally

located mitral regurgitant jet, moderate-severe secondary left atrial dilation on 2D imaging and moderately-severely increased LA:Ao ratio on M-mode imaging, mild eccentric low velocity tricuspid regurgitation with mildly elevated estimated right ventricular pressures consistent with mild pulmonary hypertension, mild right ventricular and right atrial dilation, normal left and right ventricular outflow velocities, moderately to severely depressed indices of systolic function (FS% and EF% by modified Simpson's - LV DI 144ml/m², LV SI 90ml/m²), increased EPSS, elevated transmitral inflow velocities and E:A wave ratio on spectral Doppler tracings, normal TDI E':A' ratio of the lateral mitral annulus, no masses, effusions or heartworms observed.
ECG during echocardiogram: Normal sinus rhythm. No ventricular ectopy noted.

Comments

Dear (b) (6),

Thank you for sending (b) (6) to see us with (b) (6) today. Sadly, (b) (6) has dilated cardiomyopathy with moderate to severe systolic dysfunction and moderate to severe left atrial dilation. This places her at a high risk of developing congestive heart failure and with the progression in her cough I am concerned that we may be dealing with congestive heart failure at this time. We have begun therapy to control congestive heart failure, support cardiac function, slow down the progression of the heart disease and improve survival. We are now seeing more dogs on specialized diets that are developing taurine deficiency and we have discussed submission of taurine levels to evaluate whether this may be a contributing factor to (b) (6) condition. (b) (6) is interested in pursuing this test at your clinic, taurine levels should be drawn and placed in a heparinized tube (green top) and should be frozen and submitted to (b) (6) (who sends it to UC Davis). It will be interesting to see if this is a contributing factor to (b) (6) condition.

We will continue to closely monitor (b) (6) heart disease via serial echocardiography and institute further therapy when progression is noted. While on this course of medication, it is important to monitor the chemistry profiles and blood pressures. Dogs with dilated cardiomyopathy are at a higher risk of developing ventricular arrhythmias. None were noted today; however, it will be important to monitor for arrhythmias periodically in the future. Unfortunately, the prognosis is guarded after the onset of congestive heart failure, and we discussed with the (b) (6) family that the average survival is ~ 6-12 months.^{1,2} Survival time is highly individually variable depending on response to therapy.

We appreciate your continued referrals and the trust you place in CVCA to co-manage your cardiac patients. We look forward to working with you on this case and others. In an effort to continue to improve CVCA's service to both you and your clients, please visit our website at www.cvcavets.com and complete our online referring veterinarian survey.

Sincerely,

(b) (6) - Cardiology

From: Palmer, Lee Anne
To: Jones, Jennifer L
Cc: Rotstein, David; Carey, Lauren
Subject: FW: Zignature Kangaroo Formula: (b) (6) - EON-351031
Date: Thursday, April 12, 2018 1:39:10 PM
Attachments: 2045676-report.pdf

Hi Jen – were you expecting this one? Thx - LA

From: PFR Event [mailto:ppreventcreation@fda.hhs.gov]
Sent: Thursday, April 12, 2018 1:36 PM
To: Cleary, Michael * <Michael.Cleary@fda.hhs.gov>; HQ Pet Food Report Notification <HQPetFoodReportNotification@fda.hhs.gov>; (b) (6)
Subject: Zignature Kangaroo Formula: (b) (6) - EON-351031

A PFR Report has been received and PFR Event [EON-351031] has been created in the EON System

A "PDF" report by name "2045676-report.pdf" is attached to this email notification for your reference

Below is the summary of the report:

EON Key: EON-351031

ICSR #: 2045676

EON Title: PFR Event created for Zignature Kangaroo Formula; 2045676

AE Date	02/22/2018	Number Fed/Exposed	1
Best By Date		Number Reacted	1
Animal Species	Dog	Outcome to Date	Stable
Breed	Retriever - Golden		
Age	6 Years		
District Involved	PFR (b) (6) DO		

Product information

Individual Case Safety Report Number: 2045676

Product Group: Pet Food

Product Name: Zignature Kangaroo Formula

Description: (b) (6) Patient presented to the cardiology service at (b) (6) for tachypnea. He was diagnosed with dilated cardiomyopathy and left side congestive heart failure. Whole blood taurine level was 119 (ref 200-350, critical level <150). At the time, patient consuming Zignature Kangaroo Formula and was advised to change

Submission Type: Initial

Report Type: Adverse Event (a symptom, reaction or disease associated with the product)

Outcome of reaction/event at the time of last observation: Stable

Number of Animals Treated With Product: 1

Number of Animals Reacted With Product: 1

Product Name	Lot Number or ID	Best By Date
--------------	------------------	--------------

Zignature Kangaroo Formula		
----------------------------	--	--

Sender information

(b) (6)

Owner information

(b) (6)

To view this PFR Event, please click the link below:
<https://eon.fda.gov/eon/browse/EON-351031>

To view the PFR Event Report, please click the link below:
<https://eon.fda.gov/eon/> (b) (6)

This email and attached document are being provided to you in your capacity as a Commissioned Official with the U.S. Department of Health and Human Services as authorized by law. You are being provided with this information pursuant to your signed Acceptance of Commission.

This email message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential. Any

dissemination, distribution, or copying is strictly prohibited

The information is provided as part of the Federal-State Integration initiative. As a Commissioned Official and state government official, you are reminded of your obligation to protect non-public information, including trade secret and confidential commercial information that you receive from the U.S. Food and Drug Administration from further disclosure. The information in the report is intended for situational awareness and should not be shared or acted upon independently. Any and all actions regarding this information should be coordinated through your local district FDA office.

Failure to adhere to the above provisions could result in removal from the approved distribution list. If you think you received this email in error, please send an email to FDAREportableFoods@fda.hhs.gov immediately.

Report Details - EON-351031

ICSR:	2045676		
Type Of Submission:	Initial		
Report Version:	FPSR.FDA.PETF.V.V1		
Type Of Report:	Adverse Event (a symptom, reaction or disease associated with the product)		
Reporting Type:	Voluntary		
Report Submission Date:	2018-04-12 13:26:01 EDT		
Reported Problem:	Problem Description:	(b) (6) Patient presented to the cardiology service at (b) (6) for tachypnea. He was diagnosed with dilated cardiomyopathy and left side congestive heart failure. Whole blood taurine level was 119 (ref 200-350, critical level <150). At the time, patient consuming Zignature Kangaroo Formula and was advised to change.	
	Date Problem Started:	02/22/2018	
	Concurrent Medical Problem:	Yes	
	Pre Existing Conditions:	History of swallowing disorder; on Prednisone 10mg every other day since 2015 following biopsy of nodule on larynx (granulomatous)	
	Outcome to Date:	Stable	
Product Information:	Product Name:	Zignature Kangaroo Formula	
	Product Type:	Pet Food	
	Lot Number:		
	Package Type:	BAG	
	Possess Unopened Product:	No	
	Possess Opened Product:	No	
	Product Use Information:	Description:	Owner feeding for 2-3 years prior to diagnosis.
		Last Exposure Date:	03/01/2018
		Time Interval between Product Use and Adverse Event:	3 Years
		Product Use Stopped After the Onset of the Adverse Event:	Yes
		Perceived Relatedness to Adverse Event:	Possibly related
		Other Foods or Products Given to the Animal During This Time Period:	Yes
	Manufacturer /Distributor Information:		
	Purchase Location Information:	Name:	Chewy.com
Animal Information:	Name:	(b) (6)	
	Type Of Species:	Dog	
	Type Of Breed:	Retriever - Golden	
	Gender:	Male	
	Reproductive Status:	Neutered	
	Weight:	40 Kilogram	

FDA-CVM-FOIA-2019-1704-000716

	Age: 6 Years																						
	Assessment of Prior Health: Good																						
	Number of Animals Given the Product: 1																						
	Number of Animals Reacted: 1																						
	Owner Information:	<table border="1"> <tr> <td>Owner Information provided:</td> <td>Yes</td> </tr> <tr> <td>Contact:</td> <td> <table border="1"> <tr> <td>Name:</td> <td>(b) (6)</td> </tr> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> </table> </td> </tr> <tr> <td>Address:</td> <td> <table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">United States</td> </tr> </table> </td> </tr> </table>	Owner Information provided:	Yes	Contact:	<table border="1"> <tr> <td>Name:</td> <td>(b) (6)</td> </tr> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> </table>	Name:	(b) (6)	Phone:	(b) (6)	Address:	<table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">United States</td> </tr> </table>	(b) (6)		United States								
	Owner Information provided:	Yes																					
	Contact:	<table border="1"> <tr> <td>Name:</td> <td>(b) (6)</td> </tr> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> </table>	Name:	(b) (6)	Phone:	(b) (6)																	
	Name:	(b) (6)																					
	Phone:	(b) (6)																					
	Address:	<table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">United States</td> </tr> </table>	(b) (6)		United States																		
(b) (6)																							
United States																							
Healthcare Professional Information:	<table border="1"> <tr> <td>Practice Name:</td> <td>(b) (6)</td> </tr> <tr> <td>Contact:</td> <td> <table border="1"> <tr> <td>Name:</td> <td>(b) (6)</td> </tr> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> </table> </td> </tr> <tr> <td>Address:</td> <td> <table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">States</td> </tr> </table> </td> </tr> <tr> <td>Type of Veterinarian:</td> <td>Referred veterinarian</td> </tr> <tr> <td>Date First Seen:</td> <td>(b) (6)</td> </tr> </table>	Practice Name:	(b) (6)	Contact:	<table border="1"> <tr> <td>Name:</td> <td>(b) (6)</td> </tr> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> </table>	Name:	(b) (6)	Phone:	(b) (6)	Address:	<table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">States</td> </tr> </table>	(b) (6)		States		Type of Veterinarian:	Referred veterinarian	Date First Seen:	(b) (6)				
Practice Name:	(b) (6)																						
Contact:	<table border="1"> <tr> <td>Name:</td> <td>(b) (6)</td> </tr> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> </table>	Name:	(b) (6)	Phone:	(b) (6)																		
Name:	(b) (6)																						
Phone:	(b) (6)																						
Address:	<table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">States</td> </tr> </table>	(b) (6)		States																			
(b) (6)																							
States																							
Type of Veterinarian:	Referred veterinarian																						
Date First Seen:	(b) (6)																						
Sender Information:	<table border="1"> <tr> <td>Name:</td> <td>(b) (6)</td> </tr> <tr> <td>Address:</td> <td> <table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">United States</td> </tr> </table> </td> </tr> <tr> <td>Contact:</td> <td> <table border="1"> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> <tr> <td>Email:</td> <td>(b) (6)</td> </tr> </table> </td> </tr> <tr> <td>Reporter Wants to Remain Anonymous:</td> <td>No</td> </tr> <tr> <td>Permission To Contact Sender:</td> <td>Yes</td> </tr> <tr> <td>Preferred Method Of Contact:</td> <td>Email</td> </tr> <tr> <td>Reported to Other Parties:</td> <td>None</td> </tr> </table>	Name:	(b) (6)	Address:	<table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">United States</td> </tr> </table>	(b) (6)		United States		Contact:	<table border="1"> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> <tr> <td>Email:</td> <td>(b) (6)</td> </tr> </table>	Phone:	(b) (6)	Email:	(b) (6)	Reporter Wants to Remain Anonymous:	No	Permission To Contact Sender:	Yes	Preferred Method Of Contact:	Email	Reported to Other Parties:	None
Name:	(b) (6)																						
Address:	<table border="1"> <tr> <td colspan="2">(b) (6)</td> </tr> <tr> <td colspan="2">United States</td> </tr> </table>	(b) (6)		United States																			
(b) (6)																							
United States																							
Contact:	<table border="1"> <tr> <td>Phone:</td> <td>(b) (6)</td> </tr> <tr> <td>Email:</td> <td>(b) (6)</td> </tr> </table>	Phone:	(b) (6)	Email:	(b) (6)																		
Phone:	(b) (6)																						
Email:	(b) (6)																						
Reporter Wants to Remain Anonymous:	No																						
Permission To Contact Sender:	Yes																						
Preferred Method Of Contact:	Email																						
Reported to Other Parties:	None																						
Additional Documents:																							

From: Darcy Adin
To: Joshua A Stern: (b) (6); fries. Ryan C; (b) (6)
Cc: freeman. Lisa; Jones. Jennifer L
Subject: fwd: hold-FDA call w/ NCSU & Tufts re: DCM
Date: Tuesday, August 07, 2018 7:09:27 AM

Hi Josh, (b) (6). Ryan and (b) (6),

I know it is short notice but if any of you are available to conference with Dr. Jones and her group at the FDA (b) (5)

Thanks!
Darcy and Lisa

----- Forwarded Message-----

From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Date: Mon, Aug 6, 2018 at 10:58 AM
Subject: hold-FDA call w/ NCSU & Tufts re: DCM
To: "Noffis, Anne" <Anne.Noffis@fda.hhs.gov>, DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>, "Rotstein, David" <David.Rotstein@fda.hhs.gov>, "Palmer, Lee Anne" <LeeAnne.Pahner@fda.hhs.gov>, "Carey, Lauren" <Lauren.Carey@fda.hhs.gov>, Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>, "Ceric, Olgica" <Olgica.Ceric@fda.hhs.gov>, "Nemser, Sarah" <Sarah.Nemser@fda.hhs.gov>, Darcy Adin <dbadin@ncsu.edu>, Lisa Freeman <lisa.freeman@tufts.edu>

-- Do not delete or change any of the following text. --

Join Webex meeting

Meeting number (access code) (b) (6)
Meeting password: (b) (6)

Join by phone

+1-210-795-0506 US Toll

+1-877-465-7975 US Toll Free

[Global call-in numbers](#) | [Toll-free calling restrictions](#)

[Can't join the meeting?](#)

If you are a host, [go here](#) to view host information.

IMPORTANT NOTICE: Please note that this Webex service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

--

Darcy B. Adin, DVM, DACVIM (Cardiology)
Clinical Assistant Professor of Cardiology
North Carolina State University
NC State Veterinary Hospital
1060 William Moore Drive
Raleigh, NC 27607
919-513-6032

From: [Freeman, Lisa](#)
To: [Jones, Jennifer L](#)
Subject: ideas for dcm issue
Date: Wednesday, August 08, 2018 4:48:09 PM
Attachments: [ideas 8-1-18 for fda.docx](#)
[van vleet ferrans myocardial diseases of animals am j pathol 1986.pdf](#)

Attached is an article and the various nutritional deficiencies and nutritional toxicities that can cause myocardial disease
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

(b) (6)



(b) (6)



***Review
Article***

MYOCARDIAL DISEASES
OF ANIMALS

CONTENTS

Introduction	98
Myocardial Diseases With Known or Suspected Heritability	98
Hereditary Cardiomyopathy (Muscular Dystrophy) in Hamsters	99
Hereditary Cardiomyopathies of Mice	99
Hereditary Cardiomyopathy of Rats	101
Hereditary Cardiomyopathy ("Round Heart Disease") of Turkeys	101
Hereditary Cardiomyopathies of Cattle	102
Myocardial Alterations in Glycogenosis	102
Myocardial Calcification in Mice and Other Laboratory Animals	103
Myocardial Lipofuscinosis (Xanthosis)	103
Myocardial Diseases Produced by Nutritional Deficiencies	103
Selenium-Vitamin E Deficiency	103
Potassium Deficiency	111
Copper and/or Iron Deficiency	111
Thiamine Deficiency	112
Magnesium Deficiency	113
Protein Deficiency and Protein-Calorie Malnutrition (Kwashiorkor, Marasmus)	113
Tryptophan Deficiency	113
Choline Deficiency	113
Myocardial Diseases of Unknown Etiology	113
Hypertrophic Cardiomyopathy in Cats, Dogs, and Pigs	113
Dilated (Congestive) Cardiomyopathy in Cats, Dogs, and Pigs	116
Restrictive Cardiomyopathy and Endomyocardial Diseases in Cats and Rats	118
Cardiomyopathy of Chickens and Geese	119
Atrial Thrombosis in Hamsters and Mice	119
Spontaneous Rupture of the Left Atrium in Dogs	120
Myocardial Fibrosis in Aged Rats	120
Myocardial Degeneration and Fibrosis in Aged Horses	121
Basophilic Degeneration of Myocardium	121
Myocardial Diseases of Toxic Etiology	121
Toxicity of Metallic Salts	121
Lead Cardiotoxicity	122
Cobalt Cardiotoxicity	122
Catecholamine Cardiotoxicity	123
Histamine Cardiotoxicity	125
Cardiotoxicity of Minoxidil and Other Vasodilating Antihypertensives	125
Methylxanthine Cardiotoxicity	127
Cardiotoxicity of Monensin and Other Ionophores	128
Doxorubicin and Daunorubicin Cardiotoxicity	129
Cardiotoxicity of Other Antineoplastic Agents	136
Mitoxanthrone	136
Cyclophosphamide	136
5-Fluorouracil	136
Vincristine	136
AMSA	136
Furazolidone Cardiotoxicity in Poultry	136
Sodium Chloride Cardiotoxicity in Poultry	137
Myocardial Diseases Induced by Poisonous Plants	137
Myocardial Alterations From Vitamin D Toxicosis and Calcinogenic Plants	140
Myocardial Damage in Blister Beetle Poisoning of Horses	140

Cardiotoxicity of High Erucic Acid Rapeseed Oil	140
Cardiotoxicity of Brominated Vegetable Oils.....	140
Cardiotoxicity of Rancid Fat in Mice	140
Gossypol Cardiotoxicity	140
Myocardial Alterations Induced by Chloroquine.....	140
Carbon Monoxide and Cigarette Smoke Cardiotoxicity	140
Cardiotoxicity of T-2 Mycotoxin	143
Papain-Induced Myocardial Necrosis in Rats	143
Paraphenylenediamine-Induced Myocardial Necrosis	144
Cardiotoxicity of Brown FK.....	144
Allylamine Cardiotoxicity	144
Plasmocid Cardiotoxicity.....	144
Hyperoxia Cardiotoxicity.....	145
Ethanol Cardiotoxicity	145
Emetine Cardiotoxicity.....	145
Renal Failure	145
Myocardial Diseases Associated With Physical Injuries and Shocka.....	145
Central Nervous System Lesions and Trauma	146
Stress	146
Overexertion	147
Radiation	148
Electrical Defibrillation	148
Acceleration Stress	148
Hemorrhagic Shock	149
Myocardial Diseases Associated With Endocrine Disorders	149
Glucocorticoid Excess	149
Functional Pheochromocytomas.....	150
Diabetes Mellitus	150
Hyperthyroidism.....	150
Hypothyroidism (Myxedema) in Dogs	151
Growth Hormone Excess	151
Myocarditis	151
Coxsackie Viral Myocarditis.....	151
Encephalomyocarditis Viral Myocarditis in Pigs, Primates, and Mice	152
Canine Parvoviral Myocarditis	152
Other Canine Viral Myocarditides	154
Foot-and-Mouth Disease Viral Myocarditis.....	154
Other Viral Myocarditides in Laboratory Animals	154
Viral Myocarditides in Birds.....	154
Myocarditis in Tyzzer's Disease	155
Toxoplasmal Myocarditis	155
Trypanosomal Myocarditis (Chagas' disease).....	155
Summary	155
References	157

Myocardial Diseases of Animals

JOHN F. VAN VLEET, DVM, PhD, and
VICTOR J. FERRANS, MD, PhD

*From the Pathology Branch, National Heart, Lung and Blood Institute,
National Institutes of Health, Bethesda, Maryland*

INTEREST in the cardiomyopathies first developed in the 1960s, at which time the terms "primary myocardial disease," "cardiomyopathy," and "myocardiopathy" were proposed to identify a series of disorders that affected primarily the myocardium. More recently it was suggested that the use of the term "cardiomyopathy" be restricted to myocardial diseases of unknown etiology, and that cardiomyopathies of known etiology be referred to as "myocardial diseases" associated with a given specific entity or causative factor. In this review, we use the term "myocardial diseases" in its original connotation to refer to all disorders that affect primarily the heart muscle by producing degeneration, necrosis, or inflammation. A wide spectrum of such disorders has been demonstrated in human patients. However, a much larger number of myocardial diseases occur, either spontaneously or experimentally induced, in animals. The myocardial diseases of animals provide many unique opportunities to explore diverse aspects of cardiovascular medicine. Some of these diseases correspond closely to conditions known to affect humans; others constitute model systems for specific aspects of certain human disorders; and still others represent situations of intrinsic genetic, morphologic, toxicologic, or pharmacologic interest. We have attempted to emphasize many disorders that have received only limited attention in the literature; and, whenever possible, we have referred the reader to extensive reviews that have been published recently on some types of myocardial diseases of animals. In keeping with the definitions given above, we have excluded from consideration in

this review the following groups of disorders: ischemic heart disease; valvular, pericardial, and endocardial diseases; diseases of the conduction system; congenital malformations; and diseases caused by metazoan parasites.

Myocardial Diseases With Known or Suspected Heritability

This group of diseases continues to expand, with recent descriptions of examples in the rat, cow, and mouse. The cardiomyopathies in hamsters, mice, rats, turkeys, cattle, and animals with glycogenosis may have progressive clinical courses and some morphologic alterations similar to those in certain cardiomyopathies in human patients and may provide useful models for the human diseases. The hamster model, especially, has been used extensively for studies on the morphologic and biochemical alterations of cardiomyopathies and the development of potential therapeutic agents. For the most part, these diseases may be eliminated from animal populations by selective breeding or may be maintained as models by breeding of affected or carrier animals.

Address reprint requests to Dr. John F. Van Vleet, Department of Pathology, School of Veterinary Medicine, Purdue University, West Lafayette, IN 47907.

Hereditary Cardiomyopathy (Muscular Dystrophy) in Hamsters

In 1962, Homburger reported the coexistence of cardiomyopathy and skeletal myopathy in Syrian golden hamsters of the BIO 1.50 line. Numerous reports have followed on this hereditary polymyopathy in other lines such as BIO 14.6, 40.54, 82.62, 53.58, CHF146, CHF 147, and UM-X7.1¹⁻¹² The cardiac disease is more severe than the skeletal muscle involvement in dystrophic hamsters. The condition is inherited as an autosomal recessive trait and affects both sexes. Some of the affected lines of hamsters, such as 40.54, survive for approximately one-third of the usual 600-day life span of nondystrophic hamsters. However, considerable variability exists in the rate of progression of the disease in various affected lines. Clinical signs of the disease include subcutaneous edema, muscle weakness, exercise intolerance, poor growth, ascites, hyperpnea, cyanosis, and death.

Numerous studies have characterized the myocardial pathology in affected hamsters.^{2-4,9,13,14} In general, these studies have divided the disease into four phases: 1) preneurotic, 2) neurotic, 3) hypertrophic, and 4) terminal. Most hamsters survive until they die in the terminal phase with congestive heart failure, cardiac dilatation, atrial thrombi, and multifocal pale areas of myocardial fibrosis. The initial histopathologic alterations were prominent by 30–50 days of age as focal myolysis and focal necrosis with myocyte calcification, macrophagic invasion, and postnecrotic fibrosis. By 100 days of age, myocardial hypertrophy had developed.

Ultrastructural study of the hearts of fetal hamsters from affected lines and young hamsters in the preneurotic phase of the disease revealed increased numbers of cardiomyoblasts in fetal hearts, prolonged postnatal myocyte mitotic activity, increase in number and size of myocyte mitochondria, abnormal myofibril formation, focal myofibrillar lysis, increased numbers of polysomes, and edema of myocytes and the interstitium.^{9,12,13,15}

The biochemical pathogenesis and the pathophysiologic alterations in the myocardium of the cardiomyopathic hamster have been studied extensively, and many hypotheses have been proposed to account for the observed changes. Most recently, the myocardial damage has been attributed to: 1) microvascular spasm produced by catecholamine release; 2) an inherited hypersensitivity of cardiac and smooth muscle to catecholamine stimulation; 3) repeated episodes of ischemia, reperfusion, and eventual necrosis of hypersusceptible myocytes; 4) secondary hypertrophy of surviving myocytes; and 5) a final stage of cardiac decompensation with congestive heart failure.^{6,11} Myo-

cardial protection was provided by verapamil administration.^{6,16,17} Other studies have shown protection against the development of this cardiomyopathy by administration of α -adrenergic blockers, β -adrenergic blockers, verapamil, or taurine.^{14,18-20} Potentiation of the cardiomyopathy is seen in affected hamsters fed diets low in potassium or magnesium. Affected hamsters are strikingly susceptible to catecholamine-induced myocardial necrosis. Myocardial calcium accumulation, defective carnitine transport, abnormalities in contractile proteins, altered distribution of myosin isoenzymes, and decreased sarcolemmal Na^+ , K^+ -adenosine-triphosphatase activity and adenosine triphosphate-independent Ca^{2+} binding capacity have been reported in cardiomyopathic hamsters.²⁰⁻²⁵

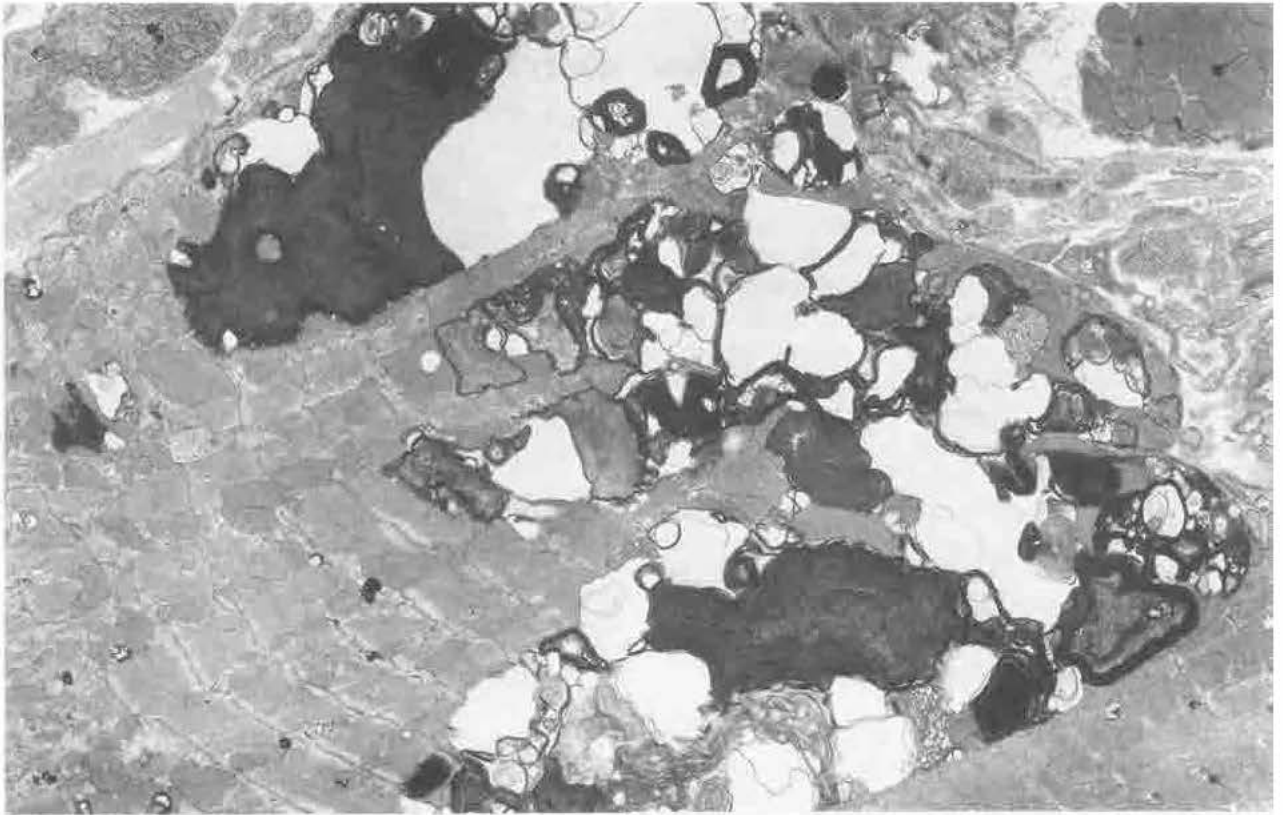
Muscular dystrophy occurs in the hamster, mouse, chicken, dog, turkey, mink, and sheep; however, among these species only in the hamster and mouse has concurrent cardiomyopathy been shown to develop.²⁶

Hereditary Cardiomyopathies of Mice

Mice with hereditary muscular dystrophy may have accompanying myocardial alterations. Dystrophy was originally described as an autosomal recessive trait in mice of the inbred strain 129/ReJ in 1955 at the Bar Harbor laboratory and later was also reported in C57BL/6J mice.²⁶⁻³⁰ Affected mice show poor growth, muscular atrophy, and gradual onset of ataxia and posterior paresis. Most animals die by 1–6 months of age. Some mice have microscopic and ultrastructural alterations in the myocardium.³¹⁻³³ In Strain 129 mice, myocytes have fatty change, SR dilatation, and mitochondrial swelling with accompanying edema and fibrosis.^{31,32} Delayed myofibrillogenesis was observed in the hearts of C57BL/6J-dydy mice.³³

An inherited cardiomyopathy has also been described³³ in KK mice, a strain in which diabetes mellitus and spontaneous soft tissue calcification also occur.³⁴⁻³⁸ However, morphologic study of the myocardial alterations indicated that the cardiac lesions develop prior to the onset of diabetes mellitus.³³ The myocardial lesions were extensive at 8 and 11 weeks of age and were characterized by myofibrillar lysis, focal necrosis, and calcification and postnecrotic fibrosis (Figures 1 and 2).^{33,39} Some affected myocytes had cytoplasmic inclusions with the appearance of nemaline rods. No thickening of capillary basement membranes was observed, suggesting that the myocardial lesions of the KK mouse are not secondary to diabetes mellitus.³⁹ However, Tomita⁴⁰ described focal thickening and dispersion of the glycocalyx of cardiac myocytes in 40-week-old KK mice (Figure 3). The severity of the cardiomyopathy in

1



2

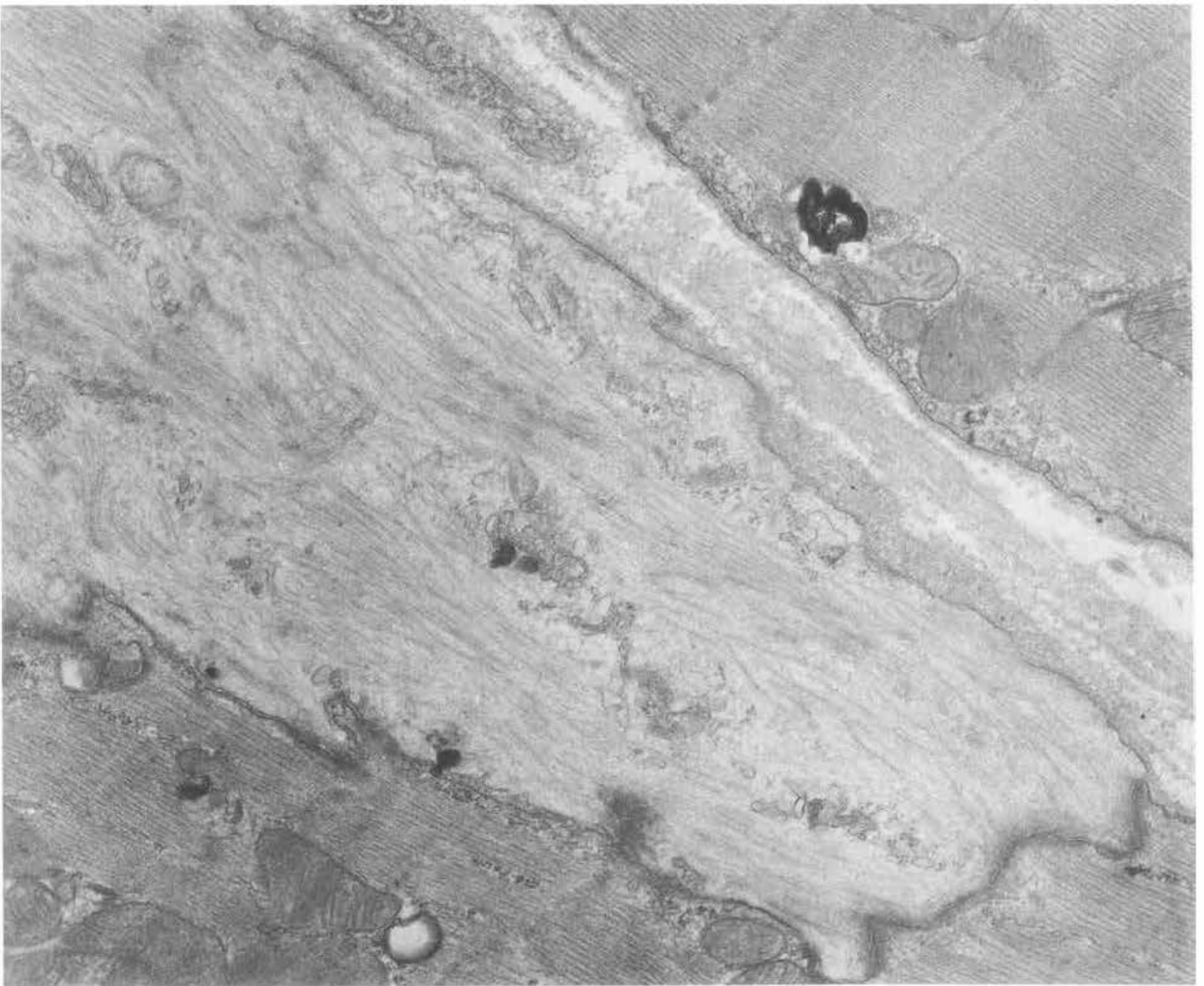




Figure 3—Hereditary cardiomyopathy, KK mouse (40-week-old male). Reduplicated external lamina is present adjacent to a capillary. (Ruthenium red, $\times 28,000$)

KK mice was found to be considerably reduced by treatment with diltiazem, a calcium channel blocker.⁴⁰

Hereditary Cardiomyopathy of Rats

Rubin et al⁴¹ recently described cardiomyopathy with congestive failure in SHR/N-cp rats. Affected rats had subcutaneous and facial edema, dyspnea, cyanosis, and malaise and survived from 5 to 14 days after the onset of clinical signs. Hypertension was present in 100% of the animals, and 25% were obese. Congestive heart failure developed in 75% of males 11 months of age or older and in 25% of females 24 months of age or older. At necropsy, lesions included hydrothorax, ascites, cardiomegaly, thickened ventricular walls, left atrial dilatation, and thrombosis, and hepatomegaly. Microscopic findings were myocardial hypertrophy and interstitial fibrosis. Ultrastructural study revealed altered Z bands.

Hereditary Cardiomyopathy ("Round Heart Disease") of Turkeys

Sporadic death losses from "round heart disease" occur in turkey poults. The literature on this disease was recently reviewed.⁴² The frequency of the cardiac disease in several commercial turkey flocks in Canada varied from 3% to 28%.⁴³ However, an inbred flock of tur-

keys maintained at the University of Minnesota as a source of research animals had a 70% incidence of the cardiac disease at 1 month of age, with 30% mortality in the affected birds by 10 days of age. Thus, it appears that the cardiac disease is heritable, although superimposed stresses have been suggested to play a role in precipitating deaths in some affected flocks.⁴⁴ It is important to differentiate inherited cardiomyopathy of turkeys from toxic cardiomyopathies produced in this species by either furazolidone or sodium chloride, because all three diseases may result in terminal cardiac dilatation ("round heart") and congestive heart failure.⁴⁵⁻⁴⁷ The findings in furazolidone- and sodium chloride-induced cardiotoxicity are described in a later section of this review.

Clinically, turkeys with inherited cardiomyopathy have stunted growth and often have sudden, unexpected deaths. Mortality is highest in the first few weeks of life. Males are more frequently affected than females. Some affected birds will survive into adulthood but will be stunted. At necropsy, ascites and hydropericardium are often present. In poults, the hearts are dilated, especially the right ventricle, and assume a rounded shape ("round heart"). In older birds, left ventricular dilatation and hypertrophy and white, firm thickening of the left ventricular endocardium by fibroelastosis are seen.^{43,44,48-51} Epicardial vessels are congested. In contrast, ventricular dilatation, but without hypertrophy

Figure 1—Hereditary cardiomyopathy, KK mouse (40-week-old male). Degenerate myocytes have numerous myelin figures. ($\times 7,400$)

Figure 2—Hereditary cardiomyopathy, KK mouse (40-week-old male). Degenerated myocyte (center) has extensive myofibrillar lysis. ($\times 22,000$)

Figure 2—Hereditary

and endocardial fibroelastosis, occurs in furazolidone- and sodium chloride-induced cardiomyopathy in turkeys.^{45,46}

Microscopic alterations described in poult have varied from interstitial myocarditis with focal myocardial necrosis⁵¹ to myocardial congestion and hemorrhage and epicardial fibrosis.⁴⁴ Ultrastructural study demonstrated type C viral particles in myocytes from affected hearts,^{51,52} but no further evidence for a viral etiology of the disease has been reported. Other ultrastructural alterations described include accumulation of sarcoplasmic glycogen deposits and myofibrillar lysis.⁵³

Biochemical studies also demonstrated increased myocardial glycogen concentration in affected turkey poults.⁵⁴ However, there is no convincing evidence to suggest that the biochemical pathogenesis of inherited cardiomyopathy in turkeys is related to a known form of glycogen storage disease. Other biochemical studies demonstrated altered composition and function of nuclear nonhistone proteins in the hearts of affected turkeys^{55,56} and altered plasma and tissue carnitine concentrations.⁵⁷ Decreased myocardial activities of lactic dehydrogenase, isocitric dehydrogenase, and creatine phosphokinase were also described.⁵⁸ Studies of regional myocardial blood flow in affected turkeys indicated decreased subendocardial perfusion and led to the suggestion that this alteration may play a role in the development of endocardial fibroelastosis.⁵⁹ Daily administration of propranolol to newly hatched turkey poults from an inbred flock with a high incidence of hereditary cardiomyopathy delayed, but did not prevent, mortality from the disease.⁶⁰ The delayed mortality may have resulted from amelioration of cardiac arrhythmias and abnormal calcium transport demonstrated in young affected turkeys.^{61,62} The inducibility of ventricular tachyarrhythmias in cardiomyopathic turkeys was directly related to the extent of ventricular dilatation.⁶³

Hereditary Cardiomyopathies of Cattle

A single report has characterized a cardiomyopathy in Japanese black calves in western Japan.⁶⁴ Affected animals, usually less than 1 month old, died suddenly after the onset of dyspnea that lasted for several minutes to a few hours. At necropsy, evidence of congestive cardiac failure was present as ascites, hydropericardium, hydrothorax, pulmonary edema, and hepatic congestion. The heart showed cardiomegaly and left ventricular dilatation. Microscopically, multifocal myocardial degeneration and necrosis were present and were most frequent in the left ventricular papillary muscles. Older lesions appeared as areas of myocardial fibrosis without infiltrating inflammatory cells. The disease was inherited as an autosomal recessive trait. In 1975 bulls

suspected of being carriers for the trait were destroyed, and no further cases have been seen.

More recently, another cardiomyopathy which seems to be hereditary has been described in Holstein-Friesian cattle in Japan.⁶⁵⁻⁶⁷ The disease affects animals from 1 to 7 years of age (average, 3.3) and is manifested clinically by edema, venous distension, and hepatic congestion. The hearts of the affected animals are dilated and increased in weight, but the ventricular walls are not thickened. Histologically, hypertrophic and nonspecific degenerative changes are found, together with diffuse interstitial fibrosis involving both ventricles. Ultrastructural studies have shown splitting of myofibrils, mitochondrial swelling, intracellular edema, increase in Z-band material, and increased numbers of mitochondria that are smaller than normal. Cellular reaction (lymphocytic infiltration) was infrequently seen.

A suspected hereditary cardiomyopathy in young adult cattle, mainly Simmental/Red and White Holstein crossbreds, was reported from Switzerland.^{68,69} Affected cattle had subcutaneous edema, hydrothorax, and ascites. It was suggested that an unknown environmental factor may precipitate the clinical onset of the disease. Grossly, cardiac enlargement and dilatation were observed. Myocardial degeneration and fibrosis were present microscopically, accompanied by hepatic congestion, pulmonary edema, sclerosis of pulmonary arteries, and chronic interstitial nephritis.

A cardiomyopathy has been reported from Australia in polled Hereford calves with dense curly coats.⁷⁰ Affected calves die before 6 months of age and have severe myocardial necrosis and fibrosis.

Myocardial Alterations in Glycogenosis

The glycogenoses (glycogen storage diseases) reported in animals were recently analyzed in a comprehensive review.⁷¹ Animal models have been documented for four of the eight types identified in man: Type I, or Von Gierke's disease (glucose-6-phosphatase deficiency), in mice; Type II, or Pompe's disease (acid maltase or α -1,4-glucosidase deficiency), in Shorthorn and Brahman cattle, Corriedale sheep, Lapland dogs, and Japanese quail⁷²⁻⁸⁴; Type III, or Cori's disease (amylo-1, 6-glucosidase deficiency), in German shepherd and Akita dogs⁸⁵⁻⁸⁷; and Type VIII (phosphorylase kinase deficiency) in rats and mice. Significant myocardial involvement occurs only in animal models of Types II and III, in which myocardial glycogen accumulation has been demonstrated by light and electron microscopy and by biochemical analysis. In cattle with Type II glycogenosis, glycogen accumulated free within the sarcoplasm and within lysosomes⁷³; in dogs with Type

III glycogenosis, generalized cytoplasmic glycogen deposition was present⁸⁷; and intralysosomal glycogen deposits were described in Japanese quail with Type II glycogenosis.⁷⁸ In calves affected with Type II glycogenosis progressive muscular weakness developed, and they died at 9–16 months of age. Some animals had cardiomegaly and lesions of congestive cardiac failure at necropsy.⁸² Autosomal recessive inheritance has been described in Type II glycogenosis of cattle⁷⁴; but the mode of inheritance in Type II glycogenosis of sheep, dogs, and quail, and in Type III glycogenosis of dogs has not been established. Morphologic and biochemical study of muscle biopsy specimens from newborn calves homozygous for Type II glycogenosis revealed accumulation of free and membrane-bound glycogen.⁷³ Adult heterozygotes were detected by assay of acid α -glucosidase activity in blood lymphocytes.

Myocardial Calcification in Mice and Other Laboratory Animals

Myocardial calcification is a frequent finding (90–100% incidence) in certain inbred mouse strains and has also been described in guinea pigs and rats.^{1,88–96} Generally these cardiac lesions are clinically insignificant, but mice with severe calcification may die with congestive failure.⁹¹ Inbred mouse strains with a high incidence of cardiac calcification include DBA/2, C, C3H, BALB/c, A, CBA, and CHI. Genetic studies in DBA/2 mice indicate that cardiac mineralization is inherited as an autosomal recessive trait and that three or four alleles are involved.⁸⁹ The frequency and severity of the cardiac lesions may be modified by age, sex, parity, and diet in the affected inbred mouse strains.⁹¹ The lesions are more frequent and severe with advancing age, are generally seen at a younger age and are more severe in females than in males, are more severe in mice following multiple pregnancies than in virginal females, and are increased in frequency and severity in mice fed increasing amounts of dietary fat.

Many terms have been applied to this cardiac lesion, including “dystrophic cardiac calcinosis” (calcification), “dystrophic epicardial mineralization,” “calcareous pericarditis,” and “metastatic calcification.” Affected mice and guinea pigs often have accompanying extracardiac calcification involving the kidney, lung, testis, ovary, skeletal muscle, stomach, intestine, and aorta. The distribution of the cardiac lesions varies between the various affected mouse strains, with epicardial localization in BALB/c, myocardial involvement in C3H and C3Hf, and both epicardial and myocardial lesions in DBA/2. Grossly, multiple small white to yellow flecks of calcification are seen in the epicardium and myocardium with mild lesions; a diffuse plaque of firm, white,

gritty material is seen in the right ventricular epicardium in severe cases. Histologically and ultrastructurally, the initial alteration is focal myocyte necrosis with subsequent calcification (Figures 4 and 5); older lesions may have a mild macrophagic response and accompanying fibrosis.

Myocardial Lipofuscinosis (Xanthosis)

Myocardial lipofuscinosis, or brown atrophy, occurs in association with advanced age or cachexia in animals.^{1,97} Affected myocytes have perinuclear accumulations of residual bodies that appear as yellowish-brown granules by light microscopy of hematoxylin and eosin-stained sections. The pigment granules have orange-yellow autofluorescence. Several recent reports have described lipofuscinosis of cardiac and skeletal muscles of healthy adult Ayrshire and Friesian cattle in England.^{98–100} Presumably, these animals have adequate vitamin E and selenium status. The affected myocardium and skeletal muscles appeared dark brown grossly and contained abundant lipofuscin granules by light and electron microscopy. The affected cattle had observable coat color alterations with yellowing of white areas, deep brown appearance of brown areas (Ayrshires), and brown discoloration of black areas (Holsteins). Frequent occurrence (9%) in Ayrshires suggests an inherited tendency in this breed.

Myocardial Diseases Produced by Nutritional Deficiencies

Most of these diseases are produced in animals only under laboratory conditions by feeding purified diets. The exception is selenium–vitamin E (Se-E) deficiency, which has been of vast economic importance in animal production in many areas of the world. Widespread supplementation of selenium and vitamin E to animals in affected areas has largely controlled the occurrence of this disease in animals and has also proven effective in prevention of Se-E deficiency-related cardiac diseases in man (Keshan disease in China and the cardiomyopathy associated with parenteral hyperalimentation therapy).

Selenium–Vitamin E Deficiency

Necrosis of myocardium and skeletal muscles is a consistent finding in the numerous animal species in which spontaneous or experimental Se-E deficiency have been described. A number of excellent reviews^{26,97,101–112} and many specific reports on the disease in chickens,^{113–118} foals,¹¹⁹ dogs,¹²⁰ nonhuman primates,¹²¹ cats,^{122,123} rats,^{124–126} and mink^{127,128} have

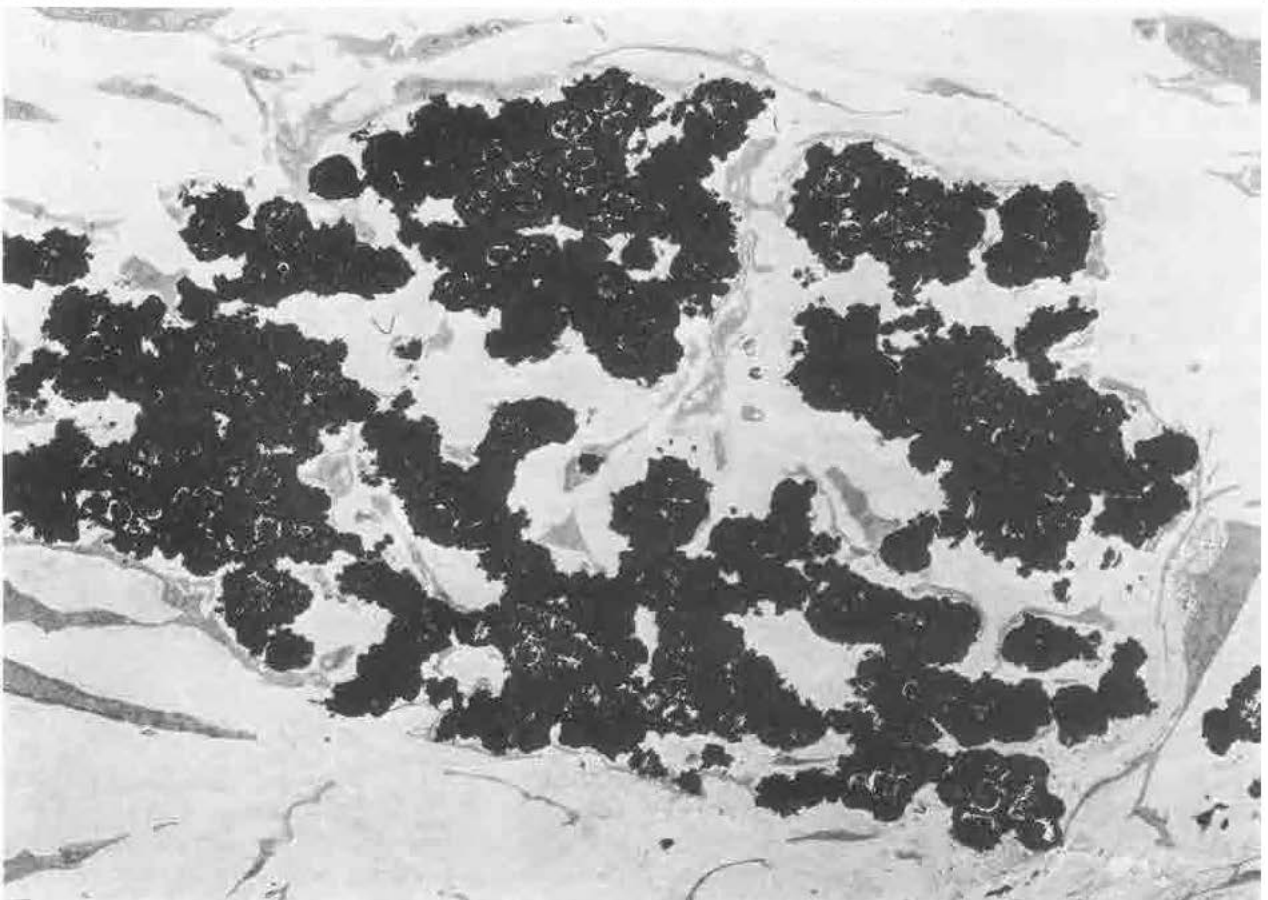
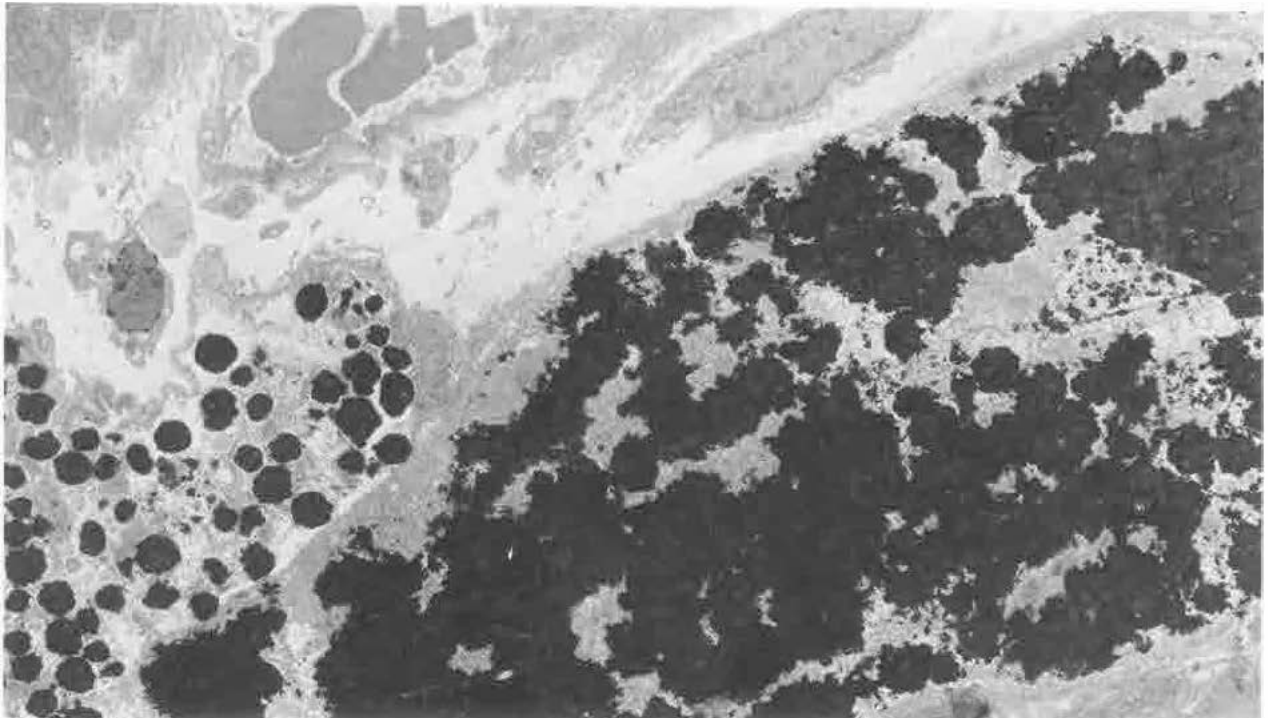


Figure 4—Hereditary calcinosis, DBA mouse. One necrotic myocyte shows mitochondrial mineralization (*left*); another myocyte has more severe confluent sarcoplasmic mineralization (*center and right*). (x6200) **Figure 5**—Hereditary calcinosis, DBA mouse. Mineralized sarcoplasmic debris of a necrotic myocyte is surrounded by cytoplasmic processes of mesenchymal cells (x6200)

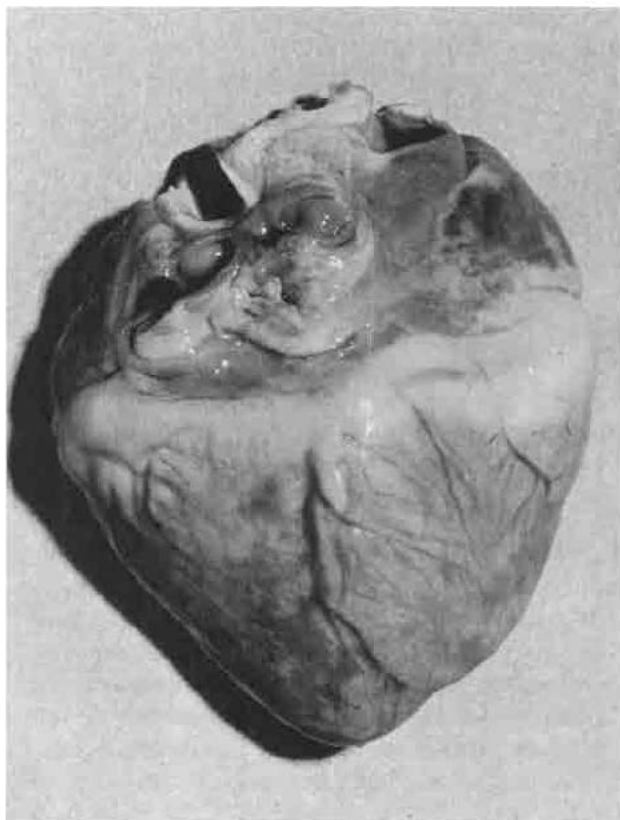
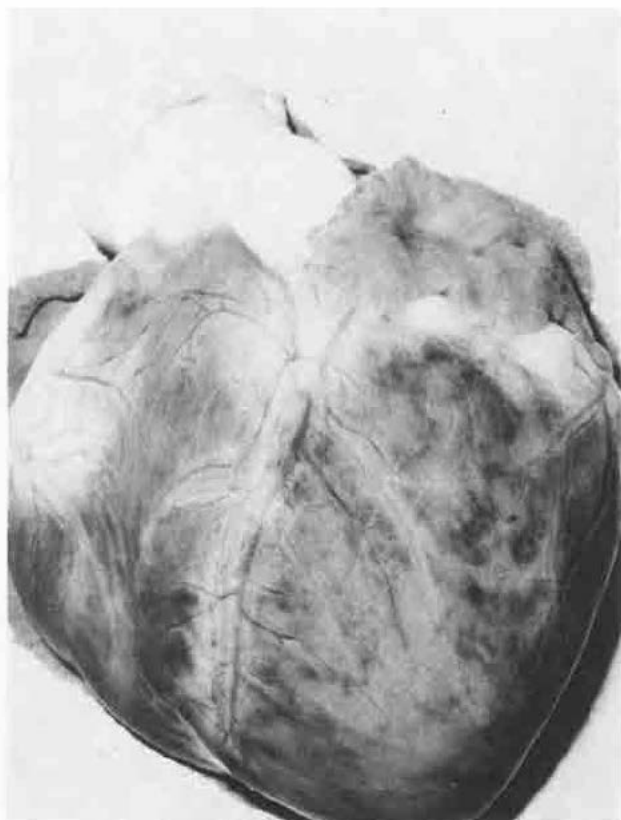


Figure 6—Selenium-vitamin E deficiency. Pig. Disseminated dark areas of epicardial and myocardial hemorrhage produce lesions termed "mulberry heart." **Figure 7**—Selenium-vitamin deficiency. Pig. Disseminated pale areas of myocardial necrosis are present in the ventricular myocardium of a pig with nonhemorrhagic cardiac lesions following experimentally induced deficiency.

described the cardiac and skeletal muscle alterations and also the variety of other lesions seen in animals with Se-E deficiency. These lesions include necrosis of gizzard and intestinal musculature in turkey poults and ducklings; hepatic necrosis in pigs, rats, and mice; gastric ulceration in pigs and rats; encephalomalacia in chicks; embryonic death and resorption in rats, mice, pigs, guinea pigs, and hamsters; testicular degeneration in rats, hamsters, guinea pigs, rabbits, dogs, monkeys, and chickens; steatitis in cats, mink, and foals; anemia in monkeys, rats, and pigs; exudative diathesis in chicks; pancreatic necrosis in chicks; incisor depigmentation in rats and hamsters; lipofuscinosis in rats and dogs; nephrosis in rats and mice; alopecia in rats, monkeys, and quail; cataract formation and pulmonary hemorrhage in rats, and localized axonal dystrophy in rats.

Etiologic factors involved in the development of these lesions include 1) low dietary levels of selenium, vitamin E, and sulfur-containing amino acids; 2) high dietary concentrations of polyunsaturated fats; 3) exposure to prooxidant compounds; and 4) intake of selenium antagonists such as silver salts and various other metals.¹²⁹⁻¹³³ Some of the above deficiency diseases (eg,

encephalomalacia in chicks; embryonic death and resorption in rats, mice, pigs, guinea pigs, and hamsters; steatitis in cats, mink, and foals; and lipofuscinosis in rats and dogs) are the result of pure vitamin E deficiency. Liu et al¹³⁴ have observed lesions of cardiomyopathy in various zoo animals, including Nyala antelopes, elephants, deer, baboons, and exotic birds, in which blood selenium levels were normal while plasma α -tocopherol levels were very low. Pure selenium deficiency only rarely produces deficiency disease (eg, alopecia in rats and monkeys and feather loss in quail). The dietary requirement for selenium and vitamin E will be increased if the animal is exposed to prooxidant conditions (eg, toxicity by ozone, oxygen, iron, various drugs such as doxorubicin, and radiation injury) or ingests excessive amounts of certain metals that act as selenium antagonists (eg, silver, mercury, copper, cobalt, cadmium, tellurium, tin, and zinc).¹²⁹

Myocardial lesions in Se-E-deficient animals are seen most frequently in calves, lambs, pigs, turkey poults and ducklings.¹³⁵⁻¹⁴³ In calves and lambs with cardiac lesions the clinical finding is generally sudden, unexpected death following vigorous exercise. At necropsy,

affected calves have extensive pale areas of necrosis and calcification in the left ventricular free wall and ventricular septum, whereas in lambs the pale lesions are present in the subendocardial myocardium of the right ventricle.^{102,108} Histologically, areas of myocardial damage have hyaline necrosis with or without accompanying calcification, subsequent macrophagic invasion, and eventual formation of areas of stromal collapse and fibrosis.

Growing pigs, usually 2 to 4 months old, with the cardiac form of Se-E deficiency are generally found dead with no premonitory signs of disease.¹⁴² At necropsy, abundant serous transudates are generally present in the body cavities, and the lungs have severe congestion and edema. The heart may have scattered pale streaks in the ventricular myocardium, but the most striking alterations are widespread epicardial and myocardial hemorrhages. These have resulted in the term "mulberry heart disease" for this lesion (Figures 6 and 7). The cardiac lesions may or may not be accompanied by multifocal massive hemorrhagic necrosis of the liver, a lesion termed "hepatosis dietetica." Skeletal muscle necrosis is also usually seen histologically but is not apparent grossly in Se-E-deficient pigs. Ulceration of the esophageal portion of the gastric mucosa is also often present in affected pigs. Histologically, the hearts have both vascular and myocyte lesions (Figure 8). Vascular changes include fibrinoid necrosis in intramyocardial arteries and arterioles and numerous fibrin microthrombi in myocardial capillaries. Myocardial hemorrhage and edema accompany the vascular lesions. Multifocal hyaline necrosis and calcification is followed by macrophagic invasion and myocardial fibrosis in some pigs with prolonged survival, but most animals have only the acute vascular and myocyte lesions. The myocardial lesions are present in the walls of all four chambers but tend to be most severe in the atria. Ultrastructural study of these hearts has demonstrated myocyte alterations that have included mitochondrial swelling and mineralization, myofibrillar lysis, and necrosis with contraction bands (Figures 9-12). Endothelial cell damage and necrosis with fibrin accumulation in the walls and lumina were observed in affected vessels (Figures 13 and 14).^{144,145}

In turkey poult and ducklings with Se-E deficiency, polymyopathy is produced.¹⁴⁰ Necrosis and calcification develop in the smooth muscle of the gizzard and intestine, in myocardium, and in skeletal muscles. Ultrastructurally, gizzard smooth muscle showed initial mitochondrial damage and subsequent myofibrillar lysis and mineralization with macrophagic invasion.¹⁴⁶ Birds with heart lesions have serous transudates in body cavities and scattered pale areas of myocardial necrosis and calcification in the ventricles (Figures 15

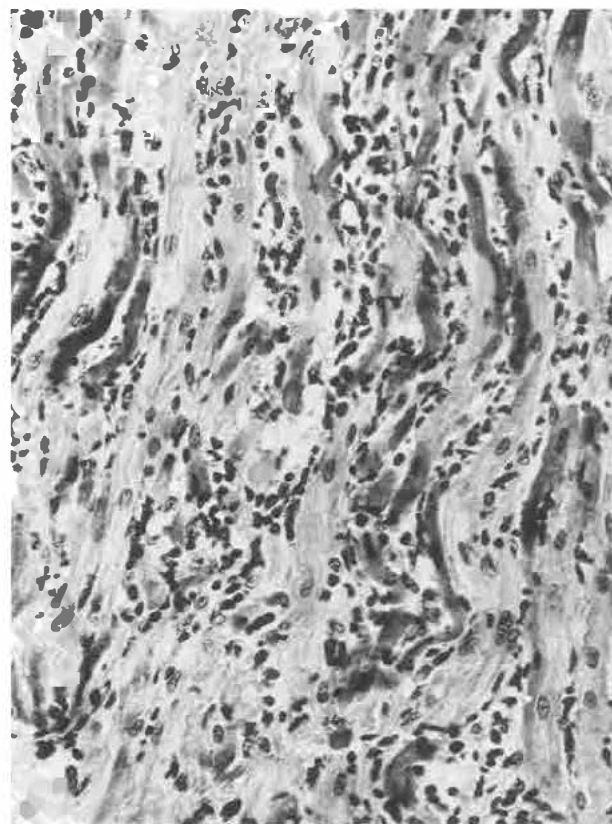
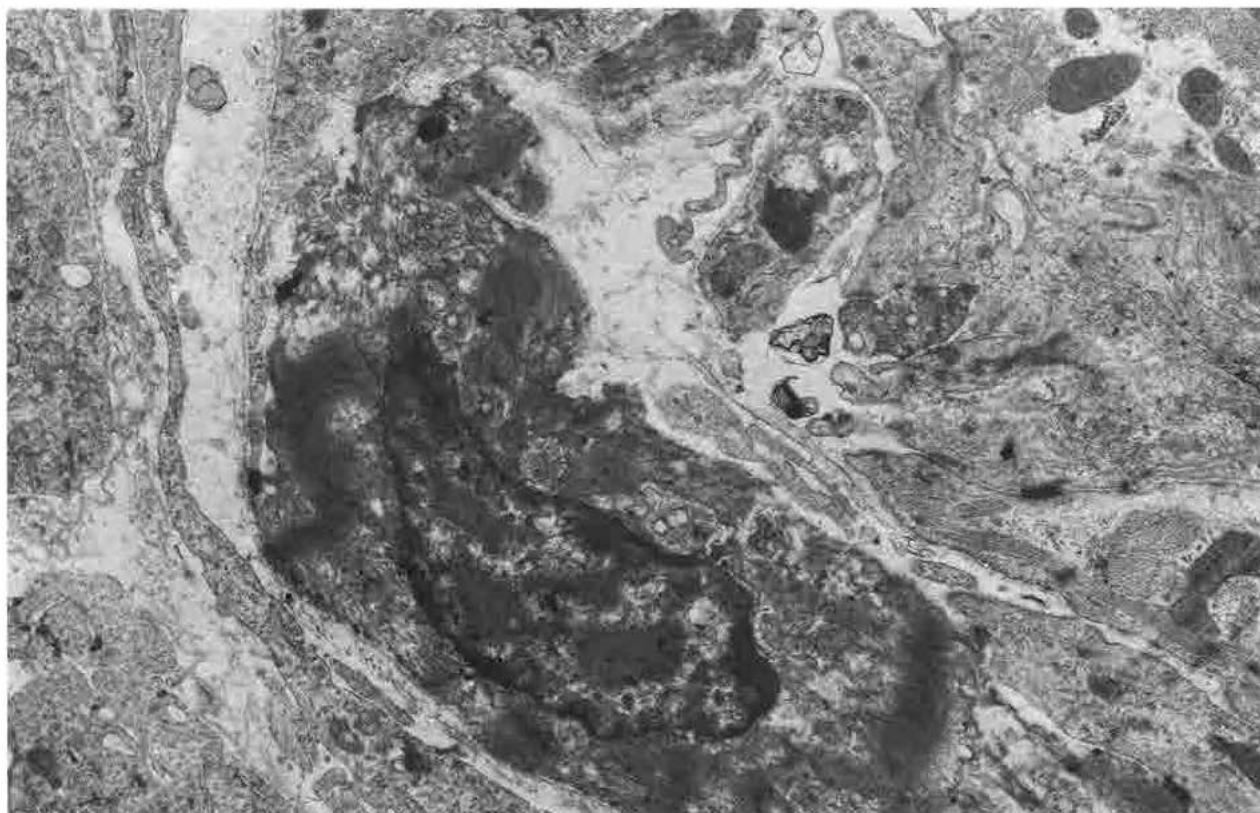


Figure 6—Selenium-vitamin E deficiency. Pig. The atrial myocardium shows numerous dark necrotic myocytes with surrounding macrophagic infiltration. (H&E, $\times 250$)

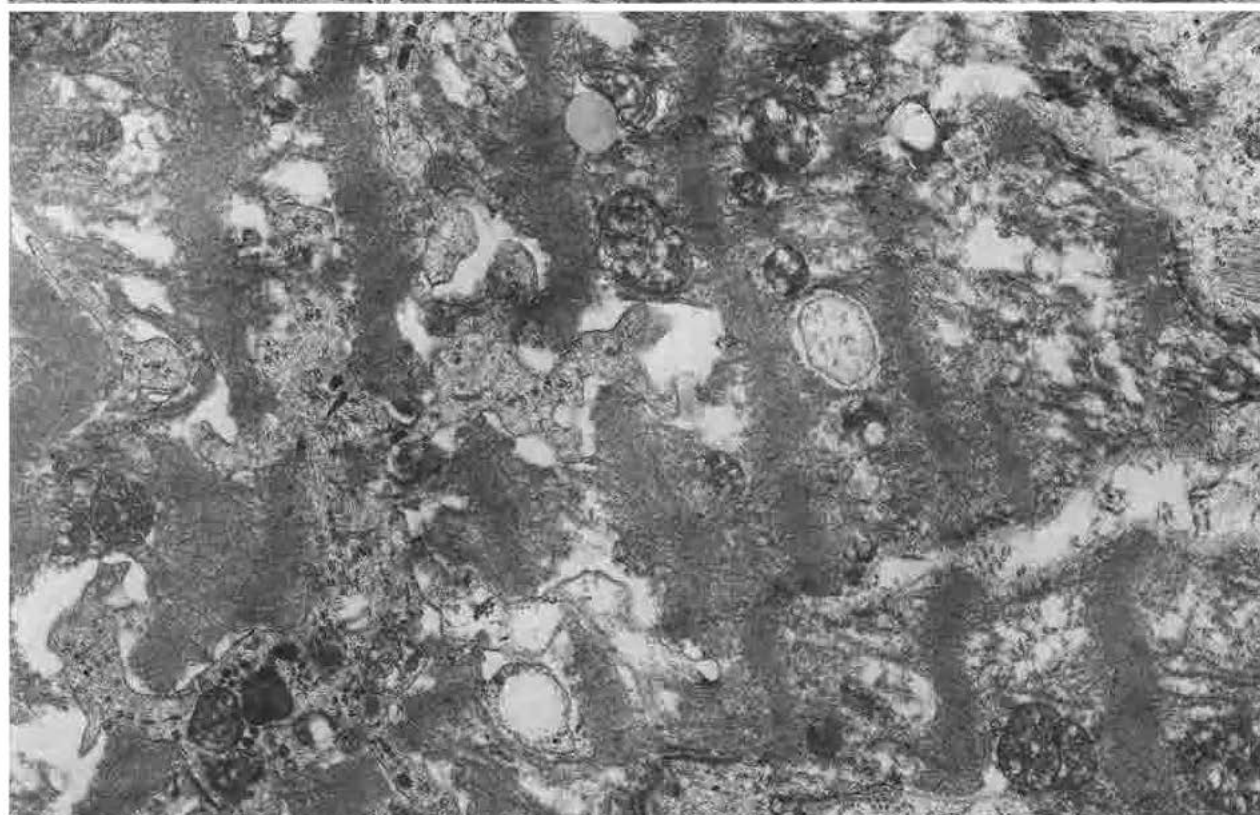
and 16). Histologically and ultrastructurally, the myocardium shows hyaline necrosis and calcification and prominent interstitial edema (Figures 17-19).¹⁴⁷

In many other species, myocardial necrosis is inconsistently observed with Se-E deficiency. In most cases the lesions are detected microscopically but are not apparent grossly. Affected species include dogs, foals, mink, rats, goats, mice, guinea pigs, rabbits, Rottneest quokka, and monkeys. Recently we produced myocardial lesions in mice fed Se-E deficient diets (Van Vleet and Ferrans, unpublished data).

It is necessary to emphasize that Se-E deficiency is an important cause of cardiomyopathy in human patients in China. Recent reports¹⁴⁸⁻¹⁵⁴ have established that selenium deficiency is associated with the development of congestive cardiomyopathy in Chinese patients with the naturally occurring form of the deficiency (Keshan disease) and in American patients maintained on long-term parenteral hyperalimentation. Keshan disease is an endemic cardiomyopathy that occurs in a belt running from the northeast to the southwest of China and results from consumption of products with low selenium concentration from the soil-plant-animal



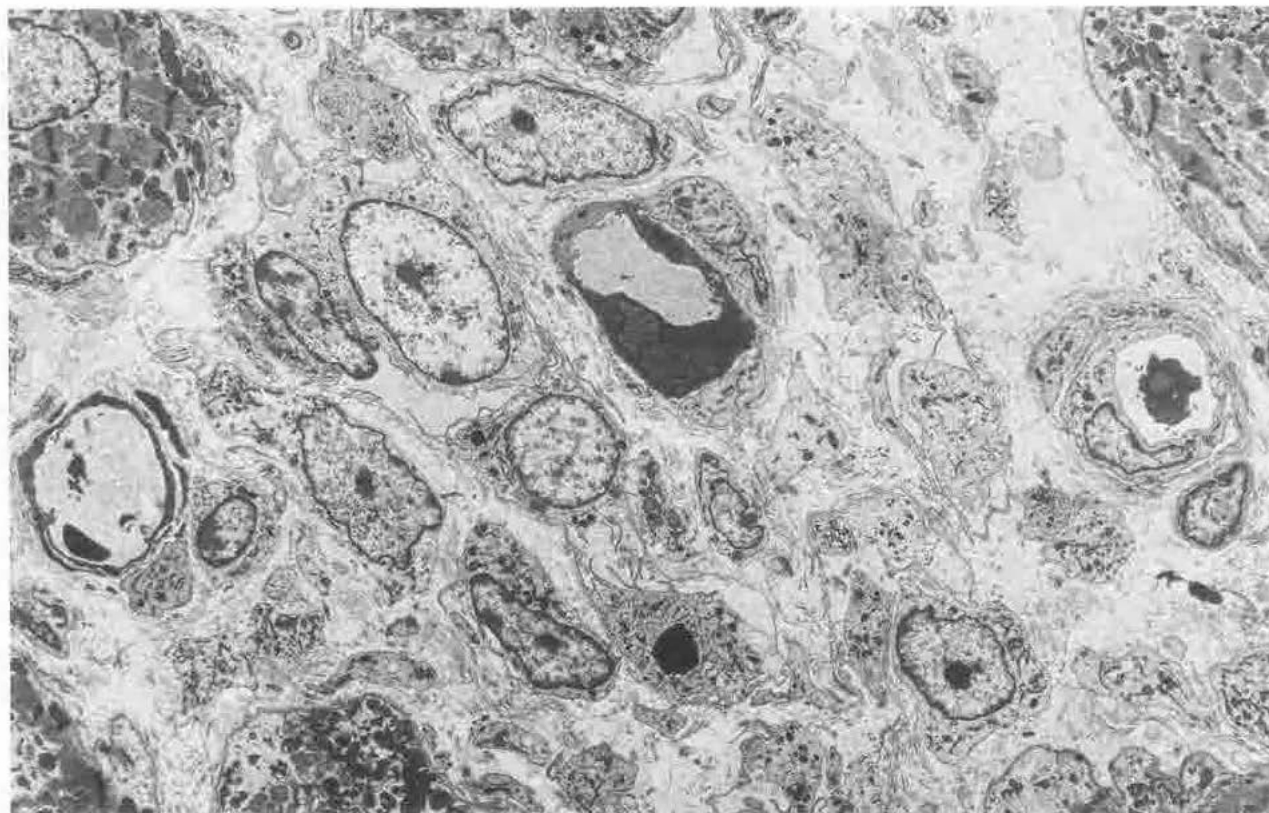
9



10

Figure 9—Selenium-vitamin E deficiency. Pig. Necrotic atrial myocyte has a dense pyknotic nucleus and dense transverse hypercontraction bands. (x12,000) **Figure 10**—Selenium-vitamin E deficiency. Pig. Necrotic myocyte with numerous lysing hypercontraction bands is invaded by a macrophage. (x18,000)

11



12

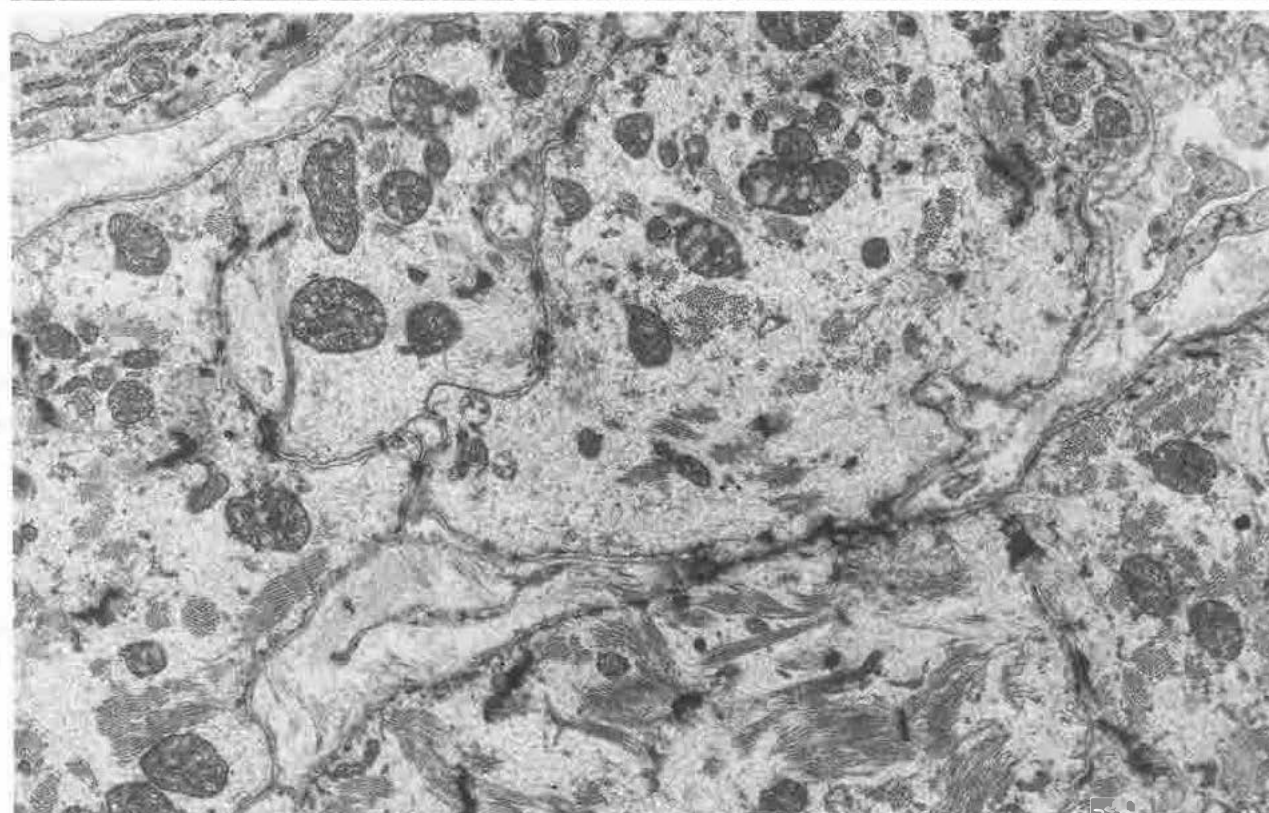
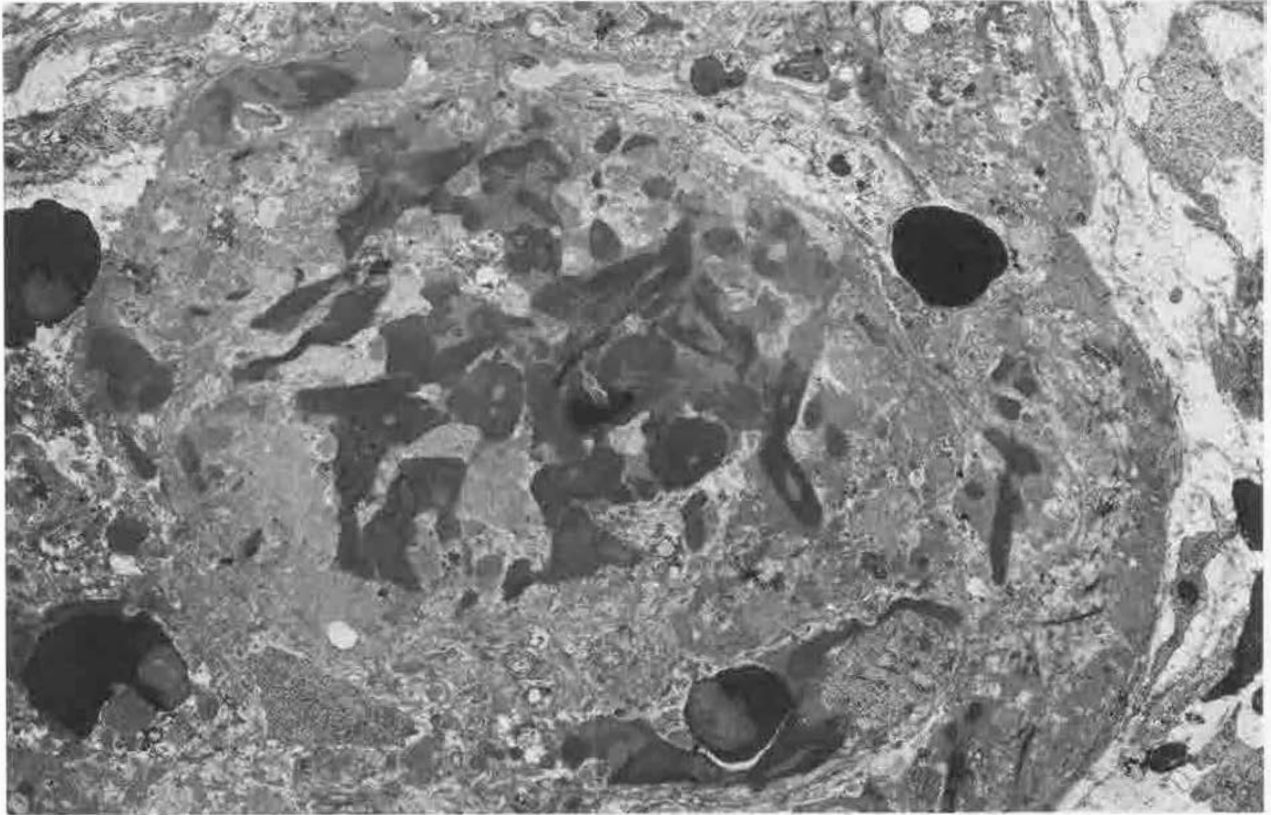
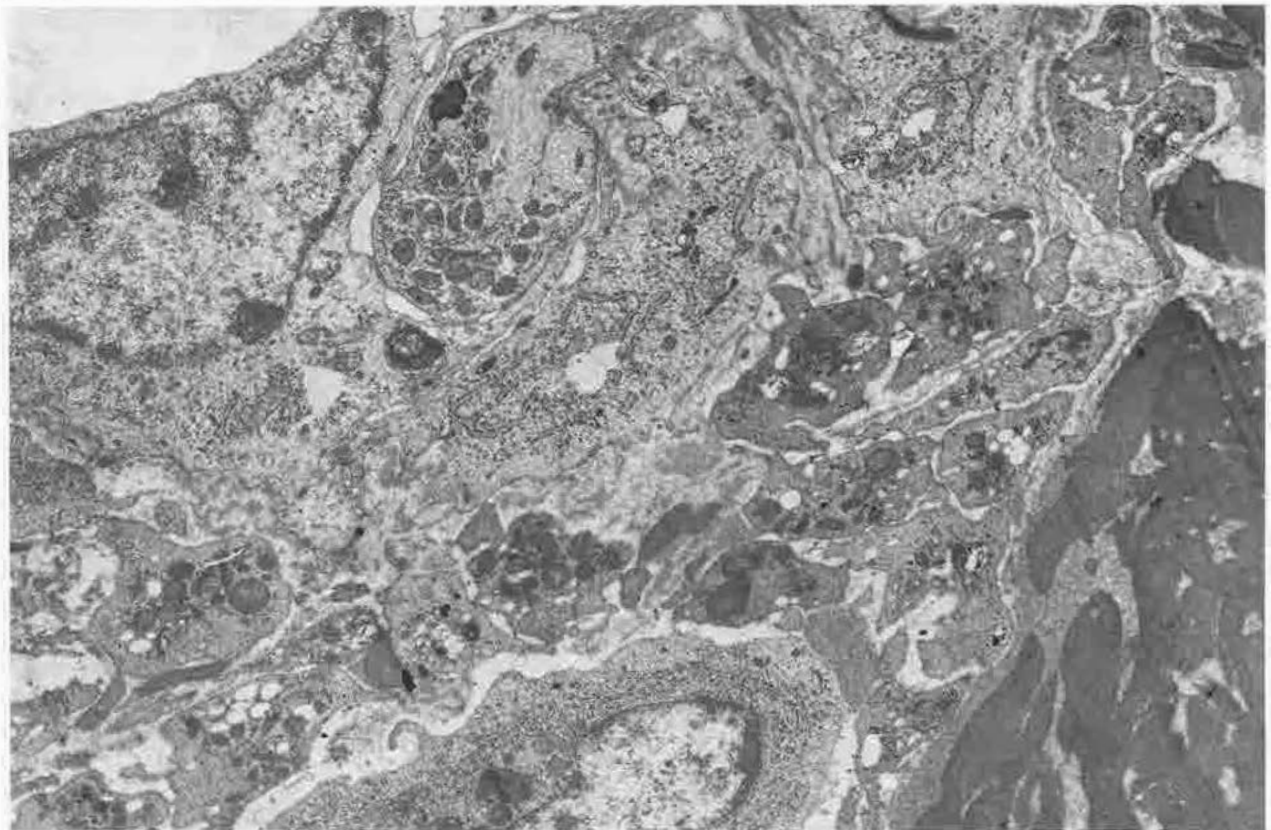


Figure 11—Selenium-vitamin E deficiency. Fig. Low magnification electron micrograph of an area of postnecrotic resolution in the atrial myocardium. Several "tubes" lined by the external lamina of missing myocytes, contain numerous macrophages. The interstitium shows edema and macrophagic invasion. (x4000) **Figure 12—**Selenium-vitamin E deficiency. Fig. Atrial myocytes show myocytolysis with numerous free myofibrils scattered throughout the sarcoplasm. (x13,000)



13



14

Figure 13—Selenium-vitamin E deficiency Pig. Low magnification micrograph of a thrombosed intramyocardial arteriole shows dense masses of fibrin and serum protein deposits in the lumen and throughout the wall. Several erythrocytes lie in the outer wall and adventitia of the affected arteriole. (x5000) **Figure 14**—Selenium-vitamin E deficiency. Pig. Inner wall of an intramyocardial arteriole with fibrinoid necrosis has large loosely-attached endothelial cells (top) with numerous underlying platelets and a dense mass of accumulated fibrin fibrils (right). (x11,000)

15



16



Figure 15—Selenium-vitamin E deficiency. Duckling. Marked hydropericardium in a bird fed tellurium (a selenium antagonist) at 500 ppm for 21 days. **Figure 16**—Selenium-vitamin E deficiency. Duckling. Extensive pale areas of myocardial necrosis in the ventricular myocardium.



mal-man food chain in affected areas. Patients have low blood and hair selenium content. Cases are generally found in peasants, mostly in children and women of childbearing age. Clinically, Keshan disease has been classified into acute, subacute, chronic, and latent types. In fatal cases, the hearts show biventricular dilatation; mural thrombi may be present. Histologically, myocardial necrosis with contraction bands and mitochondrial calcification is seen in early, acute lesions; postnecrotic fibrosis is present in chronic cases. Necrosis of skeletal muscles has been reported in some patients with Keshan disease.¹⁵¹ Administration of selenium supplements, such as sodium selenite tablets or soybean supplements, has provided protection in endemic areas of China.

Congestive cardiomyopathy has also been reported in a few human patients with low selenium status following long-term parenteral hyperalimentation.¹⁵⁵⁻¹⁵⁷ Also, cardiomyopathy may develop in human patients in whom vitamin E deficiency is presumed to be induced by chronic intestinal lipid malabsorption syndromes

Figure 17—Selenium-vitamin E deficiency. Duckling. Extensive areas of postnecrotic fibrosis and a focus of mineralized necrotic fibers (bottom) are present in the left ventricular myocardium. (H&E, $\times 100$)

17



18

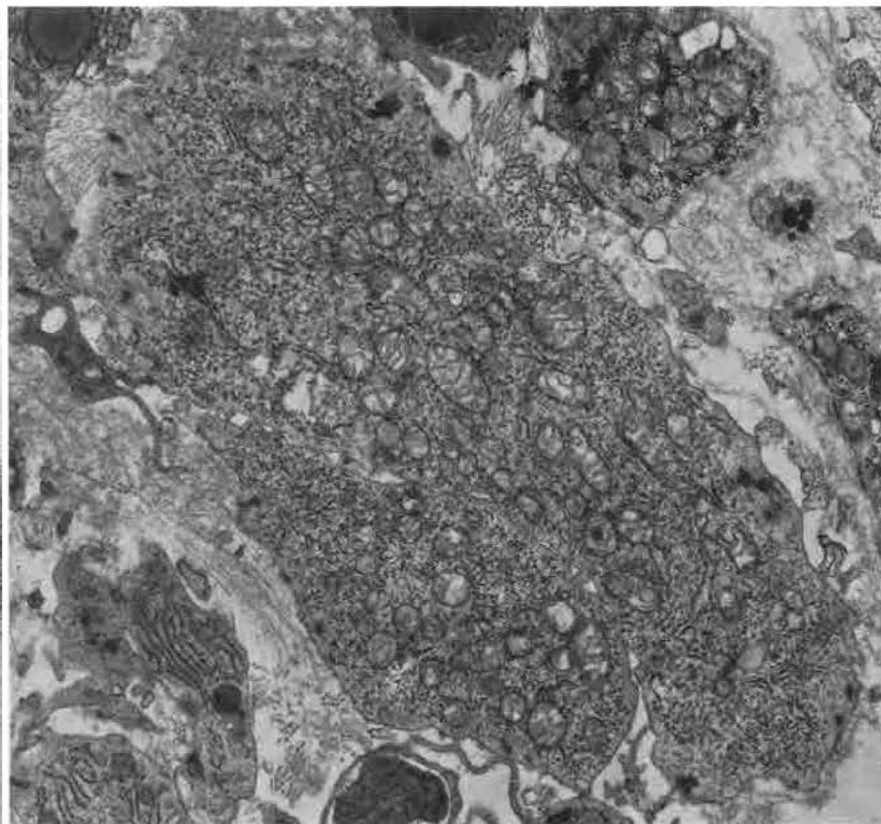


Figure 18—Selenium–vitamin E deficiency. Duckling. High magnification of a necrotic myocyte has multiple calcified mitochondria with dense granular matrix, linear profiles of cristae, and scattered lucid foci in the matrix. ($\times 20,000$) **Figure 19**—Selenium–vitamin E deficiency. Duckling. Area of resolving necrosis in the left ventricular myocardium has a dedifferentiated myocyte with numerous mitochondria and polysomes and a few scattered masses of Z-band material at the periphery. ($\times 12,000$)

such as cystic fibrosis, Byler's disease, and Bassen-Kornzweig syndrome.^{158–161}

Potassium Deficiency

Multifocal myocardial necrosis has been produced in rats, pigs, and dogs by potassium deficiency caused either by feeding potassium deficient diets, by inducing hypokalemia by administering glucocorticoids, or by hemodialysis.^{162–174} In potassium-deficient calves, degenerative alterations were described in Purkinje fibers.¹⁷⁵ In dogs, the cardiac lesions were accompanied by renal and skeletal muscle lesions.¹⁷² Myocardial lesions were present mainly in the left ventricular free wall and ventricular septum. In rats, histologic study showed foci of myocytolysis and scattered mononuclear cells in the interstitium; ultrastructural study showed myofibrillar lysis in damaged myocytes, with restoration of the myocardium, but without accompanying fibrosis, upon repletion with potassium.¹⁶⁹ These findings were interpreted to indicate that damaged myocytes underwent dedifferentiation during potassium

depletion and were restored to their mature form upon repletion.

Copper and/or Iron Deficiency

Naturally occurring copper (Cu) deficiency is seen in adult cattle maintained on copper-deficient pastures. The disease has been described in Australia, Europe, and the southeastern United States.^{176–179} Affected cattle suffer weight loss and anemia and die unexpectedly. Because animals may literally "drop dead," the disease has been termed "falling disease." At necropsy, the hearts are atrophic, pale, and flabby. Extensive myocardial fibrosis is present microscopically.

Experimentally induced Cu deficiency was produced in newborn pigs fed deficient diets for 61–127 days.^{180–182} Anemia developed, and 20 of 33 pigs died with hemo-pericardium from rupture of the myocardium, pulmonary, or coronary arteries. Rupture of papillary muscles, with or without atrial rupture, was seen in 6 pigs. Myocardial hypertrophy was present.

In rabbits with experimental Cu deficiency, myocar-

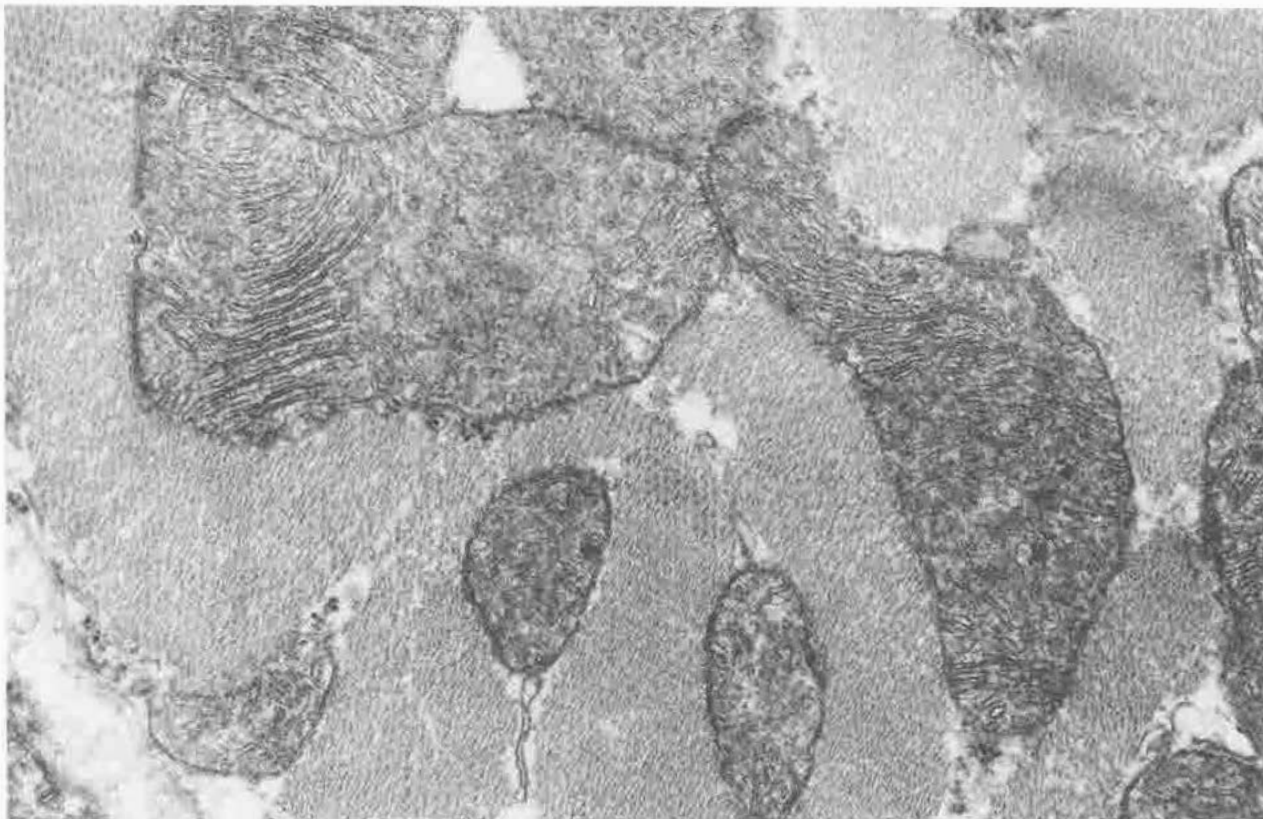


Figure 20—Copper deficiency. Rat. Ventricular myocyte has several enlarged mitochondria. ($\times 22,500$)

dial necrosis and calcification were present together with degenerative changes in elastic fibers of large blood vessels.¹⁸³

Rats fed diets deficient in copper, iron (Fe), or both, developed myocardial hypertrophy.¹⁸⁴⁻¹⁸⁷ In rats with combined Cu and Fe deficiency, severe anemia and congestive heart failure developed after 8-10 weeks. At necropsy, transudation was seen as hydrothorax, hydropericardium, ascites, and subcutaneous edema; and biventricular hypertrophy was present. Microscopically, multiple foci of myocardial degeneration, necrosis with calcification, infiltration with mononuclear leukocytes, and fibrosis were present. These lesions were concentrated in the inner third of the left ventricular wall and were attributed to anoxic injury from severe anemia. Development of myocardial hypertrophy appeared to precede the onset of severe anemia and was characterized ultrastructurally by an increase in the number and in the cell volume fraction of mitochondria (Figure 20).¹⁸⁴⁻¹⁸⁷ An increased ratio of Type III to Type I collagen was demonstrated in the hearts of Cu-deficient rats.¹⁸⁶ Young rats born of Cu-deficient dams had heart failure.¹⁸⁸ The hearts were hypertrophied and pale. Ventricular aneurysms and hemopericardium were occasionally seen. Microscopi-

cally, diffuse myocardial lipidosis and hypertrophy with focal necrosis was present. Extensive myocardial necrosis and hemorrhage occurred in the walls of the ventricular aneurysms.

Neonatal pigs with chronic Fe deficiency-induced anemia developed cardiac dilatation and hypertrophy.¹⁸⁹ Weanling mice with Cu deficiency developed anemia, atrial thrombosis and rupture, hemopericardium, hemothorax, and pleural effusion.¹⁹⁰

Thiamine Deficiency

Cardiac lesions may accompany the neural lesions in animals with severe thiamine deficiency and have been reported in the rat, mouse, pigeon, pig, fox, sea lion, dog, and monkey.^{191,192} Clinical signs of deficiency in the rat included weight loss, anorexia, and death.¹⁹³ The gross lesions in the hearts of thiamine deficient pigs were dilatation and scattered pale streaks of necrosis in the myocardium.¹⁹⁴ Histologically, multifocal myocardial necrosis was present in the atria and ventricles. Pigeons with chronic thiamine deficiency developed congestive heart failure and myocardial necrosis.¹⁹⁵ Affected dogs and foxes had multifocal myocardial necrosis and fibrosis.^{196,197} Several ultrastructural studies of the hearts of

thiamine deficient rats have shown early mitochondrial alterations of swelling or condensation and later formation of vesicles and myelin figures from damaged mitochondria. Scattered, severely damaged myocytes had contraction band necrosis in rats fed the deficient diet for 28 days.^{193,198,199} Rats with moderate thiamine deficiency were resistant to the cardiotoxic effect of isoproterenol.¹⁹¹

Magnesium Deficiency

Experimentally induced magnesium deficiency has been produced in rats, dogs, calves, and hamsters.²⁰⁰⁻²⁰⁷ The clinical signs of deficiency in rats and dogs were slow growth, alopecia, cutaneous edema and erythema, hyperirritability, convulsions, and death.^{201,206} At necropsy, myocardial lesions were usually present as scattered foci of necrosis with calcification; the lesions occasionally involved the full thickness of the ventricular wall. Selective involvement of the inner myocardium was seen. The extent of myocardial damage was increased in rats subjected to concurrent cold stress but was decreased in hamsters with concurrent thiamine deficiency.²⁰³⁻²⁰⁵

Microscopic and ultrastructural study of the myocardial lesions revealed initial alterations in mitochondria with swelling and vacuolation.²⁰⁰⁻²⁰² Affected necrotic myocytes had extensive mineralization of mitochondria. Areas of necrosis were infiltrated by mononuclear leukocytes, and healing of the lesions resulted in residual areas of fibrosis.

Protein Deficiency and Protein-Calorie Malnutrition (Kwashiorkor, Marasmus)

Monkeys fed a protein-deficient diet for 12 weeks lost approximately 20% of their body weight.²⁰⁸ At necropsy, the hearts were atrophic, pale, and flabby. Microscopically, myocytes were atrophic; and multiple foci of myocardial degeneration, necrosis, and fibrosis were present. Fibrosis was most extensive in the atria.

Experimental protein-calorie malnutrition for 7 weeks in dogs resulted in approximately 40% weight loss, lethargy, and the death of 4 of 19 animals from superimposed sepsis.^{209,210} The dogs that died had bronchopneumonia, hemorrhagic enterocolitis, hepatic lipodosis, ascites, edema of skeletal muscles, and depletion of fat depots. All of the starved dogs had cardiac atrophy with decreased heart weight and decreased myocardial glycogen content. Histologic and ultrastructural study of the hearts revealed atrophy of myocytes and prominent interstitial edema. Physiologic studies showed decreased left ventricular function, which was attributed to decreased cardiac compliance from myo-

cardial edema and to decreased myocardial contractility from atrophy.

Tryptophan Deficiency

In rats fed maize and bean diets containing nutritionally inadequate amounts of tryptophan for 15-30 months congestive heart failure developed with cardiomegaly.^{211,212} At necropsy, the hearts had dilatation and hypertrophy and thick, opaque, left ventricular endocardium. Microscopically, endocardial and myocardial fibrosis was present. Feeding low tryptophan and low protein diets containing large amounts of plantain produced endocardial fibrosis, but not myocardial lesions, in rats and guinea pigs; however, these diets did not produce cardiac lesions in monkeys.^{211,213,214} It was suggested that the high content of 5-hydroxytryptamine in plantains offers protection from the myocardial damage associated with feeding tryptophan-deficient diets. Adding supplements of tryptophan to the ration of rats after they had been fed the deficient diet for 1 year did not cause regression of the cardiac lesions.

Choline Deficiency

In rats fed choline-deficient diets, with or without added ethyl laurate, myocardial lipidosis initially developed, followed by multifocal myocardial necrosis.²¹⁵⁻²²⁰ Affected rats died suddenly and had hydropericardium and fatty livers at necropsy. The cardiac lesions were accentuated by feeding large amounts of fats and were more severe in males than in females. Administration of choline supplements protected against the cardiac lesions.

Myocardial Diseases of Unknown Etiology

This group of diseases is heterogeneous in clinical course and morphologic alterations. The idiopathic or primary cardiomyopathies in animals offer progressive diseases with many clinical and pathologic similarities to the human diseases. However, the value of these animal models of cardiomyopathy is limited by our present inability to reproduce the diseases for laboratory studies. Other diseases in this group include age-related lesions that are seen in various animal species and a syndrome of sudden cardiac failure observed in birds.

Hypertrophic Cardiomyopathy in Cats, Dogs, and Pigs

Although this disease is known to occur in several species of animals, hypertrophic cardiomyopathy has been studied most extensively in humans, in which it occurs mostly as a genetically transmitted disorder

21



22

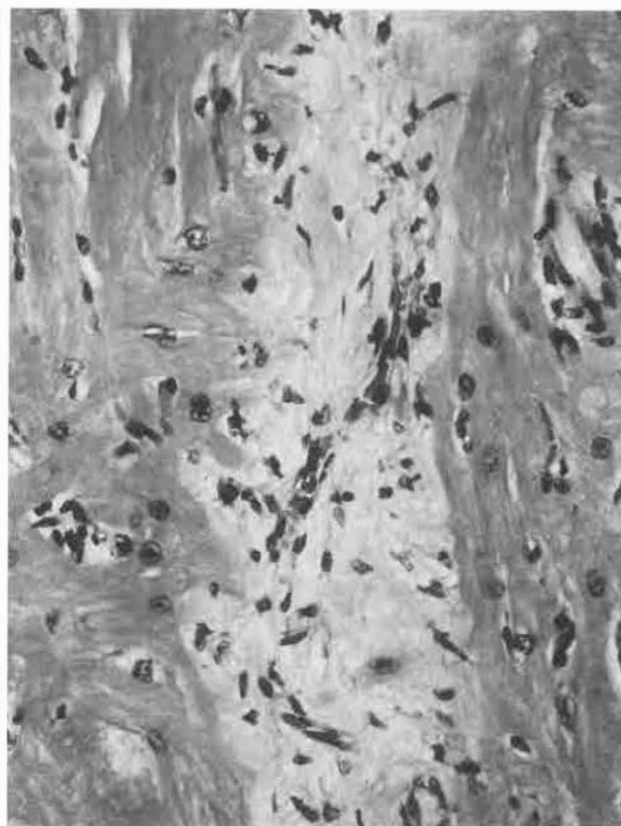


Figure 21—Hypertrophic cardiomyopathy, Cat. Cross-section of ventricles reveals prominent myocardial hypertrophy in the left and right free walls and septum. **Figure 22**—Hypertrophic cardiomyopathy, Cat. Section of left ventricle has interweaving hypertrophied myocytes with extensive perivascular fibrosis. (H&E, $\times 300$)

characterized by 1) severe hypertrophy that affects all chambers, but particularly the left ventricle; 2) asymmetric hypertrophy of the ventricular septum, the maximal thickness of which exceeds that of the left ventricular free wall (measured in the posterolateral region, at the level of the free margin of the posterior mitral leaflet) by a ratio of 1.3 (normal, 1.0); 3) a small, abnormally shaped left ventricular cavity; 4) relatively frequent occurrence (about 25%) of obstruction to left ventricular outflow (caused by narrowing of the left ventricular outflow tract by hypertrophic septal muscle and by abnormal anterior systolic motion of the anterior mitral leaflet); 5) widespread disarray of ventricular myocytes (which in the majority of patients involves $>5\%$ of the myocytes in the ventricular septum and in the left ventricular free wall); and 6) a high incidence of fibromuscular intimal and medial thickening and adventitial fibrosis involving small, intramural coronary arteries.²²¹ The presence of fibrous plaque-like lesions in the septal endocardium of the left ventricular outflow tract is regarded as evidence of contact between the anterior mitral leaflet and the ventricular septum (thus

indicating the occurrence of obstruction). A small minority of cases of hypertrophic cardiomyopathy in humans have diffuse, symmetric hypertrophy, rather than the asymmetric hypertrophy described above. However, it is believed that these are two variants of the same disease, rather than two different, unrelated entities, because they coexist in some families.²²² Other uncommon anatomic variants of hypertrophic cardiomyopathy, including the midventricular obstruction^{223,224} and the apical hypertrophy syndromes,^{225,226} form part of the anatomic spectrum of this disorder in humans.²²⁷⁻²²⁹

Hypertrophic cardiomyopathy occurs frequently in cats and occasionally in dogs,²³⁰ but only a single report²³¹ has described the disease in pigs. Numerous reports of series of cases in cats and dogs at the Animal Medical Center in New York over the past 13 years have characterized the clinical and pathologic aspects of the disease.^{230,232-242} Early reports called all cases of primary myocardial disease in cats and dogs idiopathic cardiomyopathy; however, in publications since 1977, Liu has classified these cardiac diseases into hyper-

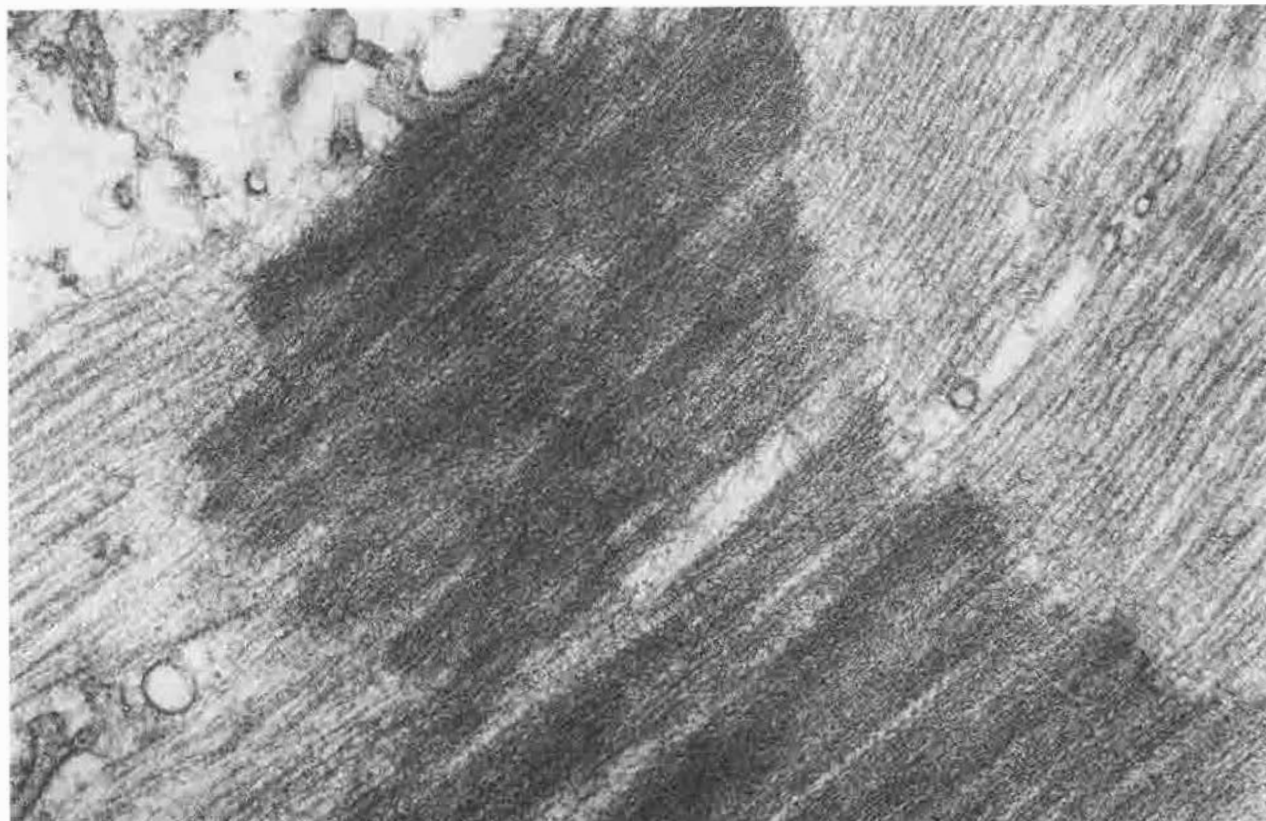


Figure 23—Hypertrophic cardiomyopathy. Cat. Thick block of Z-band material in right ventricular myocyte. ($\times 60,000$)

trophic, congestive, and restrictive cardiomyopathies in the cat and hypertrophic and congestive cardiomyopathies in the dog.

Hypertrophic cardiomyopathy in cats tends to affect middle-aged males most frequently. The disease is three times more frequent in males than females. However, the age range of affected cats may be wide, as seen in a large series ($n = 128$) of affected cats that ranged from 8 months to 16 years of age.²³² The etiology is unknown, but the occurrence of cases in related cats suggests an hereditary role.²³⁰ Clinically, affected cats generally present with sudden onset of congestive heart failure with dyspnea, anorexia, and lethargy. Approximately half of affected cats will have aortic thromboembolism and posterior paresis. Some cats may have sudden, unexpected death without previous clinical signs. At necropsy, extracardiac findings include aortic thromboembolism, renal infarction, and pulmonary congestion and edema. Affected hearts are enlarged and have diffuse hypertrophy of the left ventricular free wall, ventricular septum, and left ventricular papillary muscles, marked dilatation and hypertrophy of the left atrium, and a narrow left ventricular cavity (Figure 21). In a few cats, asymmetric septal hypertrophy is observed,

as manifested by a septal/free wall thickness ratio of 1.1 or greater (rather than by the 1.3 or greater ratio used to classify the human cases). Histologically, diffuse hypertrophy, myocyte disarray (disarray occurs mostly in association with asymmetric septal hypertrophy), interstitial fibrosis, and fibromuscular hyperplasia of small intramural coronary arteries are seen (Figure 22). Of 129 cat hearts with hypertrophic cardiomyopathy, 44% had foci of myocyte disarray in the ventricular septum; in 31% the disarray involved at least 5% of the myocytes in the section.²³² Ultrastructural study confirmed the presence of myocyte hypertrophy, disarray, interstitial fibrosis, lipofuscin accumulation, focal myofibrillar lysis, accumulation of masses of Z-band material, and distension of elements of sarcoplasmic reticulum (Figure 23).^{243,244}

Hypertrophic cardiomyopathy in dogs predominates in males. German shepherds are most frequently affected, but cases in dogs of small breeds have also been reported.^{230,232,236,237,239,241} Approximately 50% of the dogs had sudden unexpected death (which occurred in some dogs during routine surgical procedures); the remaining dogs had evidence of congestive cardiac failure with dyspnea and cough. At necropsy, the hearts

were enlarged and showed ventricular hypertrophy, decreased left ventricular cavity size, and left atrial dilatation. Asymmetric septal hypertrophy (septal/free wall thickness ratio, >1.1) was often present. Microscopically, myocyte disarray was seen in the ventricular septum of 20% of the dogs.

In a series of 1906 necropsy cases of pigs at the Pig Research Institute of Taiwan, 32 cases of hypertrophic cardiomyopathy were reported.²³¹ Twenty-three of these had the symmetric form, and 9 the asymmetric form (which was defined by a septal/free wall thickness ratio of 1.1, rather than by the 1.3 ratio used in classifying the human disorder). Relative heart weights were increased by 50%. The ventricular walls were severely thickened, and the left ventricular cavity was small in size and abnormal in shape. Microscopic study revealed consistent myocyte hypertrophy; however, only some cases had disarray of myocytes. Thus, it seems that hypertrophic cardiomyopathy in pigs (and also in dogs and cats) is more frequently of the symmetric type and is less frequently associated with myocyte disarray than is the case in humans. A pattern of inheritance for hypertrophic cardiomyopathy has not been established in animals and is only incompletely understood in humans.²⁴⁵

The pathogenesis of hypertrophic cardiomyopathy in humans and animals is unclear. The nature of the basic defect in this disease is unknown. It has been suggested that the disease may result from a disturbance of the delicate interaction between immature, myocardial adrenergic receptor sites and extracardiac catecholamines, leading to myocyte hypertrophy and disarray.²⁴⁶ Ferrans and Rodriguez²⁴⁷ have postulated an abnormal sensitivity to hypertrophic stimuli. In dogs infused with subhypertensive doses of norepinephrine for 12–63 weeks left ventricular hypertrophy develops, and these dogs may offer a model for hypertrophic cardiomyopathy.^{248,249}

Dilated (Congestive) Cardiomyopathy in Cats, Dogs, and Pigs

Congestive (or ventricular-dilated) cardiomyopathy is a group of conditions in which systolic pump failure and ventricular cavity dilatation are common denominators. In many cases the cause of the disorder cannot be established, and it is termed "idiopathic." In others, congestive cardiomyopathy occurs in association with pregnancy or the postpartum period, toxic agents, and nutritional deficiency states.^{221,247}

The heart is flabby and dilated and may show some degree of endocardial fibroelastotic thickening. Mural thrombi are common. Inflammatory reaction is absent

or very scanty; variable degrees of fibrosis and small foci of myocytolysis may be present.^{221,247}

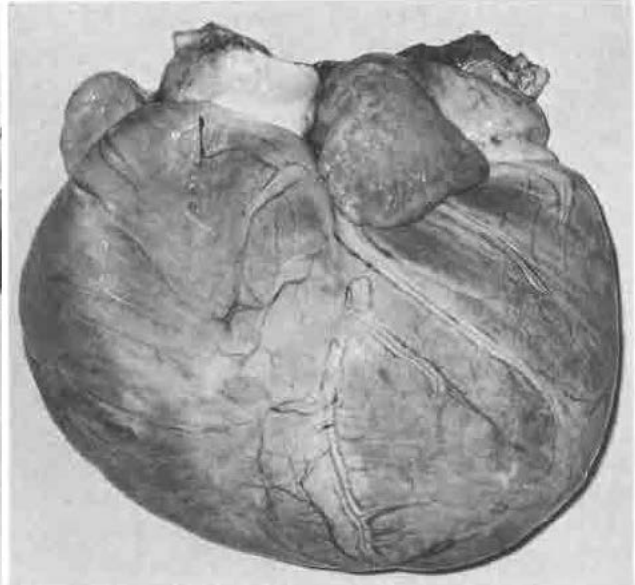
Idiopathic congestive cardiomyopathy occurs frequently in cats and somewhat less frequently in dogs²³⁰; a single report²³¹ has described the disease in pigs. In cats, the disease predominates in males (approximately 3 male/1 female), affects middle-aged cats (range, 3–16 years of age), and has no specific breed predilection.^{230,239,242,244,250–252} Hydrothorax was present in 74% of 133 cats. Presenting features were dyspnea (60%), anorexia (30%), and posterior paresis from aortic thromboembolism (25%). At necropsy, the hearts showed cardiomegaly, with increase in heart weight and marked dilatation of all chambers (Figure 24). The papillary muscles and ventricular trabeculas were atrophic. Mild interstitial edema and fibrosis and occasional foci of myocytolysis were seen in the ventricular myocardium by light- and electron-microscopic study.^{232,239,244} Extensive microscopic and ultrastructural alterations were described in severely dilated atria, including myocyte degeneration and hypertrophy and interstitial fibrosis.²⁴² Atrial tachyarrhythmias were associated with the left atrial lesions.

Numerous reports of congestive cardiomyopathy in dogs have been published since 1970.^{230,232,239,240,253–262} The disease predominates in males (approximately 3 males/1 female) of middle age (range, 2–9 years of age). Generally, dogs of large breeds are affected, especially Doberman pinschers.^{253,257} However, English cocker spaniels in western Australia also are affected.^{256,261} In New England, cardiomyopathy occurs frequently in Boxers.²⁶³ Frequent involvement of specific breeds suggests an inherited basis for the disease in the dog. Detweiler et al²⁶⁴ have suggested that some cases of canine cardiomyopathy are the result of an autoimmune reaction that follows canine parvoviral myocarditis. Clinical signs include ascites, weight loss, weakness, dyspnea, and cough. Atrial fibrillation was detected in 90% of 57 affected dogs.²³² At necropsy, ascites and hydrothorax were present. The hearts had markedly dilated ventricles with opaque endocardium and dilated atria with a rough granular epicardial surface (Figure 25). Pulmonary and hepatic congestion were present. Microscopically, multifocal myocardial fibrosis and medial hyperplasia of intramyocardial arteries were observed. Ultrastructurally, nonspecific alterations in myocytes were present as myocytolysis, lipofuscin accumulation, myelin figures, proliferation of sarcoplasmic reticulum, and altered mitochondria (Figures 26 and 27).^{254,260,262}

In pigs, 17 cases of congestive cardiomyopathy were reported from Taiwan.²³¹ However, all 17 pigs had accompanying aortic stenosis, pericarditis, or vegetative

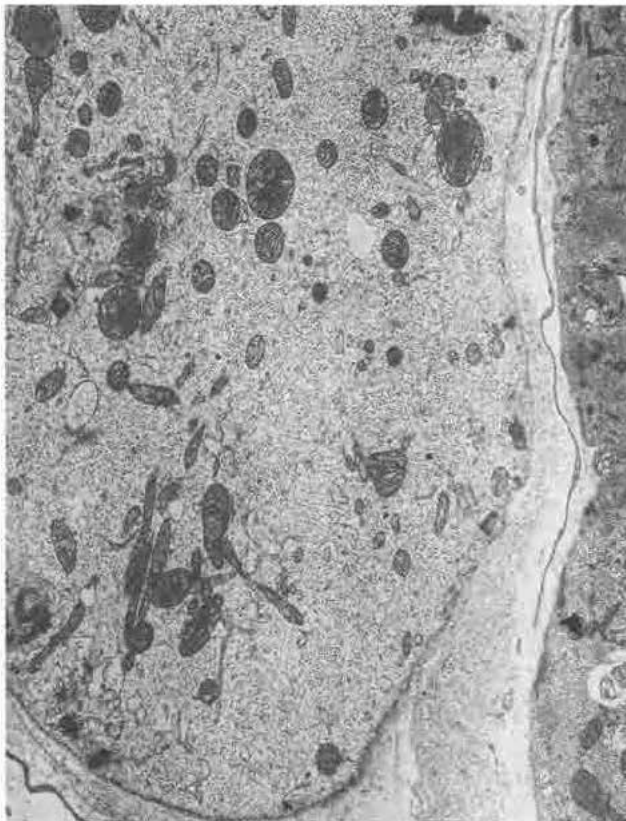


24

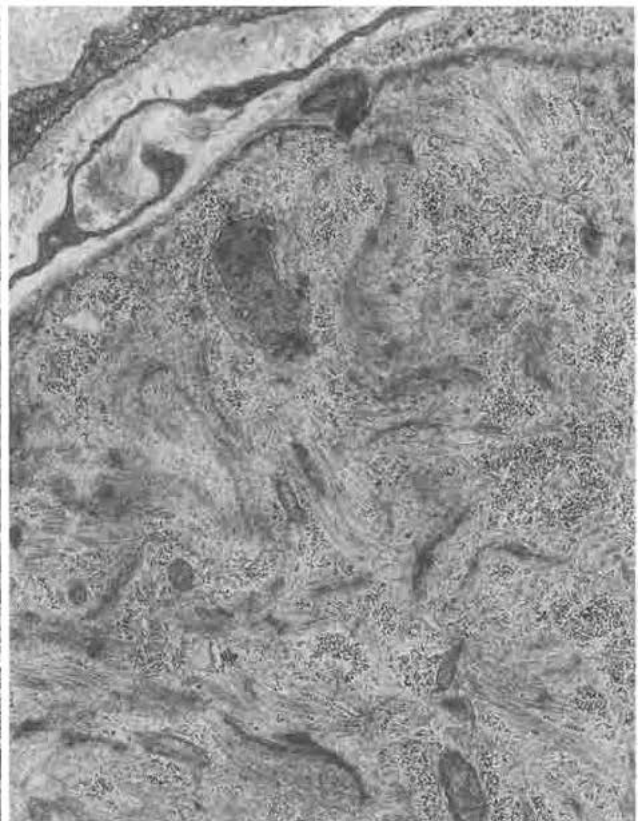


25

Figure 24—Congestive cardiomyopathy. Cat. The left ventricle is dilated and the wall is thin. **Figure 25**—Congestive cardiomyopathy. The heart from a 1-year-old Great Dane with congestive heart failure has cardiomegaly and a rounded shape from biventricular dilatation.



26



27

Figure 26—Congestive cardiomyopathy. Dog. Myocyte of left atrium has extensive myofibrillar lysis. The sarcoplasm contains numerous free filaments, scattered mitochondria, and a few lipofuscin granules. (x9000) **Figure 27**—Congestive cardiomyopathy. Dog. Sarcoplasm of a left atrial myocyte contains lysed myofibrils and numerous glycogen granules. (x18,000)

endocarditis; thus, they may have had end-stage cardiac disease with nonspecific, terminal cardiac dilatation, rather than congestive cardiomyopathy.

In a recent case report,²⁶⁵ acute congestive heart failure was described in a 6-week postpartum Doberman pinscher dog. The animal had been normal at two physical examinations during the pregnancy. The onset of cardiac failure was rapid, and the dog collapsed and died upon admission to a veterinary hospital. At necropsy, the dog had ascites, pulmonary and hepatic congestion, and biventricular dilatation. Microscopically, the myocardium showed multifocal degeneration, necrosis, and fibrosis. The lesions were most extensive in the left ventricle. The authors concluded that the clinicopathologic picture in this dog was compatible with the diagnosis of postpartum cardiomyopathy, which has been the subject of a number of reports in humans and which represents a clinically distinctive type of dilated cardiomyopathy.^{247,266}

Restrictive Cardiomyopathy and Endomyocardial Diseases in Cats and Rats

The term "restrictive cardiomyopathy" designates a group of disorders characterized by impairment of ventricular filling by unyielding endocardial, subendocardial, or myocardial tissue.²⁴⁷ Restrictive cardiomyopathy may be primary or may be due to infiltrative disorders (such as amyloidosis), endocardial fibroelastosis (in which both collagen and elastic fibers are abundant in the thickened endocardium), or endomyocardial fibrosis (in which the endocardial thickening is due to deposition of collagen). In humans, endomyocardial fibrosis often occurs in association with blood and tissue hypereosinophilia²⁶⁷; however, we are not aware of such an association in animals.

In cats, restrictive cardiomyopathy occurs less frequently than hypertrophic and congestive cardiomyopathy. In 47 cases, middle-aged male cats were generally affected, and no breed predilection was observed.²³² Clinically, dyspnea, anorexia, and posterior paresis from aortic thromboembolism were observed. At necropsy, two types of cardiac lesions have been characterized in feline restrictive cardiomyopathy.^{230,232-234,238,239,268} In the first type, the left ventricle shows diffuse, marked endocardial fibrosis, which appears as a thick, white, firm covering, especially over the inflow and outflow tracts, papillary muscles, and chordae tendineae. Massive left atrial enlargement is present. Histologically, the affected endocardium shows marked fibrosis with focal chondroid metaplasia. Myocardial hypertrophy and fibrosis also may be present. Intimal and medial hyperplasia of intramural coronary arteries are seen. Focal myocyte disarray has been found

in the ventricular septum of some affected cats. In the second type of restrictive cardiomyopathy, increased numbers of left ventricular moderator bands were found to be the cause of the disease.²⁶⁸ Left atrial dilatation and hypertrophy were present, with left ventricular hypertrophy in younger affected cats and left ventricular dilatation in older cats. Pulmonary edema was prominent. The anomalous development of these moderator bands is presumed to represent a congenital defect with delayed onset of clinical cardiac disease.

A disease termed "endocardial disease" or "subendocardial fibrosis" has been described in five strains of rats and may represent an example of restrictive cardiomyopathy.²⁶⁹⁻²⁷³ The incidence of the lesion varied from 1% to 7% in the various strains examined and was increased in older rats. Some affected rats had terminal congestive cardiac failure with chronic pulmonary and hepatic congestion. Grossly, the left ventricular endocardium was white and thick. Histologic and ultrastructural study revealed uniform diffuse or focal tumorlike masses of fibroblastic proliferation and collagen deposition in the subendocardium.

Endomyocardial fibrosis developed in Sprague-Dawley rats that were treated for 1-14 weeks with the carcinogen N-nitrosomorpholine.²⁷⁴ The incidence of the lesion was 5% and 20% in rats examined at 29-78 and 79-108 weeks after exposure, respectively. The lesion was usually limited to the left ventricle, the endocardium of which was diffusely involved; but a few rats had focal involvement with polypoid endocardial masses. Some rats had accompanying myocardial hypertrophy.

Endocardial fibroelastosis is characterized by diffuse thickening of mural endocardium by fibrous and elastic tissue. Mitral valvular endocardium also may be involved. The condition can be either primary (when it is congenital and not associated with other cardiovascular anomalies or myocardial lesions) or secondary (when it is associated with other disorders, including storage diseases, myocardial necrosis, radiation injury, and turbulent flow in the ventricular cavity after cardiac valvular replacement).²⁷⁵ Several reports have documented the occurrence of primary endocardial fibroelastosis as an inherited congenital anomaly in Burmese cats,²⁷⁶⁻²⁷⁸ and other reports have described sporadic cases of this disorder in dogs and cats.^{279,280} The disease is manifested by tachycardia, gallop rhythm, systolic murmur, cardiomegaly, and signs of congestive heart failure, especially dyspnea and often terminal cyanosis. The onset is commonly precipitated by a respiratory infection at between 3 weeks and 4 months of age. Sudden death is common. The mode of inheritance is complex. The left atrium and left ventricle are severely dilated; in Burmese cats with endocardial fibro-

elastosis the endocardium is opaque and thickened (up to 200 μ) by a subendothelial layer of collagenous and elastic fibers, which are thicker and more organized in the areas adjacent to the myocardium. The diameters of both the elastic and collagenous fibers are larger than normal. Endocardial edema and dilated lymph vessels are seen in the endocardium in early stages, suggesting that lymphatic obstruction is involved in the pathogenesis of the disorder. This also has been suggested by the results of studies of experimental obstruction of cardiac lymphatics in dogs²⁸¹ and monkeys.²¹³ Other studies have suggested that viral infection of the heart can be a cause of endocardial fibroelastosis in humans^{282,283} as well as in dogs.²⁸⁴

Cardiomyopathy of Chickens and Geese

A syndrome of sudden collapse and death, usually at the time of excitement or exertion, occurs in chickens and geese. Many names have been applied to this disease, including "round heart disease," "enzootic syncope," "toxic heart degeneration," "Eierherz" ("egg-heart"), "Kugelherz" ("bullet-heart"), "yellow heart degeneration," "idiopathic cardiac dilatation of hens," "toxic heart disease," and "enzootic Herztod."²⁸⁵⁻²⁹⁵ The etiology of this cardiac syndrome is unknown. A wide spectrum of cardiac lesions has been described, including cardiomegaly with rounded apex, left ventricular hypertrophy, and myocardial pallor. Mild ascites and hydropericardium may be present, with pulmonary and hepatic congestion. Microscopically, the hearts have acute alterations of myocardial degeneration and necrosis.

Recently a similar clinical syndrome was described in 24-30-week-old broiler-breeder hens in Australia.²⁹⁶⁻²⁹⁸ The birds collapsed and died unexpectedly. Necropsy showed edema of the head, mild ascites, hydropericardium, visceral congestion, cardiomegaly, and ventricular hypertrophy with and without dilatation. Microscopically, the lesions were concentrated in the left atrium and consisted of myocardial degeneration, inflammatory cell infiltration, and prominent endocardial fibroelastosis. Intramyocardial arteries in the left atrium showed medial hypertrophy, adventitial fibrosis, and focal fibrinoid deposits in the walls. The syndrome was reproduced experimentally in broiler-breeders fed a diet low in potassium, phosphorus, protein, and caloric content.²⁹⁷

Recent reports have demonstrated the economic importance of a cardiac failure syndrome in growing broiler chickens.²⁹⁹⁻³⁰¹ The disease has been termed "sudden death syndrome," "acute death syndrome," and "flip-over" by poultry diagnosticians. The etiology is unknown, but mortality is greater in males than in fe-

males, tends to be increased in heavier birds of the same age, is increased by continuous lighting, and tends to peak at 3-4 weeks of age. Affected hearts tended to be enlarged. Generalized visceral congestion was present. Microscopic studies have revealed inconsistent myocardial alterations varying from absence of lesions to hearts with extensive edema and interstitial leukocytic infiltration.^{299,301}

Broiler chickens are also affected by heart failure due to a condition termed "hydropericardium-ascites syndrome," "edema disease," "toxic fat syndrome," or "water belly."^{302,303} Severe ascites and cardiac dilatation are consistent findings. Suggested etiologies include toxic factors in dietary fats and polychlorinated biphenyl toxicosis.

Chickens raised at high altitudes may suffer high death losses from "high altitude disease." Necropsy findings include edema, hydropericardium, cardiac dilatation and hypertrophy, and visceral congestion.^{304,305}

Atrial Thrombosis in Hamsters and Mice

Atrial thrombosis is the most common cardiovascular lesion seen in aged Syrian hamsters and also occurs frequently in certain strains of mice.^{1,306,307} Affected hamsters may have hyperpnea, tachycardia, and cyanosis for up to a week prior to death. At necropsy, the thrombosed atria in both hamsters and mice are swollen, firm, and mottled. The atrial wall may have pale areas of scarring. The exposed thrombus is gray to tan, often laminated, and may be large enough to extend into the orifice of the mitral valve. Rarely atrial rupture occurs in mice. The left atrium is usually affected in hamsters and mice, but occasionally both atria are thrombosed and ventricular thrombi may be seen in some animals with atrial lesions. In mice with atrial thrombosis induced by feeding a high fat, low protein, and hypolipotropic diet the thrombi are found with equal frequency in both atria.^{308,309} Hamsters may also have pulmonary edema and pleural effusion at necropsy.

Microscopically, the atrial thrombi vary from recently formed layered masses of fibrin to mature organized thrombi with fibrous connective tissue and occasionally metaplastic foci of cartilage and bone.¹ Atrial myocarditis may be present, but opinions vary as to whether this lesion is the cause or the effect of thrombosis.^{308,310} Hamsters with atrial thrombosis frequently have accompanying myocardial hypertrophy, degeneration, and fibrosis.³¹⁰ Thus, it has been suggested that cardiac failure develops initially, with subsequent stasis of blood and initiation of thrombosis.³¹⁰

The sequential cardiac ultrastructural alterations were studied in mice fed a high fat, low protein, and hypolipotropic diet.³¹¹ The atrial endocardium had ini-

tial alterations after 4 weeks, with subendothelial edema and thickening and duplication of the endothelial basement membrane. At 5 and 7 weeks, degeneration was present in the atrial endothelium. By 8–9 weeks, early thrombosis was seen over the severely damaged endothelium. Endothelial damage and disruption were observed by scanning electron microscopy prior to thrombus formation.³¹²

Multiple factors are thought to be involved in the development of atrial thrombosis, including heredity, sex, age, diet, and number of pregnancies. In hamsters, females are affected at a younger age than males, but eventually both sexes may have 70–75% involvement.³¹⁰ Endocrine studies showed that thrombosis was inhibited by testosterone injections in both sexes and was enhanced by castration of males.³¹³ In mice, the BALB/c strain has a high frequency of left atrial thrombosis; 65% of inactive female breeder animals are affected.³⁰⁶ In three mouse strains fed high fat, low protein, and hypolipotropic diets for 40 weeks, the incidence of atrial thrombosis was 64% in the TS strain, 48% in the RF strain, and 10% in the C strain.³⁰⁸ DBA mice fed the same diet for 12 weeks had a 50% frequency of atrial thrombosis, but betaine-supplemented mice had increased involvement, with an 80% incidence.⁸⁸ However, C strain mice fed the thrombogenic diet with and without choline supplementation had no difference in frequency of atrial thrombosis.³¹⁴ The frequency of atrial thrombosis was also increased in BALB/c mice after multiple pregnancies³⁰⁶ and in pregnant versus nonpregnant RF mice.³¹⁵ Male and female TS mice had a similarly high frequency of atrial thrombosis, but gonadectomized mice of both sexes given estrone had a low incidence of thrombosis.³¹⁶ Feeding the thrombogenic diet with lard as 6%, 28%, and 40% of the diet resulted in 30%, 36%, and 65% frequency of atrial thrombosis, respectively.³¹⁷ In comparing the effect of various types of fats, mice fed butter had the highest frequency of atrial thrombi (92%), and those fed cod liver oil had the lowest (20%).³¹⁸

Further studies in mice fed the thrombogenic diet have demonstrated that the affected animals develop severe anemia concurrently with atrial thrombi, that administration of erythropoietin or packed erythrocytes prevents anemia and thrombosis,^{319–321} and that feeding a normal diet to affected mice leads to remission of the lesions.³²² A recent report has shown that the thrombogenic diet is deficient in copper and that adding supplements of copper prevents the formation of atrial thrombi.³²³ Mice with experimental copper deficiency have a high incidence of atrial thrombosis and rupture, with hemopericardium and hemothorax.¹⁹⁰

Spontaneous Rupture of the Left Atrium in Dogs

Two autopsy series have reported a total of 41 cases of left atrial rupture in dogs.^{324,325} In one series, 11 cases were found in 4033 canine necropsies.³²⁵ In the other report, 30 cases were detected over a 5-year period.³²⁴ The lesion was consistently found in old dogs, with males predominating. Dachshunds and cocker spaniels were the most frequently affected breeds. All affected dogs had extensive endocardiosis (noninflammatory valvular thickening by fibrous and myxomatous tissue) of the mitral valve, and most cases also involved ruptured chordae tendineae. At necropsy, three types of lesions were observed. In the first type, seen in 17 of 30 affected dogs, nonperforating left atrial endocardial or endomyocardial splits were present and were often apparent by an elongated zone of subepicardial hemorrhage before the atrium was opened. In 2 of these dogs, atrial thrombi were attached to splits. In the second type of lesion (9 of 30 dogs), perforations of the lateral wall were associated with hemopericardium. In the third type (4 of 30 dogs), the atrial septum had perforated, which resulted in acquired atrial septal defects.

The pathogenesis of atrial rupture in these dogs is not certain. Consistent concurrent lesions were 1) valvular endocardiosis, often with mitral regurgitation and “jet lesions” of the atrial endocardium, 2) ruptured chordae tendineae and 3) intimal thickening of intramural coronary arteries. The event initiating atrial rupture may be rupture of a chorda tendinea. Buchanan³²⁴ has suggested that genetically influenced degeneration of collagen may be involved in the development of the atrial lesion.

Myocardial Fibrosis in Aged Rats

Myocardial fibrosis is the most common cardiac disease of rats.^{1,271,326–329} The lesion is age-related; it is seen initially at approximately 13 months of age. Males are somewhat more susceptible than females. The lesion develops earlier in males, and they have more severe involvement than do females at a given age. In several large necropsy series on aged rats, the frequency of myocardial fibrosis varied from 60% in Wistar (mean age 31 months) and inbred albino rats (mean age 24 months) to 90% in Wistar and BN/Bi rats (mean age greater than 37 months).^{271,326,329}

Clinical evidence of cardiac disease has not been reported in rats with myocardial fibrosis. At necropsy, the lesions usually are not detected grossly, but in cases with severe lesions, areas of pallor may be scattered in the left ventricular myocardium.¹ Microscopically, the

lesions are concentrated in the left ventricular papillary muscles, the left ventricular free wall, and the ventricular septum. The fibrotic areas often are detected initially at either the base or the apex of the left ventricle.³²⁹ The inner third of the left ventricular free wall is selectively affected. The lesions may be focal or disseminated and appear as prominent interstitial fibrosis with atrophy and degeneration of adjacent myocytes. Scattered lesions of myocardial necrosis and mineralization may be seen and probably represent early alterations that would be expected to progress to myocardial fibrosis.³²⁸

The pathogenesis of myocardial fibrosis in aged rats is unclear. It has been proposed that the lesion is secondary to chronic renal disease or coronary arteriosclerosis, lesions that are also found frequently in aged rats.^{328,329} However, myocardial fibrosis may be present in the absence of these two lesions.

Myocardial Degeneration and Fibrosis in Aged Horses

In several studies of hearts from horses, which either had been normal clinically or had had arrhythmias, myocardial fibrosis was observed at a frequency varying from 15% to 80%.³³⁰⁻³³⁵ In a clinical study of 2477 horses, 63 (2.5%) were found to have atrial fibrillation.³³⁴ Necropsy of 45 of the animals with atrial fibrillation revealed gross atrial lesions of patchy or diffuse fibrosis and dilatation in 80% of the hearts. In a large study of 2076 healthy horses, ponies, and donkeys, 14.3% had focal myocardial fibrosis.³³⁰ Most reports of myocardial fibrosis in equine hearts have described the affected hearts to have concurrent lesions of arteriosclerosis in the intramyocardial arteries.^{330,333,335,336} In general, the vascular lesions and myocardial scarring were present more frequently in horses with advancing age. Rarely, atrial rupture has occurred in horses with severe atrial damage.^{337,338}

Grossly, the areas of myocardial fibrosis are usually apparent as pale, depressed streaks or foci on the epicardial surface. The lesions tend to be most frequent toward the base of the ventricle. Microscopically, the affected areas have central myocyte loss with replacement fibrosis, and adjacent myocytes have degenerative alterations such as sarcoplasmic vacuolation and myocytolysis.^{330,333-339} The pathogenesis of the myocardial lesions remains unclear but may be due to focal ischemic injury associated with intramyocardial vascular lesions like those that occur in dogs.³⁴⁰ Another proposed mechanism attributes the myocardial lesions to microembolization from *Strongylus vulgaris*-induced lesions of endarteritis of the proximal aorta.³³⁰

Basophilic Degeneration of Myocardium

Basophilic degeneration of cardiac muscle cells was described as a frequent finding in the atria and ventricles of horses with atrial fibrillation or with chronic myocardial disease.^{5,335} This lesion is occasionally present in the myocardium of dogs with chronic mitral endocardiosis and myocardial hypertrophy.⁵ Affected cells have a mass of perinuclear basophilic material that gives a positive reaction with the periodic acid-Schiff (PAS) stain.

No ultrastructural studies of this material have been reported in animals; however, it appears histologically similar to the basophilic, finely fibrillar carbohydrate material that has been described as a nonspecific finding in the hearts of elderly humans.^{341,342} Similar fibrils of basophilic, PAS-positive material also have been found in human myocardium in the Lafora type of myoclonic epilepsy (Lafora's disease, in which the metabolic defect is unknown), in Type IV glycogen storage disease (branching enzyme deficiency), and in phosphofructokinase deficiency.³⁴²⁻³⁴⁴ Lafora's disease has been described in dogs,³⁴⁵ but myocardial alterations were not reported in these animals. Type IV glycogen storage disease and phosphofructokinase deficiency have not been described in animals.

Myocardial Diseases of Toxic Etiology

In this large group of diseases various biochemical mechanisms elicit morphologic evidence of cardiotoxicity as degeneration (myofibrillar lysis, vacuolar degeneration, fatty degeneration, lipofuscin deposition) and contraction band necrosis with or without mineralization. Many of these diseases have been utilized as models for studies of myocardial injury. Similar human diseases of toxic origin exist for many of these examples, including toxicity by cobalt, catecholamines, antihypertensives, antineoplastic agents, vitamin D, ethanol, uremia, and various infrequently used drugs. The cardiotoxic properties of many of these compounds were recognized in animals during drug safety studies. It is necessary to emphasize that a number of these cardiotoxicities have emerged as important naturally occurring diseases in animals including toxicities by ionophores, antineoplastic agents, furazolidone, poisonous plants, and vitamin D.

Toxicity of Metallic Salts

Numerous metallic compounds, including salts of lithium, cadmium, nickel, barium, lanthanum, man-

ganese, vanadium, lead, and cobalt, are known to have cardiotoxic properties.³⁴⁶ However, detailed structural studies of the changes induced by these compounds have been made only with respect to lead and cobalt.

Lead Cardiotoxicity

The cardiotoxicity induced by intake of excessive amounts of lead has received relatively little attention, although it is of biochemical interest because this metal interferes with certain actions of calcium.³⁴⁷ Moore et al³⁴⁸ observed various minor mitochondrial changes in rats given 1 mg lead per liter of drinking water for 1 year. In rats given 1% lead acetate in the drinking water for 6 weeks, Asokan³⁴⁹ observed myofibrillar fragmentation, intracellular edema, dilatation of sarcoplasmic reticulum, and twofold to threefold swelling of mitochondria with deformed, loosely packed cristae. The animals showing these changes had plasma lead levels of $112 \pm 5 \mu\text{g}/100 \text{ ml}$, which were considered comparable to those in mild, clinical lead poisoning. In mice, Khan et al³⁵⁰ found a correlation between blood lead levels and cardiac ultrastructural changes. No changes were detected in animals with blood levels $<20 \mu\text{g}/100 \text{ ml}$. Animals having levels $>20 \mu\text{g}/100 \text{ ml}$ showed clumping of nuclear chromatin and nucleolar disorganization. Those having levels $>40 \mu\text{g}/100 \text{ ml}$ also had sarcotubular dilatation and mitochondrial changes consisting of mitochondrial enlargement, disarray of the crista, and an increase in intramitochondrial matrix. Animals with lead levels $>60 \mu\text{g}/100 \text{ ml}$ also had focal myofibrillar degeneration, focal areas of separation of the apposed membranes of the intercalated disks, and appearance of increased numbers of lysosomal-like cytoplasmic dense bodies.

Cobalt Cardiotoxicity

"Beer-drinkers' cardiomyopathy," characterized by acute cardiac failure with myopericarditis and lactic acidosis, occurred in human patients in Canada, the United States, and Belgium in the 1960s, when cobalt salts were added to some beers to improve the quality of the foam.³⁵¹⁻³⁵³ Cobalt cardiotoxicity has been induced experimentally in rats, rabbits, dogs, and guinea pigs,³⁵⁴⁻³⁶² but with the use of much larger doses of cobalt than those ingested by patients in whom beer-drinkers' cardiomyopathy developed. Animal experiments led to the conclusion that coexisting protein deficiency played an important role in the pathogenesis of the cardiomyopathy observed in humans, by increasing absorption of cobalt from the gastrointestinal tract.³⁶⁰ In an effort to develop a large animal model for cobalt cardiotoxicity, we administered cobalt sulfate, in doses of 125 mg/kg of body weight daily for 3 days, to weanling conventional pigs.³⁶³ Surviving pigs

were euthanatized 2 days later. The pigs showed anorexia, lethargy, vomiting, and diarrhea; and 6 of 20 treated pigs died. Serum activities of creatine phosphokinase and aspartate aminotransferase were markedly increased after administration of cobalt.

At necropsy, the affected pigs had mild to moderate hydropericardium and pale atria (Figure 28). Microscopically, the atria showed diffuse myocardial necrosis and calcification. The affected fibers showed necrosis with contraction bands and basophilic granular sarcoplasm from mitochondrial calcification. Within 2-3 days after necrosis, numerous macrophages had invaded the necrotic cells and the adjacent interstitium. The interstitium also showed edema and fibroblastic proliferation.

Ultrastructurally, cardiac muscle cells with mild injury had loss of glycogen granules, dilated elements of sarcoplasmic reticulum, and focal myofibrillar lysis. Myocytes with severe damage had necrosis, with contraction bands, pyknotic nuclei, damaged mitochondria, and ruptured plasma membranes (Figure 29). The damaged mitochondria showed swelling, striking accumulations of dense granular deposits containing large amounts of calcium and phosphorus, and disrupted membranes (Figure 30). The interstitium showed edema,

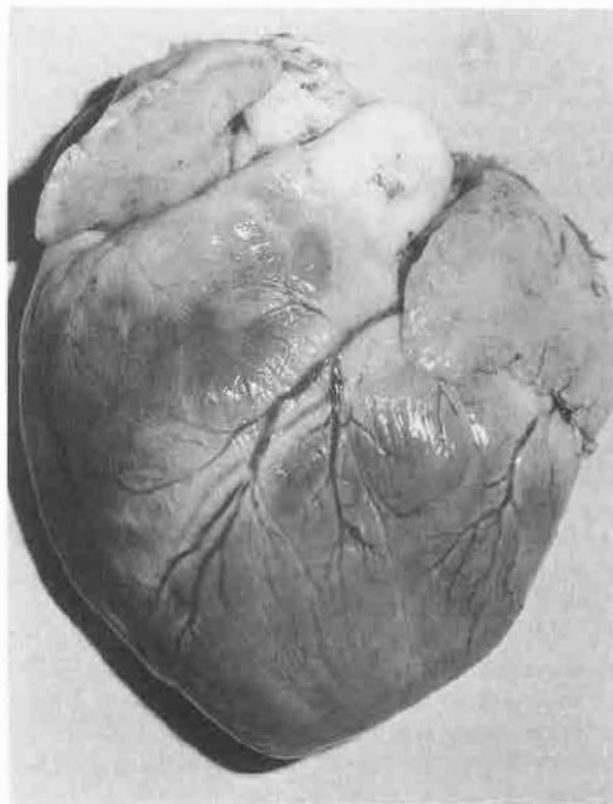


Figure 28—Cobalt cardiotoxicity. Pig. Extensive necrosis of the atrial myocardium is evident by pallor of both atria.

29



Figure 29—Cobalt cardiotoxicity. Pig. Necrotic myocytes in atria have dense transverse hypercontraction bands and either dense granular calcified mitochondria or swollen mitochondria. (x6000) **Figure 30**—Cobalt cardiotoxicity. Pig. Calcified mitochondrion has dense granular matrical deposits and scattered lucent foci. (x50,000)

30

deposits of serum protein, occasional strands of fibrin, invading macrophages, and activated fibroblasts.

In this pig model of cobalt cardiotoxicity, the severity of the cardiac disease was markedly decreased in animals given selenium-vitamin E by injection 24 hours before cobalt administration. Pigs with inherited stress susceptibility had more severe cobalt-induced cardiac damage than did animals without this trait.

In the dog model, lesions of a dilated cardiomyopathy were produced by intravenous infusions of cobalt with or without feeding of a protein- and thiamine-deficient diet.^{361,364,365} The myocardium was pale grossly, and myocyte degeneration and necrosis were scattered in both the ventricles and the atria.

The biochemical lesion in cobalt cardiotoxicity was demonstrated to involve blocking of the oxidation of α -ketoglutarate and pyruvate by complexes formed between cobalt and the sulfhydryl groups of α -lipoic acid.³⁶⁶ Thus, myocardial energy metabolism is compromised as in thiamine deficiency. Cobalt cardiotoxicity was potentiated in rats by increasing age, thiamine deficiency, protein deficiency, thyroidectomy, and preexisting cardiac disease (see Ferrans et al for review).³⁶²

Catecholamine Cardiotoxicity

Several recent reviews have summarized the voluminous literature on the cardiotoxicity of catecholamines.³⁶⁷⁻³⁷¹ The myocardial lesions produced by endogenous and synthetic catecholamines have generally similar features. Most animal studies have utilized isoproterenol, but reports on epinephrine, norepinephrine, salbutamol, terbutaline and ephedrine are also numerous. Most pathologic studies have been done in rats, rabbits, and dogs.³⁷¹⁻³⁸¹ In these species, the typical lesions are multifocal myocardial necroses with concentration of the damage in the left ventricular subendocardium and papillary muscles (Figures 31 and 32). Histologically and ultrastructurally, the damage is characterized by necrosis with contraction bands, with subsequent macrophagic invasion and fibrosis (Figure 32). Endocardial fibrous thickening and left ventricular aneurysms develop when the lesions are very extensive, as in the case of isoproterenol-induced necrosis in rats.³⁷¹ Catecholamine-induced cardiac lesions have also been described in poikilotherms.³⁸²

Catecholamine cardiotoxicity was induced in swine

by administration of large doses of isoproterenol (125 mg/kg) intraperitoneally to weanling pigs.³⁶³ Dyspnea, vomiting, ataxia, anorexia, and lethargy developed; and the pigs were reluctant to rise for 6–8 hours after treatment. Cutaneous alterations were evident as piloerection and patchy erythema. Moderate increases in serum creatine phosphokinase and aspartate aminotransferase activity were present. Twelve of 20 pigs died within 5 days of treatment.

At necropsy, the cardiac lesions included hydropericardium; scattered pale areas of myocardial necrosis, especially in the left ventricular papillary muscles; and focal left ventricular endocardial hemorrhages (Figure 31). Microscopically, hyaline necrosis was frequent in left ventricular subendocardial myocardium and was only occasionally present in atrial myocardium. Some necrotic myocytes had mineralized deposits. At 4–5 days after isoproterenol injection, the necrotic areas were evident as empty sarcolemmal tubes invaded by numerous macrophages and surrounded by proliferating fibroblasts. The severity of this cardiotoxicity was not affected by pretreatment with selenium-vitamin E but was increased in stress-susceptible pigs.³⁶³

Numerous studies have been done for evaluation of procedures used to modify isoproterenol cardiotoxicity.^{367–388} Cardiac damage is potentiated by cold exposure, long-term isolation, administration of corticosteroids or thyroxine, diets high in fat and carbohydrates, and using obese animals. Protection against isoproterenol cardiotoxicity has been demonstrated with induction of hypocalcemia³⁸⁴ and administration of propranolol and other β -adrenergic receptor blockers, verapamil, ribose, and adenosine.³⁸⁹ Also, resistance to induction of myocardial necrosis with further doses of isoproterenol occurs in animals after production of an initial focus of myocardial damage.^{367, 390, 391} Decreased severity of isoproterenol cardiotoxicity was seen in rats in which body weight was reduced by limiting food intake,³⁸³ in rats fed normal diets after malnutrition for the first 7 weeks of life, and in exercised rats.^{386, 392} Recent studies have shown that the cardiotoxicity of isoproterenol is considerably reduced, compared with that in normal animals, in rats made diabetic by administration of streptozotocin³⁹³ and in mice with alloxan-induced or with genetically transmitted diabetes mellitus.³⁹⁴ In mice, treatment with insulin was shown

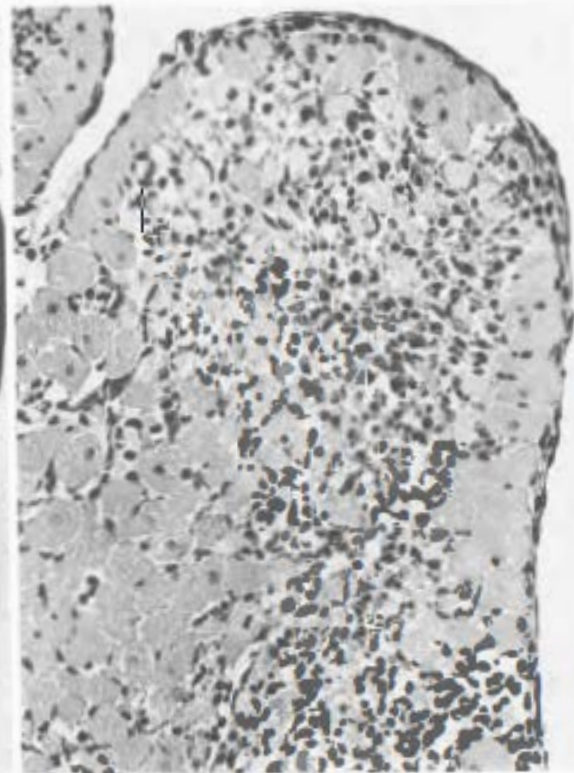
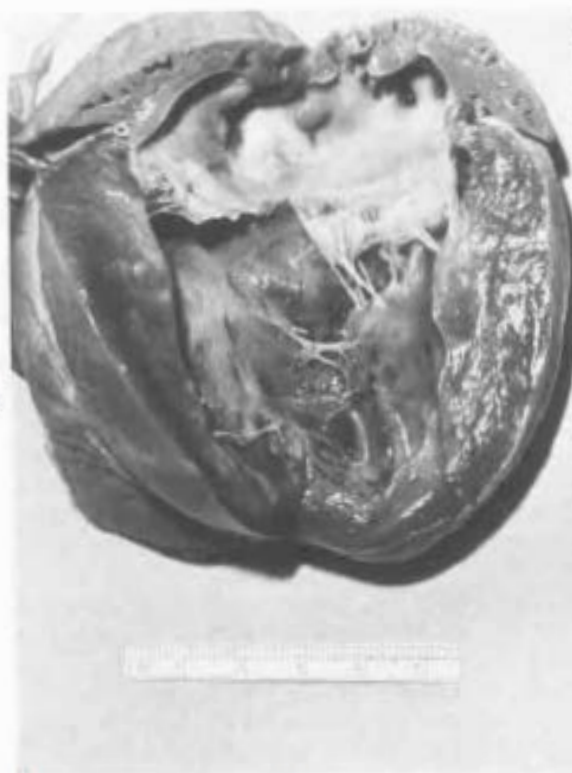


Figure 31—Isoproterenol cardiotoxicity. Pig. Incised left side of the heart shows multiple pale areas of myocardial necrosis in the inner half of the left ventricular wall. **Figure 32**—Isoproterenol cardiotoxicity. Rat. Area of necrosis in the left ventricular subendocardial myocardium is invaded by mononuclear leukocytes. (H&E, $\times 250$)

to correct the diabetes and to restore the sensitivity to the cardiotoxic effects of isoproterenol.

Other recent studies have suggested that free radical injury may be one of the factors mediating isoproterenol cardiotoxicity.^{395,396} Vitamin E-deficient rats had increased susceptibility to isoproterenol-induced myocardial damage; and animals pretreated with vitamin E, an antioxidant, or Zn, a membrane-stabilizing agent, also showed evidence of protection.³⁹⁶

Histamine Cardiotoxicity

In rabbits given histamine multifocal myocardial necrosis developed, with concentration of the lesions in the right ventricle, ventricular septum, and papillary muscles.^{397,398} Microscopically, the lesions showed edema and hemorrhage and necrosis with contraction bands. During resolution, a mixed population of inflammatory cells was present, and late lesions showed stromal collapse and fibrosis. The myocardial lesions were not prevented by adrenergic blockade, which suggests that the damage was caused directly by histamine and was not mediated by catecholamines.

Cardiotoxicity of Minoxidil and Other Vasodilating Antihypertensives

Minoxidil is a vasodilating antihypertensive drug that is useful in human patients with refractory hypertension. In animal safety testing it was demonstrated that minoxidil produced hemorrhagic right atrial lesions in dogs given doses as low as 1 mg/kg.³⁹⁹⁻⁴⁰² Minoxidil can also produce left ventricular papillary muscle necroses and superficial endocardial and epicardial hemorrhages in various regions of the heart. The hemorrhagic atrial lesions were associated with fibrinoid necrosis of arterioles, focal myocyte damage, and epicardial inflammation; they progressed to eventual fibrosis. Protection against minoxidil-induced lesions in dogs was provided by pretreatment for several days with furosemide, but not with propranolol or hydrochlorothiazide.⁴⁰⁰ The mechanism of this protection is unknown.

In miniature swine, administration of minoxidil, 10 mg/kg/day for 2 days, produced tachycardia and hypotension.⁴⁰³ At necropsy, 24 hours after minoxidil treatment, the cardiac lesions were diffuse left atrial epicardial hemorrhage and focal pale areas of myocar-

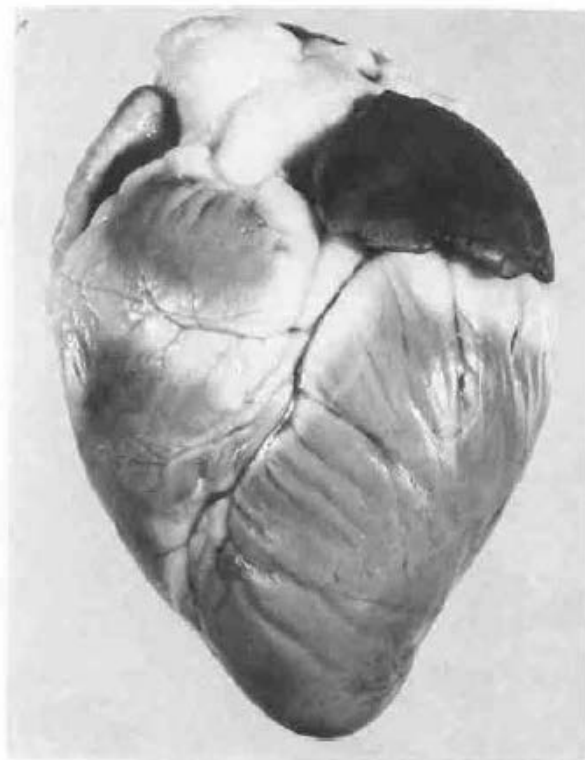
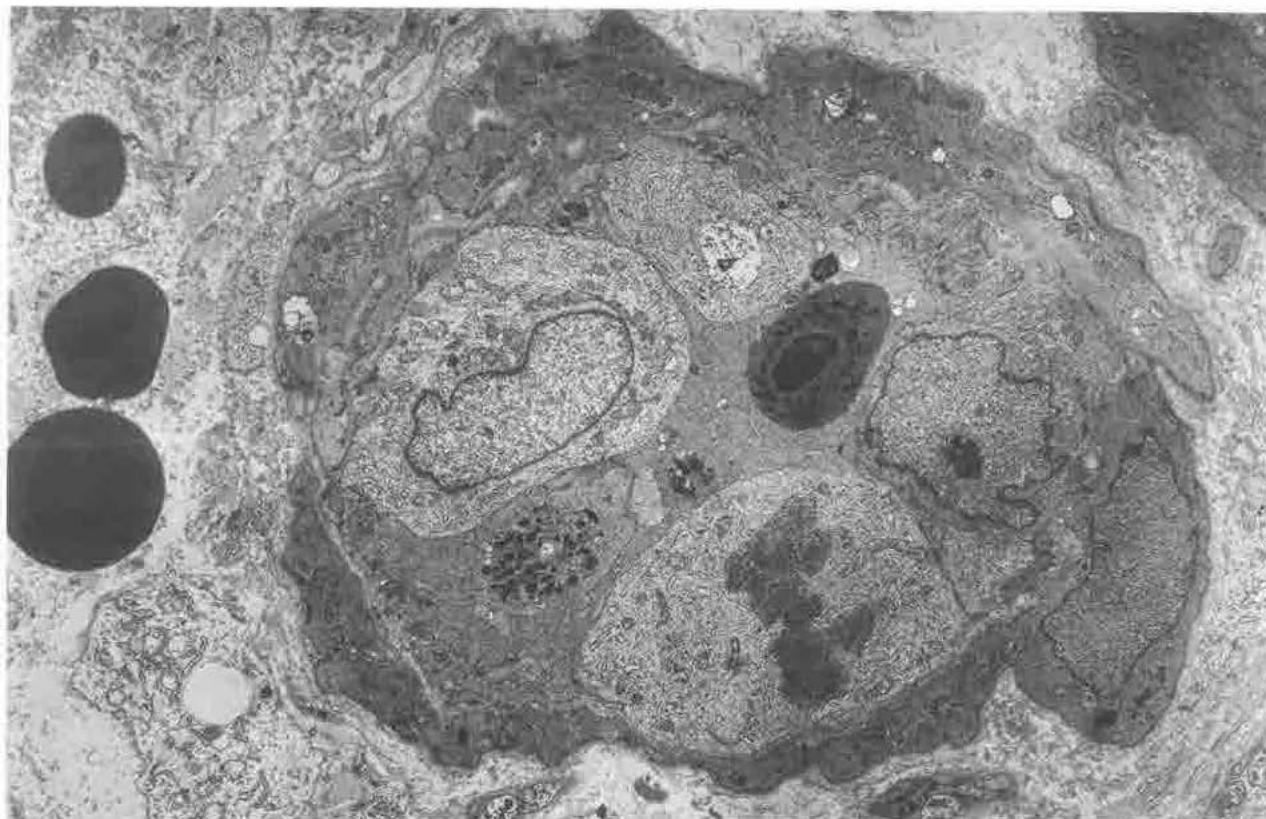


Figure 33—Minoxidil cardiotoxicity. Pig. The left atrium has diffuse hemorrhage. Endothelial thickening is present in an arteriole (center).



Figure 34—Minoxidil cardiotoxicity. Pig. Scattered dark necrotic myocytes are present in the left atrium. Endothelial thickening is present in an arteriole (center). (Plastic-embedded section 1 μ thick, alkaline toluidine blue, $\times 700$)

35



36



Figure 35—Minoxidil cardiotoxicity. Pig. Damaged arteriole in the left atrial epicardium has endothelial swelling, an endothelial cell in mitosis, and several leukocytes in the lumen. The surrounding interstitium has hemorrhage and edema. (x4000) **Figure 36**—Minoxidil cardiotoxicity. Pig. Myocytes with coagulation necrosis surround a capillary occluded by leukocytes and erythrocytes in the left ventricular papillary muscle. Lysis of I bands is extensive, and mitochondria contain flocculent densities. (x5000)

dial necrosis in the left ventricular papillary muscles (Figure 33).

Microscopic and ultrastructural study of the porcine cardiac lesions revealed vascular damage in the hemorrhagic left atria. Arterioles were selectively injured and showed endothelial swelling with prominent transmural and perivascular accumulations of leukocytes, fibrin deposits, and edema fluid (Figures 34 and 35). Thrombosis and endothelial necrosis were not present in damaged arterioles. The interstitium was edematous and had activated fibroblasts. In necrotic areas of left ventricular papillary muscles, myocytes had necrosis with contraction bands. The necrotic cells had pyknotic nuclei, mitochondrial matrical densities, and accumulations of sarcoplasmic lipid droplets (Figures 36 and 37). These studies demonstrate that the pig offers a suitable model for producing minoxidil cardiotoxicity and that the regional distributions of the cardiac lesions caused by this agent in the dog and in the pig are different.⁴⁰⁴

Other vasodilating antihypertensive drugs, such as hydralazine, diazoxide, and SK&F 24260, produce left ventricular lesions similar to those produced by minoxidil.^{347,358,405,406} However, these agents are not known to produce atrial hemorrhagic lesions such as those in-

duced by minoxidil and theobromine.⁴⁰⁷ The left ventricular papillary muscle lesions are thought to result from a decrease in vascular perfusion.

Methylxanthine Cardiotoxicity

Cardiotoxicity has been demonstrated for the methylxanthine compounds theobromine, theophylline, and caffeine. Long-term theobromine administration produced a distinctive lesion in the right atrium of dogs.⁴⁰⁷ The affected atria developed hemorrhage, myocardial necrosis, and residual fibrosis. Grossly, the atria were red. Arteries and arterioles in the right atrium had medial hyperplasia and perivascular fibrosis and inflammatory cell infiltration. Similar hemorrhagic lesions were present in both atria in pigs with acute theobromine toxicity (Figure 38) (Herman et al, unpublished data).

Acute theophylline and caffeine toxicity in rats caused extensive myocardial necrosis.^{408,409} Lesions were concentrated in the left ventricular subendocardium and were similar to those produced by isoproterenol cardiotoxicity. In pigs, theophylline toxicity induced prominent endocardial hemorrhage (Figure 39).

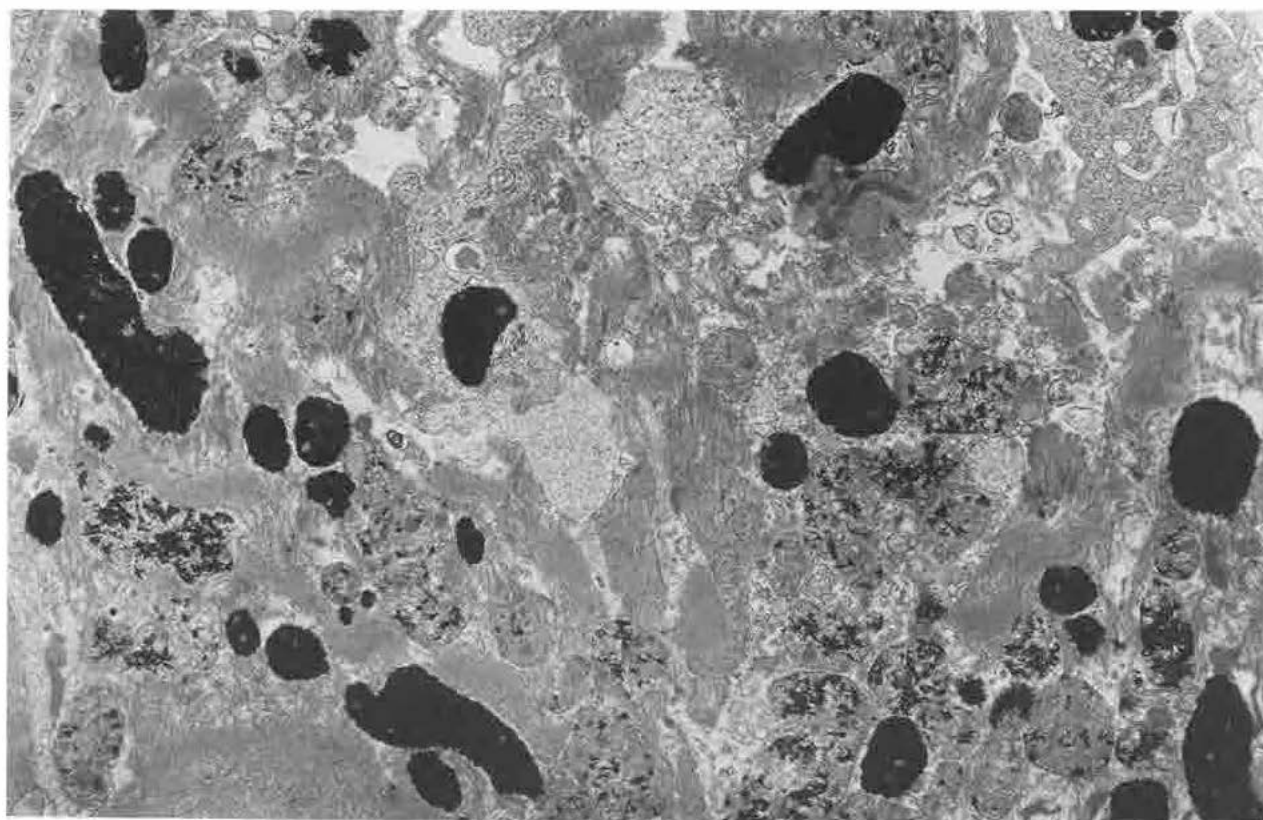
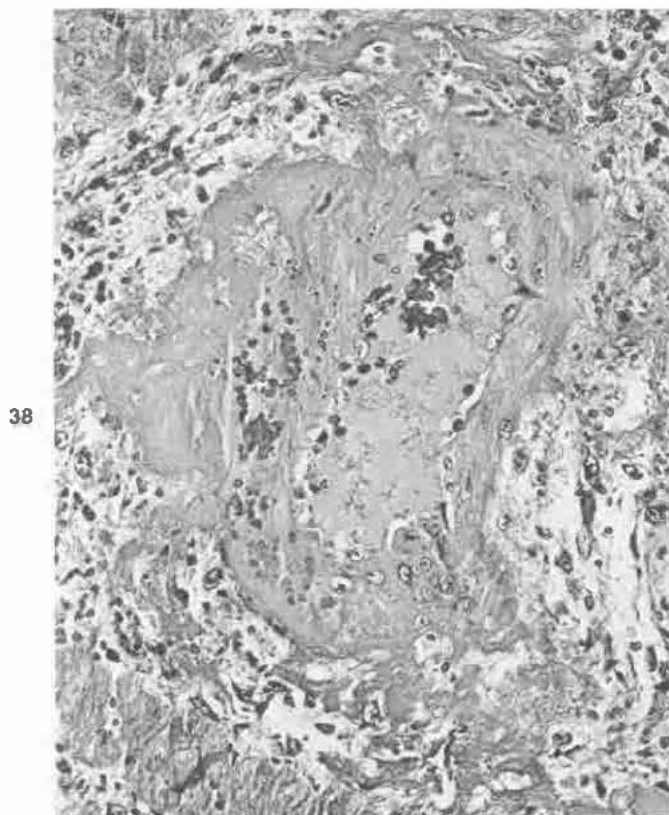


Figure 37—Minoxidil cardiotoxicity. Pig. Necrotic myocyte in the left ventricular papillary muscle has dense calcified mitochondria, clumps of disrupted contractile material, and multiple cytoplasmic processes of an invaded macrophage (×12,000)

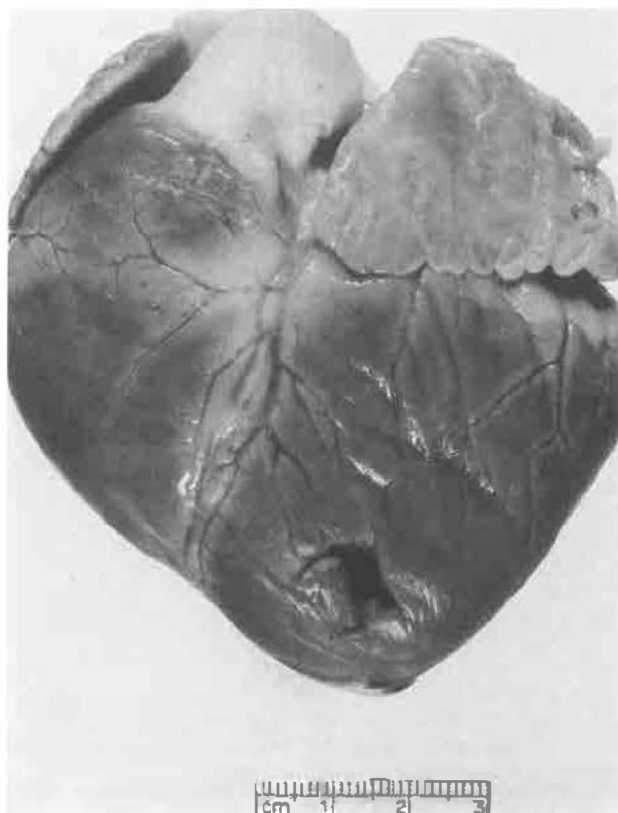


38



39

Figure 38—Theobromine cardiotoxicity. Pig. Fibrinoid necrosis and hemorrhage in the wall of an artery in the left atrial epicardium. (H&E, $\times 160$) **Figure 39**—Theophylline cardiotoxicity. Pig. Extensive endocardial hemorrhage is present in the left ventricle. (H&E, $\times 100$)



Cardiotoxicity of Monensin and Other Ionophores

Monensin, a Na^+ -selective carboxylic ionophore, is used extensively in veterinary medicine as a coccidiostat for poultry and as a growth-promoting agent for cattle. Reports of toxicosis in horses, cattle, sheep, pigs, dogs, and poultry have emphasized the occurrence of necrosis of skeletal and cardiac muscle.⁴¹⁹⁻⁴⁴⁷ Because few studies have been made of monensin toxicosis in pigs, we experimentally induced this toxicosis in weanling swine and characterized its clinical and pathologic features.⁴⁴⁰⁻⁴⁴² The severity of clinical signs of toxicosis was dose-related. These signs occurred in pigs given 20, 30, 40, or 50 mg/kg of monensin orally and included dyspnea, lethargy, anorexia, ataxia, muscular weakness, myoglobinuria, and death. Serum activities of creatine phosphokinase and aspartate aminotransferase were increased.

At necropsy, the skeletal muscles had consistent lesions of pallor from myonecrosis. Less frequently, cardiac damage was apparent as pallor of the left atrium (Figure 40). Some pigs died within 24 hours and had generalized myocardial mottling. Histologic and ultra-

~

Figure 40—Monensin cardiotoxicity. Pig. Left atrium appears pale, indicating myocardial necrosis.

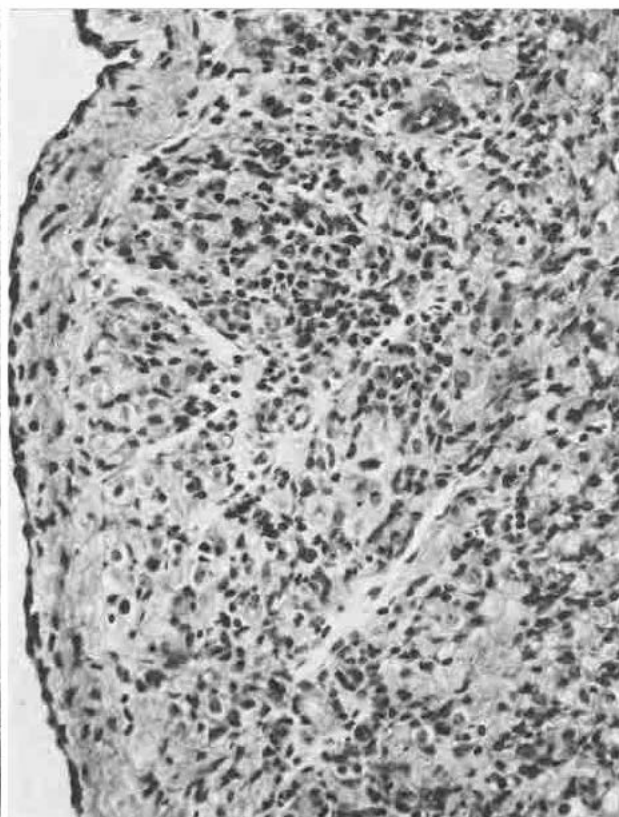
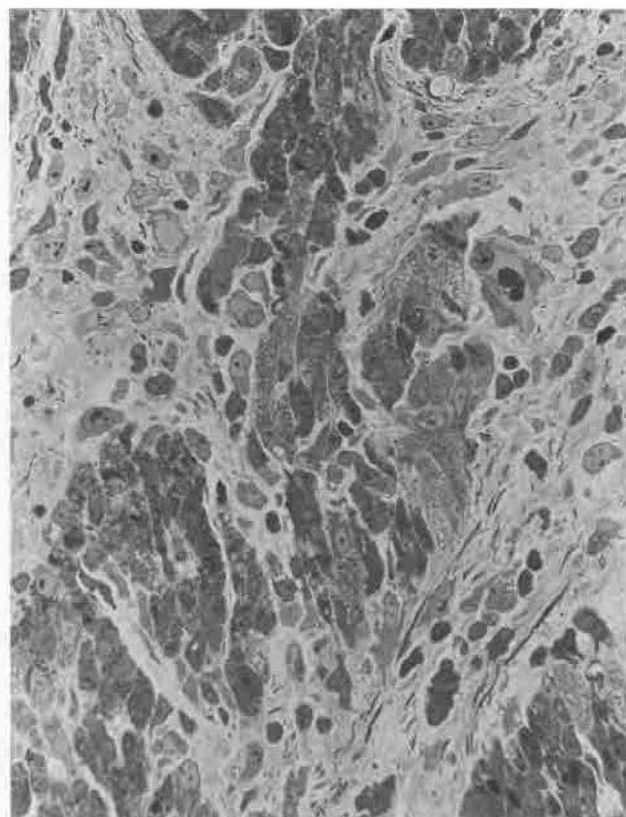


Figure 41—Monensin cardiotoxicity. Pig. Left atrium contains numerous dense necrotic myocytes with contraction bands at 1 day after monensin administration. (Plastic-embedded section 1 μ thick, alkaline toluidine blue, $\times 400$) **Figure 42**—Monensin cardiotoxicity. Pig. Atrium has extensive infiltration of mononuclear leukocytes into an area of myocardial necrosis. (H&E, $\times 250$)

structural study of the left atrial lesions demonstrated myocytes with contraction band necrosis (Figures 41–44). By Day 2 after monensin administration, numerous macrophages had invaded the necrotic myocytes and had engulfed sarcoplasmic debris. On Day 16 after treatment, the areas of necrosis of left atrial myocardium showed lysis of myocytes and persistent tubes of myocyte external lamina within supporting stromal tissue. Myocytes with sublethal injury had mitochondrial alterations, focal myofibrillar lysis, and sarcoplasmic vacuolation. Administration of selenium–vitamin E, 24 hours prior to monensin, provided protection against the development of necrosis of skeletal and cardiac muscle.

Our studies of monensin toxicosis in cattle^{439,443} have shown that initial signs of intoxication were anorexia, diarrhea, and lethargy. Cardiac and skeletal muscle damage was reflected by marked elevations of serum aspartate aminotransferase and creatine phosphokinase activities. One of 12 calves given monensin at 40 mg/kg died 7 days later from acute congestive heart failure. At necropsy, the myocardial lesions were disseminated pale yellowish brown areas of necrosis in the ventricles

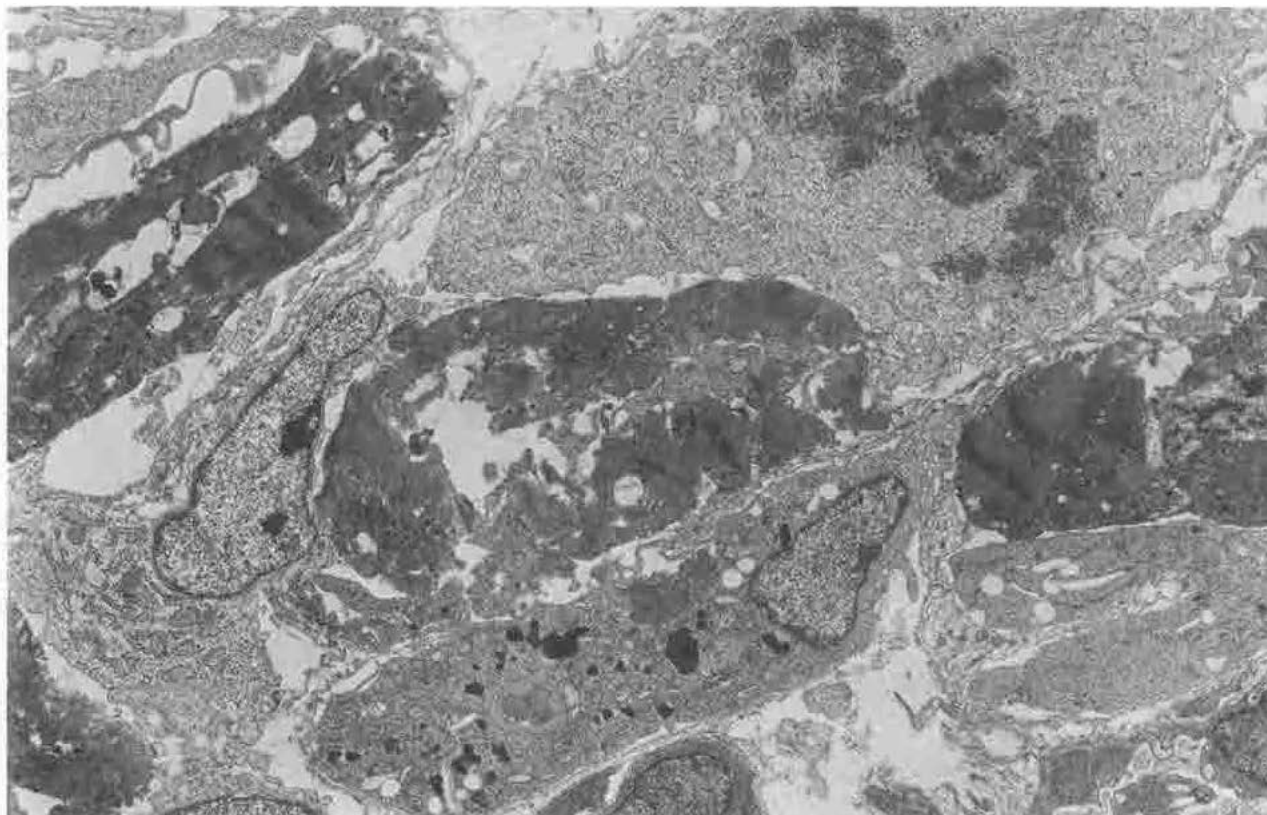
(Figure 45). Microscopic and ultrastructural study showed early sarcoplasmic vacuolation from lipid droplet accumulation and mitochondrial swelling (Figure 46). Numerous myelin figures were present by Day 4. Myocyte necrosis was present at 4 days after monensin administration. Necrotic fibers had disrupted contractile material and contraction bands (Figures 47–49). Macrophages invaded areas of necrosis and engulfed fragments of sarcoplasmic debris.

Cardiotoxicity has also been demonstrated for other ionophores including lasalocid in horses and cattle,^{448,449} A204 in rats,⁴⁵⁰ and salinomycin and narasin in turkeys.^{451,452}

Doxorubicin and Daunorubicin Cardiotoxicity

Doxorubicin (Adriamycin; Adria Laboratories, Inc., Columbus, Ohio) is an antineoplastic compound that is used widely in human patients. However, a significant complication of long-term therapy with this agent, and with daunorubicin, a closely related compound, is the development of a dose-related chronic cardiotoxicity characterized by congestive heart failure. Suitable ani-

43



44

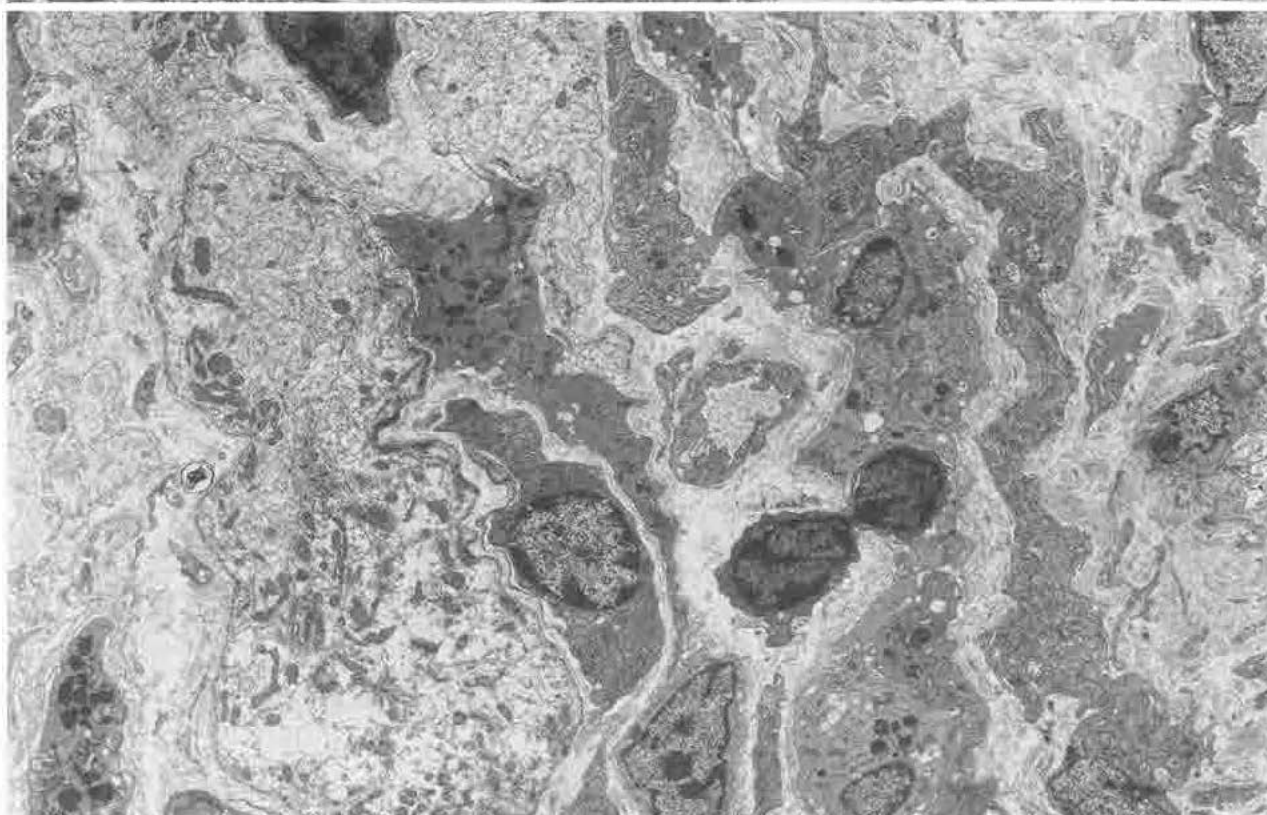
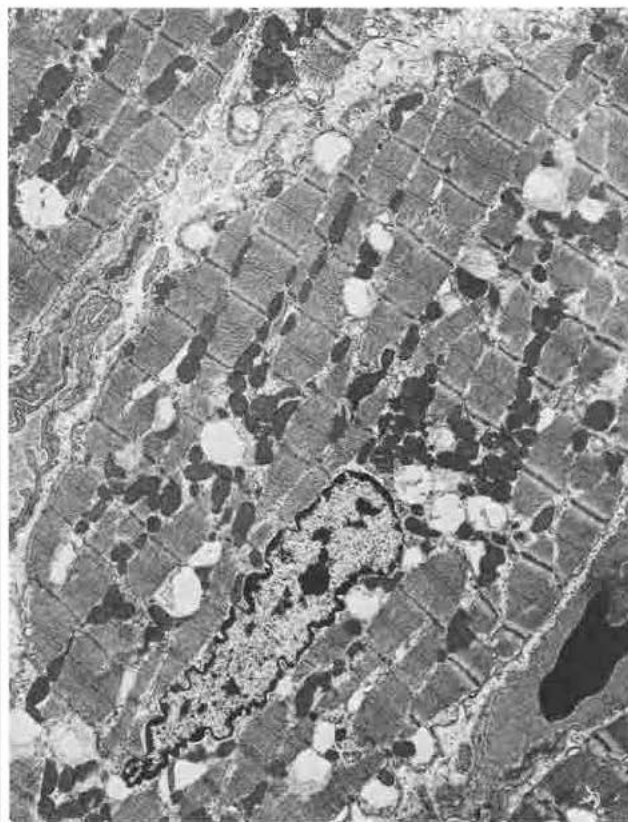


Figure 43—Monensin cardiotoxicity. Pig. Dense necrotic left atrial myocytes are invaded by macrophages at 2 days after monensin administration. (x6000) **Figure 44—Monensin cardiotoxicity.** Pig. Left atrial myocardium at 4 days after monensin administration has several myocytes at the right with extensive myofibrillar lysis. Macrophages lie within the external lamina of necrotic myocytes. (x4500)

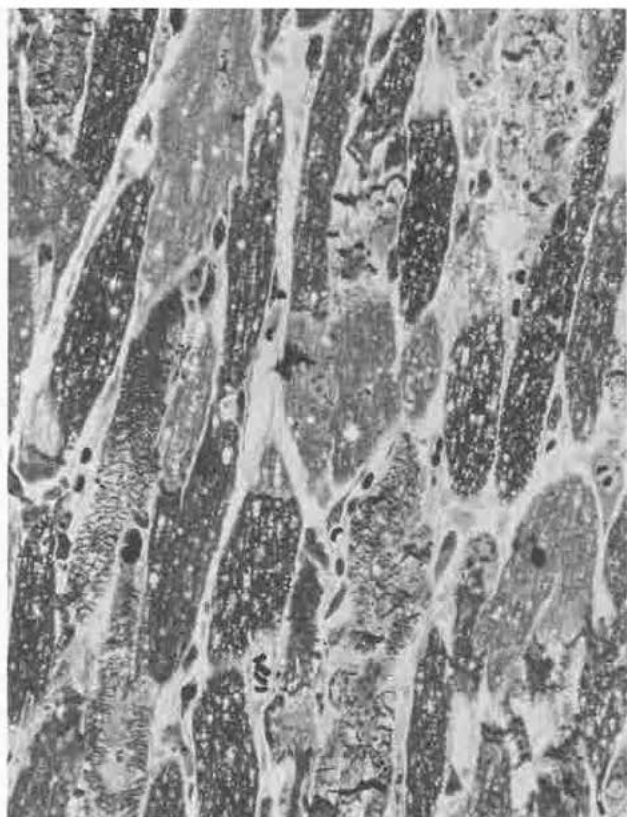
45



46



47



48

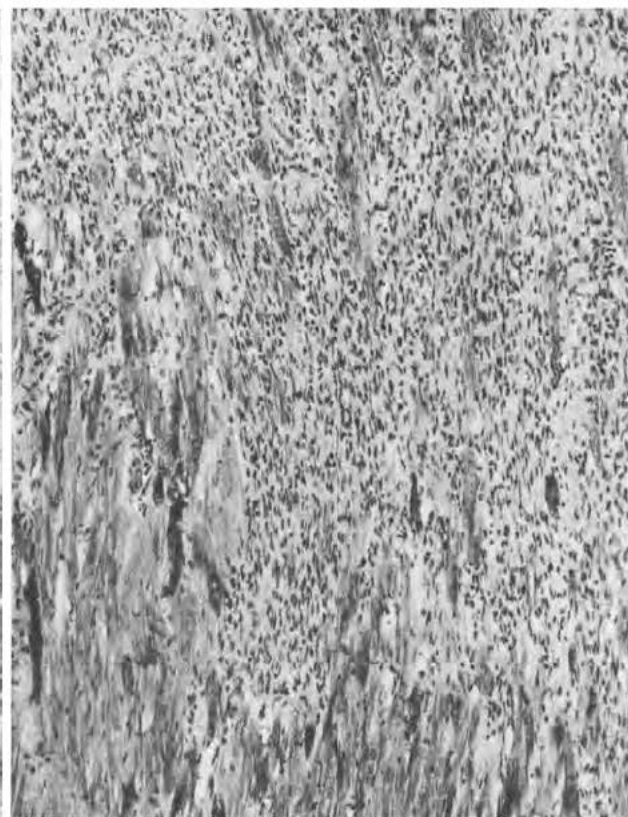


Figure 45—Monensin cardiotoxicity. Cow. Disseminated pale areas of myocardial necrosis are present in this transverse slice of the ventricles from a calf given monensin 4 days previously. **Figure 46**—Monensin cardiotoxicity. Cow. Left ventricular myocytes have moderate sarcoplasmic vacuolation at 2 days after monensin administration. (x6000) **Figure 47**—Monensin cardiotoxicity. Cow. Numerous dark necrotic myocytes are present in the left ventricle. Affected fibers have sarcoplasmic vacuolation and transverse hypercontraction bands. (Plastic-embedded section 1 μ thick, alkaline toluidine blue, x500) **Figure 48**—Monensin cardiotoxicity. Cow. Area of resolving myocardial necrosis in ventricular septum has prominent fibroblastic stroma with a few scattered dark necrotic myocytes in an adjacent area of myocardium. (Phosphotungstic acid hematoxylin, x150)

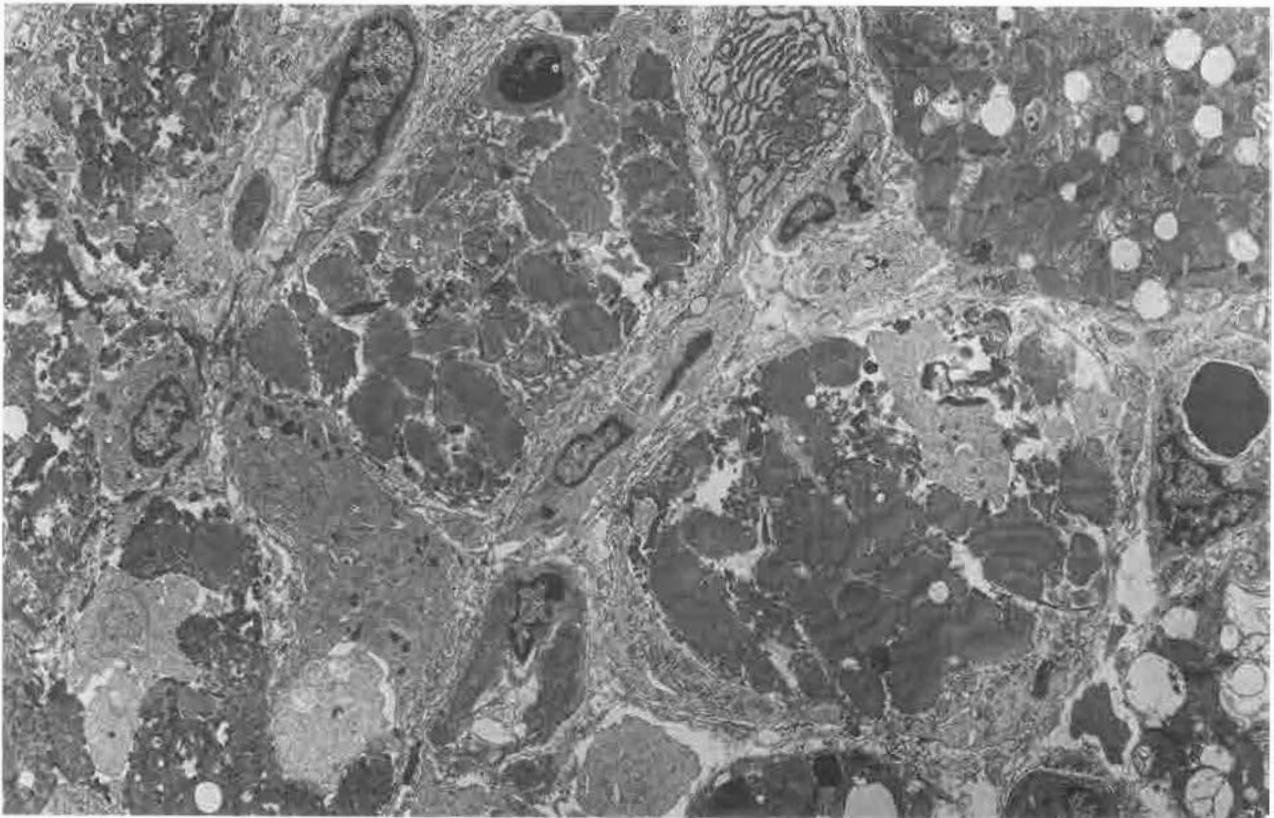


Figure 49—Monensin cardiotoxicity. Cow. Several necrotic myocytes have dense clumps of disrupted contractile material. Numerous macrophages lie in the interstitium and invade necrotic myocytes. Myocytes at left have prominent sarcoplasmic vacuolation. ($\times 4500$)

mal models of chronic doxorubicin-induced cardiotoxicity are used for studying the prevention and management of this complication. Studies in the mouse, rat, rabbit, dog, and monkey have revealed development of chronic cardiotoxicity similar to that seen in human patients with prolonged administration of doxorubicin.⁴⁵³⁻⁴⁷³ The dog has been shown in a number of studies⁴⁵⁴⁻⁴⁵⁷ to provide an excellent model for studies of chronic doxorubicin cardiotoxicity. Characteristic myocardial lesions have been consistently produced in dogs by weekly doses of 1 mg/kg for 15 or 20 weeks or with administration of 1.75 mg/kg every 3 weeks for 7 doses. In rodents, chronic administration of doxorubicin produces not only cardiotoxicity but also renal toxicity and a nephrotic syndrome.^{470,471} Spontaneously hypertensive rats (SHRs) are much more sensitive than Kyoto-Wistar rats to the cardiotoxic effects of doxorubicin.⁴⁵⁸

In our initial studies in pigs, we observed that conventional pigs were susceptible to damage to the alimentary tract and myeloid and lymphoid tissue if large doses of doxorubicin were given.⁴⁵⁹ However, pigs given 0.64, 1.0, or 1.6 mg/kg once a week or 1.6 or 2.4 mg/kg every 3 weeks (mean cumulative dose, 520 mg/sqm) had

prolonged survival and frequently developed subacute or chronic doxorubicin cardiotoxicity. Miniature pigs given doxorubicin, 2.4 mg/kg every 3 weeks for six doses (cumulative dose, 475 mg/sqm), developed consistent lesions of cardiomyopathy with good survival.^{455,460}

Gross lesions of cardiotoxicity in pigs, rabbits, and dogs were hydropericardium, hydrothorax, and ascites. In occasional pigs, fibrinous pericarditis was present. The myocardium was pale, and the hearts were dilated when compared with control hearts (Figures 50 and 51); however, many animals had no gross evidence of cardiotoxicity at necropsy. The microscopic and ultrastructural alterations in the myocardium of pigs, rabbits, and dogs with chronic doxorubicin cardiotoxicity were similar to those in humans and in other species of animals.^{453,457,461-473}

The three major lesions observed in myocytes were 1) sarcoplasmic vacuolization, 2) myocytolysis, and 3) hyaline necrosis (Figures 52-56). The distinctive vacuolar lesions resulted from distention of elements of the sarcoplasmic reticulum and the T-tubules. In mildly affected myocytes, the vacuoles varied from 0.1 to 1 μ in diameter, but in severely affected cells the vacuoles were 1-5 μ in diameter. Myocytolysis was present in

50



51

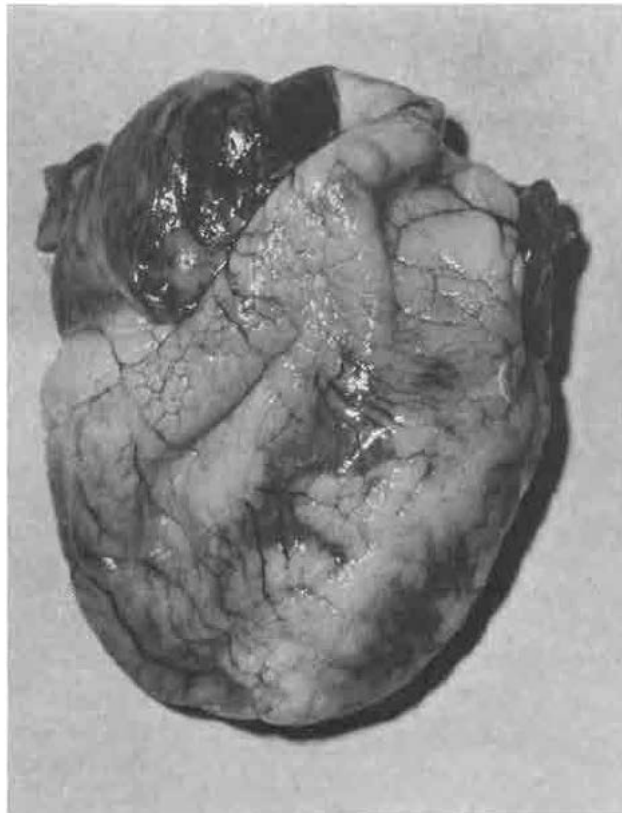


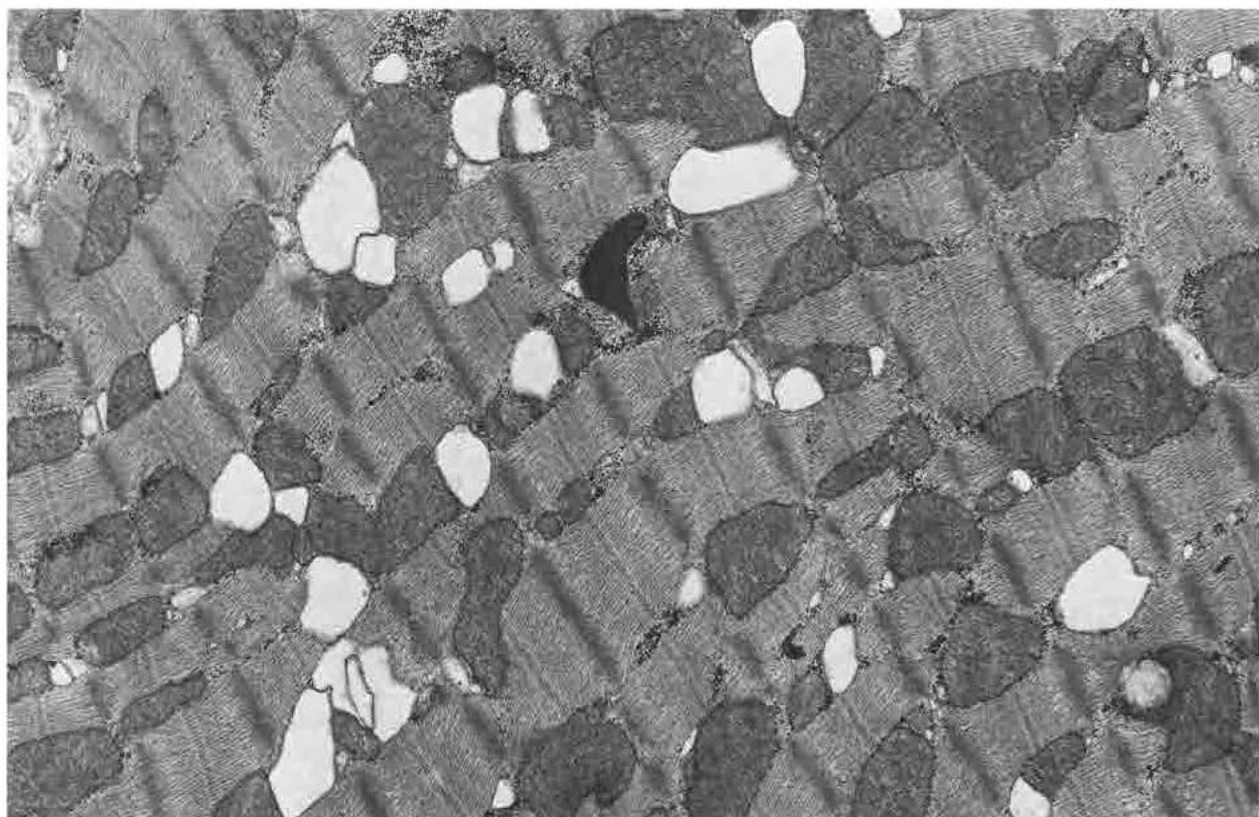
Figure 50—Chronic doxorubicin cardiotoxicity. Rabbit. The heart has marked biventricular dilatation, diffuse pallor, and depleted epicardial fat deposits. **Figure 51**—Heart of a control rabbit has abundant epicardial fat deposits and normal shape.

damaged myocytes either with or without sarcoplasmic vacuolization. Thick myofilaments were preferentially lysed, and irregular clumps of Z-band material were present. Accumulation of glycogen granules and elements of sarcoplasmic reticulum occurred in some fibers undergoing myofibrillar lysis. Affected myocytes also had mitochondrial alterations, consisting of swelling and disruption of membranes, and scattered accumulations of residual bodies. Occasional myocytes showed hyaline necrosis with dense masses of disrupted contractile elements, pyknotic nuclei, and macrophagic invasion. The interstitium showed edema, activated fibroblasts, and a few invading macrophages. Vacuolar degeneration and myocytolysis also were present in Purkinje fibers.

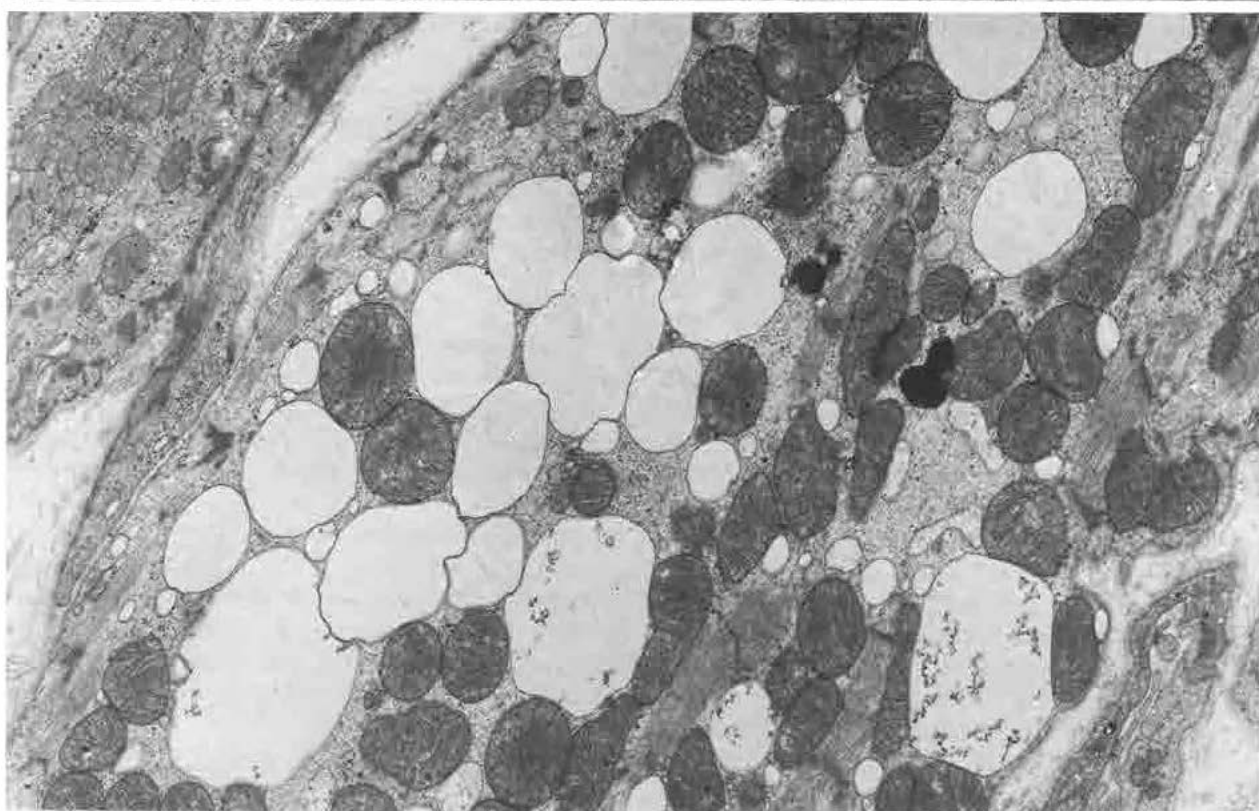
Rabbits, dogs, and pigs have been utilized to evaluate the ability of various compounds such as ICRF-187, vitamin E, selenium, N-acetylcysteine, and thyroxine and lysosomal encapsulation to ameliorate the chronic cardiac lesions.^{454-457,460,474-479} These studies have further established these species as suitable animal models for studies of the cardiotoxicity produced



Figure 52—Chronic doxorubicin cardiotoxicity. Rabbit. Prominent sarcoplasmic vacuolation is present in the left ventricular myocardium. (Plastic-embedded section 1 μ thick, alkaline toluidine blue, $\times 350$)



55



56

Figure 55—Chronic doxorubicin cardiotoxicity. Dog. Mild vacuolation of a left ventricular myocyte has resulted from distention of elements of sarcoplasmic reticulum. ($\times 18,000$) **Figure 56**—Chronic doxorubicin cardiotoxicity. Dog. Marked myofibrillar lysis and sarcoplasmic vacuolation is present in left ventricular myocytes ($\times 15,000$)

by doxorubicin and by other compounds of the anthracycline family.

Cardiotoxicity of Other Antineoplastic Agents

In addition to anthracyclines, other antineoplastic agents are capable of producing myocardial dysfunction and/or anatomic lesions. Among these drugs are mitoxanthrone, cyclophosphamide, 5-fluorouracil, vincristine, and amsacrine (m-AMSA).

Mitoxanthrone

Mitoxanthrone is a synthetic anthraquinone that shares some of the biochemical effects of doxorubicin on nucleic acids. Chronic administration of mitoxanthrone to mice⁴⁸⁰ and monkeys⁴⁸¹ produced myocardial alterations similar in type and severity to those induced by doxorubicin. Affected myocytes showed degeneration and sarcoplasmic vacuolization due to dilatation of sarcoplasmic reticulum. Similar changes were found in myocardial biopsies from human patients receiving mitoxanthrone.^{482,483} However, previous safety studies in dogs had failed to demonstrate significant myocardial morphologic alterations from mitoxanthrone.⁴⁸⁴

Anthracenedione diacetate (NSC-287513), an analog of mitoxanthrone, was found to exert significant acute depression of cardiovascular function in dogs. When administered over 12 weeks, this agent was judged to be less toxic than doxorubicin, but it produced cardiomyopathy in 5 of 6 rabbits and renal toxicosis in 3 of 6.⁴⁸⁵

Cyclophosphamide

Cyclophosphamide, a widely used alkylating agent, produces a syndrome of acute cardiac failure associated with myocardial edema and hemorrhage and fibrinous pericarditis when given to human patients in large doses (45 mg/kg/day for 4–6 days) in order to ablate bone marrow in preparation for bone marrow transplantation.^{486–490} Similar myocardial hemorrhagic necrosis has been produced by cyclophosphamide in dogs⁴⁹¹ and monkeys.⁴⁹² This toxicity is thought to be mediated by damage to endothelial cells, with transudation of the drug and its toxic metabolites into the extravascular compartment. In rhesus monkeys, cyclophosphamide and ifosfamide cause hypotension, bradycardia, cardiac depression, and histamine release.⁴⁹³ Recent evidence suggests that formation of acrolein, a by-product of the metabolism of cyclophosphamide, is an important factor in the pathogenesis of these toxic effects and that they can be ameliorated by disulfiram.⁴⁹⁴ In inbred female ACI rats, cyclophosphamide (three intraperitoneal doses of 150 mg/kg) produced a less acute syndrome

of cardiotoxicity characterized by myocyte vacuolization and hypertrophy, vascular damage, marked lymphocytic infiltration, focal calcification, interstitial fibrosis, and cartilaginous metaplasia.⁴⁹⁵

5-Fluorouracil

Focal myocardial necroses and associated inflammatory reaction were produced in 3–6-month-old Wistar rats by administration of large doses of 5-fluorouracil (125 mg/kg daily for 3 days).⁴⁹⁶ This compound accumulates in myocardium, but to a lesser extent than in other organs,⁴⁹⁷ and is an infrequent cause of cardiac complications (which consist mainly of anginal pain) in humans.^{498–502}

Vincristine

In 3-month-old male CBA/Kw mice, weighing 20–30 g, given 0.4 or 0.8 mg/kg/day of vincristine sulfate for 1–12 days, cardiac ultrastructural changes developed, consisting of focal mitochondrial lysis, increased amounts of autophagic vacuoles, accumulation of myelin figures, dilatation of sarcoplasmic reticulum, and widening of the intercalated disks, with separation of the apposed membranes.⁵⁰³ Another electron-microscopic study showed that administration of single large doses (3 mg/kg) of vincristine or vinblastine to male 250–280-g Wistar rats produced degeneration of noradrenergic nerves (cholinergic nerves were unaffected) and a marked decrease in norepinephrine content in the atria within 24–48 hours.⁵⁰⁴ However, the administration of vincristine to human patients only very rarely has been associated with cardiovascular dysfunction, which has consisted of manifestations suggestive of ischemic heart disease.⁵⁰⁵

AMSA

AMSA (m-amsacrine, 4'-(9-acridinylamino) methanesulfon-m-aniside), an acridine compound effective in the therapy of some refractory leukemias and lymphomas, has been shown to produce severe ventricular arrhythmias, particularly in patients with hypokalemia.^{506–513} In mice, dogs, monkeys, and rabbits, this agent had significant hemodynamic and electrophysiologic effects but did not produce histologic changes.^{514–518} Animal studies failed to support the suggestion that the solvent mixture (containing dimethylacetamide and lactic acid) used in the formulation of AMSA was responsible for the cardiotoxic effects.

Furazolidone Cardiotoxicity in Poultry

Congestive cardiomyopathy is produced in turkeys, ducklings, and chickens by excessive intake of furazoli-

done (FZ).^{42,45,47,53,57,519-542} This disease was first reported by Jankus et al⁴⁵ in 1972 in turkey poultts accidentally exposed to excessive amounts of this antibacterial drug. Since then, numerous studies have been reported on the clinical, pathologic, and biochemical alterations of FZ-induced cardiomyopathy.^{42,519,532} The disease is produced readily by oral administration or feed supplementation of FZ.^{47,528} In turkeys, the gross appearance of the heart is similar in the inherited cardiomyopathy ("round heart disease") described above and in FZ-induced cardiomyopathy.

In ducklings, FZ induced dose-related frequency and severity of clinical disease.^{47,540-542} Signs were growth retardation, ascites, and death. Ducklings fed 750 mg FZ/kg of feed for 28 days developed a high incidence of cardiomyopathy and a low mortality. Cessation of FZ feeding resulted in regression of ascites and reversal of the cardiomyopathy. At necropsy, congestive heart failure was manifested as severe ascites and hydropericardium. The lungs and liver were congested. The hearts were large, with marked biventricular dilatation and thin ventricular walls ("round heart") (Figures 57-60). However, light-microscopic study of the myocardium failed to demonstrate necrosis, inflammation, or fibrosis and instead revealed myocytolysis with pale sarcoplasm (Figure 61). Ultrastructurally, the outstanding alteration was myofibrillar lysis (Figures 62-64). Affected myocytes showed a loss of intact myofibrils, with scattered masses of free thick and thin filaments, clumps of Z-band material, and accumulations of cytoskeletal filaments. Numerous polyribosomes were present in the areas of myofibrillar lysis. It is not known whether the myofibrillar lysis results from FZ-induced decreased synthesis, increased degradation, or disaggregation of contractile proteins. FZ-induced cardiotoxicity in ducklings offers an attractive model for studies of congestive cardiomyopathy.

The clinical and pathologic features of FZ cardiotoxicity appear to be similar in turkey poultts and ducklings. Turkeys are slightly more sensitive to the cardiotoxicity; the disease was produced in this species by feeding 300 mg of FZ/kg of feed. Cardiac dilatation in turkeys developed initially in the right ventricle, with subsequent left ventricular distention.⁵¹⁹ Numerous biochemical studies in FZ-fed turkeys have suggested that FZ may induce 1) inhibition of monoamine oxidase activity, 2) altered carbohydrate metabolism, 3) altered protein metabolism, 4) decreased myocardial content of taurine, and 5) altered lipid metabolism.^{57,525-528,535-537,539} In ducklings, feeding supplements of taurine, selenium, and vitamin E have not ameliorated the cardiotoxicity.⁵⁴⁰ However, administration of propranolol to FZ-fed turkey poultts provided protec-

tion against the development of cardiomyopathy.⁵³¹ Further studies are needed to establish the primary biochemical alterations induced by FZ in the myocardium of birds.

Sodium Chloride Cardiotoxicity in Poultry

Cardiotoxicity with ventricular dilatation ("round heart") and ascites occurs in turkey poultts and broiler chicks with sodium chloride toxicity.^{46,543-546} Turkey poultts with experimental disease, induced by drinking water containing 0.75% NaCl for 3 days, had ultrastructural alterations of myocytes with glycogen accumulation, myofibrillar lysis, and disruption of intercalated disks.⁴⁶ The cardiac lesions were suggested to be mediated via hypertension.

Myocardial Diseases Induced by Poisonous Plants

Numerous syndromes of cardiac failure, with or without skeletal muscle involvement, have been described in grazing ruminants in many areas of the world.⁵⁴⁷⁻⁵⁶⁰ Fluoroacetate toxicity is the poisonous principle involved in a disease described in Australia as "gidyea poisoning" or "Georgina River poisoning" and is produced by *Acacia georginae*, *Gastrolobium* spp. and *Oxylobium* spp. In South Africa the same syndrome is produced by *Dichapetalum cymosum* and is called "gifblaar." Also in South Africa, ruminants may develop a toxic congestive cardiomyopathy called "gousiekte" ("quick disease") from ingestion of *Pachystigma pygmaeum*, *Pachystigma thamnus*, *Pavetta harborii*, *Pavetta schumaniana* and *Fadogia monticola*. In the United States, toxic cardiomyopathy has occurred in ruminants following consumption of *Cassia occidentalis* (coffee senna), *Cassia obtusifolia*, *Karwinskia humboldtiana* (coyotillo), and *Vicia villosa* (hairy vetch). Other plants implicated as cardiotoxic were *Trigonella foenum-graecum* in Israel and *Palicourea marcgravi* in South America. The toxic compound(s) involved with poisoning by the above plants and their mechanisms of cardiotoxicity are generally not known except for those plants containing fluoroacetate, a compound that interferes with cellular aerobic metabolism by blockade of the tricarboxylic acid cycle.

Clinically, most of these plant poisonings are characterized by the sudden onset of congestive cardiac failure. At necropsy, hydropericardium, hydrothorax, and ascites are generally observed. The heart may appear mottled, with dilatation and subserosal hemorrhage. Microscopically, the findings vary, depending on the time of cardiotoxic exposure prior to death. Acute damage will produce multifocal necrosis, and older lesions

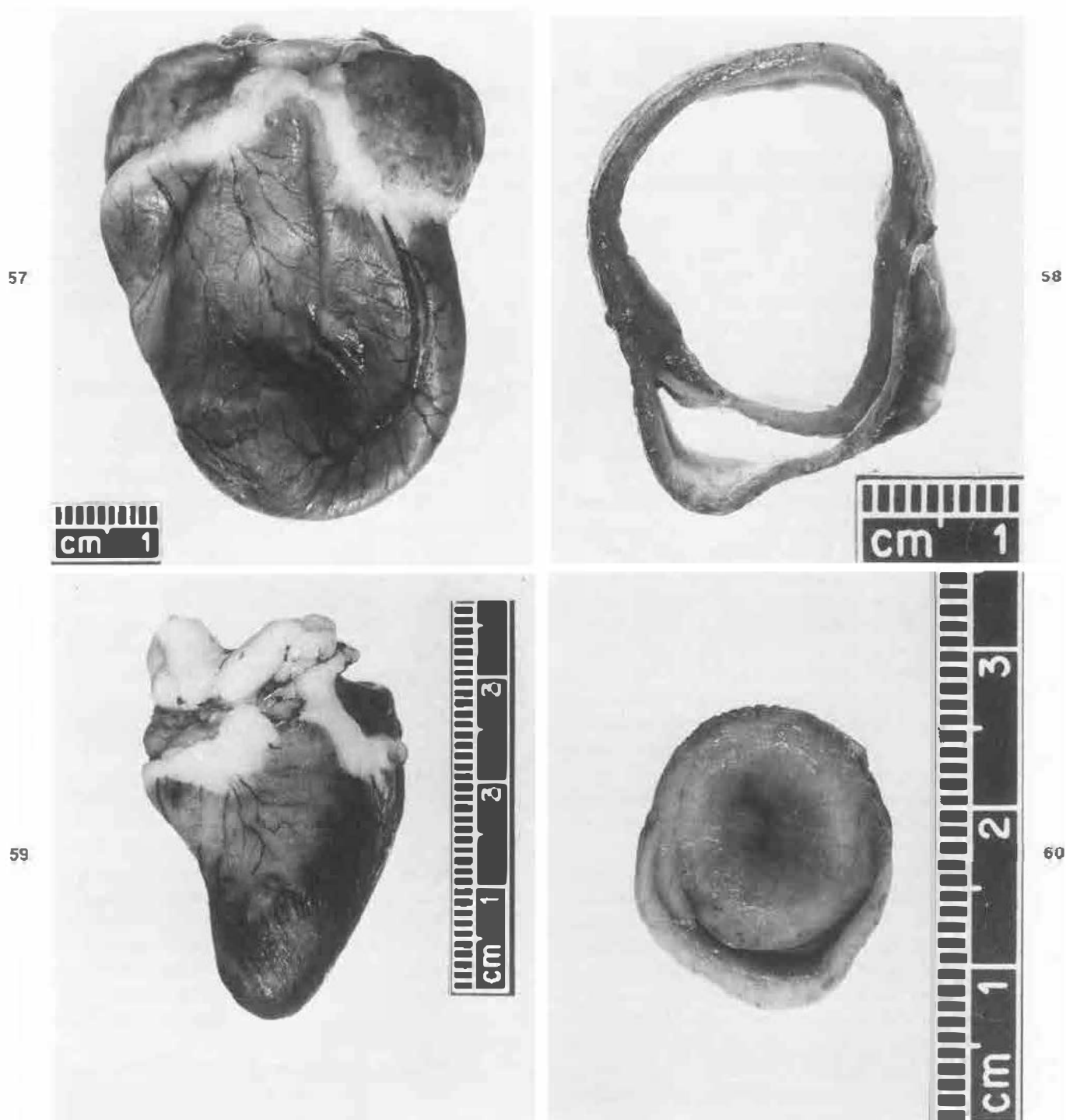
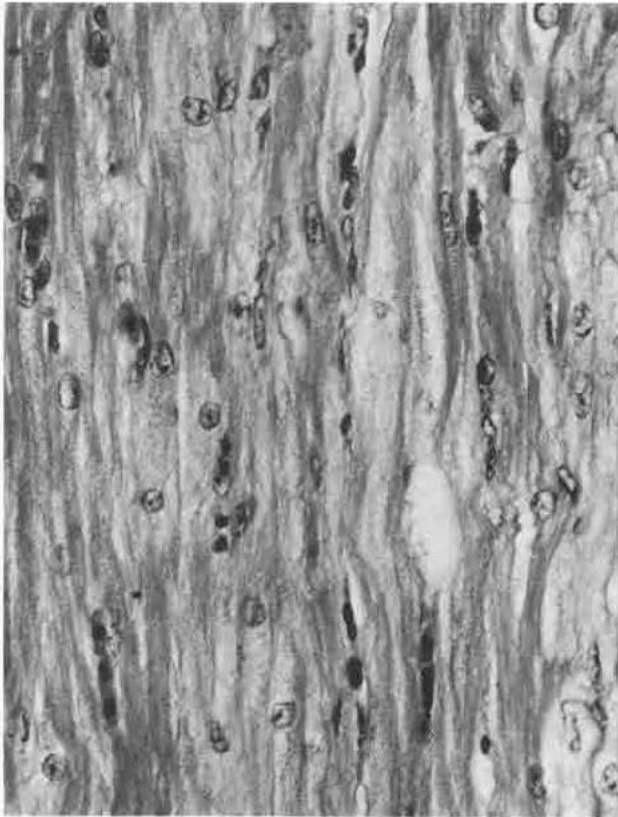
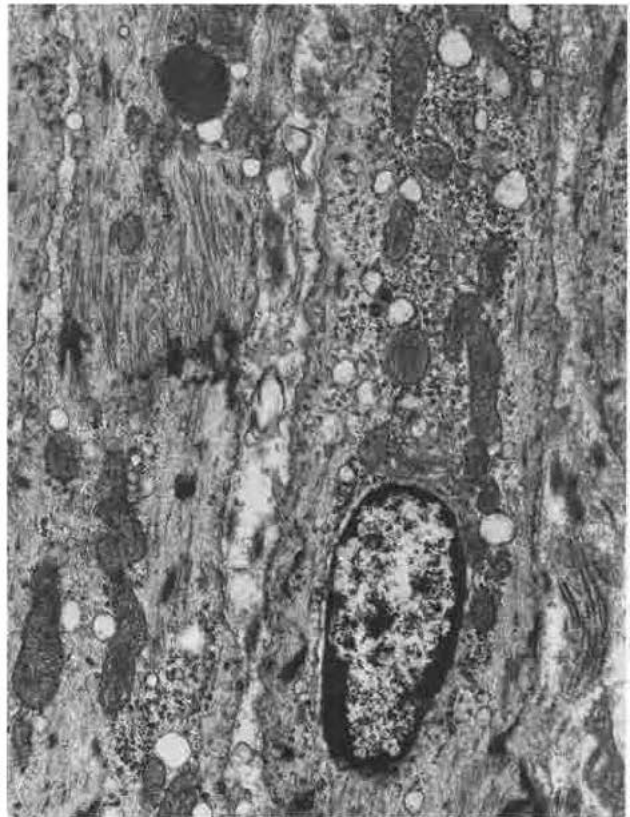


Figure 57—Furazolidone cardiotoxicity. Duckling. Marked cardiomegaly and biventricular dilatation are present. **Figure 58**—Furazolidone cardiotoxicity. Duckling. Transverse section of the ventricular walls of the heart in **Figure 57** shows marked dilatation of the ventricular chambers and thinned walls. **Figure 59**—Heart from a control duckling has normal size and shape. **Figure 60**—Transverse section of the ventricles of the heart in **Figure 59** shows normal chamber size and wall thickness.

61



62



63



64

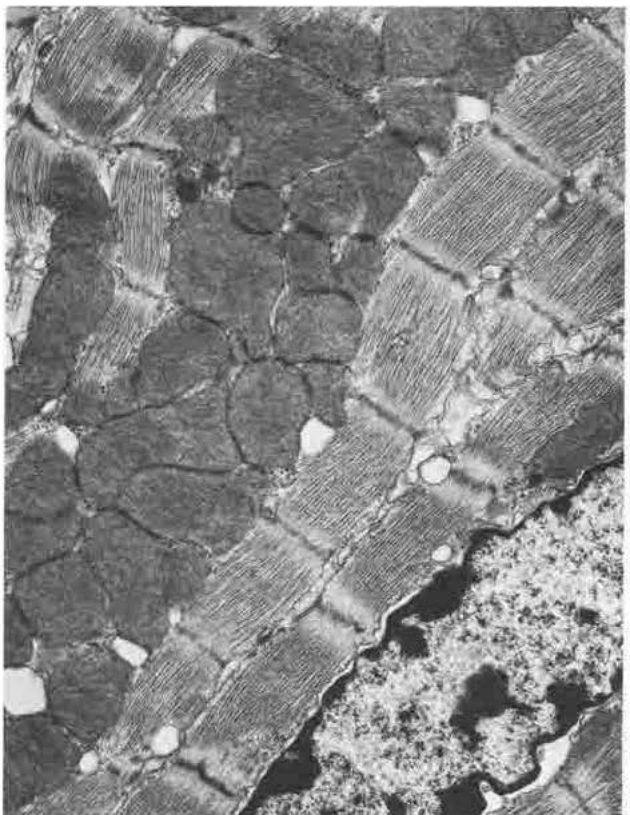


Figure 61—Furazolidone cardiotoxicity Duckling. Left ventricular myocardium shows extensive myofibrillar lysis. (H&E, x500) **Figure 62**—Furazolidone cardiotoxicity Duckling. Diffuse myofibrillar lysis is present in left ventricular myocytes. The sarcoplasm contains scattered free myofilaments and dense clumps of Z-band material and numerous polysomes and mitochondria. (x14,000) **Figure 63**—Furazolidone cardiotoxicity Duckling. Myocytes with early myofibrillar lysis shows abundant intermediate filaments and elements of sarcoplasmic reticulum lying between lysed myofibrils. (x35,000) **Figure 64**—Myocytes from the left ventricle of a control duckling have intact myofibrils and numerous mitochondria. (x14,000)

may show mild inflammatory cell infiltration and replacement fibrosis.

Myocardial Alterations From Vitamin D Toxicosis and Calcinogenic Plants

Myocardial calcification has occurred in pigs fed a calcinogenic plant (*Cestrum diurnum*)⁵⁶¹ or large amounts of vitamin D.^{562,563} The lesions consist of multifocal myocardial calcification and focal calcification of smooth muscle cells in the walls of intramyocardial arteries.

Extensive endocardial mineralization occurs in cattle and horses following prolonged ingestion of calcinogenic plants.⁵⁶⁴⁻⁵⁶⁶ Many names have been applied to this disease in cattle throughout the world, including "Manchester wasting disease" in Jamaica, "enzootic calcinosis" in European countries, "naalehu" in Hawaii, "enteque seco" in Argentina, and "espichamento" in Brazil. The implicated plants include *Solanum malacoxylon*, *Solanum torvum*, *Trisetum flavescens* and *Cestrum diurnum*. The endocardial lesions are accompanied by extensive mineralization of the aorta, lungs, and tendons.

Vitamin D toxicosis in rats produced extensive myocardial damage.⁵⁶⁷⁻⁵⁷⁴ Necrosis and calcification were seen as patchy white areas in the myocardium. Microscopically and ultrastructurally, dense spherical calcified bodies, representing calcified mitochondria, were present in intact and necrotic myocytes (Figures 65 and 66).⁵⁷⁴ Calcification was also present within valves and the walls of intramyocardial arteries (Figures 67 and 68).

Myocardial Damage in Blister Beetle Poisoning of Horses

Ingestion of baled hay contaminated with dead striped blister beetles (*Epicauta*) was reported to produce myocardial, gastrointestinal, and urinary lesions.⁵⁷⁵ The affected myocardium showed pale patches grossly; and necrosis, with or without calcification, was observed microscopically.

Cardiotoxicity of High Erucic Acid Rapeseed Oil

Myocardial lesions occur in rats, rabbits, monkeys, gerbils, turkeys, chickens, ducklings, and pigs fed diets containing long-chain monoenoic fatty acids such as erucic acid, which is found in rapeseed oil.⁵⁷⁶⁻⁵⁸⁴ Male rats were more susceptible than females to the cardiac lesions.⁵⁷⁸ Light- and electron-microscopic studies revealed early lesions of myocardial lipidosis. Later lesions were focal myocardial necrosis, macrophagic invasion, and fibrosis. Ducklings and chicks, but not

turkey poults, were highly susceptible to the cardiotoxicity and developed prominent hydropericardium, ascites, and myocardial pallor.⁵⁸¹ New varieties of rape plants produce rapeseed oil that contains only small amounts of erucic acid.

Cardiotoxicity of Brominated Vegetable Oils

Brominated vegetable oils have been used in North America for nearly 50 years to adjust the density of essential flavoring oils used in the manufacture of citrus-flavored beverages. Safety studies in rats have demonstrated that feeding large amounts of various brominated vegetable oils, including cottonseed oil, corn oil, sesame oil, and olive oil, will induce myocardial lesions.⁵⁸⁵⁻⁵⁹⁰ The earliest myocardial alteration was lipid droplet accumulation; the liver and kidney also showed lipidosis. Later myocardial alterations were multifocal necrosis and myocytolysis.

Cardiotoxicity of Rancid Fat in Mice

Mice inadvertently fed rancid powdered purified diets developed high mortality and cardiac lesions.⁵⁹¹ Affected hearts appeared mottled grossly and had necrotizing hemorrhagic myocarditis on microscopic study. Many animals had hemothorax. Elevated levels of lipoperoxides were detected in feed samples, but selenium and vitamin E concentrations were adequate.

Gossypol Cardiotoxicity

Pigs are very susceptible to poisoning by gossypol, which is found in cottonseed meal, a protein supplement used in swine rations. In affected pigs, congestive heart failure develops, with prominent ventricular dilatation and pulmonary edema.^{103,592} Hepatic necrosis and pale degenerated skeletal muscles also may be present. Microscopically, myocardial necrosis is seen. Similar lesions have been described in dogs with gossypol poisoning.^{593,594}

Myocardial Alterations Induced by Chloroquine

Myocardial alterations were produced in rabbit, rat, and fetal mouse hearts by chloroquine.⁵⁹⁵⁻⁵⁹⁷ In rabbits, multifocal myocardial necrosis was seen. In rat and mouse hearts, numerous myelin figures were found by light and electron microscopy. In rats, the myocardial alterations were shown to be reversible.

Carbon Monoxide and Cigarette Smoke Cardiotoxicity

Myocardial damage has been produced by exposure

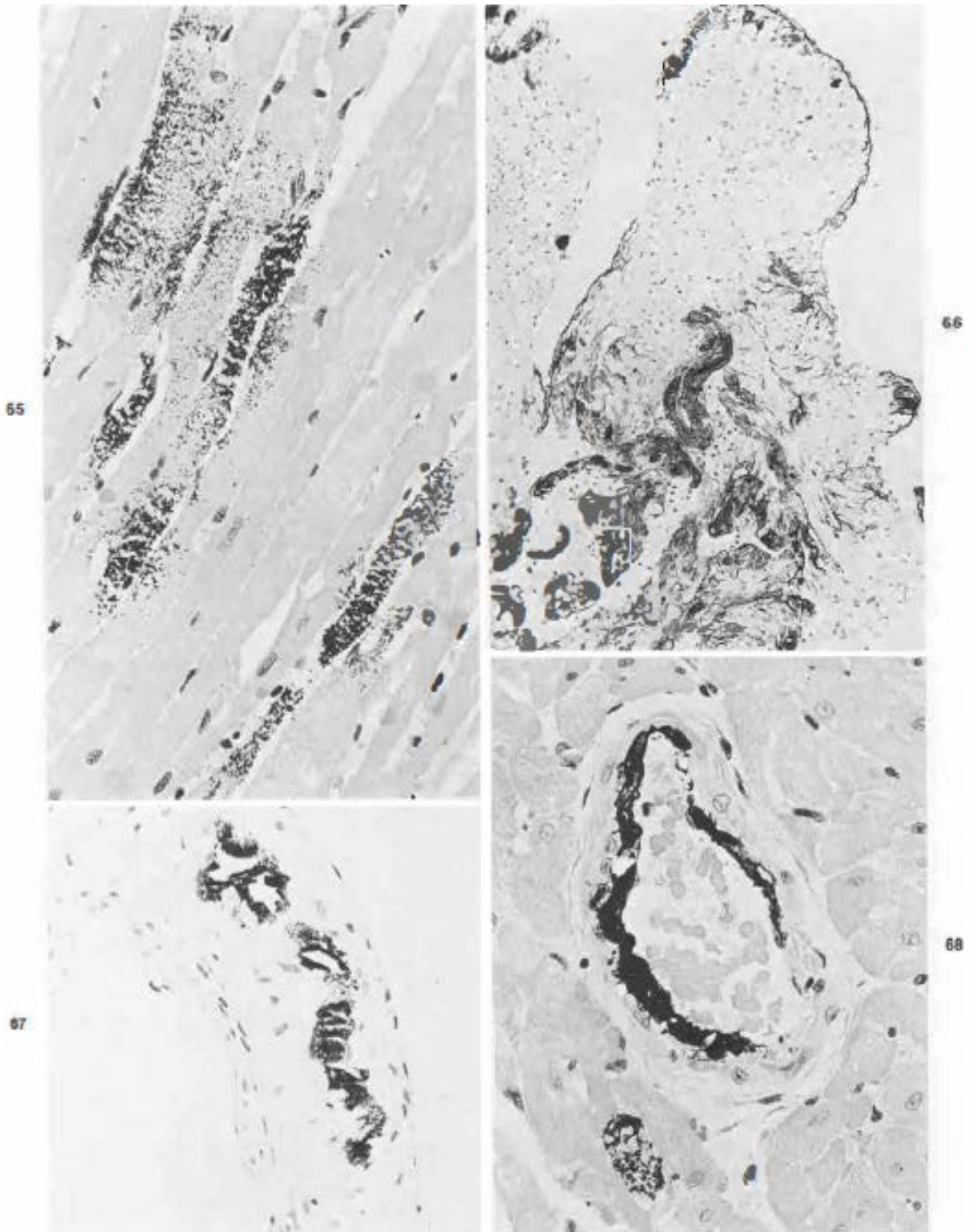
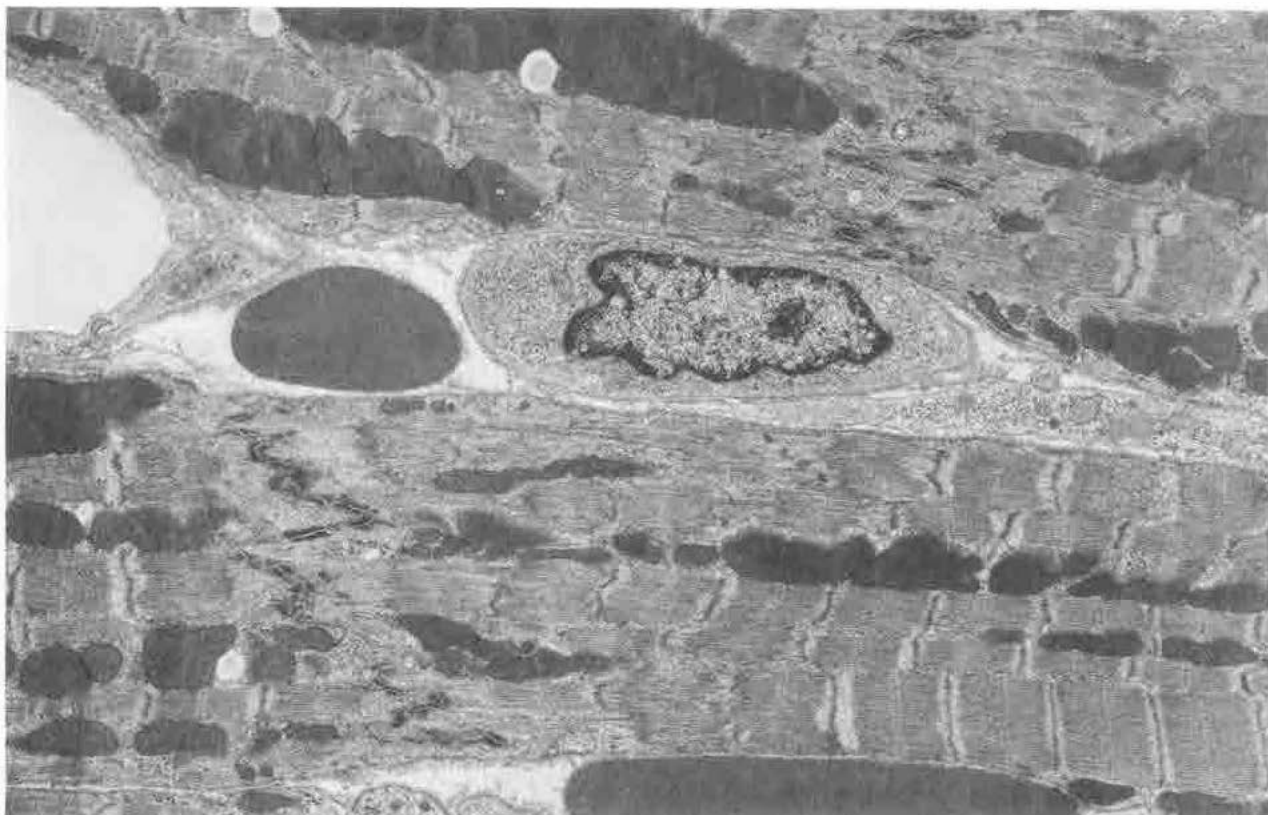


Figure 65—Vitamin D toxicity, Rat. Scattered left ventricular myocytes have granular deposits of mineral. (von Kossa, $\times 350$) **Figure 66**—Vitamin D toxicity, Rat. Extension mineralization is present in left atrial myocardium and endocardium. (von Kossa, $\times 100$) **Figure 67**—Vitamin D toxicity, Rat. Focal mineralization is present in the mitral valve leaflet. (von Kossa, $\times 350$) **Figure 68**—Vitamin D toxicity, Rat. Prominent mineralization is seen in the inner wall of an intramyocardial artery. (von Kossa, $\times 400$)

69



70

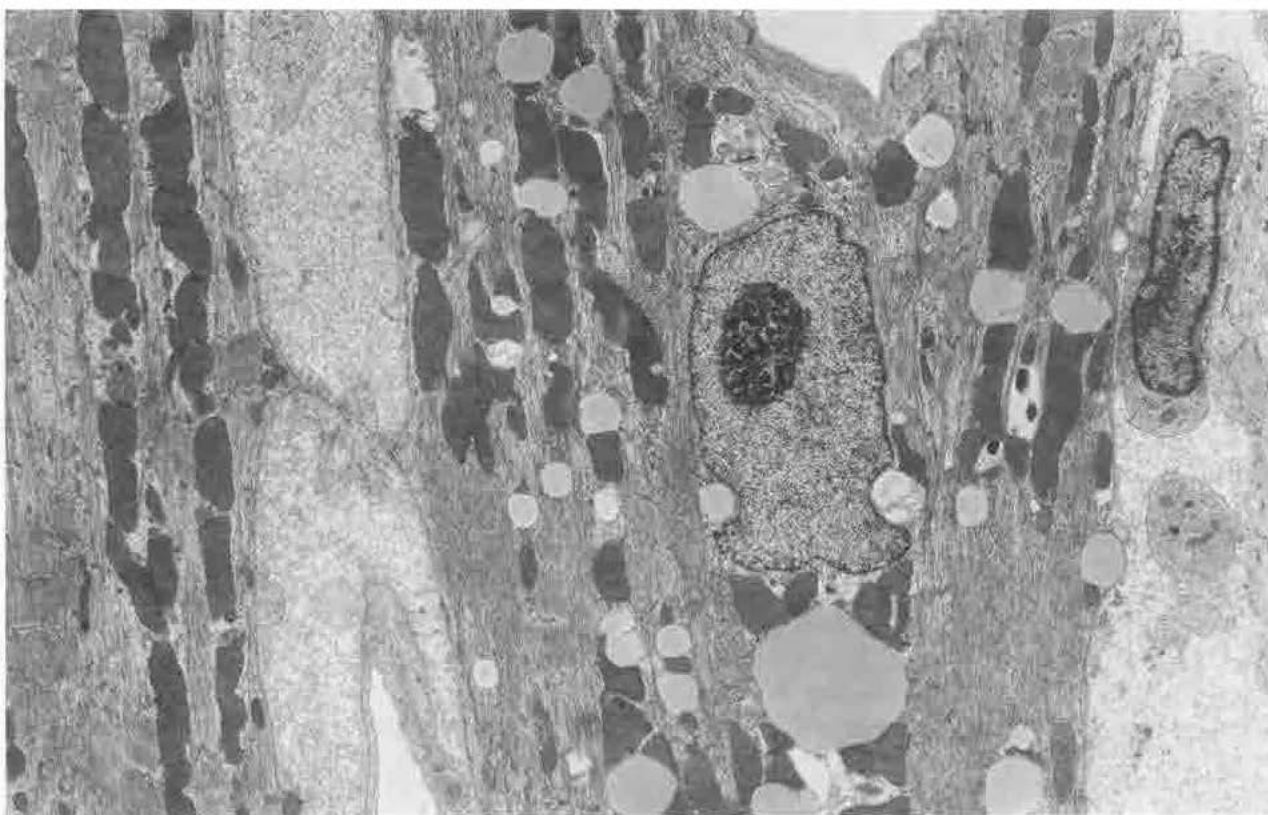


Figure 69—Allylamine cardiotoxicity Rat. Early damage is seen as myofibrillar lysis in areas adjacent to intercalated disks. ($\times 15,000$) **Figure 70**—Allylamine cardiotoxicity Rat. Myocytes with more advanced injury (compare with Figure 69) have diffuse myofibrillar lysis and lipid droplet accumulation. The interstitium shows severe edema. ($\times 15,000$)

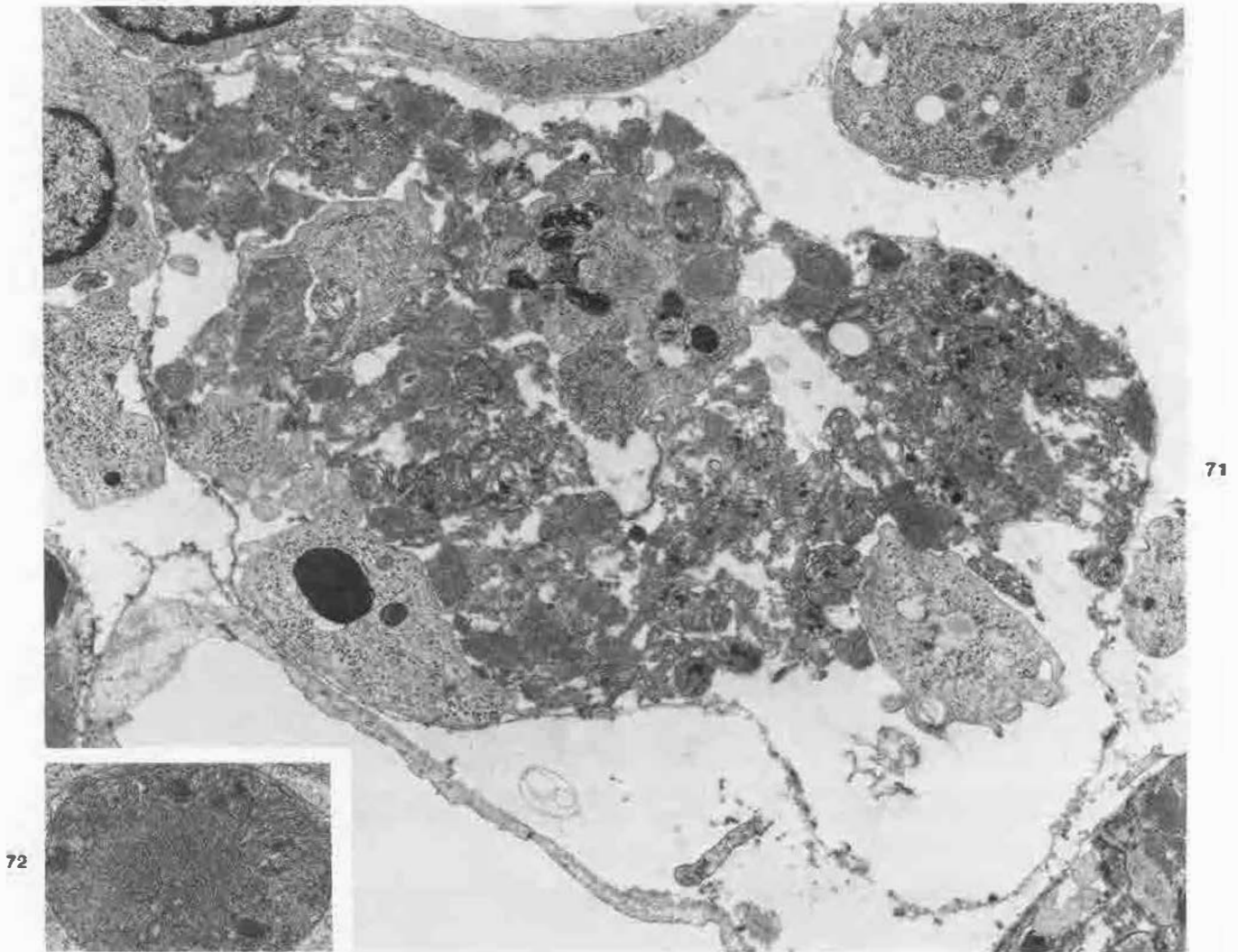


Figure 71—Allylamine cardiotoxicity. Rat. Necrotic myocyte has disrupted contractile material and mitochondria with metrical densities. Macrophages are in the interstitium and within the "tube" of external lamina of the necrotic myocyte ($\times 11,000$). **Figure 72**—Allylamine cardiotoxicity. Rat. Malrical densities are seen in a mitochondrion of a necrotic myocyte ($\times 20,000$).

to carbon monoxide in dogs and rabbits.⁵⁹⁸⁻⁶⁰² In dogs, myocardial degeneration and fibrosis were described. Ultrastructural study of the hearts of exposed rabbits demonstrated myocyte alterations, including contraction bands, myofibrillar lysis, myelin figures, and dehiscence of intercalated disks.

Cigarette smoke inhalation by guinea pigs produced ultrastructural alterations in cardiac muscle cells, including mitochondrial damage, lipid droplet accumulation, and increased numbers of myelin figures and residual bodies.⁶⁰⁰ These alterations were attributed to carbon monoxide exposure.

Cardiotoxicity of T-2 Mycotoxin

Rats given single or multiple doses of T-2 mycotoxin

developed myocardial lesions concentrated in the left ventricular subendocardium.⁶⁰³ Microscopic and ultrastructural study showed myocardial edema and necrosis with subsequent fibrosis.

Papain-Induced Myocardial Necrosis in Rats

Intravenous administration of the proteolytic enzyme papain produced myocardial necrosis in rats.^{604,605} The necrotic foci were observed as yellow-grey areas scattered throughout the myocardium but most numerous in the left ventricle. Microscopic and ultrastructural study showed interstitial edema and myocyte damage with myofibrillar lysis and sarcolemmal disruption. Necrotic myocytes were invaded by inflammatory cells, and late lesions showed fibrosis.



Figure 73—Allylamine cardiotoxicity. Rat. Late lesion of focal calcification of the left ventricular endocardium is seen as a large, dense deposit. ($\times 9000$) **Figure 74**—Allylamine cardiotoxicity. Rat. High magnification of calcified lesion in Figure 73 shows calcification of collagen fibrils. ($\times 24,000$)

Paraphenylenediamine-Induced Myocardial Necrosis

In rats administered paraphenylenediamine cardiac and skeletal muscle lesions developed.^{606,607} Necrotic foci were concentrated in the subendocardium. Microscopic study revealed necrosis, cellular infiltration, and residual fibrosis.

Cardiotoxicity of Brown FK

Brown FK, a food-coloring agent, produces cardiac and skeletal muscle lesions in rats.⁶⁰⁸ In rats given massive doses, myocytes showed myofibrillar lysis and necrosis. Macrophagic invasion and fibrosis subsequently occurred in the necrotic foci. With lower doses of Brown FK, myocardial lipofuscinosis was produced.

Allylamine Cardiotoxicity

Allylamine, an aliphatic amine used in the production of pharmaceuticals and polymers, produces myocardial and vascular alterations in rats.⁶⁰⁹⁻⁶¹³ The myocardial alterations are multifocal necrosis concentrated in the left ventricular subendocardium. These necrotic

areas undergo resolution with extensive fibrosis to form aneurysmal scars in the left ventricular and right ventricular apices. Ultrastructurally, the myocardial damage is evident as interstitial edema with prominent cellular activation and numerous mitoses in interstitial cells and capillary endothelium (Figures 69 and 70).⁶⁰⁹ Severely damaged myocytes develop contraction band necrosis with lipid droplet accumulation (Figures 71 and 72). Erythrocytes are present in the interstitium. Extensive macrophagic invasion occurs into the areas of myocardial necrosis. Endocardial thickening, calcification, and cartilaginous metaplasia also are found in late stages of the lesions (Figures 73 and 74).⁶¹¹

Calves given allylamine developed acute vascular injury and thrombosis with multiple foci of myocardial ischemic damage.⁶¹³ In rats the vascular lesions led to severe fibromuscular intimal thickening in intramural coronary arteries.^{610,612}

Plasmocid Cardiotoxicity

Rats administered toxic amounts of plasmocid had myocardial and skeletal muscle necrosis.⁶¹⁴⁻⁶¹⁶ The myo-

cardiac damage was most severe in the subendocardium of the left ventricle; and microscopic and ultrastructural study showed early mitochondrial alterations, lipid droplet accumulation, and necrosis of myocytes. Macrophagic invasion occurred into necrotic areas. At lower doses, damaged atrial myocytes showed selective lysis of I bands and Z-band alterations; but ventricular myocytes showed intact myofibrils.⁶¹⁴

Hyperoxia Cardiotoxicity

Myocardial lesions have been produced in rats, rabbits, guinea pigs, and hamsters subjected to prolonged normobaric and hyperbaric hyperoxia.⁶¹⁷⁻⁶¹⁹ Animals that die may have lesions of congestion cardiac failure with cardiac dilatation and visceral congestion. Multifocal myocardial necrosis is present, and the most severe lesions are concentrated in the left ventricular papillary muscles and subendocardium. Microscopic and ultrastructural studies showed prominent mitochondrial alterations, dilatation of elements of sarcoplasmic reticulum, lipid droplet accumulation, and necrosis with contraction bands.⁶¹⁹ Macrophagic invasion and fibrosis occur in resolving areas of necrosis.

Ethanol Cardiotoxicity

Numerous attempts have been made to establish an animal model of alcoholic cardiomyopathy in humans. Some reports have demonstrated various myocardial alterations in animals fed large amounts of ethanol, with and without various superimposed nutritional deficiencies.⁶²⁰⁻⁶²⁵ Biochemical and morphologic alterations produced in myocardium of experimental animals by ethanol appear to be numerous⁶²⁶⁻⁶³⁴ and include dilatation of sarcoplasmic reticulum, separation of intercalated disks, alterations in mitochondrial structure, formation of megamitochondria, decreased volume fraction of mitochondria, presence of increased amounts of glycoprotein material in myocardial interstitium, triglyceride deposits within myocytes, depression of myocardial contractility, diminished calcium content and reduction in the uptake and binding of calcium to the sarcoplasmic reticulum, and decrease in protein synthesis (an effect mediated by acetaldehyde). However, Ferrans et al³⁵² reviewed the literature of alcoholic cardiomyopathy in humans and animals and concluded 1) that considerable variability existed in the morphologic data on the cardiotoxicity of ethanol in different studies of a given animal species and among different species, and 2) that none of the animal studies has produced cardiac morphologic alterations comparable to those found in humans with alcoholic cardiomyopathy.

Administration of ethanol potentiated the cardiac

damage in animals with isoproterenol cardiotoxicity, Cocksackie B₃ myocarditis, and *T. cruzi* myocarditis.^{635,636} Administration of 3-amino-1,2,4-triazole, an inhibitor of catalase, caused considerable worsening of morphologic changes caused by ethanol in rat myocardium.⁶³⁶

Emetine Cardiotoxicity

Administration of emetine to rabbits, cats, and dogs, but not rats, produced myocardial lesions.⁶³⁷⁻⁶⁴¹ In rabbits, affected hearts were pale grossly, and microscopic and ultrastructural study showed contraction-band necrosis. Mitochondrial damage has been observed in myocardial biopsies from human patients with emetine cardiotoxicity.⁶³⁹ Myocardial necrosis and fibrosis was described in rabbits and cats with emetine cardiotoxicity.^{637,640}

Renal Failure

Cardiac lesions have been described in animals with experimentally induced and spontaneously occurring renal disease.^{108,642-650} Myocardial necrosis is consistently found in rats, dogs, and rabbits with experimentally induced acute renal hypertension.^{643-645,648,650} Procedures used to create renal hypertension have included unilateral renal ischemia, bilateral nephrectomy with administration of crude kidney extracts, and angiotensin administration. Focal myocardial necrosis with contraction bands was especially prominent in the left ventricular subendocardium.⁶⁴⁵ In early lesions, hemorrhage and edema were present; mononuclear leukocytic infiltration was prominent in the necrotic foci after several days. The myocardial lesions may be the direct effect of angiotensin or may be mediated by increased release of endogenous catecholamines.⁶⁴³

Other cardiac lesions occur in uremic dogs with experimental toxic nephroses and spontaneous nephritis.^{108,642,646,649} In acute renal insufficiency, distinctive necrotizing ulcerative lesions are present in the left atrial endocardium and intima of the proximal aorta and pulmonary arteries. In dogs that recover, raised, firm, rough healed lesions remain as residual alterations in the left atrium, aorta, and pulmonary artery. Dogs with chronic renal disease may have cardiac hypertrophy.^{647,649} Uremic pericarditis, although frequent in human patients, occurs only rarely in dogs and cats.¹⁰⁸

Myocardial Diseases Associated With Physical Injuries

This group of diseases represents a wide variety of insults that produce myocardial necrosis. In general, similar diseases have been seen in man. In animals, these

diseases occur sporadically under natural conditions or are solely recognized as experimental diseases.

Central Nervous System Lesions and Trauma

Myocardial necrosis and/or hemorrhage has been described in animals with spontaneous and experimentally induced central nervous system (CNS) lesions. King et al⁶⁵¹ reported 59 cases in dogs, sheep, cows, goats, pigs, and horses. Occasionally the cardiac lesions produced death by arrest or resulted in arrhythmias, but generally the cardiac damage was detected as an incidental finding at necropsy following euthanasia or natural death from irreversible CNS disease. The CNS lesions found in animals with heart lesions included trauma associated with vertebral and skull fractures, infections, and degenerative diseases. Cardiac lesions have been produced experimentally by intracranial injection of blood in mice,⁶⁵²⁻⁶⁵⁴ rats,⁶⁵⁵ and dogs,⁶⁵⁶ and by electrical stimulation of stellate ganglia in dogs,^{657,658} mesencephalic reticular formation in cats,⁶⁵⁹ vagus nerve in baboons,^{660,661} and hypothalamus in cats and monkeys.⁶⁶²⁻⁶⁶⁵

In a clinical study of 10 dogs with development of cardiac arrhythmias (premature ventricular contractions and ventricular tachycardia) from 1 to 48 hours after trauma, disseminated myocardial necrosis was observed in a dog that died 4 days after trauma.⁶⁶⁶ Eight of 10 affected dogs had been hit by an automobile, and most of the dogs had multiple skeletal fractures.

The cardiac lesions associated with this group of injuries were multiple pale foci or streaks of necrosis and calcification with preferential involvement of the left ventricular subendocardium and left ventricular papillary muscles and left ventricular subendocardial hemorrhage. Light-microscopic and ultrastructural studies revealed myocardial necrosis with contraction bands, infiltration of mononuclear leukocytes, and proliferation of fibroblasts.

The cardiac lesions are presumed to result from sympathetic overactivity and local catecholamine release in the myocardium.⁶⁶⁷ The myocardial lesions are similar to those produced by administration of excessive doses of catecholamines. Protection studies in mice with experimentally induced intracranial hemorrhage showed cardioprotection by reserpine (blocked catecholamine release) and partial protection by atropine, propranolol, and adrenalectomy.^{654,655}

Stress

Cardiac necroses, which occur in association with various forms of stress in animals, can be divided into two groups: those in which cardiac lesions develop with-

out coexisting lesions in skeletal muscle and those in which skeletal muscle lesions are associated with cardiac lesions and constitute a predominant or important aspect of the clinicopathologic picture. This latter group includes the exertional rhabdomyolysis, or "capture myopathy" syndrome, and the porcine stress syndrome.

Stress-induced cardiac necroses without accompanying skeletal muscle lesions (the latter, however, may not have been specifically searched for) have been observed in immobilization or restraint in rats,⁶⁶⁸ overcrowding in rats⁶⁶⁹ and rabbits,^{670,671} repeated small electric shocks in rats⁶⁷² and squirrel monkeys,⁶⁷³⁻⁶⁷⁵ exposure to cold in kangaroo rats,⁶⁷⁶ exposure to heat in rats,⁶⁷⁷ restraint and water immersion in rats,^{678,679} various emotional and painful stresses in rats,⁶⁸⁰⁻⁶⁸³ conflictive situations in rats with borderline hypertension,⁶⁸⁴ the stress associated with acceleration in pigs and a variety of other species,⁶⁸⁵ auditory stimuli (tape recording of hissing cats and squealing rats) in wild rats and to a much lesser extent in domesticated rats,⁶⁸⁶ gastric dilatation/volvulus in dogs,^{32,687-689} and sudden death with focal myocardial necroses in calves.⁶⁹⁰⁻⁶⁹²

The cardiac lesions in rabbits subjected to overcrowding progressed to myocardial fibrosis, endocardial thickening, and ventricular dilatation. Of 44 rabbits subjected to crowding, only 9 survived more than 10 months; 20 died during the first month, and 15 died between the second and ninth months.⁶⁷¹ No necrosis was found in animals subjected to prolonged isolation⁶⁹³; however, these animals had a greatly increased sensitivity to the cardiotoxicity of isoproterenol,^{694,695} epinephrine,⁶⁹³ and d-amphetamine.⁶⁹⁶

Perret⁶⁹⁷ made histologic investigations over a 10-year period on 164 lesser mouse lemurs (*Microcebus murinus*) that died spontaneously in captivity. The principal lesions found were chronic nephrosis with nephritis (which affected 90% of the animals), focal areas of myocardial necrosis or fibrosis in the left ventricular wall, various changes in the endocrine glands, and a variety of other abnormalities. Analysis of the data led to the conclusion that the whole captive population of lesser mouse lemurs suffered from a syndrome leading to renal insufficiency and premature death. Most of the pathologic changes observed in this syndrome were of the type considered to be associated with aging in mammals. Perret hypothesized that these changes were due to an overload of cortico- and meduloadrenal secretions, and that they could be induced by stress factors occurring in captivity.⁶⁹⁷

Gastric dilatation, with or without associated volvulus, is a potentially fatal disease of humans, dogs, and other animals.⁶⁸⁸ Large-breed dogs are commonly affected. The mortality is high and is attributable to hypovolemic and neurogenic shock, endotoxemia, dis-

seminated intravascular coagulation with secondary fibrinolysis, acid-base and electrolyte imbalance, circulating myocardial depressant factors, and a surprisingly high incidence (42%) of cardiac arrhythmias. The latter were generally ventricular in origin (ventricular tachycardia in 23 of 48 dogs) and were considered to be due to reduced cardiac output (decreased venous return as a consequence of compression of the caudal vena cava and the portal vein by the dilated stomach). Nevertheless, of 13 dogs with gastric dilatation/volvulus, 8 had cardiac arrhythmias and cardiac necrosis with contraction bands.⁶⁸⁹ One dog had cardiac lesions with arrhythmias; 2 had arrhythmias without lesions, and 2 had neither. Thus, myocardial damage (whether due to ischemia, to stimulation of the autonomic nervous system, or to a combination of these factors) also must be considered a potential contributing factor in the pathogenesis of these arrhythmias.

Five of 8 dogs in which experimental gastric distention was induced for 20 minutes had gross and microscopic lesions of myocardial necrosis, especially in the left ventricular myocardium, 3 days later. The lesions were evident as yellow to white subendocardial areas in the papillary muscles and free wall of the left ventricle.⁶⁸⁷

Overexertion

Captured wild animals may die from stress-associated necrosis of skeletal and cardiac muscle. This syndrome has been termed capture myopathy, exertional rhabdomyolysis, and overstraining disease.⁶⁹⁸⁻⁷⁰⁰ Cases have been described in nonhuman primates, 22 different African ungulates, deer, mountain goats, antelopes, seals, and flamingoes. In affected animals generalized muscle weakness and dyspnea develop. Some animals die within several hours after overexertion, most die after 2-4 days, and a few die 1-4 weeks after stressing. Necropsy reveals generalized pallor of necrotic skeletal muscles, myoglobinuria, myoglobinuric nephrosis, and multifocal myocardial necrosis. Cardiac lesions attributed to capture have been reported in some species in the absence of massive skeletal muscle necrosis.⁷⁰¹

In Chacma baboons, Weber et al⁷⁰² found a high incidence of focal myocardial necroses in various stages of evolution. Adrenal cortical necroses were common in animals with cardiac lesions. Stress was considered to be an etiologic factor; however, this could not be clarified, because many of the animals in this study had been used for various surgical procedures.

Exertional rhabdomyolysis has long been recognized in horses, and myocardial necrosis may be present in fatal cases, along with skeletal muscle necrosis, myoglobinuria and myoglobinuric nephrosis.^{97,103,703} Vari-

ous terms have been applied to the disease, including azoturia, paralytic myoglobinuria, and exertional rhabdomyolysis. Similar lesions have also been described in cattle and sheep with transport myopathy, a syndrome produced by overexertion.^{26,102} The clinical disease in horses is often precipitated shortly after the onset of muscular exertion that followed a period of several days of rest.

Focal myocardial necrosis was reported in 15-30% of nonhuman primates that underwent necropsy after death from various spontaneous diseases and experimental procedures.^{701,702,704} Microscopic examination revealed myocardial necrosis with contraction bands, mitochondrial mineralization, invasion of a few mononuclear leukocytes, and resolving lesions with fibrosis. The etiology of these lesions has not been established, although a relationship to stress has been postulated.

A syndrome of sudden death with myocardial necrosis precipitated by intense, excitement, such as that produced at feeding time, has been described in calves.^{680-692,705,706} The disease is sporadic but may occur repeatedly in affected herds. Affected calves are generally 1-8 weeks old and die within several minutes to several hours following the onset of dyspnea, bawling, and hemorrhagic nasal discharge. At necropsy, lesions of acute congestive failure may be seen, including pulmonary edema, hydrothorax, and hepatic congestion. Grossly, the hearts may be dilated and show pale areas of myocardial necrosis, especially in the subendocardium of the left ventricular free wall and the ventricular septum. Microscopic and ultrastructural study reveals damaged myocytes with hyaline necrosis or necrosis with contraction bands. In some cases, myocardial necrosis is not detected in paraffin-embedded hematoxylin and eosin (H&E)-stained sections but is observed in sections stained by hematoxylin-basic fuchsin-picric acid and in semithin sections of plastic-embedded tissue stained with toluidine blue. Skeletal muscle lesions have not been found, and the selenium status of other animals in affected herds was either deficient or adequate. Etiologic factors suggested have included enterotoxemia and inherited susceptibility, but as yet the syndrome must be considered idiopathic.

Myocardial necrosis may occur in pigs dying of porcine stress syndrome (PSS) or malignant hyperthermia and in swine subjected to restraint stress.^{5,101,564,707-712} A high degree of heritability has been shown for PSS in several breeds, and the basic metabolic defect apparently involves abnormal Ca^{2+} movement in cardiac and skeletal muscle cells. The clinical syndrome may be precipitated in susceptible pigs by administration of halothane or succinylcholine or by various emotional and physical stresses such as transportation, high am-

bient temperatures, high humidity, running, fighting, or mating. Affected pigs show exhaustion, collapse, dyspnea, hyperthermia, patchy cutaneous congestion, muscular rigidity, severe lactic acidosis, and death within minutes. At necropsy, the skeletal muscles may be pale and moist; and some pigs will show cardiac lesions of scattered pale areas in the left ventricular myocardium and epicardial and endocardial hemorrhages. Microscopic and ultrastructural studies of myocardium show either hyaline necrosis or necrosis with contraction bands.

Restraint stress, produced by administration of muscle relaxants and subsequent electrical stimulation, resulted in extensive myocardial necrosis with elevated blood catecholamine concentrations. Amygdalectomy and administration of propranolol prevented the development of cardiac lesions and the increase in catecholamine levels.^{710,713} Affected hearts had pale areas of necrosis in the left ventricular free wall, with selective involvement of the inner third of the myocardium and the papillary muscles and multiple areas of epicardial, endocardial, and myocardial hemorrhage. Pharmacologic restraint induced by succinylcholine produced more severe myocardial and skeletal muscle necrosis in stress-susceptible than in non-stress-susceptible pigs.⁷¹⁴

Cardiac failure precipitated by stress is increasing in frequency in modern swine after continual genetic selection for prominent carcass musculature because the PSS trait and prominent muscularity are transmitted by similar genes. The hearts of these pigs have limited reserve capacity, due, in part, to the relatively low cardiac weight.⁷¹⁵

A syndrome of malignant hyperthermia also occurs in humans, most often on a familial basis, and has many clinical and pathologic similarities to the syndrome in pigs, including having stress and anesthesia (halothane and succinylcholine) as precipitating factors⁷¹⁶ and the occurrence of myocardial necrosis with contraction bands.^{717,718}

Radiation

Rabbits and rats exposed to single or fractionated doses (2000 rads) of roentgen radiation developed myocardial fibrosis with congestive cardiac failure.⁷¹⁹⁻⁷²⁹ The severity of myocardial damage was dose-dependent. Sequential morphologic studies revealed an initial acute pancarditis followed by a latent phase from 2 to 70 days after irradiation and a late phase of progressive cardiac disease after 70 days. Ultrastructural study showed selective damage to blood capillary endothelium in the myocardium. Fibrin and platelet microthrombi were present in damaged vessels, and ischemic injury was ini-

tiated in the myocardium. Slowly progressive myocardial fibrosis followed, and congestive heart failure developed terminally.

A synergistic effect of combined cardiac X-radiation and doxorubicin-induced cardiotoxicity produced myocardial damage in rabbits⁷¹⁹ at considerably lower cumulative doses of doxorubicin than in rabbits given doxorubicin alone.

Cardiac irradiation in dogs produced dose-related severity of cardiac damage.⁷³⁰⁻⁷³² Grossly, the pericardium was thickened by fibrosis. Accumulation of serosanguinous pericardial fluid resulted from vascular damage, and both atrial appendages showed hemorrhage and fibrosis. Microscopically, dose-related fibrosis was present in the epicardium, endocardium, and myocardium; and decreased capillary volume was seen in the myocardium. In a previous study of radiation injury in dogs, it was reported that selective damage with hemorrhage and fibrosis occurred in the right atrium.⁷³³ However, this selective damage apparently resulted from a greater irradiation dose having been given to the right atrium than to the other portions of the heart.

Electrical Defibrillation

In dogs, administration of strong shocks of intensity several times greater than threshold intensity by electrodes positioned on the thoracic wall, on the epicardium, or against the endocardium produces lesions of myocardial necrosis.⁷³⁴⁻⁷⁴⁷ By 2 hours after shock, pale areas of myocardial necrosis are seen grossly in areas of high current density. Such areas are either adjacent to the electrodes on the serosal surfaces of the heart or within a path between the electrodes placed on the thoracic wall. By 2 days after shock, the necrotic myocardium is calcified and appears yellowish-white. Microscopically and ultrastructurally, the damaged fibers have necrosis with contraction bands and mitochondrial mineralization. Macrophagic invasion is prominent at 4 days after shock. At 2 and 8 weeks after shock, the residual lesions of shock-induced damage are focal loss of myocytes and stromal collapse.

Factors that increase the severity of shock-induced myocardial necrosis are 1) application of shocks of increased strength, 2) use of small electrodes, 3) delivery of multiple shocks, and 4) application of several shocks with short intervals between each shock.

Acceleration Stress

In pigs exposed to acceleration stress cardiac lesions developed that were similar to those seen after restraint stress.^{685,748-752} At necropsy, prominent subendocardial

bient temperatures, high humidity, running, fighting, or mating. Affected pigs show exhaustion, collapse, dyspnea, hyperthermia, patchy cutaneous congestion, muscular rigidity, severe lactic acidosis, and death within minutes. At necropsy, the skeletal muscles may be pale and moist; and some pigs will show cardiac lesions of scattered pale areas in the left ventricular myocardium and epicardial and endocardial hemorrhages. Microscopic and ultrastructural studies of myocardium show either hyaline necrosis or necrosis with contraction bands.

Restraint stress, produced by administration of muscle relaxants and subsequent electrical stimulation, resulted in extensive myocardial necrosis with elevated blood catecholamine concentrations. Amygdalectomy and administration of propranolol prevented the development of cardiac lesions and the increase in catecholamine levels.^{710,713} Affected hearts had pale areas of necrosis in the left ventricular free wall, with selective involvement of the inner third of the myocardium and the papillary muscles and multiple areas of epicardial, endocardial, and myocardial hemorrhage. Pharmacologic restraint induced by succinylcholine produced more severe myocardial and skeletal muscle necrosis in stress-susceptible than in non-stress-susceptible pigs.⁷¹⁴

Cardiac failure precipitated by stress is increasing in frequency in modern swine after continual genetic selection for prominent carcass musculature because the PSS trait and prominent muscularity are transmitted by similar genes. The hearts of these pigs have limited reserve capacity, due, in part, to the relatively low cardiac weight.⁷¹⁵

A syndrome of malignant hyperthermia also occurs in humans, most often on a familial basis, and has many clinical and pathologic similarities to the syndrome in pigs, including having stress and anesthesia (halothane and succinylcholine) as precipitating factors⁷¹⁶ and the occurrence of myocardial necrosis with contraction bands.^{717,718}

Radiation

Rabbits and rats exposed to single or fractionated doses (2000 rads) of roentgen radiation developed myocardial fibrosis with congestive cardiac failure.⁷¹⁹⁻⁷²⁹ The severity of myocardial damage was dose-dependent. Sequential morphologic studies revealed an initial acute pancarditis followed by a latent phase from 2 to 70 days after irradiation and a late phase of progressive cardiac disease after 70 days. Ultrastructural study showed selective damage to blood capillary endothelium in the myocardium. Fibrin and platelet microthrombi were present in damaged vessels, and ischemic injury was ini-

tiated in the myocardium. Slowly progressive myocardial fibrosis followed, and congestive heart failure developed terminally.

A synergistic effect of combined cardiac X-radiation and doxorubicin-induced cardiotoxicity produced myocardial damage in rabbits⁷¹⁹ at considerably lower cumulative doses of doxorubicin than in rabbits given doxorubicin alone.

Cardiac irradiation in dogs produced dose-related severity of cardiac damage.⁷³⁰⁻⁷³² Grossly, the pericardium was thickened by fibrosis. Accumulation of serosanguinous pericardial fluid resulted from vascular damage, and both atrial appendages showed hemorrhage and fibrosis. Microscopically, dose-related fibrosis was present in the epicardium, endocardium, and myocardium; and decreased capillary volume was seen in the myocardium. In a previous study of radiation injury in dogs, it was reported that selective damage with hemorrhage and fibrosis occurred in the right atrium.⁷³³ However, this selective damage apparently resulted from a greater irradiation dose having been given to the right atrium than to the other portions of the heart.

Electrical Defibrillation

In dogs, administration of strong shocks of intensity several times greater than threshold intensity by electrodes positioned on the thoracic wall, on the epicardium, or against the endocardium produces lesions of myocardial necrosis.⁷³⁴⁻⁷⁴⁷ By 2 hours after shock, pale areas of myocardial necrosis are seen grossly in areas of high current density. Such areas are either adjacent to the electrodes on the serosal surfaces of the heart or within a path between the electrodes placed on the thoracic wall. By 2 days after shock, the necrotic myocardium is calcified and appears yellowish-white. Microscopically and ultrastructurally, the damaged fibers have necrosis with contraction bands and mitochondrial mineralization. Macrophagic invasion is prominent at 4 days after shock. At 2 and 8 weeks after shock, the residual lesions of shock-induced damage are focal loss of myocytes and stromal collapse.

Factors that increase the severity of shock-induced myocardial necrosis are 1) application of shocks of increased strength, 2) use of small electrodes, 3) delivery of multiple shocks, and 4) application of several shocks with short intervals between each shock.

Acceleration Stress

In pigs exposed to acceleration stress cardiac lesions developed that were similar to those seen after restraint stress.^{685,748-752} At necropsy, prominent subendocardial

hemorrhages were present in the left ventricle. The cardiac hemorrhages were more prominent in adult miniature swine than in adult conventional pigs. Microscopically, extravasated erythrocytes surrounded Purkinje fibers; and areas of necrosis with contraction bands were present in the left ventricular subendocardial myocardium, especially in the papillary muscles. The hemorrhagic lesions were prevented by propranolol, but not by atropine. The cardiac lesions may have been the result of emotional stress sustained by the pigs during the manipulations related to the acceleration procedure, because control pigs that were handled similarly but were not exposed to the acceleration had lesions that were similar to those in pigs exposed to high, sustained acceleration.⁷⁵²

Cardiac lesions have also been produced in rats and chickens exposed to acceleration stress.^{753,754}

Hemorrhagic Shock

Myocardial lesions consistently develop in dogs, cats, rabbits, pigs, and monkeys subjected to hemorrhagic shock and may play a major role in the evolution of irreversible shock.⁷⁵⁵⁻⁷⁶² Numerous studies in dogs have characterized the pathophysiologic and pathologic alterations involved in development of this cardiac damage. Two types of myocardial lesions are induced by shock, and the severity of the lesions is related to the duration of shock and subsequent survival time. Subendocardial hemorrhage and necrosis are concentrated in the ventricular subendocardium and are especially pronounced in the papillary muscles of both ventricles and in the middle of the ventricular septum. These lesions are related to hypoxia and are prevented by administration of hyperbaric oxygen.⁷⁶¹ The second type of myocardial alteration is reversible and has been termed "zonal lesions." Zonal lesions are the result of hypercontraction of cardiac muscle cells and are characterized microscopically and ultrastructurally by an organelle-free zone that is adjacent to intercalated disks and results from longitudinal displacement of the myofibrils and mitochondria.⁷⁶⁰ Zonal lesions are more extensive and widespread in hearts than are subendocardial hemorrhage and necrosis. The zonal lesions are most frequent in the subendocardial myocardium and in the ventricular papillary muscles. Zonal lesions are not due to hypoxia and hyperbaric oxygen is not protective. However, zonal lesions are ameliorated either by administration of β -adrenergic blockers or by prevention of tachycardia by surgical production of complete heart block.⁷⁵⁹ Several papers^{755,759,762} have suggested that zonal lesions appear to be the result of mechanical injury to myocytes from the tachycardia and the small intraven-

tricular volumes that are present in severe hemorrhagic shock.

The myocardial lesions of hemorrhagic shock vary somewhat among species. Subendocardial hemorrhage and necrosis develop in dogs, pigs, cats, and monkeys, but not in rabbits. Zonal lesions are prominent in dogs, cats, pigs, and are less obvious in rabbits, and are not present in monkeys with hemorrhagic shock.⁷⁵⁵ These differences remain unexplained.

Myocardial Diseases Associated With Endocrine Disorders

In animals, most of these diseases are induced experimentally but may serve as models of similar diseases that occur naturally in man. A recently recognized, spontaneously occurring disease of some importance in cats is hyperthyroidism.

Glucocorticoid Excess

A few reports have demonstrated myocardial damage in rabbits, mice, and rats given large doses of glucocorticoids.⁷⁶³⁻⁷⁶⁸ Heart weights were often increased. The major microscopic and ultrastructural alterations were accumulation of lipid droplets, increased numbers of mitochondria, degenerative changes in mitochondria, and myofibrillar lysis.^{763,765-768} The severity of the myocardial alterations varied considerably among studies using different animal species and dose regimens of corticosteroids. Cardiac lesions have not been described in Cushing's disease of animals, although it represents an important disease of dogs. It would appear that rodents are more sensitive than humans to the cardiotoxic effects of corticosteroids.

Numerous studies have demonstrated the role of corticosteroids in the production of myocardial necrosis in rats with so-called electrolyte-steroid cardiopathy or necrotizing cardiomyopathies.⁷⁶⁹⁻⁷⁷⁸ These studies have demonstrated the interaction of endocrine, nutritional, and toxic factors in cardiac injury. Exposure to many experimental stresses has produced myocardial necrosis in these studies. Such necroses appear to be mediated via a combination of excessive cardiac work and altered concentrations of endogenous catecholamines, adrenal cortical hormones, and electrolytes. In rats, similar cardiac lesions may be induced by a wide variety of exogenous manipulations, including administration of glucocorticoids, aldosterone, and various sodium salts and by producing deficiencies of potassium, magnesium, and chlorine. The production of a common cardiac lesion by these numerous manipulations suggests mediation of the injury via a common pathogenetic mechanism, such as exposure to excessive

amounts of endogenous catecholamines or potentiation of the toxic effects of these agents.

Functional Pheochromocytomas

Pheochromocytomas occur in dogs, in which they may be functional neoplasms, and produce clinical and pathologic alterations suggestive of hypertension.⁷⁷⁹ Affected dogs showed lethargy and weakness, periods of incoordination, cardiac arrhythmias, and respiratory distress. Vascular degenerative alterations of arteriolar sclerosis and medial hyperplasia were observed in the kidneys, lungs, and spleen. However, myocardial lesions of necrosis with contraction bands seen in human patients (see McAllister⁷⁸⁰ for review) have not been described in animals with this tumor. In two case reports, myocardial lipidosis was described in dogs with pheochromocytomas.^{781,782}

Diabetes Mellitus

Cardiomyopathy has been reported in human diabetes patients in the absence of coronary atherosclerosis. However, the morphologic findings in these patients have not been completely correlated with the functional changes. These findings include thickening of the basement membranes of cardiac capillaries and myocytes, and microaneurysms.^{780,783} Animal models utilized in the study of this myocardial disease include mice with genetically transmitted diabetes, rats with streptozotocin-induced diabetes, and dogs and rabbits with alloxan-induced diabetes.^{7,783-795} Ultrastructural studies of the hearts from C57BL/KsJ db+/db+ genetically diabetic mice showed progressive damage to ventricular myocytes.⁷⁹⁰ The initial alteration was lipidosis. Mitochondria had dense matrical material, numerous residual bodies were present, and myofibrillar lysis resulted in atrophied myocytes. Myocardial capillaries had reduplication of their external laminae. Similar alterations developed in the hearts of rats given a single dose of 65 mg streptozotocin/kg body weight.⁷⁹⁴

In rats with streptozotocin-induced diabetes, the myocardial lesions were markedly increased in animals with concurrent renovascular hypertension.⁷⁸⁵⁻⁷⁸⁸ In animals with diabetes alone, the cardiac muscle cells had increased lipid droplets and mild focal myofibrillar lysis. In diabetic-hypertensive rats, loss of myocytes was produced, with fibrosis and proliferation of basal lamina.

Myocardium of dogs with alloxan diabetes had lipidosis but vascular lesions and myocardial fibrosis were not observed.⁷⁹² In alloxan-diabetic rabbits, myocytolysis with replacement fibrosis was described.⁷⁹⁵

Hyperthyroidism

Hyperthyroidism has been described in various animal species, including the rat, cat, dog, rabbit, and guinea pig.⁷⁹⁶⁻⁸¹⁵ Cardiac hypertrophy was consistently produced and regressed after restoration of normal thyroid functional status.^{811,812} Cats given l-thyroxine (0.75 mg/kg/day for 10 months) had biventricular hypertrophy with weight increases of 86% in the left ventricle and 60% in the right ventricle.⁸¹² Light-microscopic and ultrastructural studies have demonstrated hypertrophy of cardiac muscle cells and increased numbers of mitochondria that showed densely packed cristalline membranes.^{801,802}

Hyperthyroidism in cats has recently been recognized as occurring frequently, and the clinical and pathologic features have been characterized. Affected cats usually have functional thyroidal adenomatous hyperplasia, but occasionally have functional thyroid adenocarcinomas. Clinically, the cats are middle- to old-aged; each sex is equally affected. They have weight loss, polyphagia, increased activity, polydipsia, polyuria, vomiting, tachycardia, and marked increases in serum T₃ and T₄ concentrations.^{799,804} Congestive heart failure with pulmonary edema and pleural effusion occurred in 12% of 131 hyperthyroid cats.⁸⁰⁵ Liu et al⁸⁰⁰ has recently described the cardiac pathology of 23 hyperthyroid cats. Ventricular hypertrophy was symmetric in the left ventricular free wall and ventricular septum in 20 cats and asymmetric in 3 animals. Microscopic study showed myofiber hypertrophy, interstitial fibrosis, endocardial fibrosis, and fibrosis of the atrioventricular node. Disorganization of cardiac muscle cells was found in the 3 cases with asymmetric hypertrophy (ventricular septal/left ventricular free wall thickness >1.1). The cardiac alterations in these 3 cats may have resulted either from the effects of hyperthyroidism alone or from hyperthyroidism with concurrent idiopathic hypertrophic cardiomyopathy (which, as mentioned previously, is relatively frequent in cats).

Clinical hyperthyroidism is rarely seen in dogs and is difficult to produce experimentally. The condition was successfully produced in dogs given 1.2 mg/kg of l-thyroxine daily for several months; and in 13 of 30 treated dogs cardiac failure developed.^{806,807}

The offspring of pregnant rats administered triiodothyroacetic acid (TRIAC), a thyroid hormone analog had hypertrophy and myofibrillar disarray of cardiac muscle cells, but only hypertrophy was seen in young rats treated with TRIAC.^{797,803,815} Administration of propranolol to TRIAC-treated dams prevented the development of myofibrillar disarray, but not of the hypertrophy, in the hearts of the offspring.^{797,803} The significance of these findings for the pathogenesis of hypertrophic cardiomyopathy is unclear.

Hypothyroidism (Myxedema) in Dogs

Several of 19 dogs administered antithyroid medication for 4 to 7 years developed clinical signs of myxedema.⁸¹⁶ Ultrastructural study of myocardium and skeletal muscle showed marked thickening of capillary basement membranes. Myocytes had mitochondrial alterations, lipid droplet accumulation, and myelin figures.

Spontaneous cases of hypothyroidism occur frequently in dogs, but accompanying cardiac lesions have not been described.⁸¹⁷

Growth Hormone Excess

In rats implanted with a growth hormone-secreting tumor cardiomegaly develops with prominent ventricular hypertrophy.^{818,819} Similar cardiac lesions occur in human patients with acromegaly.⁷⁸⁰

Myocarditis

Many studies of myocarditis in animals have addressed the role of various host and infectious agent factors in the pathogenesis of the disease. In particular, many such studies have utilized experimental infection of laboratory animals with Coxsackie or encephalomyocarditis viruses. Another group of diseases with myocarditis represents naturally occurring infections in various animal species.

Coxsackie Viral Myocarditis

Several excellent reviews have summarized the virologic and pathologic findings in viral myocarditis of humans and have also considered the results of numerous studies done in animal models of viral myocarditis.⁸²⁰⁻⁸²⁷ The majority of animal studies have been done in the mouse and have utilized Coxsackie B viruses, the viruses most frequently isolated from affected human patients. Some studies have also been done with hamsters, monkeys, and chimpanzees. In mice, yellowish-white foci of myocarditis may be present on the ventricular surface. Microscopically, non-suppurative myocarditis or perimyocarditis is present, with necrosis and calcification of myocytes. Ultrastructural studies have demonstrated viral crystals in some infected myocytes.⁸²⁸ However, this is not a consistent finding. Damaged myocytes have myofibrillar lysis and mitochondrial alterations. Myocyte necrosis is followed by macrophagic invasion and phagocytosis of debris.⁸²⁸⁻⁸³³ In animals that survive the early stages of the disease extensive myocardial fibrosis and calcification develop.⁸³⁴⁻⁸³⁷ Ventricular aneurysms have been ob-

served in mice and hamsters with late lesions.⁸³⁸⁻⁸⁴⁰ Ventricular aneurysms also have been reported in humans with viral myocarditis.⁸⁴¹

Numerous animal studies have been done to determine the effect of many variables on the severity of viral myocarditis. In studies of Coxsackie B infections in mice, the cardiac disease was enhanced by young age, male sex, pregnancy, poor nutrition, whole-body ionizing radiation, cold environmental temperatures, alcohol ingestion, exercise, cortisone administration, and in certain strains of mice.^{822,826} Also, considerable variation in cardiotropism and virulence was seen between different viral isolates.

The model of Coxsackie B₃ viral myocarditis developed by Woodruff, Huber, and associates⁸⁴²⁻⁸⁴⁸ in male BALB/c mice is of particular interest in that it has revealed a number of complexities in the immunologic response to viral infections of the heart. This model also has provided a system for investigating the possibility that Coxsackie viral infections are involved in the pathogenesis of chronic congestive (ventricular dilated) cardiomyopathy by inducing immunologic reactions which are directed against normal myocyte antigens and which persist after the viral infection has subsided. The histologic lesions produced by viral inoculation in this model system are very similar to those found in the human disease. Evidence has been presented to show that in this model most of the cardiac injury is produced by an immune, rather than by viral, mechanism: 1) cardiac cellular necrosis starts after the concentration of virus in the myocardium has begun to decrease; 2) virus is not detected in myocardium at the time when cellular and humoral immunity are maximal; and 3) studies on variant strains of Coxsackie B₃ and B₄ suggest that viral replication in the heart is not a direct cause of the necrosis. Cytolytic T lymphocytes from mice inoculated with Coxsackie B₃ virus have been found to lyse primary cultures of both virus-infected and noninfected myocytes. Huber and Lodge⁸⁴⁶ demonstrated the existence of two distinct populations of cytolytic T lymphocytes in the infected animals. One population preferentially absorbed to and lysed uninfected myocytes (autoreactive cytolytic T lymphocytes), whereas the other absorbed to and lysed virus-infected myocytes (virus-specific cytolytic T lymphocytes). Neither population of cells adsorbed to monolayers of HeLa, L929, or umbilical cord endothelial cells or to myocytes infected with a related but nonmyocarditis variant of Coxsackie B₃. Inoculation of T-lymphocyte-deficient mice with the virus failed to induce significant myocarditis, even though equivalent concentrations of virus were isolated from the hearts of T-lymphocyte-deficient and control animals. Both autoreactive and virus-specific cytolytic T lymphocytes induced myocarditis *in vivo*,

but the lesions produced by the autoreactive cells were more extensive and necrotizing than those produced by virus-specific cells. Thus, these results support the hypothesis that Coxsackie B₂-induced myocarditis results in part from autoimmunity to myocyte antigens. It remains to be determined whether these mechanisms become operational in myocarditides induced by other types of viruses.

Encephalomyocarditis Viral Myocarditis in Pigs, Primates, and Mice

Spontaneous outbreaks of encephalomyocarditis virus (EMCV) infection occur in swine and nonhuman primates.^{106,849-853} Initially described in 1945 in gibbons and chimpanzees, the disease was recognized in swine in 1958 in Panama, in 1960 in Florida, and in 1970 in Australia and New Zealand. Rats serve as the reservoir host of infection. Young pigs are particularly susceptible and die unexpectedly of acute cardiac failure. At necropsy, effusions with or without small amounts of fibrin are found in the body cavities. The affected hearts are dilated, and scattered white streaks are present in the right ventricular myocardium. Microscopically, lymphocytic myocarditis is found, with myocyte necrosis and calcification. Pigs that survive beyond the acute phase of the disease have scattered areas of resolving necrosis that initially appear as red highly vascular streaks and eventually form white fibrous scars. Inclusion bodies are not present.

Experimental infection of mice by the M variant of EMCV resulted in necrotizing myocarditis on Days 5-14, deaths with lesions of congestive heart failure on Days 10-14, and myocardial fibrosis on Days 28 and 90.⁸⁵⁴⁻⁸⁵⁷ Ultrastructural findings in infected mice included early nuclear alterations, occasional viral crystals, myocyte necrosis, and inflammatory cell infiltration (Figure 75).^{829,857-859} These workers have proposed the experimental disease in the mouse as a suitable model for congestive cardiomyopathy. Attempts to produce myocarditis in various mouse strains showed that A/J and C57BL were resistant and BALB/c, C3H, and DBA were susceptible.⁸⁶⁰ Right ventricular aneurysms which were considered morphologically similar to the findings in right ventricular dysplasia or Uhl's anomaly were occasionally seen in mice 8-10 months after infection.⁸⁶¹

Canine Parvoviral Myocarditis

This disease is relatively new; outbreaks were first recognized in 1978.⁸⁶² Manifestations in affected dogs usually are hemorrhagic diarrhea and vomiting associated with a viral-induced necrotizing enteritis. Similar en-

teric lesions are present in cats with infection by feline parvovirus, which is antigenically similar to the canine parvovirus but does not infect dogs. Myocarditis develops in approximately 5% of dogs with parvovirus infection. Dogs with the cardiac form of the disease are generally free of enteric lesions, although in some animals cardiac disease develops several weeks after recovery from the enteric disease.

It has become apparent that several syndromes may develop in dogs with parvoviral myocarditis.⁸⁶³⁻⁸⁷² In the peracute form that is seen most frequently, several puppies in a litter are affected suddenly with dyspnea and either die soon after clinical signs of disease are observed or may be found dead without any premonitory signs. Necropsy reveals lesions of acute congestive failure with pulmonary edema, hepatic congestion, ascites, and hydrothorax. The heart is dilated and diffusely pale or may have discrete white streaks in the ventricular myocardium. Histopathologic alterations in the myocardium are diagnostic and consist of diffuse lymphocytic myocarditis and scattered myocytes with large basophilic intranuclear inclusion bodies. Occasional necrotic myocytes are present. Increased numbers of fibroblasts are present in the interstitium.

In the delayed-onset clinical form congestive heart failure may develop rapidly with underlying chronic parvoviral myocarditis. Most cases have been approximately 5 months old and were littermates of puppies that suffered clinical signs of parvovirus infection, often fatal, at 3-8 weeks of age. Necropsy reveals lesions of congestive heart failure with pulmonary edema, hepatic congestion, ascites, and hydrothorax. The hearts are dilated and scattered white streaks of myocardial fibrosis are apparent beneath the ventricular epicardium. Microscopically, scattered foci of necrosis are present without accompanying leukocytic infiltration or viral inclusion bodies.

In a litter of puppies experimentally given injections *in utero* 8 days before parturition, 2 puppies died unexpectedly at 3-4 weeks of age with acute parvoviral myocarditis, and 2 puppies remained clinically normal but had multifocal chronic myocarditis without inclusion bodies when euthanized at 3 and 4½ months of age.⁸⁷³ In another report, 3 clinically normal 6-8-month-old beagle dogs with high serum titers indicative of previous natural infection with parvovirus were found to have electrocardiographic alterations when screened for use in drug safety studies. The dogs were necropsied and had scattered gray streaks in the ventricular myocardium. Microscopically, multifocal chronic myocarditis was present with myocyte degeneration, fibrosis, and sparse infiltrates of lymphocytes and plasma cells.⁸⁷⁴ Experimental infection of 5-day-old pups produced myocyte degeneration and necrosis with inclu-

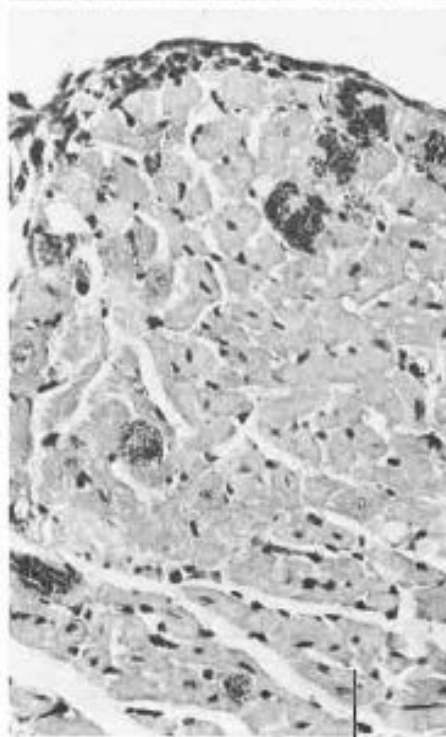
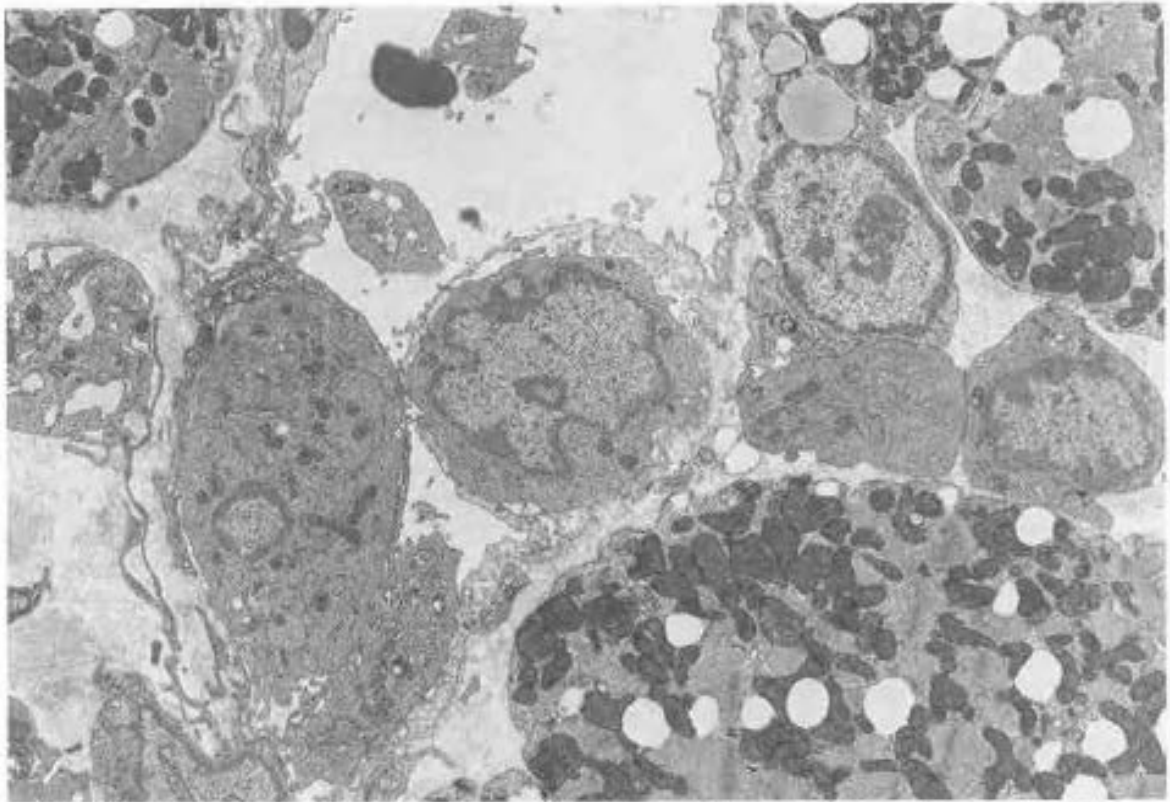


Figure 75—Encephalomyocarditis viral myocarditis. Mouse. Left ventricular subendocardium 10 days after experimental infection with EMC virus, showing endothelial cell damage, interstitial edema, accumulation of lipid droplets in myocytes, and lymphocytic infiltration. (x9000) **Figure 76—*T. cruzi* myocarditis. Mouse. Clusters of darkly stained parasites are present within left ventricular myocytes. Inflammatory reaction is mild. (Giemsa, x250)** **Figure 77—*T. cruzi* myocarditis. Mouse. High-magnification view showing myocyte necrosis and amastigotes of *T. cruzi* within the cytoplasm of other, adjacent myocytes. (Giemsa, x1000)** **Figure 78—*T. cruzi* myocarditis. Mouse. Intracellular parasites have differentiated from amastigotes to trypomastotes, assuming elongated shapes. (Giemsa, x1000)**

sion bodies at 4 weeks after infection, lymphocytic myocarditis at 8 weeks, and multifocal myocardial fibrosis at 16 weeks.⁸⁷⁵ A third clinical presentation of canine parvoviral myocarditis was described recently with development of fatal acute myocarditis, with inclusion bodies, in an adult 3½-year-old dog.⁸⁷⁶ The dog initially developed fever, lethargy, and vomiting, and died unexpectedly on the eighth day of the illness.

Other Canine Viral Myocarditides

Young puppies that die with multisystemic lesions of canine distemper may have myocarditis. Cardiac lesions developed in puppies that were infected experimentally at 5–7 days of age but not those which were infected at 10–21 days of age.⁸⁷⁷ Grossly, scattered pale foci were observed. Microscopically, focal necrosis, with or without calcification, and minimal inflammatory cell infiltration were present. Electron-microscopic study showed infected myocytes with occasional sarcoplasmic inclusion bodies that contained aggregates of virus particles.

Experimental intrauterine infection of puppies during the second trimester of pregnancy with canine herpesvirus (CHV) resulted in fetal and perinatal deaths with disseminated lesions of CHV infection. Focal necrotizing myocarditis with intranuclear inclusion bodies was present.⁸⁷⁸

Infection with the herpesvirus of pseudorabies in naturally infected swine and in experimentally infected dogs and cats may result in multifocal necrotizing myocarditis.⁸⁷⁹

Foot-and-Mouth Disease Viral Myocarditis

Foot-and-mouth disease (FMD) is a disease of domesticated and wild cloven-footed animals and is of great historic and international importance.^{103,880} Currently the disease does not exist in North America, Central America, Australia, or New Zealand; and rigorous regulatory procedures are followed to prevent entry of infected animals into these areas. The causative virus is a picornavirus. Generally, the disease in adults produces high morbidity with mucocutaneous vesicular lesions, but mortality is low. However, myocarditis develops frequently in affected young calves, lambs, pigs, and goats, and 50% mortality may result. In some cases, outbreaks caused by FMD virus type C also have produced a high mortality from myocarditis in adult animals.

Gross lesions in the heart are multiple pale streaks in the ventricular myocardium, resulting in the term "tiger heart." The atria are only rarely affected. Microscopically, lymphocytic myocarditis is present,

with hyaline necrosis and scattered neutrophils. Similar cardiac lesions are produced by experimental infection of mice and guinea pigs.

Other Viral Myocarditides in Laboratory Animals

Myocarditis was produced in mice by experimental infections with adenovirus, reovirus, vaccinia virus, and herpes simplex virus.^{881–884} Adenoviral myocarditis was characterized by scattered pale foci in the myocardium with hydropericardium and hydrothorax. Microscopically, multifocal nonsuppurative myocarditis with myocardial necrosis and calcification and intranuclear viral inclusion bodies were present. Mice infected with herpes simplex Type 1 and 2 had more severe disease in sucklings than in weanlings. Myocardial lesions included focal necrosis with scant inflammatory reaction and intranuclear viral inclusion bodies in several cell types, including cardiac muscle cells. In reovirus-infected mice, gray-yellow foci were scattered in the ventricular myocardium. Histologically, multifocal nonsuppurative myocarditis was accompanied by myocardial necrosis and calcification, interstitial fibrosis, and intracytoplasmic eosinophilic viral inclusion bodies. Experimental infection of mice with vaccinia virus produced similar gross and microscopic myocardial alterations, except that inclusion bodies were not observed by light microscopy (although viral particles were seen in myocytes by electron microscopy).

Rocio virus, an arbovirus associated with outbreaks of human encephalitis in South America, produced extensive myocardial necrosis with infiltration of mononuclear leukocytes in experimentally infected suckling hamsters.⁸⁸⁵ Damaged myocytes were seen to contain numerous virus particles by electron microscopy. Myocardial lesions have also been described with infection by St. Louis encephalitis virus in suckling hamsters⁸⁸⁶ and by Venezuelan equine encephalomyelitis virus in newborn mice.⁸⁸⁷

A febrile disease with myocardial lesions developed in rabbits experimentally infected with an agent thought to be a coronavirus.⁸⁸⁸ Grossly, multiple red foci were seen throughout the epicardium and endocardium, and hydrothorax was present. Microscopically, multifocal myocardial necrosis with minimal accompanying inflammatory reaction was observed. Electron microscopy failed to demonstrate viral particles in the hearts.

Viral Myocarditides in Birds

A disease occurred in geese in Europe that was termed infectious myocarditis or goose influenza.⁸⁸⁹ Intranuclear inclusion bodies were present in cardiac muscle cells. The causative virus was characterized as a par-

vovirus. A single outbreak of myocarditis, with accompanying intranuclear inclusion bodies in myocytes, was described in adult chickens at a research facility in Maryland.⁸⁹⁰ The affected birds died unexpectedly with ascites. The hearts were pale grossly and had diffuse lymphocytic myocarditis with Feulgen-positive intranuclear inclusions in myocytes. Ultrastructural study showed virus particles 18–20 nm in diameter suggestive of parvovirus.

In chicks with experimentally induced avian encephalomyelitis, diffuse lymphocytic myocarditis was consistently present in the atria and affected the ventricular myocardium less frequently.⁸⁹¹

Chicks experimentally infected with an arthritis-inducing reovirus that was recovered from an adult chicken had extensive myocarditis, with infiltration of heterophils and mononuclear leukocytes.⁸⁹²

Focal nonsuppurative myocarditis was present in chickens with experimental infection with Newcastle disease.⁸⁹³

Myocarditis was a frequent finding in an outbreak of Eastern and Western encephalitis in chukar partridges in Florida. The affected hearts had multiple pale myocardial foci grossly and, microscopically, nonsuppurative myocarditis.⁸⁹⁴

Turkeys with experimental influenza A infection developed multifocal myocarditis.⁸⁹⁵ Multiple pale foci were evident grossly in the myocardium. Extensive ultrastructural alterations in myocytes were described, with myofibrillar lysis, mitochondrial alterations, and sarcolemmal disruption.

Myocarditis in Tyzzer's Disease

Prominent myocardial lesions have been reported in several outbreaks of Tyzzer's disease in mice, rabbits, rats, and hamsters.^{896–900} The gross lesions varied from bulging, large (0.2–0.5 cm in diameter) white foci in the myocardium of affected weanling Syrian hamsters to thin pale streaks in the left ventricular apical myocardium of nursing rabbits.^{896,900} Microscopically, degeneration and necrosis of myocytes was accompanied by a mixed inflammatory cell infiltrate. Intact organisms of *Bacillus piliformis* were demonstrated in cardiac muscle cells by light and electron microscopy.⁸⁹⁹

Toxoplasma Myocarditis

Toxoplasmosis occurs in a wide range of animal hosts. In clinical cases, disseminated lesions are often found in the myocardium. Cardiac lesions are described most commonly in dogs and cats. Scattered pale foci are seen grossly, and the microscopic findings are necrotizing myocarditis with scattered pseudocysts.⁹⁰¹ In

experimentally infected mice, multifocal myocardial necrosis with infiltration of mononuclear leukocytes was seen.⁹⁰²

Trypanosomal Myocarditis (Chagas' Disease)

Trypanosomiasis (Chagas' disease) is an important disease in animals in South America and is enzootic in wild animals in the southern United States.⁹⁰³ The experimental disease has been produced in mice, rabbits, monkeys, and dogs.^{904–913} Affected dogs in a Texas study died with evidence of right ventricular failure.⁹¹⁴ The hearts had right ventricular and right atrial dilation with scattered pale foci in the myocardium. Microscopically, the lesions were those of necrotizing granulomatous myocarditis associated with scattered intracellular and extracellular amastigotes of *Trypanosoma cruzi*. In dogs with experimental chronic disease, microscopic lesions were demonstrated in the conduction system as well as in ordinary myocardium.^{905,906}

In experimental infection of mice, gross findings included cardiomegaly with right ventricular dilation, mural thrombi in the right atrium and right ventricle, hydrothorax, and pulmonary and hepatic congestion.^{909,911,915} Microscopically and ultrastructurally, acute myocarditis with necrosis, neutrophilic infiltration and intramyocytic pseudocysts containing amastigotes were seen until 50 days after infection (Figures 76–79). Fibrosis accompanied by histiocytic invasion was present after 50 days, with the most severe damage in the right ventricular myocardium.

Summary

In this review we have attempted a comprehensive compilation of the cardiac morphologic changes that occur in spontaneous and experimental myocardial diseases of animals. Our coverage addresses diseases of mammals and birds and includes these diseases found in both domesticated and wild animals. A similar review of the myocardial diseases in this broad range of animal species has not been attempted previously. We have summarized and illustrated the gross, microscopic, and ultrastructural alterations for these myocardial diseases; and, whenever possible, we have reviewed their biochemical pathogenesis.

We have arranged the myocardial diseases for presentation and discussion according to an etiologic classification with seven categories. These include a group of idiopathic or primary cardiomyopathies recognized in man (hypertrophic, dilated, and restrictive types) and a large group of secondary cardiomyopathies with known causes, such as 1) inherited tendency; 2) nutritional deficiency; 3) toxicity; 4) physical injury

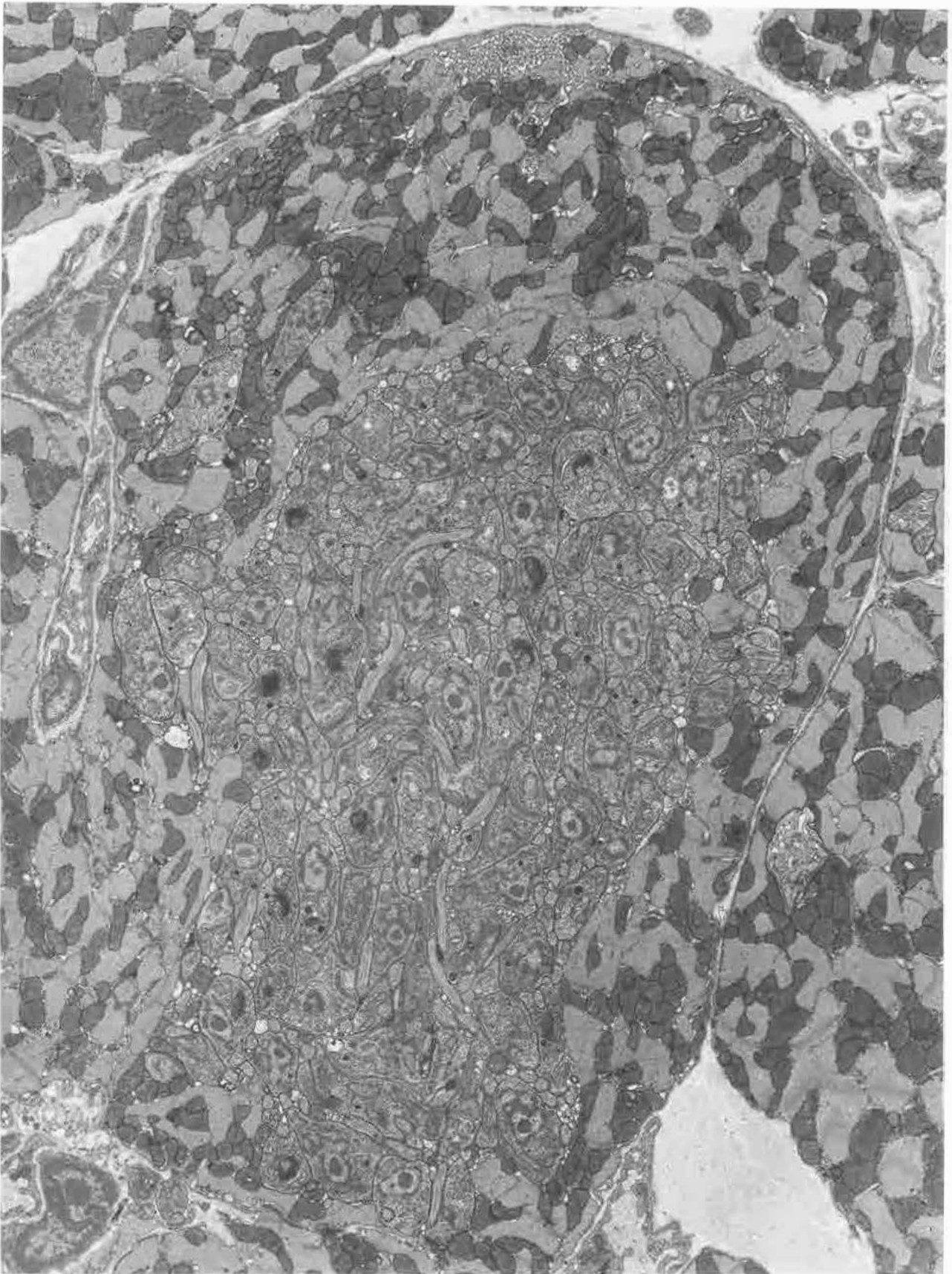


Figure 79—*T. cruzi* myocarditis. Mouse. low magnification electron micrograph showing transverse section of a myocyte that contains numerous amastigotes of *T. cruzi* that are beginning to differentiate into trypomastigote forms. Note the lack of structural abnormalities in cytoplasmic organelles of the invaded myocyte. One single parasite is evident in the cytoplasm of another myocyte (lower right). (x6000)

and shock; 5) endocrine disorders, and 6) myocarditides of viral, bacterial, and protozoal causation. Considerable overlap exists between each of the etiologic groups in the spectrum of pathologic alterations seen in the myocardium. These include various degenerative changes, myocyte necrosis, and inflammatory lesions. However, some diseases show rather characteristic myocardial alterations such as vacuolar degeneration in anthracycline cardiotoxicity, myofibrillar lysis in furazolidone cardiotoxicity, calcification in calcinosis of mice, glycogen accumulation in the glycogenoses, lipofuscinosis in cattle, fatty degeneration in erucic acid cardiotoxicity, myofiber disarray in hypertrophic cardiomyopathy, and lymphocytic inflammation with inclusion bodies in canine parvoviral myocarditis.

The myocardial diseases represent the largest group in the spectrum of spontaneous cardiac diseases of animals. Pericardial and endocardial diseases and congenital cardiac diseases are seen less frequently; and, in contrast to man, coronary artery disease and myocardial ischemia are rather infrequent in animals. The present review shows clearly that the spectrum of myocardial diseases in animals is enlarging and that many newly recognized diseases are emerging and assuming considerable importance. For example, various heritable cardiomyopathies have recently been described in the KK mouse, cattle, and rats. Increasingly recognized myocardial diseases include cardiomyopathies in cats, dogs, and birds; anthracycline cardiotoxicity; furazolidone cardiotoxicity; ionophore cardiotoxicity; myocardial damage associated with central nervous system injuries; myocardial hypertrophy in hyperthyroid cats; and parvoviral myocarditis in dogs.

References

1. Ayers KM, Jones SR: The cardiovascular system, Pathology of Laboratory Animals. Vol I. Edited by K Benirschke, FM Garner, TC Jones. New York, Springer-Verlag, 1978, pp 1-69
2. Bajusz E: Hereditary cardiomyopathy: A new disease model. *Am Heart J* 1969, 77:686-696
3. Bajusz E, Baker JR, Nixon CW, Homburger F: Spontaneous hereditary myocardial degeneration and congestive heart failure in a strain of Syrian hamster. *Ann NY Acad Sci* 1969, 156:105-129
4. Bajusz E, Homburger F, Baker JR, Opie LH: The heart muscle in muscular dystrophy with special reference to involvement of the cardiovascular system in the hereditary myopathy of the hamster. *Ann NY Acad Sci* 1966, 138:213-229
5. Bishop SP: Cardiovascular system, Spontaneous Animal Models of Human Disease. Vol I. Edited by EJ Andrews, BC Ward, NH Altman. New York, Academic Press, 1979, pp 39-79
6. Factor SM, Minase T, Cho S, Dominitz R, Sonnenblick EH: Microvascular spasm in the cardiomyopathic Syrian hamster: A preventable cause of focal myocardial necrosis. *Circulation* 1982, 66:342-354
7. Factor SM, Sonnenblick EH: The pathogenesis of clinical and experimental congestive cardiomyopathies: Recent concepts. *Prog Cardiovasc Dis* 1985, 27:395-420
8. Hunter EG, Hughes V, White J: Cardiomyopathic hamsters, CHF146 and CHF147: A preliminary study. *Can J Physiol Pharmacol* 1984, 62:1423-1428
9. Jasmin G, Eu HY: Cardiomyopathy of hamster dystrophy. *Ann NY Acad Sci* 1979, 317:46-58
10. Liu S-K, Tilley LP: Animal models of primary myocardial diseases. *Yale J Biol Med* 1980, 53:191-211
11. Sole MJ, Factor SM: Hamster cardiomyopathy: A genetically-transmitted sympathetic dystrophy? (Abstr) *Univ Manitoba Med J* 1984, 54:49
12. Strobeck JE, Factor SM, Bhan A, Sole M, Liew CC, Fein F, Sonnenblick EH: Hereditary and acquired cardiomyopathies in experimental animals: Mechanical, biochemical, and structural features. *Ann NY Acad Sci* 1979, 317:59-87
13. Büchner F, Onishi S, Wada A: Cardiomyopathy Associated with Systemic Myopathy: Genetic Defect of Actomyosin Influencing Muscular Structure and Function. Baltimore, Urban & Schwarzenberg, 1978, pp 7-95
14. Jasmin G, Proschek L: Hereditary polymyopathy and cardiomyopathy in the Syrian hamster: I. Progression of heart and skeletal muscle lesions in the UM-X7.1 line. *Muscle Nerve* 1982, 5:20-25
15. Wada A, Fushimi H, Takemura K, Inui Y, Onishi S: Cardiomyocytes in the embryonal stage of Syrian hamsters with a hereditary cardiomyopathy. *J Mol Cell Cardiol* 1977, 9:799-805
16. Jasmin G, Solymoss B: Prevention of hereditary cardiomyopathy in the hamster by verapamil and other agents. *Proc Soc Exp Biol Med* 1975, 149:193-198
17. Lossnitzer K, Mohr W, Konrad A, Guggenmoos R: Hereditary cardiomyopathy in the Syrian golden hamster: Influence of verapamil as calcium antagonist, Cardiomyopathy and Myocardial Biopsy. Edited by M Kaltenbach, F Loogen, EGJ Olsen. New York, Springer-Verlag, 1978, pp 27-37
18. Azari J, Brumbaugh P, Huxtable R: Prophylaxis by taurine in the hearts of cardiomyopathic hamsters. *J Mol Cell Cardiol* 1980, 12:1353-1366
19. Factor SM, Cho S: Alpha adrenergic blockade of the cardiomyopathic Syrian hamster: Further evidence for the microvascular etiology of micronecrosis. (Abstr) *Fed Proc* 1983, 42:920
20. York CM, Cantrell CR, Borum PR: Cardiac carnitine deficiency and altered carnitine transport in cardiomyopathic hamsters. *Arch Biochem Biophys* 1983, 221:526-533
21. Malhotra A, Karell M, Scheuer J: Multiple cardiac contractile protein abnormalities in myopathic Syrian hamsters (BIO 53:58). *J Mol Cell Cardiol* 1985, 17:95-107
22. Panagia V, Singh JN, Anand-Srivastava MB, Pierce GN, Jasmin G, Dhalla NS: Sarcolemmal alterations during the development of genetically determined cardiomyopathy. *Cardiovasc Res* 1984, 18:567-572
23. Proschek L, Jasmin G: Hereditary polymyopathy and cardiomyopathy in the Syrian hamster. II. Development of heart necrotic changes in relation to defective mitochondrial function. *Muscle Nerve* 1982, 5:26-32
24. Saffitz JE, Barzilai B, Williamson E, Sedlis SP, Ahumada G, Sobel BE, Perez JE: Accumulation of calcium anteceding ultrastructural damage and its implication regarding pathogenesis of the Syrian hamster cardiomyopathy. (Abstr) *J Am Coll Cardiol* 1983, 1:583
25. Wiegand V, Stroh E, Henniges A, Lossnitzer K, Kreuzer H: Altered distribution of myosin isoenzymes in the cardiomyopathic Syrian hamster (BIO 8.262). *Basic Res Cardiol* 1983, 78:665-670
26. Hadlow WJ: Diseases of skeletal muscle, Comparative Neuropathology. Edited by JRM Innes, LZ Saunders. New York, Academic Press, 1962, pp 147-243

27. Douglas WB: Murine muscular dystrophy,⁵ Vol II, pp 86-90
28. Harman PJ, Tassoni JB, Curtis RL, Hollinshead MB: Muscular dystrophy in the mouse, *Muscular Dystrophy in Man and Animals*. Edited by GH Bourne, MN Golarz. New York, Hafner Publishing Co, 1963, pp 407-456
29. Meier H, Southard JL: Muscular dystrophy in the mouse caused by an allele at the dy-locus. *Life Sci* 1970, 9:137-144
30. Russell ES, Silvers WK, Loosli R, Wolfe HG, Southard JL: New genetically homogeneous background for dystrophic mice and their normal counterparts. *Science* 1962, 135:1061-1062
31. Forbes MS, Sperelakis N: Ultrastructure of cardiac muscle from dystrophic mice. *Am J Anat* 1972, 134:271-290
32. Jasmin G, Bajusz E: Myocardial lesions in strain 129 dystrophic mice. *Nature* 1962, 193:181-182
33. Nishi S: A study on animal model for cardiomyopathy: Histopathological investigations of the heart in KK mice and dystrophic mice. *J Clin Electron Microsc* 1977, 10:77-108
34. Camerini-Davalos RA, Oppermann W, Mittl R, Ehrenreich T: Studies of vascular and other lesions in KK mice. *Diabetologia* 1970, 6:324-329
35. Dulin WE, Wyse BM: Diabetes in the KK mouse. *Diabetologia* 1970, 6:317-323
36. Fujimoto K, Sakaguchi T, Ui M: Adrenergic mechanisms in the hyperglycaemia and hyperinsulinaemia of diabetic KK mice. *Diabetologia* 1981, 20:568-572
37. Hamuro Y, Shino A, Suzuoki Z: Acute induction of soft tissue calcification with transient hyperphosphatemia in the KK mouse by modification in dietary contents of calcium, phosphorus, and magnesium. *J Nutr* 1970, 100:404-412
38. Nakamura M, Yamada K: Studies on a diabetic (KK) strain of the mouse. *Diabetologia* 1967, 3:212-221
39. Saito K, Nishi S, Kashima T, Tanaka H: Histologic and ultrastructural studies on the myocardium in spontaneously diabetic KK mice: A new animal model of cardiomyopathy. *Am J Cardiol* 1984, 53:320-323
40. Tomita Y: A histo-pathological study on the myocardial lesions in KK mice. With special reference to its causative factors and prevention of deteriorating the disease condition. *J Nippon Med School* 1984, 51:601-614
41. Ruben Z, Miller JE, Rohrbacher BA, Walsh GM: A potential model for a human disease: Spontaneous cardiomyopathy-congestive heart failure in SHR/N-cp rats. *Human Pathol* 1984, 15:902-903
42. Czarnecki CM: Cardiomyopathy in turkeys. *Comp Biochem Physiol* 1984, 77A:591-598
43. Hunsaker WB: Round heart disease in four commercial strains of turkeys. *Poult Sci* 1971, 50: 1720-1724
44. Sautter JH, Newman JA, Kleven SH, Larsen CT: Pathogenesis of the round heart syndrome in turkeys. *Avian Dis* 1968, 12:614-628
45. Jankus EF, Noren GR, Staley NA: Furazolidone-induced cardiac dilatation in turkeys. *Avian Dis* 1972, 16:958-961
46. Onderka DK, Bhatnager R: Ultrastructural changes of sodium chloride-induced cardiomyopathy in turkey poults. *Avian Dis* 1982, 26:835-841
47. Van Vleet JF, Ferrans VJ: Congestive cardiomyopathy induced in ducklings fed graded amounts of furazolidone. *Am J Vet Res* 1983, 44:76-85
48. Einzig S, Jankus EF, Moller JH: Round heart disease in turkeys: A hemodynamic study. *Am J Vet Res* 1972, 33:557-561
49. Hunsaker WB, Robertson A, Magwood SE: The effect of round heart disease on the electrocardiogram and heart weight of turkey poults. *Poult Sci* 1971, 50: 1712-1720
50. Magwood SE, Bray DF: Disease condition of turkey poults characterized by enlarged and rounded hearts. *Can J Comp Med Vet Sci* 1962, 26:268-272
51. Noren GR, Staley NA, Jankus EF, Stevenson JE: Myocarditis in round heart disease of turkeys: A light and electron microscopic study. *Virchows Arch [Pathol Anat]* 1971, 352:285-295
52. Gough AW, Pinn S, Hulland TJ, Thomson RG, de la Iglesia F: Spontaneous cardiomyopathy: Histopathologic and ultrastructural alterations in turkey heart tissue. *Am J Vet Res* 1981, 42:1290-1297
53. Czarnecki CM: Furazolidone-induced cardiomyopathy-Biomedical model for the study of cardiac hypertrophy and congestive heart failure. *Avian Dis* 1980, 24:120-138
54. Czarnecki CM, Jankus EF: Observations on cardiac glycogen in spontaneous round heart disease. *Avian Dis* 1974, 18:614-618
55. Limas CJ, Einzig S, Noren G: Contrasting effects of spontaneous and induced cardiomyopathy on the nucleoproteins of turkey hearts. *Cardiovasc Res* 1982, 16:263-268
56. Limas CJ, Einzig S, Noren GR: Nucleoprotein changes in the hearts of cardiomyopathic turkeys. *Cardiovasc Res* 1982, 16:225-232
57. Pierpont MM, Judd D, Borgwardt B, Noren GR, Staley NA, Einzig S: Carnitine alterations in spontaneous and drug-induced turkey congestive cardiomyopathy. *Pediatr Res* 1985, 19:415-420
58. Bogin E, Ratner D, Avidar Y: Biochemical changes in blood and tissues associated with round heart disease in turkey poults. *Avian Pathol* 1983, 12:437-442
59. Einzig S, Staley NA, Mettler E, Nicoloff DM, Noren GR: Regional myocardial blood flow and cardiac function in a naturally occurring congestive cardiomyopathy of turkeys. *Cardiovasc Res* 1980, 14:396-407
60. Staley NA, Noren GR, Einzig S, Rublein TG: Effect of early propranolol treatment in an animal model of congestive cardiomyopathy: I. Mortality and Ca transport in sarcoplasmic reticulum. *Cardiovasc Res* 1984, 18:371-376
61. Einzig S, Detloff BLS, Borgwardt BK, Staley NA, Noren GR, Benditt DG: Cellular electrophysiological changes in "round heart disease" of turkeys: A potential basis for dysrhythmias in myopathic ventricles. *Cardiovasc Res* 1981, 15:643-651
62. Staley NA, Noren GR, Einzig S: Early alterations in the function of sarcoplasmic reticulum in a naturally occurring model of congestive cardiomyopathy. *Cardiovasc Res* 1981, 15:276-281
63. Dunnigan A, Noren GR, Einzig S, Benditt DG, Staley NA, Benson DW Jr: Inducible ventricular arrhythmias in a naturally occurring model of cardiomyopathy. *Cardiovasc Res* 1984, 18:645-650
64. Watanabe S, Akita T, Itakura C, Goto M: Evidence for a new lethal gene causing cardiomyopathy in Japanese black calves. *J Hered* 1979, 70:255-258
65. Matsukawa K, Chihaya Y, Okada H, Ohtsuyama A: Hereditary cardiomyopathy in the dairy cattle: Pathomorphological study. *Proceedings of the 4th Annual Meeting of the Federation of Asian Veterinary Association, Taipei, Taiwan (In press)*
66. Nomura T, Une Y, Shiota K: Dilated cardiomyopathy in Holstein cattle. *International Symposium on Cardiomyopathy and Myocarditis*, December 12-15, 1984, Tokyo, Abstract S-33
67. Sonoda M, Takahashi K, Kurosawa T, Matsukawa K, Chiyada Y: Clinical and clinico-pathological studies on idiopathic congestive cardiomyopathy in cattle. *Proceedings of the XII World Congress on Diseases of Cattle*, 1982, pp 1187-1191
68. Martig J: Eine neue Herzerkrankung beim Rind (Abstr).

- Mitt Schweiz Verb Kunstl Besamung Schweiz Arbeitsgem 1983, 21:45
69. Martig J, Tschudi P, Perritaz C, Tontis A, Luginbühl H: Gehäufte Fälle von Herzinsuffizienz beim Rind: Vorläufige Mitteilung. Schweiz Arch Tierheilk 1982, 124:69-82
 70. Cook RW: Cardiomyopathy and woolly hair coat in Poll Hereford calves. Australian Veterinary Association Yearbook. Edited by MG Cooper, JC Holt. 1981, p. 210
 71. Walvoort HC: Glycogen storage diseases in animals and their potential value as models of human disease. J Inher Metab Dis 1983, 6:3-16
 72. Edwards JR, Richards RB: Bovine generalized glycogenosis type II: A clinico-pathological study. Br Vet J 1979, 135:338-348
 73. Howell J McC, Dorling PR, Cook RD: Generalised glycogenosis type II. Comp Pathol Bull 1983, 15:2-4
 74. Howell J McC, Dorling PR, Cook RD, Robinson WF, Bradley S, Gawthorne JM: Infantile and late onset form of generalized glycogenosis type II in cattle. J Pathol 1981, 134:267-277
 75. Jolly RD, Van-de-Water NS, Richards RB, Dorling PR: Generalized glycogenosis in beef Shorthorn cattle-heterozygote detection. Aust J Exp Biol Med Sci 1977, 55:141-150
 76. Manktelow BW, Hartley WJ: Generalized glycogen storage disease in sheep. J Comp Pathol 1975, 85:139-145
 77. Murakami H, Takagi A, Nonaka S, Ishiura S, Sugita H, Mizutani M: Glycogenosis II in a Japanese quail. Exp Anim (Tokyo) 1980, 29:475-478
 78. Matsui T, Kuroda S, Mizutani M, Kiuchi Y, Suzuki K, Ono T: Generalized glycogen storage disease in Japanese quail (*Coturnix coturnix japonica*). Vet Pathol 1983, 20:312-321
 79. Mostafa IE: A case of glycogenic cardiomegaly in a dog. Acta Vet Scand 1970, 11:197-208
 80. O'Sullivan BM, Healy PJ, Fraser IR, Nieper RE, Whittle RJ, Sewell CA: Generalized glycogenosis in Brahman cattle. Aust Vet J 1981, 57:227-229
 81. Richards RB, Edwards JR, Cook RD, White RR: Bovine generalized glycogenosis. Neuropathol Appl Neurobiol 1977, 3:45-56
 82. Robinson WF, Howell J McC, Dorling PR: Cardiomyopathy in generalised glycogenosis type II in cattle. Cardiovasc Res 1983, 17:238-242
 83. Walvoort HC, Slec RG, Koster JF: Canine glycogen storage disease type II: A biochemical study of an acid α -glucosidase deficient Lapland dog. Biochim Biophys Acta 1982, 715:63-69
 84. Walvoort HC, Van der Ingh TSGAM, Van Nes JJ: Glycogenosis type II in the dog (Abstr). Berl Munch Tierarztl Wochenschr 1981, 94:39
 85. Ceh L, Hauge JG, Svenkerud R, Strande A: Glycogenosis type III in the dog. Acta Vet Scand 1976, 17:210-222
 86. Otani T, Mochizuki H: Glycogen storage disease (III?) in a dog. Exp Anim (Tokyo) 1977, 26:172-173
 87. Rafiquzzaman M, Svenkerud R, Strande A, Hauge JG: Glycogenosis in the dog. Acta Vet Scand 1976, 17:196-209
 88. Ball CR, Williams WL: Spontaneous and dietary-induced cardiovascular lesions in DBA mice. Anat Rec 1965, 152:199-210
 89. Brownstein DG: Genetics of dystrophic epicardial mineralization in DBA/2 mice. Lab Anim Sci 1983, 33:247-248
 90. DiPaolo JA, Strong LC, Moore GE: Calcareous pericarditis in mice of several genetically related strains. Proc Soc Exp Biol Med 1964, 115:496-497
 91. Eaton GJ, Custer RP, Johnson FN, Stabenow KT: Dystrophic cardiac calcinosis in mice. Genetic, hormonal and dietary influences. Am J Pathol 1978, 90:173-186
 92. Galloway JH, Glover D, Fox WC: Relationship of diet and age to metastatic calcification in guinea pigs. Lab Anim Care 1964, 14:6-12
 93. Highman B, Daft FS: Calcified lesions in C3H mice given purified low-protein diets. Arch Pathol 1951, 52:221-229
 94. Nabors CE, Ball CR: Spontaneous calcification in hearts of DBA mice. Anat Rec 1969, 164:153-162
 95. Rings RW, Wagner JE: Incidence of cardiac and other soft tissue mineralized lesions in DBA/2 mice. Lab Anim Sci 1972, 22:344-352
 96. Sparschu GL, Christie JR: Metastatic calcification in a guinea pig colony: A pathological survey. Lab Anim Care 1968, 18:520-526
 97. Hulland TJ: Muscles and tendons, Pathology of Domestic Animals. 3rd edition. Vol 1. Edited by KJV Jubb, PC Kennedy, N Palmer. New York, Academic Press, 1985, pp 139-199
 98. Bradley R, Duffell SJ: The pathology of the skeletal and cardiac muscles of cattle with xanthosis. J Comp Pathol 1982, 92:85-97
 99. Duffell SJ, Edwardson R: Xanthosis in cattle. Vet Rec 1978, 102:269-270
 100. Hayward AHS, Baker-Smith J: Xanthosis: An abnormal pigmentation of cattle. Vet Rec 1978, 102:96-97
 101. Bradley R, Fell BF: Myopathies in animals, Disorders of Voluntary Muscle. Edited by J Walton. 4th edition. New York, Churchill Livingstone, 1981, pp 824-872
 102. Hadlow WJ: Myopathies of animals, The Striated Muscle. International Academy of Pathology Monograph No. 12. Baltimore, Williams & Wilkins Co, Baltimore, 1973, pp 364-409
 103. Jones TC, Hunt RD: Veterinary Pathology. 5th edition. Philadelphia, Lea & Febiger, 1983, pp 385-388, 925-927, 1044-1050, 1135-1161, 1250-1293
 104. Lannek N, Lindberg P: Vitamin E and selenium deficiencies (VESD) of domestic animals. Adv Vet Sci Comp Med 1976, 19:127-164
 105. Mason K: Effects of nutritional deficiency on muscle, The Structure and Function of Muscle. 2nd edition. Vol 4. Edited by GH Bourne. New York, Academic Press, 1973, pp 155-206
 106. Mason KE, Horwitt MK: Effects of deficiency in animals, The Vitamins: Chemistry, Physiology, Pathology, Methods. Edited by WH Sebrell Jr, RS Harris. New York, Academic Press, 1972, pp 272-292
 107. Nelson JS: Pathology of vitamin E deficiency, Vitamin E: A Comprehensive Treatise. Edited by LJ Machlin. New York, Marcel Dekker, 1980, pp 397-428
 108. Robinson WF, Maxie MG: The cardiovascular system,⁹⁷ Vol 3, pp 1-81
 109. Shamberger RJ: Selenium deficiency diseases in animals, Biochemistry of Selenium. New York, Plenum Press, 1983, pp 31-58
 110. Subcommittee on Selenium, Committee on Animal Nutrition, Board on Agriculture, National Research Council. Selenium in Nutrition. Revised edition. Washington, DC, National Academy Press, 1983, pp 77-106
 111. Telford IR: Experimental Muscular Dystrophies in Animals: A Comparative Study. Springfield, IL, Charles C Thomas, 1971, pp 3-243
 112. Underwood EJ: Selenium, Trace Elements in Human and Animal Nutrition. 4th edition. New York, Academic Press, 1977, pp 302-346
 113. Cheville NF: The pathology of vitamin E deficiency in the chick. Pathol Vet 1966, 3:208-225
 114. Gries CL, Scott ML: Pathology of selenium deficiency in the chick. J Nutr 1972, 102:1287-1296
 115. Jungherr EL: Ten year incidence of field encephalomalacia in chicks and observations on its pathology. Ann NY Acad Sci 1959, 52:104-112

116. Wolf A, Pappenheimer AM: The histopathology of nutritional encephalomalacia of chicks. *J Exp Med* 1931, 54:399-406
117. Young PA, Taylor JJ, Yu W-H, Yu MC, Tureen LL: Ultrastructural changes in chick cerebellum induced by vitamin E deficiency. *Acta Neuropathol* 1973, 25:149-160
118. Yu W-H, Yu MC, Young PA: Ultrastructural changes in the cerebrovascular endothelium induced by a diet high in linoleic acid and deficient in vitamin E. *Exp Mol Pathol* 1974, 21:289-299
119. Schougaard H, Basse A, Gessel-Nielsen G, Simesen MG: Nutritional muscular dystrophy (NMD) in foals. *Nord Vet Med* 1972, 24:67-84
120. Van Vleet JF: Experimentally induced vitamin E-selenium deficiency in the growing dog. *J Am Vet Med Assoc* 1975, 166:769-774
121. Muth OA, Weswig PH, Whanger PD, Oldfield JE: Effect of feeding selenium-deficient ration to the subhuman primate (*Saimiri sciureus*). *Am J Vet Res* 1971, 32:1603-1605
122. Dennis JM, Alexander RW: Nutritional myopathy in a cat. *Vet Rec* 1982, 111:195-196
123. Gershoff SN, Norkin SA: Vitamin E deficiency in cats. *J Nutr* 1962, 77:303-308
124. Lin CT, Chen LH: Ultrastructural and lysosomal enzyme studies of skeletal muscle and myocardium in rats with long-term vitamin E deficiency. *Pathology* 1982, 14:375-382
125. Machlin LJ, Filipski R, Nelson J, Horn LR, Brin M: Effects of a prolonged vitamin E deficiency in the rat. *J Nutr* 1977, 107:1200-1208
126. Porta EA, de la Iglesia FA, Hartroft WS: Studies on dietary hepatic necrosis. *Lab Invest* 1968, 18:283-297
127. Nordstoga K: Muscular and myocardial degeneration in rapidly growing male mink kits. *Acta Vet Scand* 1983, 24:321-324
128. Stowe HD, Whitehair CK: Gross and microscopic pathology of tocopherol-deficient mink. *J Nutr* 1963, 81:287-300
129. Hoekstra WG: Biochemical function of selenium and its relation to vitamin E. *Fed Proc* 1975, 34:2083-2089
130. Van Vleet JF: Amounts of twelve elements required to induce selenium-vitamin E deficiency in ducklings. *Am J Vet Res* 1982, 43:851-857
131. Van Vleet JF: Amounts of eight combined elements required to induce selenium-vitamin E deficiency in ducklings and protection by supplements of selenium and vitamin E. *Am J Vet Res* 1982, 43:1049-1055
132. Van Vleet JF, Boon GD, Ferrans VJ: Induction of lesions of selenium-vitamin E deficiency in weanling swine fed silver, cobalt, tellurium, zinc, cadmium, and vanadium. *Am J Vet Res* 1981, 42:789-799
133. Van Vleet JF, Boon GD, Ferrans VJ: Induction of lesions of selenium-vitamin E deficiency in ducklings fed silver, copper, cobalt, tellurium, cadmium, or zinc: Protection by selenium or vitamin E supplements. *Am J Vet Res* 1981, 42:1206-1217
134. Liu SK, Dolensek EP, Tappe JP, Stover J, Adams CR: Cardiomyopathy associated with vitamin E deficiency in seven gelada baboons. *J Am Vet Med Assoc*, 1984, 185:1347-1350
135. Bradley R: Selenium deficiency and bovine myopathy. *Vet Annu* 1975, 15:27-36
136. Grant CA: Morphological and etiological studies of dietetic microangiopathy in pigs ("mulberry heart disease") *Acta Vet Scand (Suppl 2)* 1961, 2:1-107
137. McMurray CH, Rice DA, Kennedy S: Experimental models for nutritional myopathy, *Biology of Vitamin E*. London, Pitman Books, 1983, pp 201-223
138. Nafstad I, Tollersrud S: The vitamin E-deficiency syndrome in pigs: I. Pathological changes. *Acta Vet Scand* 1970, 11:452-480
139. Obel AL: Studies on the morphology and etiology of so-called toxic liver dystrophy (hepatosis dietetica) in swine. *Acta Pathol Microbiol Scand (Suppl)* 1953, 94:1-118
140. Scott ML, Olson G, Krook L, Brown WR: Selenium-responsive myopathies of myocardium and of smooth muscle in the young poult. *J Nutr* 1967, 91:573-583
141. Van Vleet JF: Comparative efficacy of five supplementation procedures to control selenium-vitamin E deficiency in swine. *Am J Vet Res* 1982, 43:1180-1189
142. Van Vleet JF, Carlton W, Olander HJ: Hepatosis dietetica and mulberry heart disease associated with selenium deficiency in Indiana swine. *J Am Vet Assoc* 1970, 157:1208-1219
143. Vawter LR, Records E: Muscular dystrophy (white muscle disease) in young calves. *J Am Vet Med Assoc* 1947, 110:152-157
144. Van Vleet JF, Ferrans VJ, Ruth GR: Ultrastructural alterations in nutritional cardiomyopathy of selenium-vitamin E deficient swine: I. Fiber lesions. *Lab Invest* 1977, 37:188-200
145. Van Vleet JR, Ferrans VJ, Ruth GR: Ultrastructural alterations in nutritional cardiomyopathy of selenium-vitamin E deficient swine: II. Vascular lesions. *Lab Invest* 1977, 37:201-211
146. Van Vleet JF, Ferrans VJ: Ultrastructural alterations in gizzard smooth muscle of selenium-vitamin E-deficient ducklings. *Avian Dis* 1977, 21:531-542
147. Van Vleet JF, Ferrans VJ: Myocardial ultrastructural alterations in ducklings fed tellurium. *Am J Vet Res* 1982, 43:2000-2009
148. Chen XS: Selenium and Keshan disease. *Ann NY Acad Sci* 1982, 393:224-225
149. Chen X, Yang G, Chen J, Chen X, Wen Z, Ge K: Studies on the relations of selenium and Keshan disease. *Biol Trace Elem Res* 1980, 2:91-107
150. Ge K, Xue A, Bai J, Wang S: Keshan disease: An endemic cardiomyopathy in China. *Virchows Arch Pathol Anat*, 1983, 401:1-15
151. Gu B: Pathology of Keshan disease. A comprehensive review. *Chin Med J* 1983, 96:251-261
152. Levander OA: Clinical consequences of low selenium intake and its relationship to vitamin E. *Ann NY Acad Sci* 1982, 393:70-82
153. Li G, Wang F, Kang D, Li C: Keshan Disease: An endemic cardiomyopathy in China. *Human Pathol* 1985, 16:602-609
154. Yu W-H: A study of nutritional and bio-geochemical factors in the occurrence and development of Keshan disease. *Jpn Circ J* 1982, 46:1201-1207
155. Collip PJ, Chen SY: Cardiomyopathy and selenium deficiency in a two-year-old girl. *N Engl J Med* 1981, 304:1304-1305
156. Fleming CR, Lie JT, McCall JT, O'Brien JR, Baillie EE, Thistle JL: Selenium deficiency and fatal cardiomyopathy in a patient on home parenteral nutrition. *Gastroenterology* 1982, 83:689-693
157. Johnson RA, Baker SS, Fallon JT, Maynard EP, Ruskin JN, Wen Z, Ge K, Cohen HJ: An occidental case of cardiomyopathy and selenium deficiency. *N Engl J Med* 1981, 304:1210-1212
158. Dische MR, Porro RS: The cardiac lesions in Bassen-Kornzweig syndrome. *Am J Med* 1970, 49:568-571
159. Hide DW, Martlew R: Cystic fibrosis and myocardial fibrosis. *Arch Dis Child* 1977, 52:163
160. Nezelof C, LeSec G: Multifocal myocardial necrosis and fibrosis in pancreatic diseases of children. *Pediatrics* 1979, 63:361-368
161. Saito K, Matsumoto S, Yokoyama T, Okaniwa M, Kamoshita S: Pathology of chronic vitamin E deficiency in fatal familial intrahepatic cholestasis (Byler's disease). *Virchows Arch [Pathol Anat]* 1982, 396:319-330

162. Darrow DC, Miller HC: The production of cardiac lesions by repeated injections of deoxycorticosterone acetate. *J Clin Invest* 1942, 21:601-612
163. Follis RH Jr, Orent-Keiles E, McCollum EV: The production of cardiac and renal lesions in rats by a diet extremely deficient in potassium. *Am J Pathol* 1942, 18:29-35
164. French JE: A histological study of the heart lesions in potassium-deficient rats. *Arch Pathol* 1952, 53:485-496
165. Macpherson CR: Myocardial necrosis in the potassium-depleted rat: A reassessment. *Br J Exp Pathol* 1956, 37:279-285
166. Molnar Z, Larsen K, Spargo B: Cardiac changes in the potassium-depleted rat. *Arch Pathol* 1962, 74:339-347
167. Newberne PM: Cardiorenal lesions of potassium depletion steroid therapy in the rat. *Am J Vet Res* 1964, 25:1256-1265
168. Poche R: Submikroskopische Beitrage zur Pathologie der Herzmuskelzelle bei Phosphorvergiftung, Hypertrophie, Atrophie und Kaliummangel. *Virchows Arch [Pathol Anat]* 1958, 331:165-248
169. Sarkar K, Levine DZ: Repair of the myocardial lesion during potassium repletion of kaliopenic rats: An ultrastructural study. *J Mol Cell Cardiol* 1979, 11:1165-1172
170. Sarkar K, Levine DZ: Persistence of a basallamina-like structure following DOCA-induced myofibrillar degeneration in rats. *Cardiology* 1976, 61:112-121
171. Schrader GA, Prickett CO, Salmon WD: Symptomatology and pathology of potassium and magnesium deficiencies in the rat. *J Nutr* 1937, 14:85-110
172. Tate CL, Bagdon WJ, Bokelman DL: Morphologic abnormalities in potassium-deficient dogs. *Am J Pathol* 1978, 93:103-116
173. Thomas RM, Mylon E, Winternitz MC: Myocardial lesions resulting from dietary deficiency. *Yale J Biol Med* 1940, 12:345-360
174. Tucker VL, Hanna H, Kaiser CJ, Darrow DC: Cardiac necrosis accompanying potassium deficiency and administration of corticosteroids. *Circ Res* 1963, 13:420-431
175. Sykes JF, Moore LA: Lesions of the Purkinje network of the bovine heart as a result of potassium deficiency. *Arch Pathol* 1942, 33:467-471
176. Bennetts HW, Beck AB, Harley R: The pathogenesis of "falling disease": Studies on copper deficiency in cattle. *Aust Vet J* 1948, 24:237-244
177. Bennetts HW, Hall HTB: "Falling disease" of cattle in the southwest of western Australia. *Aust Vet J* 1939, 15:152-159
178. Bennetts HW, Harley R, Evans ST: Studies on copper deficiency of cattle: The fatal termination ("falling disease"). *Aust Vet J* 1942, 18:50-63
179. Van den Ingh TSGAM, Lenghaus C: Myocardfibrose: een geval van falling disease. *Tijdschr Diergeneesk* 1975, 100:327-329
180. Coulson WF: Copper deficiency, with special reference to the cardiovascular system. *Methods Achiev Exp Pathol* 1972, 6:111-138
181. Shields GS, Coulson WF, Kimball DA, Carnes WH, Cartwright GE, Wintrobe MM: Studies on copper metabolism: XXXII. Cardiovascular lesions in copper-deficient swine. *Am J Pathol* 1962, 41:603-621
182. Waisman J, Cancilla PA, Coulson WF: Cardiovascular studies on copper-deficient swine: XIII. The effect of chronic copper deficiency on the cardiovascular system of miniature pigs. *Lab Invest* 1969, 21:548-554
183. Hunt CE, Carlton WW: Cardiovascular lesions associated with experimental copper deficiency in the rabbit. *J Nutr* 1965, 87:385-393
184. Datta BN, Silver MD: Cardiomegaly in chronic anemia in rats: An experimental study including ultrastructural, histometric, and stereologic observations. *Lab Invest* 1975, 32:503-514
185. Datta BN, Silver MD: Cardiomegaly in chronic anemia in rats: Gross and histologic features. *Ind J Med Res* 1976, 64:447-458
186. Dawson R, Milne G, Williams RB: Changes in the collagen of rat heart in copper-deficiency-induced cardiac hypertrophy. *Cardiovasc Res* 1982, 16:559-565
187. Goodman JR, Warsaw JB, Dallman PR: Cardiac hypertrophy in rats with iron and copper deficiency: quantitative contribution of mitochondrial enlargement. *Pediatr Res* 1970, 4:244-256
188. Kelly WA, Kesterson JW, Carlton WW: Myocardial lesions in the offspring of female rats fed a copper deficient diet. *Exp Mol Pathol* 1974, 20:40-56
189. Lee JC, Fagenholz SA, Downing SE: Cardiac dimensions in severely anemic neonatal pigs. *Am J Vet Res* 1983, 44:1940-1942
190. Kincaid SA, Carlton WW: Experimental copper deficiency in laboratory mice. *Lab An Sci* 1982, 32:491-494
191. Brown ML, McGrath JJ: Thiamine deficiency and experimental cardiac necrosis. *Proc Soc Exp Biol Med* 1970, 135:735-738
192. Loew FM: Effect of nutrient deficiencies in animals: thiamin, CRC Handbook series in Nutrition and Food. Section E: Nutritional Disorders. Vol II. Edited by M Rechcigl Jr. West Palm Beach, Florida, CRC Press, 1978, pp 3-25
193. Davies MJ, Jennings RB: The ultrastructure of the myocardium in the thiamine-deficient rat. *J Pathol* 1970, 102:87-95
194. Follis RH Jr, Miller MH, Wintrobe MM, Stein HJ: Development of myocardial necrosis and absence of nerve degeneration in thiamine deficiency in pigs. *Am J Pathol* 1943, 19:341-357
195. Swank RL: Avian thiamine deficiency. A correlation of the pathology and clinical behavior. *J Exp Med* 1940, 71:683-708
196. Evans CA, Carlson WE, Green RG: The pathology of Chastek paralysis in foxes: A counterpart of Wernicke's hemorrhagic polioencephalitis of man. *Am J Pathol* 1942, 18:79-91
197. Swank RL, Porter RR, Yeomans A: The production and study of cardiac failure in thiamin-deficient dogs. *Am Heart J* 1941, 22:154-168
198. Bozner A, Knieriem HJ, Meesen H, Reinauer H: Die Ultrastruktur und Biochemie des Herzmuskels der Ratte im Thiaminmangel und nach einer Gabe von Thiamin. *Virchows Arch Zellpathol* 1969, 2:125-143
199. Suzuki T: Electron microscopic study on myocardial lesions in thiamine deficient rats. *Tohoku J Exp Med* 1967, 91:249-255
200. Heggveit HA: The cardiomyopathy of magnesium-deficiency, *Electrolytes and Cardiovascular Diseases*. Edited by E Bajusz. New York, S Karger, 1965, pp 204-220
201. Heggveit HA, Herman L, Mishra RK: Cardiac necrosis and calcification in experimental magnesium deficiency. *Am J Pathol* 1964, 45:757-782
202. Heggveit HA, Nadkarni BB: Ultrastructural pathology of the myocardium. *Methods Achiev Exp Pathol* 1971, 5:474-517
203. Heroux O, Peter D, Heggveit A: Long-term effect of suboptimal dietary magnesium on magnesium and calcium contents of organs, on cold tolerance and on lifespan, and its pathological consequences in rats. *J Nutr* 1977, 107:1640-1652
204. Hirota Y, Thorp K, Abelmann WH: Protective effect of coexistent thiamine deficiency upon the experimental cardiomyopathy associated with acute magnesium

- deficiency in the Syrian Golden Hamster. *Recent Adv Stud Card Struct Metab* 1975, 10:695-706
205. Mishra RK: Studies on experimental magnesium deficiency in the albino rat: 8. The influence of stress on cardiac and renal lesions in rats on Mg-deficient diet. *Rev Can Biol* 1960, 19:175-180
 206. Vitale JJ, Hellerstein EE, Nakamura M, Lown B: Effects of magnesium-deficient diet upon puppies. *Circ Res* 1961, 9:387-394
 207. Wener J, Pintor K, Simon MA, Matola R, Friedman R, Maymen A, Schucher R: The effects of prolonged hypomagnesemia on the cardiovascular system in young dogs. *Am Heart J* 1964, 67:221-231
 208. Chauhan S, Nayak NC, Ramalingaswami V: The heart and skeletal muscle in experimental protein malnutrition in rhesus monkeys. *J Pathol Bacteriol* 1965, 90:301-309
 209. Abel RM: Nutritional aspects of myocardial disease, Drug-Induced Heart Disease. Edited by MR Bristow. New York, Elsevier/North Holland Biomedical Press, 1980, pp 341-357
 210. Abel RM, Grimes JB, Alonso D, Alonso M, Gay WA Jr: Adverse hemodynamic and ultrastructural changes in dog hearts subjected to protein-calorie malnutrition. *Am Heart J* 1979, 97:733-744
 211. McKinney B: Studies on the experimental production of endomyocardial fibrosis and cardiomegaly of unknown origin by dietary means. *Am Heart J* 1975, 90:206-214
 212. Reid JVO, Berjak P: Dietary production of myocardial fibrosis in the rat. *Am Heart J* 1966, 71:240-250
 213. McKinney B: Endocardial changes produced in Patus monkeys by the ablation of cardiac lymphatics and the administration of a plantain diet. *Am Heart J* 1976, 91:484-491
 214. McKinney B, Crawford MA: Fibrosis in guinea pig heart produced by plantain diet. *Lancet* 1965, 2:880-882
 215. Kesten HD, Salcedo J Jr, Stetten DW Jr: Fatal myocarditis in choline deficient rats fed ethyl laurate. *J Nutr* 1945, 29:171-177
 216. Rabin ER, Melnick JL: Experimental acute myocarditis. *Prog Cardiovasc Dis* 1964, 7:65-72
 217. Salmon WD, Newberne PM: Cardiovascular disease in choline-deficient rats. Effects of choline deficiency, nature and level of dietary lipids and proteins, and duration of feeding on plasma and liver lipid values and cardiovascular lesions. *Arch Pathol* 1962, 73:190-209
 218. Wilgram GF: Cardiovascular changes induced in choline-deficient rats by growth hormone. *Ann NY Acad Sci* 1959, 72:863-869
 219. Wilgram GF, Hartroft WS: Pathogenesis of fatty and sclerotic lesions in the cardiovascular system of choline-deficient rats. *Brit J Exp Pathol* 1955, 36:298-305
 220. Wilgram GF, Hartroft WS, Best CH: Dietary choline and the maintenance of the cardiovascular system in rats. *Brit Med J* 1954, 2:1-5
 221. Roberts WC, Ferrans VJ: Pathologic anatomy of the cardiomyopathies (idiopathic dilated and hypertrophic types, infiltrative types and endomyocardial disease with and without eosinophilia). *Hum Pathol* 1975, 6:287-342
 222. Ciro E, Maron BJ, Roberts WC: Coexistence of asymmetric left ventricular hypertrophy in a family with hypertrophic cardiomyopathy. *Am Heart J* 1982, 104:643-646
 223. Eslami B, Aryanpur I, Tabaezadeh AJ, Alipour M, Nazarian I, Shakibi JG: Midventricular obstruction. *Jpn Heart J* 1979, 20:117-126
 224. Falicov RE, Resnekov L, Bharati S, Lev M: Midventricular obstruction: A variant of obstructive cardiomyopathy. *Am J Cardiol* 1976, 37:432-437
 225. Maron BJ, Bonow RO, Seshagiri TN, Roberts WC, Epstein SE: Hypertrophic cardiomyopathy with ventricular septal hypertrophy localized to the apical region of the left ventricle (apical hypertrophic cardiomyopathy). *Am J Cardiol* 1982, 49:1838-1848
 226. Yamaguchi F, Nishijo T, Umeda T, Machii K: Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): Ventriculographic and echocardiographic features in 30 patients. *Am J Cardiol* 1979, 44:401-412
 227. Ferrans VJ, Rodriguez ER: Specificity of light and electron microscopic features of hypertrophic obstructive and nonobstructive cardiomyopathy: Qualitative, quantitative and etiologic aspects. *Eur Heart J (Suppl F)* 1983, 4:9-22
 228. Maron BJ, Gottdiener JS, Bonow RO, Epstein SE: Hypertrophic cardiomyopathy with unusual locations of left ventricular hypertrophy undetectable by M-mode echocardiography. *Circulation* 1981, 63:409-417
 229. Maron BJ, Gottdiener JS, Epstein SE: Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: A wide angle, two dimensional echocardiographic study of 125 patients. *Am J Cardiol* 1981, 48:418-428
 230. Tilley LP, Liu S-K, Fox PR: Myocardial disease. Textbook of Veterinary Internal Medicine. Diseases of the Dog and Cat. 2nd edition Vol I. Edited by SJ Ettinger, Philadelphia, WB Saunders, 1983, pp 1029-1051
 231. Hsu FS, Du S-J: Cardiac diseases in swine. *Pig Model for Biomedical Research*. Edited by HR Roberts and WJ Dodds. Pig Research Institute, Taiwan, Republic of China 1982, pp 134-143
 232. Liu S-K: Cardiac disease in the dog and cat, ²²¹ pp 110-133
 233. Liu S-K: Pathology of feline heart diseases. *Vet Clin N Am* 1977, 7:323-339
 234. Liu S-K: Acquired cardiac lesions leading to congestive heart failure in the cat. *Am J Vet Res* 1970, 31:2071-2088
 235. Liu S-K, Maron BJ, Tilley LP: Feline hypertrophic cardiomyopathy. Gross anatomic and quantitative histologic features. *Am J Pathol* 1981, 102:388-395
 236. Liu S-K, Maron BJ, Tilley LP: Canine hypertrophic cardiomyopathy. *J Am Vet Med Assoc* 1979, 174:708-713
 237. Liu S-K, Maron BJ, Tilley LP: Hypertrophic cardiomyopathy in the dog. *Am J Pathol* 1979, 94:497-508
 238. Liu S-K, Tashjian RJ, Patniak AK: Congestive heart failure in the cat. *J Am Vet Med Assoc* 1970, 156:1319-1330
 239. Liu S-K, Tilley LP: Animal models of primary myocardial diseases. *Yale J Biol Med* 1980, 53:191-211
 240. Maron BJ, Liu S-K, Tilley LP: Spontaneously occurring hypertrophic cardiomyopathy in dogs and cats: A potential animal model of a human disease. *Hypertrophic Cardiomyopathy*. Edited by M Kaltenbach, SE Epstein. Berlin, Springer-Verlag, 1982, pp 73-87
 241. Tilley LP, Liu S-K: Cardiomyopathy in the dog. *Recent Adv Stud Card Struct Metab* 1975, 10:641-653
 242. Tilley LP, Liu S-K, Gilbertson SR, Wagner BM, Lord PF: Primary myocardial disease in the cat. A model for human cardiomyopathy. *Am J Pathol* 1977, 86:494-522
 243. Boyden PA, Tilley LP, Albala A, Liu S-K, Fenoglio JJ Jr, Wit AL: Mechanisms for atrial arrhythmias associated with cardiomyopathy: A study of feline hearts with primary myocardial disease. *Circulation* 1984, 69:1036-1047
 244. Van Vleet JF, Ferrans VJ, Weirich WE: Pathologic alterations in hypertrophic and congestive cardiomyopathy of cats. *Am J Vet Res* 1980, 41:2037-2048
 245. Maron BJ, Nichols PF III, Pickle LW, Wesley RY, Mulvihill JJ: Patterns of inheritance in hypertrophic cardiomyopathy: Assessment by M-mode and two-dimensional echocardiography. *Am J Cardiol*, 1984 53:1087-1094
 246. Perloff AK: Pathogenesis of hypertrophic cardiomyopathy: Hypotheses and speculations. *Am Heart J* 1981, 101:219-226

247. Ferrans VJ, Rodriguez ER: The pathology of the cardiomyopathies. The Cardiomyopathies. Edited by TD Giles. New York, Wright PSG, 1986 (In press)
248. Laks MM, Morady F, Swan HJC: Myocardial hypertrophy produced by chronic infusion of subhypertensive doses of norepinephrine in the dog. *Chest* 1973, 64:75-78
249. Raum WJ, Laks MM, Garner D, Swerdloff RS: β -adrenergic receptor and cyclic AMP alterations in the canine ventricular septum during long-term norepinephrine infusion: Implications for hypertrophic cardiomyopathy. *Circulation* 1983 68:693-699
250. Fincel TJ, Hill BL: A review of primary cardiomyopathy in the cat. *Iowa State Univ Vet* 1983, 45:118-124
251. Kimman TG, Van der Molen EJ: Patholoog anatomische bevindingen bij negentien Katten mit idiopathische cardiomyopathie. *Tijdschr Diergeneeskde* 1984, 109:132-141
252. Rozengurt N, Hayward AHS: Primary myocardial disease of cats in Britain: Pathological findings in twelve cases. *J Small Anim Pract* 1984, 25:617-626
253. Calvert CA, Chapman WL Jr, Toal RL: Congestive cardiomyopathy in Doberman Pinscher dogs. *J Am Vet Med Assoc* 1982, 181:598-602
254. Darke PGG, Else RW: Canine cardiomyopathy. *Vet Annu* 1984, 24:237-249
255. Ettinger SJ, Suter PF: Acquired diseases of the myocardium. *Canine Cardiology*. Philadelphia, WB Saunders, 1970, pp 383-402
256. Gooding JP, Robinson WF, Wyburn RS, Cullen LK: A cardiomyopathy in the English Cocker Spaniel: A clinico-pathological investigation. *J Small Anim Pract* 1982, 23:133-149
257. Hazlett MJ, Maxie MG, Allen DG, Wilcock BP: A retrospective study of heart disease in Doberman Pinscher dogs. *Can Vet J* 1983, 24:205-210
258. Hill BL: Canine idiopathic congestive cardiomyopathy. *Compend Contin Educ Pract Vet* 1981, 3:615-621
259. Lombard CW: Echocardiographic and clinical signs of canine dilated cardiomyopathy. *J Small Anim Pract* 1984, 25:59-70
260. Sandusky GE Jr, Capen CC, Kerr KM: Histological and ultrastructural evaluation of cardiac lesions in idiopathic cardiomyopathy in dogs. *Can J Comp Med* 1984, 48:81-86
261. Staaden RV: Cardiomyopathy of English Cocker Spaniels. *J Am Vet Med Assoc* 1981, 178:1289-1292
262. Van Vleet JF, Ferrans VJ, Weirich WE: Pathologic alterations in congestive cardiomyopathy of dogs. *Am J Vet Res* 1981, 42:416-424
263. Harpster NK: Boxer cardiomyopathy. *Current Veterinary Therapy VIII. Small Animal Practice*. Philadelphia, WB Saunders, 1983, pp 329-337
264. Detweiler DK, Glickman LT: Parvovirus-induzierte Kardiomyopathie: Eine Hypothese. *Kleintierpraxis* 1983, 28:295-298
265. Sandusky GE, Cho D-Y: Congestive cardiomyopathy in a dog associated with pregnancy. *Cornell Vet* 1984, 74:60-64
266. Walsh JJ, Burch GE, Black WC, Ferrans VJ, Hibbs RG: Idiopathic myocardial disease of the puerperium (post-partal heart disease). *Circulation* 1965, 32:19-31
267. Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH: The idiopathic hyper-eosinophilic syndrome (HES): Clinical, pathophysiological and therapeutic considerations. *Ann Intern Med* 1982, 97:78-92
268. Liu S-K, Fox PR, Tilley LP: Excessive moderator bands in the left ventricle of 21 cats. *J Am Vet Med Assoc* 1982, 180:1215-1219
269. Boorman GA, Hollander CF: Spontaneous lesions in the female WAG/Rij (Wistar) rat. *J Gerontol* 1973, 28:152-159
270. Boorman GA, Zurcher C, Hollander CF, Feron VJ: Naturally occurring endocardial disease in the rat. *Arch Pathol* 1973, 96:39-45
271. Burek JD: Cardiovascular system. *Pathology of Aging Rats*. West Palm Beach, Florida, CRC Press, 1978, pp 75-94
272. Lewis DJ: Sub-endocardial fibrosis in the rat: A light and electron microscopical study. *J Comp Pathol* 1980, 90:577-583
273. Saegusa J, Kawai K: Six cases of endocardial disease in the rat. *Jap J Vet Sci* 1982, 44:961-966
274. Mayer D, Bannasch P: Endomyocardial fibrosis in rats treated with N-nitrosomorpholine. *Virchows Arch Pathol Anat* 1983, 401:129-135
275. Fishbein MD, Ferrans VJ, Roberts WC: Histologic and ultrastructural features of primary and secondary endocardial fibroelastosis. *Arch Pathol Lab Med* 1977, 101:49-51
276. Paasch LH, Zook BC: The pathogenesis of endocardial fibroelastosis in Burmese cats. *Lab Invest* 1980, 42:197-204
277. Zook BC, Paasch LH: Endocardial fibroelastosis in Burmese cats. *Am J Pathol* 1982, 106:435-438
278. Zook BC, Paasch LH, Chandra RS, Casey HW: The comparative pathology of primary endocardial fibroelastosis in Burmese cats. *Virchows Arch [Pathol Anat]* 1981, 390:211-227
279. Harpster NK: Cardiovascular diseases of the domestic cat. *Adv Vet Sci Comp Med* 1977, 21:39-74
280. Zook BC: Some spontaneous cardiovascular lesions in dogs and cats. *Adv Cardiol* 1974, 13:148-168
281. Miller AJ, Pick R, Katz LN: Ventricular endomyocardial changes after impairment of cardiac lymph flow in dogs. *Br Heart J* 1963, 25:182-189
282. St. Geme JW Jr, Davis CW, Noren GR: An overview of primary endocardial fibroelastosis and chronic viral cardiomyopathy. *Perspect Biol Med* 1974, 17:495-505
283. St. Geme JW Jr, Peralta H, Farias E, Davis CW, Noren GR: Experimental gestational mumps virus infection and endocardial fibroelastosis. *Pediatrics* 1971, 48:821-826
284. Levin S: Parvovirus: A possible etiologic agent in cardiomyopathy and endocardial fibroelastosis. *Hum Pathol* 1980, 11:404-405
285. Blaxland JD, Markson LM: Toxic heart degeneration, or "round heart disease" of poultry. *Ir Vet J* 1947, 103:401-405
286. Fischel WG: Enzootic fatal syncope (toxic heart degeneration) in fowl. *Aust Vet J* 1946, 22:144-149
287. Franze F: Beobachtungen über herztodähnliche Erkrankungen bei Jungenten. *Monatsch Veterinaarmed* 1961, 16:109-110
288. Kilian JG, Babcock WE, Dickinson EM: A report on round heart disease in Oregon chickens. *Avian Dis* 1964, 8:56-61
289. Levine PP: Case report: Round heart disease in the United States. *Avian Dis* 1958, 2:530-536
290. Luke D: "Round heart disease" in poultry. *Br Vet J* 1947, 103:17-20
291. Natscheff B: Beitrag zur Behandlung des enzootischen Herztodes beim Huhn. *Berl Münch Tierarztl Wochenschr* 1965, 78:334-335
292. Peckham MC: Diseases of Poultry. 7th edition. Edited by Hofstad MS, Calnek BW, Helmboldt CF, Reid WM, Yoder HW Jr, Ames, Iowa, Iowa State University Press, 1978, pp 872-893
293. Shishov N, Obreshkov C, Enchev ST: Round heart disease of the domestic fowl (*Gallus gallus*) in Bulgaria. *Pathol Vet* 1968, 5:41-50

294. Wilson JE: Round heart disease in poultry. *J Comp Pathol* 1957, 67:239-251
295. Wilson JE, Siller WG: Round heart disease in the fowl. *J Comp Pathol* 1954, 64:41-51
296. Hopkinson WI, Griffiths GL, Jessop D, Williams W: Sudden death syndrome in broiler chickens. *Aust Vet J* 1983, 60:192-193
297. Hopkinson WI, Williams W, Griffiths GL, Jessop D, Peters SM: Dietary induction of sudden death syndrome in broiler breeders. *Avian Dis* 1984, 28:352-357
298. Pass DA: A cardiomyopathy ("sudden death syndrome") of adult hens. *Avian Pathol* 1983, 12:363-369
299. Ononiwu JC, Thomson RG, Carlson HC, Julian RJ: Pathological studies of "sudden death syndrome" in broiler chickens. *Can Vet J* 1979, 20:70-73
300. Ononiwu JC, Thomson RG, Carlson HC, Julian RJ: Studies on effect of lighting on "sudden death syndrome" in broiler chickens. *Can Vet J* 1979, 20:74-77
301. Riddell C, Orr JP: Chemical studies of the blood, and histological studies of the heart of broiler chickens dying from acute death syndrome. *Avian Dis* 1980, 24:751-757
302. Bergmann V, Müller-Molenar K, Birnbaum H: Zum auftreten eines Hydroperekard-Aszites-Syndroms ("Üdemkrankheit" in Broilerstanden). *Mh Vet Med* 1979, 34:626-628
303. Lohr JE: Congestive heart failure in broilers, resembling toxic heart degeneration and chick oedema disease. *NZ Vet J* 1975, 23:200-206
304. Hall SA, Machicao N: Myocarditis in broiler chickens reared at high altitude. *Avian Dis* 1968, 12:75-84
305. Olander HJ, Burton RR, Adler HE: The pathophysiology of chronic hypoxia in chickens. *Avian Dis* 1967, 11:609-620
306. Fry RJM, Hamilton KH, Lisco H: Thrombi in the left atrium of the heart in mice. *Arch Pathol* 1965, 80:308-313
307. Schmidt RE, Eason RL, Hubbard GB, Young JT, Eisenbrandt DL: Cardiovascular system. Pathology of Aging Syrian Hamsters. Boca Raton, Florida, CRC Press, 1983, pp 3-19
308. Ball CR, Clower BR, Williams WL: Dietary-induced atrial thrombosis in mice. *Arch Pathol* 1965, 80:391-396
309. Ball CR, Williams WL, Collum JM: Cardiovascular lesions in Swiss mice fed a high-fat, low-protein diet with and without betaine supplementation. *Anat Rec* 1963, 145:49-60
310. McMartin DN: Spontaneous atrial thrombosis in aged Syrian hamsters: I. Incidence and pathology. *Thromb Haemost* 1977, 38:447-456
311. Lockwood WR, Clower BR, Hetherington F: Light and electron microscopy of diet-induced atrial thrombosis in TS mice. *Am J Anat* 1969, 126:185-200
312. Davenport WD Jr, Ball CR: Diet-induced atrial endothelial damage: A scanning electron-microscopic study. *Atherosclerosis* 1981, 40:145-152
313. Sichuk G, Bettigole RE, Der BK, Fortner JG: Influence of sex hormones on thrombosis of left atrium in Syrian (golden) hamsters. *Am J Physiol* 1965, 208:465-470
314. Thomas HM Jr, Williams WL, Clower BR: Cardiac lesions in C mice: Result of choline-deficient and choline-supplemented diets. *Arch Pathol* 1968, 85:532-538
315. Clower BR, Douglas BH: The effect of estrogen, reserpine, and pregnancy on development of diet-induced atrial thrombosis in mice. *Am J Obstet Gynecol* 1968, 102:928-931
316. Wilson JL, Ashburn AD, Williams WL: Effects of sex hormones on diet-induced atrial thrombosis. *Anat Rec* 1970, 168:331-338
317. Clower BR: Relation of levels of dietary fat to atrial thrombosis in RF mice. *J Atheroscler Res* 1968, 8:885-890
318. Wicks MS, Ball CR, Williams WL: Relation of types of dietary fat to cardiovascular damage in mice. *Am J Anat* 1969, 124:481-490
319. Ashburn AD, Weaver MM, Summers PA: Effects of red blood cell injections on diet-induced atrial thrombosis in Swiss mice. *Am J Anat* 1972, 133:341-348
320. Ball CR: Hematologic studies of mice fed a thrombogenic diet. *Arch Pathol* 1968, 85:547-553
321. Weaver MM, Ashburn AD: Effects of circulating red cell mass on diet-induced atrial thrombosis in mice. *Yale J Biol Med* 1974, 3:148-154
322. Ball CR, Westin DC: Anemia induced by thrombogenic diet and remission after normal diet. *Arch Pathol* 1970, 90:117-124
323. Klevay LM: Thrombosis, cardiac arrhythmia and sudden death in mice due to copper deficiency (Abstr). *Fed Proc* 1984, 43:844
324. Buchanan JW: Spontaneous left atrial rupture in dogs. *Adv Exp Med Biol* 1972, 22:315-334
325. Stünzi H, Ammann-Mann M: Nicht-traumatische Rupturen des Herzvorhofs beim Hund. *Zbl Vet Med A* 1973, 20:409-418
326. Boorman GA, Hollander CF: Spontaneous lesions in the female WAG/Rij (Wistar) rat. *J Gerontol* 1973, 28:152-159
327. Fairweather FA: Cardiovascular disease in rats. Pathology of Laboratory Rats and Mice. Edited by E Cotchin, FJC Roe. Blackwell Scientific Publications. Oxford, 1967, pp 213-227
328. Lehr D: Lesions of the cardiovascular system. In The Pathology of Laboratory Animals. Edited by WE Ribelin, JR McCoy, Springfield, Ill, Charles C Thomas, 1965, pp 124-159
329. Willens SL, Sproul EE: Spontaneous cardiovascular disease in the rat: I. Lesions of the heart. *Am J Pathol* 1938, 14:177-200
330. Cranley JJ, McCullagh KG: Ischaemic myocardial fibrosis and aortic strongylosis in the horse. *Equine Vet J* 1981, 13:35-42
331. Dudan F, Luginbühl H: Etude cardiovasculaire chez le cheval: Relation entre les altérations vasculaires et tissulaires du myocarde. Première partie. *Schweiz Arch Tierheilk* 1984, 126:277-286
332. Dudan F, Rossi GL, Luginbühl H: Etude cardiovasculaire chez le cheval: Relation entre les altérations vasculaires et tissulaires du myocarde. Deuxième partie. *Schweiz Arch Tierheilk* 1984, 126:527-538
333. Dudan F, Rossi GL, Luginbühl H: Etude cardiovasculaire chez le cheval: Relation entre les altérations vasculaires et tissulaires du myocarde. *Schweiz Arch Tierheilk* 1985, 127:369-378
334. Else RW, Holmes JR: Pathological changes in atrial fibrillation in the horse. *Equine Vet J* 1971, 3:56-64
335. Marcus LC, Ross JN Jr: Microscopic lesions in the hearts of aged horses and males. *Vet Pathol* 1967, 4:162-185
336. Kiryu K: Cardiopathology of arrhythmias in the horse. *Proc 26th Annu Convent Am Assoc Equine Pract* 1981, 457-468
337. Haaland MA, Davidson JP: Spontaneous left atrial rupture with associated chronic fibrotic myocarditis in a stallion. *Vet Clin North Am [Sm Anim Pract]* 1983, 78:1284-1288
338. Miller WC: Cardiovascular diseases in horses. *Vet Rec* 1962, 74:825-828
339. Else RW, Holmes JR: Cardiac pathology in the horse: 2. Microscopic pathology. *Equine Vet J* 1972, 4:57-62
340. Jonsson L: Coronary arterial lesions and myocardial infarcts in the dog: A pathologic and microangiographic study. *Acta Vet Scand (Suppl 38)* 1972, 13:1-80
341. Ferrans VJ, Boyce SW: Metabolic and familial diseases. Cardiovascular Pathology, Edited by MD Silver, New York, Churchill-Livingstone, 1982, pp 945-1004

342. Ferrans VJ, Buja LM, Jones M: Ultrastructure and cytochemistry of glycogen in cardiac diseases. *Recent Adv Stud Card Struct Metab* 1973, 3:97-144
343. Agamanolis DP, Askari AD, Di Mauro S, Hays A, Kumar K, Lipton M, Raynor A: Muscle phosphofructokinase deficiency: Two cases with unusual polysaccharide accumulation and immunologically active enzyme protein. *Muscle Nerve* 1980, 3:456-467
344. Reed GB Jr, Dixon JFP, Neustein HB, Donnell GN, Landing BH: Type IV glycogenosis: Patient with absence of a branching enzyme α -1,4-glucan: α -1,4-glucan 6-glycosyl transferase. *Lab Invest* 1968, 19:546-557
345. Holland JM, Davis WC, Prieur DJ, Collins GH: Lafora's disease in the dog: A comparative study. *Am J Pathol* 1970, 58:509-530
346. Revis NW: Relationship of vanadium, cadmium, lead, nickel, cobalt and soft water to myocardial and vascular toxicity and cardiovascular disease. *Cardiovascular Toxicology*, Edited by EW Van Stee, New York, Raven Press, 1982, pp 365-377
347. Williams BJ, Hejtmancik MR Jr, Abreu M: Cardiac effects of lead. *Fed Proc* 1983, 42:2989-2993
348. Moore MR, Goldberg A, Carr K, Toner P, Lawrie TDV: Biochemical and electron-microscopical studies of chronic lead exposure in the heart and other organs of rats. *Scott Med J* 1974, 19:155-156
349. Asokan SK: Experimental lead cardiomyopathy: Myocardial structural changes in rats given small amounts of lead. *J Lab Clin Med* 1974, 84:20-25
350. Khan MY, Buse M, Louria DB: Lead cardiomyopathy in mice: A correlative ultrastructural and blood level study. *Arch Pathol Lab Med* 1977, 101:89-94
351. Alexander CS: Cobalt-beer cardiomyopathy: A clinical and pathologic study of twenty-eight cases. *Am J Med* 1972, 53:395-417
352. Ferrans VJ, Buja LM, Roberts WC: Cardiac morphologic changes produced by ethanol. *Alcohol and Abnormal Protein Biosynthesis*. Edited by MA Rothschild, M Oratz, S Schreiber. New York, Pergamon Press, 1974, pp 139-185
353. Grice HC, Wiberg GS, Heggveit HA: Studies in food additive cardiomyopathies. *Cardiac Toxicology*. Vol II. Edited by T Balazs. Boca Raton, Florida, CRC Press, 1981, pp 189-201
354. Achenbach H, Urbaszek W, Günther K, Schneider D, Schneider D, Kronberger H, Trenckmann H, Kiessling J, Hurlbeck M, Splith G: Die Kobaltmyokardose als Experimentiermodell für hypodynamie Herz-Kreislauf-Situationen. *Z Gesamte Inn Med* 1974, 29:1-8
355. Grice HC, Munro IC, Wiberg GS, Heggveit HA: The pathology of experimentally induced cobalt cardiomyopathy: A comparison with beer drinkers' cardiomyopathy. *Clin Toxicol* 1969, 2:273-287
356. Hall JL, Smith EB: Cobalt heart disease: An electron microscopic and histochemical study in the rabbit. *Arch Pathol* 1968, 86:403-412
357. Knieriem H-J, Herbertz G: Elektronenmikroskopische Befunde sowie photometrische und aktivierungsanalytische Ergebnisse bei experimenteller Herzinsuffizienz durch Kobaltchlorid. *Virchows Arch Zellpathol* 1969, 2:32-46
358. Lin JH, Duffy JL: Cobalt-induced myocardial lesions in rats. *Lab Invest* 1970, 23:158-162
359. Mohiuddin SM, Taskar PK, Rheault M, Roy PE, Chenard J, Morin Y: Experimental cobalt cardiomyopathy. *Am Heart J* 1970, 80:532-543
360. Rona G, Chappel CI: Pathogenesis and pathology of cobalt cardiomyopathy. *Recent Adv Stud Card Struct Metab* 1973, 2:407-422
361. Unverferth DV, Crockery RW, Leier CV, Altschuld R, Pipers FS, Thomas J, Magorien RD, Hamlin RL: Canine cobalt cardiomyopathy: A model for the study of heart failure. *Am J Vet Res* 1983, 44:989-995
362. Wiberg GS, Munro IC, Meranger JC, Morrison AB, Grice HC: Factors affecting the cardiotoxic potential of cobalt. *Clin Toxicol* 1969, 1:257-271
363. Van Vleet JF, Rebar AH, Ferrans VJ: Acute cobalt and isoproterenol cardiotoxicity in swine: Protection by selenium-vitamin E supplementation and potentiation by stress-susceptible phenotype. *Am J Vet Res* 1977, 38:991-1002
364. Hossein R, Burmen SO, Casale T, Narula O, Greenberg S, Downing S, Schumer W: An experimental model of cardiomyopathy. *Surg Forum* 1976, 27:278-280
365. Sandusky GE, Crawford MP, Roberts ED: Experimental cobalt cardiomyopathy in the dog: A model for cardiomyopathy in dogs and man. *Toxicol Appl Pharmacol* 1981, 60:263-278
366. Heggveit HA, Grice HC, Wiberg GS: Cobalt cardiomyopathy: Experimental basis for the human lesion. *Pathol Microbiol* 1970, 35:110-113
367. Balazs T, Bloom S: Cardiotoxicity of adrenergic bronchodilator and vasodilating antihypertensive drugs,³⁴⁶ pp 199-220
368. Balazs T, Herman EH: Toxic cardiomyopathies. *Ann Clin Lab Sci* 1976, 6:467-476
369. Lehr D: Studies on the cardiotoxicity of α - and β -adrenergic amines,³⁵³ pp 75-112
370. Rona G: Catecholamine cardiotoxicity. *J Mol Cell Cardiol* 1985, 17:291-306
371. Rona G, Hüttner I, Boutet M: Microcirculatory changes in myocardium with particular reference to catecholamine-induced cardiac muscle cell injury. *Handbuch der Allgemeinen Pathologie*. Vol 111/7. Edited by H Meesen, Berlin, Springer-Verlag, 1977, pp 791-888
372. Balazs T, Earl FL, Bierbower GW, Weinberger MA: The cardiotoxic effects of pressurized aerosol isoproterenol in the dog. *Toxicol Appl Pharmacol* 1973, 26:407-417
373. Bloom S, Cancilla P: Myocytolysis and mitochondrial calcification in rat myocardium after low doses of isoproterenol. *Am J Pathol* 1969, 54:373-391
374. Downing SE, Chen V: Myocardial injury following endogenous catecholamine release in rabbits. *J Mol Cell Cardiol* 1985, 17:377-387
375. Downing SE, Lee JC: Contribution of α -adrenoceptor activation to the pathogenesis of norepinephrine cardiomyopathy. *Circ Res* 1983, 52:471-478
376. Dusek J, Boutet M, Rona G: Ultrastructural changes in isoproterenol-induced atrial necrosis. *Recent Adv Card Struct Metab* 1973, 2:423-432
377. Eliot RS, Todd GL, Clayton FC, Pieper GM: Experimental catecholamine-induced acute myocardial necrosis. *Adv Cardiol* 1978, 25:107-118
378. Ferrans VJ, Hibbs RG, Black WC, Weilbaecher DG: Isoproterenol-induced myocardial necrosis: A histochemical and electron-microscopic study. *Am Heart J* 1964, 68:71-90
379. Magnuson G, Hansson E: Myocardial necrosis in the rat: A comparison between isoprenaline, or ciprenaline, salbutamol, and terbutaline. *Cardiology* 1973, 58:174-180
380. Noronha-Dutra AA, Steen EM, Woolf N: The early changes induced by isoproterenol in the endocardium and adjacent myocardium. *Am J Pathol* 1984, 114:231-239
381. Todd GL, Baroldi G, Pieper GM, Clayton FC, Eliot RS: Experimental catecholamine-induced myocardial necrosis: I. Morphology, quantification and regional distribution of acute contraction band lesions. *J Mol Cell Cardiol* 1985, 17:317-338
382. Carlsten A, Poupa O, Volkmann R: Cardiac lesions in poikilotherms by catecholamines. *Comp Biochem Physiol* 1983, 76A:567-581
383. Balazs T, Arena E, Barron CN: Protection against the cardiotoxic effect of isoproterenol HCl by restricted food intake in rats. *Toxicol Appl Pharmacol* 1972, 21:237-242

384. Darsinos JT, Karli JN, Stathaki SN, Ziroyannis PN, Pistevos AC, Levis GM, Mouloupoulos SD: Effect of hypocalcemia on isoproterenol induced cardiotoxicity in dogs. *Angiology* 1984, 35:152-162
385. Parizkova J, Faltova E: Physical activity, body fat and experimental cardiac necrosis. *Br J Nutr* 1970, 24:3-10
386. Parizkova J, Faltova E, Mraz M, Spatova M: Growth, food intake, motor activity and experimental cardiac necrosis in early malnourished male rats. *Ann Nutr Metab* 1982, 26:121-128
387. Rona G, Chappel CI, Balazs T, Gaudry R: The effect of breed, age, and sex on myocardial necrosis produced by isoproterenol in the rat. *J Gerontol* 1959, 14:169-173
388. Rona G, Chappel CI, Kahn DS: The significance of factors modifying the development of isoproterenol-induced myocardial necrosis. *Am Heart J* 1963, 66:389-395
389. Wexler BC: Prolonged protective effects following propranolol withdrawal against isoproterenol-induced myocardial infarction in normotensive and hypertensive rats. *Br J Exp Pathol* 1985, 66:143-154
390. Balazs T: Development of tissue resistance to toxic effects of chemicals. *Toxicology* 1974, 2:247-255
391. Joseph X, Bloom S, Pledger G, Balazs T: Determinants of resistance to the cardiotoxicity of isoproterenol in rats. *Toxicol Appl Pharmacol* 1983, 69:199-205
392. Mitova M, Bednarik B, Cerny E, Foukal T, Krathy J, Papousek F: Influence of physical exertion on early isoproterenol-induced heart injury. *Basic Res Cardiol* 1983, 78:131-139
393. Gotzsche O: Lack of cardiotoxic effect of isoproterenol in streptozotocin diabetic rats. *Virchows Arch [Pathol Anat]* 1982, 397:83-91
394. El-Hage AN, Herman EH, Jordan AW, Ferrans VJ: Influence of the diabetic state on isoproterenol-induced cardiac necrosis. *J Mol Cell Cardiol* 1985, 17:361-369
395. Singal PK, Beamish RE, Dhalla NS: Potential oxidative pathways of catecholamines in the formation of lipid peroxides and genesis of heart disease. *Adv Exp Med Biol* 1983, 161:391-401
396. Singal PK, Kapur N, Dhillon KS, Beamish RE, Dhalla NS: Role of free radicals in catecholamine-induced cardiomyopathy. *Can J Physiol Pharmacol* 1982, 60:1390-1397
397. Kantrowitz NE, Bristow MR, Minobe WA, Billingham ME, Harrison DC: Histamine-mediated myocardial damage in rabbits. *J Mol Cell Cardiol* 1982, 14:551-555
398. Tãterka W: Vergleichende histotopographische und elektrokardiographische Untersuchungen über linksbetonte und rechtsbetonte Coronarinsuffizienz bei Collaps. *Beitr Pathol* 1938, 102:287
399. Carlson RG, Feenstra ES: Toxicologic studies with the hypotensive agent minoxidil. *Toxicol Appl Pharmacol* 1977, 39:1-11
400. Herman EH, Balazs T, Ferrans VJ, Young RSK: Divergent effects of propranolol and furosemide pretreatment on acute cardiomyopathy induced by minoxidil in beagle dogs. *Toxicology* 1981, 20:155-164
401. Herman E, Balazs T, Young R, Earl FJ, Krop S, Ferrans VJ: Acute cardiomyopathy induced by the vasodilating antihypertensive agent minoxidil. *Toxicol Appl Pharmacol* 1979, 47:493-503
402. Sobota JT, Martin WB, Carlson RG, Feenstra ES: Minoxidil: Right atrial cardiac pathology in animals and in man. *Circulation* 1980, 62:376-387
403. Van Vleet JF, Herman EH, Ferrans VJ: Cardiac morphologic alterations in acute minoxidil cardiotoxicity in swine. *Exp Mol Pathol* 1984, 41:10-25
404. Herman EH, Ferrans VJ, Balazs T: Minoxidil and cardiac lesions. *Circulation* 1981, 64:1299-1300
405. Balazs T: Cardiotoxicity of adrenergic bronchodilator and vasodilating antihypertensive drugs.³⁵³ pp 61-73
406. Balazs T, Payne BJ: Myocardial papillary muscle necrosis induced by hypotensive agents in dogs. *Toxicol Appl Pharmacol* 1971, 20:442-445
407. Gans JH, Korson R, Cater MR, Ackerly CC: Effects of short-term and long-term theobromine administration to male dogs. *Toxicol Appl Pharmacol* 1980, 53:481-496
408. Strubelt O, Hoffmann A, Siegers C-P, Sierra-Callejas J-L: On the pathogenesis of cardiac necroses induced by theophylline and caffeine. *Acta Pharmacol Toxicol* 1976, 39:383-392
409. Strubelt O, Wegener F, Siegers C-P: Zur Frage der Hepatotoxizität von Coffein und Theophyllin. *Arzneimittelforsch* 1970, 20:473-476
410. Amend JF, Mallon FM, Wren WB, Ramos AS: Equine monensin toxicosis: Some experimental clinicopathologic observations. *Comp Contin Ed Pract Vet (Suppl)* 1980, 2:173-183
411. Anderson TD, Van Alstine WG, Ficken MD, Miskimins DW, Carson TL, Osweiler GD: Acute monensin toxicosis in sheep: Light and electron microscopic changes. *Am J Vet Res* 1984, 45:1142-1147
412. Beck BE, Harries WN: The diagnosis of monensin toxicosis: A report on outbreaks in horses, cattle and chickens. *Proceedings of the 22nd Annual Meeting of the American Association of Veterinary Laboratory Diagnosticians* 1979, 269-282
413. Collery P: An outbreak of monensin poisoning in cattle. *Irish Vet J* 1983, 37:139-141
414. Collins EA, McCrea CT: Monensin sodium toxicity in cattle. *Vet Rec* 1978, 103:386
415. Confer AW, Reavis DU, Panciera RJ: Light and electron microscopic changes in cardiac and skeletal muscle of sheep with experimental monensin toxicosis. *Vet Pathol* 1983, 20:590-602
416. Dilov P, Dimitrov S, Jourov A, Nikolov A, Panchev I, Goranov H, Stoyanov K, Donev B, Dimitrov K: [Studies on the toxicity of monensin-sodium in pigs.] *Veterinar-nomeditsinski Nauki* 1981, 18:55-63
417. Donev B, Stoyanov K, Dzhurov A, Dilov P: [Acute and subacute toxicity of monensin in lambs.] *Veterinar-nomeditsinski Nauki* 1980, 17:17-25
418. Drake JN: Monensin-tiamulin interaction risk to pigs. *Vet Rec* 1981, 108:219-220
419. Geor RJ, Robinson WF: Suspected monensin toxicosis in feedlot cattle. *Aust Vet J* 1985, 62:130-131
420. Hanrahan LA, Corrier DE, Naqi SA: Monensin toxicosis in broiler chickens. *Vet Pathol* 1981, 18:665-671
421. Horrox NE: Monensin-tiamulin interaction risk to poultry. *Vet Rec* 1980, 106:278
422. Hosie BD, Rollo DG: Nutritional myopathy in cattle associated with monensin toxicosis. *Vet Rec* 1985, 116:132-133
423. Howell J, Hanson J, Onderka D, Harries WN: Monensin toxicity in chickens. *Avian Dis* 1980, 24:1050-1053
424. Janzen ED, Radostits OM, Orr JP: Possible monensin poisoning in a group of bulls. *Can Vet J* 1981, 22:92-94
425. Kemp J: Monensin poisoning in turkeys. *Vet Rec* 1978, 102:467
426. Matsuoka T: Evaluation of monensin toxicity in the horse. *J Am Vet Med Assoc* 1976, 169:1098-1100
427. Mollenhauer HH, Rowe LD, Cysewski SJ, Witzel DA: Ultrastructural observations in ponies after treatment with monensin. *Am J Vet Res* 1981, 42:35-40
428. Muylle E, Vandenhende C, Oyaert W, Thoonen H, Vlaeminck K: Delayed monensin sodium toxicity in horses. *Equine Vet J* 1981, 13:107-108
429. Nation PN, Crowe SP, Harries WN: Clinical signs and pathology of accidental monensin poisoning in sheep. *Can Vet J* 1982, 23:323-326
430. Newsholme SJ, Howerth EW, Bastianello SS, Prozesky L, Minne JA: Fatal cardiomyopathy in feedlot sheep attributed to monensin toxicosis. *J S Afr Vet Assoc* 1983, 54:29-32
431. Ordidge RM, Schubert FK, Stoker JW: Death of horses

- after accidental feeding of monensin. *Vet Rec* 1979, 104:375
432. Pott JM, Skov B: Monensin-tiamulin interactions in pigs. *Vet Rec* 1981, 109:545
 433. Potter EL, VanDuyn RL, Cooley CO: Monensin toxicity in cattle. *J Anim Sci* 1984, 58:1499-1511
 434. Schweitzer D, Kimberling C, Spraker T, Sterner FE, McChesney AE: Accidental monensin sodium intoxication of feedlot cattle. *J Am Vet Med Assoc* 1984, 184:1273-1276
 435. Stansfield DG, Lamont MN: Monensin tiamulin interactions in pigs. *Vet Rec* 1981, 109:545
 436. Stuart JC: An outbreak of monensin poisoning in adult turkeys. *Vet Rec* 1978, 102:303-304
 437. Todd GC, Novilla MN, Howard LC: Comparative toxicology of monensin sodium in laboratory animals. *J Anim Sci* 1984, 58:1512-1517
 438. Van de Kirk PL [Monensin-intoxicatie bij paarden.] *Tijdschr Diergeneeskd* 1978, 103:699-700
 439. Van Vleet JF, Ferrans VJ: Myocardial ultrastructural alterations in monensin toxicosis of cattle. *Am J Vet Res* 1983, 44:1629-1639
 440. Van Vleet JF, Ferrans VJ: Ultrastructural alterations in the atrial myocardium of pigs with acute monensin toxicosis. *Am J Pathol* 1984, 114:367-379
 441. Van Vleet JF, Amstutz HE, Weirich WE, Rebar AH, Ferrans VJ: Clinical, clinicopathologic, and pathologic alterations of monensin toxicosis in swine. *Am J Vet Res* 1983, 44:1469-1475
 442. Van Vleet JF, Amstutz HE, Weirich WE, Rebar AH, Ferrans VJ: Acute monensin toxicosis in swine: Effect of graded doses of monensin and protection of swine by pretreatment with selenium-vitamin E. *Am J Vet Res* 1983, 44:1460-1468
 443. Van Vleet JF, Amstutz HE, Weirich WE, Rebar AH, Ferrans VJ: Clinical, clinicopathologic, and pathologic alterations in acute monensin toxicosis in cattle. *Am J Vet Res* 1983, 44:2133-2144
 444. Wardrope DD, Macleod NSM, Sloan JR: Outbreak of monensin poisoning in cattle. *Vet Rec* 1983, 112:560-561
 445. Wentink GH, Vente JPh: Monensin poisoning in dairy cattle: Report of a case. *Tijdschr Diergeneeskd* 1981, 106:623-625
 446. Whitlock RH, White NA, Rowland GN, Plue R: Monensin toxicosis in horses: Clinical manifestations. *Proceedings of the Annual Convention of the American Association of Equine Practitioners* 1978, 24:473-486
 447. Wilson JS: Toxic myopathy in a dog associated with the presence of monensin in dry food. *Can Vet J* 1980, 21:30-31
 448. Galitzer SJ, Bartley EE, Oehme FW: Preliminary studies on lasalocid toxicosis in cattle. *Vet Hum Toxicol* 1982, 24:406-409
 449. Hanson LJ, Eisenbeis HG, Givens SV: Toxic effects of lasalocid in horses. *Am J Vet Res* 1981, 42:456-461
 450. Todd GC, Meyers DB, Pierce EC, Worth HM: Acute reversible myopathy produced by compound A204. *Antimicrob Agents Chemother* 1970, 361-365
 451. Davis C: Narasin toxicity in turkeys. *Vet Rec* 1983, 113:627
 452. Stuart JC: Salinomycin poisoning in turkeys. *Vet Rec* 1983, 113:597
 453. Arnold L, McGrath B, Cocks M, Sumithran E, Johnston C: Adriamycin cardiomyopathy in the rabbit: An animal model of low output cardiac failure with activation of vasoconstrictor mechanisms. *Cardiovasc Res* 1985, 19:378-382
 454. Herman EH, Ferrans VJ: Reduction of chronic doxorubicin cardiotoxicity in dogs by pretreatment with (\pm)-1,2-bis (3,5-dioxopiperazinyl-1-yl) propane (ICRF-187). *Cancer Res* 1981, 41:3436-3440
 455. Herman EH, Ferrans VJ: ICRF-187 Reduction of chronic daunorubicin and doxorubicin cardiotoxicity in rabbits, beagle dogs and miniature pigs. *Drugs Exp Clin Res* 1983, 9:483-490
 456. Van Vleet JF, Ferrans VJ, Badylak SF: Effect of thyroid hormone supplementation on chronic doxorubicin (adriamycin)-induced cardiotoxicity and serum concentrations of T₃ and T₄ in dogs. *Am J Vet Res* 1982, 43:2173-2182
 457. Van Vleet JF, Ferrans VJ, Weirich WE: Cardiac disease induced by chronic adriamycin administration in dogs and an evaluation of vitamin E and selenium as cardioprotectants. *Am J Pathol* 1980, 99:13-42
 458. Herman EH, El-Hage AN, Ferrans VJ, Ardalén B: Comparison of the severity of the chronic cardiotoxicity produced by doxorubicin in normotensive and hypertensive rats. *Toxicol Appl Pharmacol* 1985, 78:202-214
 459. Van Vleet JF, Greenwood LA, Ferrans VJ: Pathologic features of adriamycin toxicosis in young pigs: Nonskeletal lesions. *Am J Vet Res* 1979, 40:1537-1552
 460. Herman EH, Ferrans VJ: Influence of vitamin E and ICRF-187 on chronic doxorubicin cardiotoxicity in miniature swine. *Lab Invest* 1983, 49:69-77
 461. Bertazzoli C, Bellini O, Magrini U, Tosana MG: Quantitative experimental evaluation of adriamycin cardiotoxicity in the mouse. *Cancer Treat Rep* 1979, 63:1877-1883
 462. Billingham ME, Mason JW, Bristow MR, Daniels JR: Anthracycline cardiomyopathy monitored by morphologic changes. *Cancer Treat Rep* 1978, 62:865-872
 463. Cortes EP, Lutman G, Wanka J, Wang JJ, Pickren J, Wallace J, Holland JF: Adriamycin (NSC-123127) cardiotoxicity: A clinicopathologic correlation. *Cancer Treat Rep* 1975, 6:215-225
 464. Doroshow JH, Locker GY, Myers CE: Experimental animal models of adriamycin cardiotoxicity. *Cancer Treat Rep* 1979, 63:855-860
 465. Ferrans VJ: Overview of cardiac pathology in relation to anthracycline cardiotoxicity. *Cancer Treat Rep* 1978, 62:955-961
 466. Ferrans VJ: Anthracycline cardiotoxicity. *Adv Exp Med Biol* 1983, 161:519-532
 467. Jackson JA, Reeves JP, Muntz KH, Kruk D, Prough RA, Willerson JT, Buja LM: Evaluation of free radical effects and catecholamine alterations in adriamycin cardiotoxicity. *Am J Pathol* 1984, 117:140-153
 468. Jaenke RS: An anthracycline antibiotic-induced cardiomyopathy in rabbits. *Lab Invest* 1974, 30:292-304
 469. Jaenke RS: Delayed and progressive myocardial lesions after adriamycin administration in the rabbit. *Cancer Res* 1976, 36:2958-2966
 470. Mettler FP, Young DM, Ward JM: Adriamycin-induced cardiotoxicity (cardiomyopathy and congestive heart failure) in rats. *Cancer Res* 1977, 37:2705-2713
 471. Olson HM, Capen CC: Chronic cardiotoxicity of doxorubicin (adriamycin) in the rat: Morphologic and biochemical investigations. *Toxicol Appl Pharmacol* 1978, 44:605-616
 472. Solcia E, Ballerini L, Bellini O, Magrini U, Bertazzoli C, Toxana MG, Sala L, Balconi F, Rallo F: Cardiomyopathy of doxorubicin in experimental animals: Factors affecting the severity, distribution and evolution of myocardial lesions. *Tumori* 1981, 67:461-472
 473. Van Vleet JF, Ferrans VJ: Clinical and pathologic features of chronic adriamycin toxicosis in rabbits. *Am J Vet Res* 1980, 41:1462-1469
 474. Herman EH, Ferrans VJ, Jordan W, Ardalén B: Reduction of chronic daunorubicin cardiotoxicity by ICRF-187 in rabbits. *Res Commun Chem Pathol Pharmacol* 1981, 31:85-97
 475. Herman EH, Ferrans VJ, Myers CE, Van Vleet JF: Comparison of the effectiveness of (\pm)-1,2-bis (3,5 dioxopiperazinyl-1-yl) propane (ICRF-187) and N-acetylcysteine in preventing chronic doxorubicin cardiotoxicity in beagles. *Cancer Res* 1985, 45:276-281

476. Herman EH, Rehman A, Ferrans VJ, Vick JA, Schein PS: Prevention of chronic doxorubicin cardiotoxicity in beagles by liposomal encapsulation. *Cancer Res* 1983, 43:5427-5432
477. Van Vleet JF, Greenwood L, Ferrans VJ, Rebar AH: Effect of selenium-vitamin E on adriamycin-induced cardiomyopathy in rabbits. *Am J Vet Res* 1978, 39:997-1010
478. Van Vleet JF, Ferrans VJ: Evaluation of vitamin E and selenium protection against chronic adriamycin toxicity in rabbits. *Cancer Treat Rep* 1980, 64:315-317
479. Unverferth DV, Leier CV, Balcerzak SP, Hamlin RL: Usefulness of a free radical scavenger in preventing doxorubicin-induced heart failure in dogs. *Am J Cardiol* 1985, 56:157-161
480. Perkins WE, Schroeder RL, Carrano RA, Imondi AR: Myocardial effects of mitoxanthrone and doxorubicin in the mouse and guinea pig. *Cancer Treat Rep* 1984, 68:841-847
481. Iatropoulos MJ: Anthracycline cardiomyopathy: Predictive value of animal models. *Cancer Treat Symp* 1984, 3:3-17
482. Unverferth DV, Bashore TM, Magorein RD, Fetters JK, Neidhart JA: Histologic and functional characteristics of human heart after mitoxanthrone therapy. *Cancer Treat Symp* 1984, 3:47-53
483. Unverferth DV, Unverferth BJ, Balcerzak SP, Bashore TM, Neidhart JA: Cardiac evaluation of mitoxanthrone. *Cancer Treat Rep* 1983, 67:343-350
484. Sparano BM, Gordon G, Hall C, Iatropoulos MJ, Noble JF: Safety assessment of a new anticancer compound, mitoxanthrone, in beagle dogs: Comparison with doxorubicin: II. Histologic and ultrastructural pathology. *Cancer Treat Rep* 1982, 66:1145-1158
485. Grieshaber CK: Preclinical toxicity of two mitoxanthrone analogs. *Cancer Treat Symp* 1984, 3:19-23
486. Applebaum FR, Strauchen RG, Graw RG Jr, Savage DD, Kent KM, Ferrans VJ, Herzig GP: Acute lethal carditis caused by high-dose combination chemotherapy: A unique clinical and pathological entity. *Lancet* 1976, 1:58-62
487. Buja LM, Ferrans VJ, Graw RD Jr: Cardiac pathologic findings in patients treated with bone marrow transplantation. *Hum Pathol* 1976, 7:17-45
488. Gottdiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J: Cardiotoxicity associated with high-dose cyclophosphamide therapy. *Arch Intern Med* 1981, 141:758-763
489. Santos GW, Sensenbrenner LL, Burke PJ, Colvin OM, Owens AH, Bias W, Slavin R: Marrow transplants in man utilizing cyclophosphamide: Summary of Baltimore experience. *Exp Hematol* 1970, 20:78-81
490. Von Bernuth G, Adam D, Hofstetter R, Lang D, Mohr W, Kohne K, Niethammer D: Cyclophosphamide cardiotoxicity. *Eur J Pediatr* 1980, 134:87-90
491. O'Connell TX, Berenbaum MC: Cardiac and pulmonary effects of high-dose cyclophosphamide and isophosphamide. *Cancer Res* 1984, 34:1586-1591
492. Storb RC, Buckner J, Dillingham LA, Thomas ED: Cyclophosphamide regimens in rhesus monkeys with and without marrow infusion. *Cancer Res* 1970, 31:2195-2203
493. Herman EH, Mhatre RM, Waravdekar VS, Lee IP: Comparison of the cardiovascular actions of NSC-109, 724 (ifosfamide) and cyclophosphamide. *Toxicol Appl Pharmacol* 1972, 23:178-190
494. Ershler WB, Hacker MP, Newman RA, Stewart JA, Gamelli RL, Krakoff IH: Effect of disulfiram on cyclophosphamide toxicity: A clinical trial. *Cancer Treat Rep* 1983, 67:1145-1146
495. Hopkins HA, Betsill WL Jr, Hobson AS, Looney WB: Cyclophosphamide-induced cardiomyopathy in the rat. *Cancer Treat Rep* 1982, 66:1521-1527
496. Levillain R: Myocardite experimentale: Etude anatomique de 210 coeurs de rats ayant ingéré du 5-fluorouracile. *C R Acad Sci* 1972, 166:340-342
497. Liss RN, Chadwick M: Correlation of 5-fluorouracil (NSC-19893) distribution in rodents with toxicity and chemotherapy in man. *Cancer Chemother Rep* 1974, 58:777-786
498. Dent RG, McColl I: 5-FU and angina. *Lancet* 1975, 1:347
499. Pottage A, Holt S, Ludgate S, Langlands AO: Fluorouracil cardiotoxicity. *Br Med J* 1978, 1:547
500. Roth A, Kolaric K, Popovic S: Cardiotoxicity of 5-fluorouracil (NSC-19893). *Cancer Chemother Rep Part 1*, 1975, 59:1051-1053
501. Sanani S, Spaulding MD, Masud ARZ, Canty R: 5-FU cardiotoxicity. *Cancer Treat Rep* 1981, 65:1123-1125
502. Stevenson-Lange D, Mikhailidis P, Gillett DS: Cardiotoxicity of 5-fluorouracil. *Lancet* 1977, 2:406-407
503. Dabros W, Ochalska B: Vincristine-induced ultrastructural alterations of cardiac and smooth muscles in mice. *Folia Histochem Cytochem* 1979, 17:259-266
504. Bennett T, Gardiner SM, Tomlinson DR: Selective noradrenergic denervation of the heart following intravenous injection of vinblastine or vincristine. *Naunyn-Schmiedberg Arch Pharmacol* 1976, 293:175-182
505. Mandel EM: Vincristine-induced myocardial infarction. *Cancer* 1975, 36:1979-1982
506. De Lena M, Rossi A, Bonadonna G: Phase II trial of AMSA in refractory breast cancer. *Cancer Treat Rep* 1982, 66:403-404
507. Falkson G: Multiple ventricular extrasystoles following administration of 4'-(9-acridinylamino)methanesulfon-m-aniside (AMSA). *Cancer Treat Rep* 1980, 64:358
508. Legha SS, Latrelle J, McCredle KB, Bodey GP: Neurologic and cardiac rhythm abnormalities associated with 4'-(9-acridinylamino)methanesulfon-m-aniside (AMSA) therapy. *Cancer Treat Rep* 1979, 63:2001-2003
509. Omura GA, Winton EF, Vogler WR, Zuckerman KS, Grillo-Lopez AJ: Phase II study of amsacrine gluconate in refractory leukemia. *Cancer Treat Rep* 1983, 67:1131-1132
510. Riela AR, Kimball JC, Patterson RB, Land VJ: Echocardiographic and ECG abnormalities associated with AMSA in a child: A southwest oncology group study. *Cancer Treat Rep* 1981, 65:1121-1123
511. Steinherz LJ, Steinherz PG, Mangiacasale D, Tan C, Miller DR: Cardiac abnormalities after AMSA administration. *Cancer Treat Rep* 1982, 66:483-488
512. Von Hoff DD, Elson D, Polk G, Colman C Jr: Acute ventricular fibrillation and death during infusion of 4'-(9-acridinylamino)methanesulfon-m-aniside (AMSA). *Cancer Treat Rep* 1980, 64:356-358
513. Vorobiof DA, Iturralde M, Falkson G: Amsacrine cardiotoxicity: Assessment of ventricular function by radionuclide angiography. *Cancer Treat Rep* 1983, 67:1115-1117
514. Flandina C, Leto G, Tumminello FM, Messina L: Effects of amsacrine (m-AMSA), a new aminoacridine antitumor drug, on the rabbit heart. *Cancer Treat Rep* 1983, 67:467-474
515. Hamlin RL, Pipers FS, Nguyen K, Mihalko P, Folk RM: Acute cardiovascular effects of acridinyl aniside (NSC-249992) following continuous intravenous infusion to anesthetized beagle hounds. PB2464120/AS, US Dept of Commerce, Springfield, Va, National Technical Information Service, 1976
516. Lowe MC: In vitro evaluation of the cardiotoxic potential of AMSA. *Cancer Treat Rep* 1982, 66:1571-1573
517. Van Echo DA, Chiuten DF, Gormley PE, Lichtenfeld JL, Scoltoch M, Wiernik PH: Phase I clinical and pharmacological study of 4'-(9-acridinylamino)methanesulfon-m-aniside using an intermittent biweekly schedule. *Cancer Res* 1979, 39:3881-3884

518. Will J, Splitter G, Lulich J, Dennis S, Dennis W: Adriamycin cardiotoxicity: A comparison with m-AMSA (NSC-249992). PB81-110421, US Dept of Commerce, Springfield, Va, National Technical Information Service, 1980
519. Czarnecki CM: Animal models of drug-induced cardiomyopathy. *Comp Biochem Physiol* 1984, 79C:9-14
520. Czarnecki CM, Bautch MP, Fletcher TF: Quantitation of cardiac gross morphology during the development of FZ-induced cardiomyopathy in turkey poults. *Avian Dis* 1983, 27:188-195
521. Czarnecki CM, Evanson OA: Myocardial calcium levels in furazolidone-induced cardiomyopathy in turkey poults. *Comp Biochem Physiol* 1983, 75C:207-209
522. Czarnecki CM, Grahn DA: A morphometric study of myocardial mitochondria and myofibrils in turkey poults during development of furazolidone-induced cardiomyopathy. *Avian Dis* 1980, 24:955-970
523. Czarnecki CM, Jankus EF: Effect of furazolidone on heart weights and myocardial moisture content in turkey poults. *Avian Dis* 1965, 19:622-625
524. Czarnecki CM, Jankus EF, Hultgren BD: Effects of furazolidone on the development of cardiomyopathies in turkey poults. *Avian Dis* 1974, 18:125-133
525. Czarnecki CM, Jegers A, Jankus EF: Characterization of glycogen in selected tissues of turkey poults with spontaneous round heart disease and furazolidone-induced cardiomyopathy. *Acta Anat* 1979, 102:33-39
526. Czarnecki CM, Reneau JK, Jankus EF: Effect of furazolidone on glycogen deposition in the left ventricle of turkey hearts. *Avian Dis* 1974, 18:551-558
527. Czarnecki CM, Reneau JK, Jankus EF: Blood glucose and tissue glycogen levels in turkey poults with spontaneous round heart disease and furazolidone-induced cardiomyopathy. *Avian Dis* 1975, 19:773-780
528. Czarnecki CM, Salam A, Caldwell R, Jankus EF: Activity of alpha-1,4-glucosidase in furazolidone-induced glycogenosis. *Poult Sci* 1978, 57:301-303
529. Feron VJ, van Stratum PGC: The effect of furazolidone on broiler chickens fed rations containing amprolium or zoalene: II. Intoxication phenomena at continuous administration during six weeks. *Tijdschr Diergeenskd* 1966, 9:571-579
530. Good AL, Czarnecki CM: The production of cardiomyopathy in turkey poults by the oral administration of furazolidone. *Avian Dis* 1980, 24:980-988
531. Gwathmey JK, Hamlin RL: Protection of turkeys against furazolidone-induced cardiomyopathy. *Am J Cardiol* 1983, 52:626-628
532. Hamlin RL: Animal models of dilated cardiomyopathy. *Dilated Cardiomyopathy*. Edited by DV Unverferth, Mount Kisco, New York, Futura Publ, 1985, pp 257-283
533. Jensen LS, Chang CH, Washburn KW: Differential response in cardiomyopathy of chicks and turkeys to furazolidone toxicity. *Avian Dis* 1975, 19:596-602
534. Mustafa AI, Idris SO, Ali BH, Mahdi BM, Abu Elgasim AI: Furazolidone poisoning associated with cardiomyopathy in chickens. *Vet Rec* 1984, 115:251
535. Powers MD, Good AL, Czarnecki CM, Evanson OA: Monoamine oxidase inhibition and furazolidone-induced cardiomyopathy in turkey poults. *Poult Sci* 1983, 62:1850-1855
536. Schaffer SW, Czarnecki CM, Cawthray M, Chovan JP: Cardiac taurine levels and sarcolemmal calcium binding activity in furazolidone-induced cardiomyopathy. *Comp Biochem Physiol* 1981, 69:149-151
537. Schaffer SW, Czarnecki CM, McClune J: Role of taurine in furazolidone-induced cardiomyopathy. *Comp Biochem Physiol* 1982, 72C:137-140
538. Simpson CF, Rollinghoff W, Preisig R, Fisher MJ: Hepatitis, cardiomyopathy and hemodynamics in furazolidone-induced round heart disease of turkeys. *Can J Comp Med* 1979, 43:345-351
539. Staley NA, Noren GR, Bandt CM, Sharp HL: Furazolidone-induced cardiomyopathy in turkeys: Association with a relative-antitrypsin deficiency. *Am J Pathol* 1978, 91:531-544
540. Van Vleet JF, Ferrans VJ: Furazolidone-induced congestive cardiomyopathy in ducklings: Lack of protection from selenium, vitamin E and taurine supplements. *Am J Vet Res* 1983, 44:1143-1148
541. Van Vleet JF, Ferrans VJ: Furazolidone-induced congestive cardiomyopathy in ducklings: Regression of cardiac lesions after cessation of furazolidone ingestion. *Am J Vet Res* 1983, 44:1007-1013
542. Van Vleet JF, Ferrans VJ: Furazolidone-induced congestive cardiomyopathy in ducklings: Myocardial ultrastructural alterations. *Am J Vet Res* 1983, 44:1014-1023
543. Bigland CH: Ascites and edema in brooded turkey poults in Alberta. *Can J Comp Med* 1950, 14:144-156
544. Dewar WA, Siller WG: Sodium toxicity resulting from feeding hen egg albumen powder to turkey poults. *Br Poult Sci* 1971, 12:535-543
545. Scrivner LH: Edema and ascites in poults. *J Am Vet Med Assoc* 1946, 108:27-32
546. Sibbald IR, Pepper WF, Slinger SJ: Sodium chloride in the feed and drinking water of chicks. *Poult Sci* 1962, 41:541-545
547. Adler JH, Nobel TA, Egyed M, Neuman F: Some effects of feeding *Trigonella foenum-graecum* straw to cattle. *Refuch Vet* 1960, 17:166-171
548. Dewan ML, Henson JB, Dollahite JW, Bridges CH: Toxic myodegeneration in goats produced by feeding mature fruits from the coyotillo plant (*Karwinskia humboldtiana*). *Am J Pathol* 1965, 46:215-226
549. Dollahite JW, Henson JB: Toxic plants as the etiologic agent of myopathies in animals. *Am J Vet Res* 1965, 26:749-752
550. Henson JB, Dollahite JW: Toxic myodegeneration in calves produced by experimental *Cassia occidentalis* intoxication. *Am J Vet Res* 1966, 27:947-949
551. Henson JB, Dollahite JW, Bridges CH, Rao RR: Myodegeneration in cattle grazing *Cassia* species. *J Am Vet Med Assoc* 1965, 147:142-145
552. Harter LR, Naude TW, Adelaar TF, Smit JD, Codd LE: Suggestion of the plant *Fadogia monticola* Robyns as an additional cause of gousiekte in ruminants. *Onderstepoort J Vet Res* 1972, 39:71-82
553. Marais JSC: Monofluoroacetic acid, the toxic principle of "gifblaar" *Dichapetalum cymosum* (Hook) Engl. *Onderstepoort J Vet Res* 1944, 20:67-73
554. Mercer HD, Neal FC, Himes JA, Edds GT: *Cassia occidentalis* toxicosis in cattle. *J Am Vet Med Assoc* 1967, 151:735-741
555. O'Hara PJ, Pierce KR, Read WK: Degenerative myopathy associated with ingestion of *Cassia occidentalis* L.: Clinical and pathologic features of the experimentally induced disease. *Am J Vet Res* 1969, 30:2173-2180
556. Panciera RJ, Johnson L, Osburn BI: A disease of cattle grazing hairy vetch pasture. *J Am Vet Med Assoc* 1966, 148:804-808
557. Pretorius PJ, Terblanche M, Van der Welt JD, Van Rysen CJ: Cardiac failure in ruminants caused by gousiekte. *Recent Adv Stud Card Struct Metab* 1973, 2:385-397
558. Schultz RA, Coetzer JAW, Kellerman TS, Naude TW: Observations on the clinical, cardiac and histopathological effects of fluoroacetate in sheep. *Onderstepoort J Vet Res* 1982, 49:237-245
559. Snyman LD, Van der Walt JJ, Pretorius PJ: A study on the function of some subcellular systems of the sheep myocardium during gousiekte: I. The energy production system. *Onderstepoort J Vet Res* 1982, 49:215-220
560. Whitten JH, Murray LR: The chemistry and pathology of Georgina River poisoning. *Aust Vet J* 1963, 39:168-173

561. Kasali OB, Krook L, Pond WG, Wasserman RH: *Cestrum diurnum* intoxication in normal and hyperparathyroid pigs. *Cornell Vet* 1977, 67:190-221
562. Long GG: Acute toxicosis in swine associated with excessive dietary intake of vitamin D. *J Am Vet Med Assoc* 1984, 184:164-170
563. Quarterman J, Dalgarno AC, Adam A, Fell BF, Boyne R: The distribution of vitamin D between the blood and the liver in the pig, and observations on the pathology of vitamin D toxicity. *Br J Nutr* 1964, 18:65-77
564. Blood DC, Radostits OM, Henderson JA: *Veterinary Medicine*, 6th edition, London, Baillière and Tindall, 1983, pp 1179-1180
565. Krook L, Wasserman RH, McEntee K, Brokken TD, Tieglund MB: *Cestrum diurnum* poisoning in Florida cattle. *Cornell Vet* 1975, 65:557-575
566. Krook L, Wasserman RM, Shively JN, Tashjian AH Jr, Brokken TD, Morton JF: Hypercalcemia and calcinosis in Florida horses: Implication of the shrub, *Cestrum diurnum*, as the causative agent. *Cornell Vet* 1975, 65:26-56
567. Gillman T, Grant RA, Hathorn M: Histochemical and chemical studies of calciferol-induced vascular injuries. *Br J Exp Pathol* 1960, 41:1-18
568. Grant RA, Gillman T, Hathorn M: Prolonged chemical and histochemical changes associated with widespread calcification of soft tissues following brief acute calciferol intoxication. *Br J Exp Pathol* 1963, 44:220-232
569. Ham AW: Mechanism of calcification in the heart and aorta in hypervitaminosis D. *Arch Pathol* 1932, 14:613-626
570. Hass GM, Truheart RE, Taylor CB, Stampe M: An experimental histologic study of hypervitaminosis D. *Am J Pathol* 1958, 34:395-431
571. Shohl AT, Goldblatt H, Brown HB: The pathologic effects upon rats of excess irradiated ergosterol. *J Clin Invest* 1930, 8:505-531
572. Takeo S, Schraven E, Keil M, Nitz R-E: Vitamin D-induced myocardial lesions and the protection by carbocromen. *Arzneim Forsch/Drug Res* 1982, 32:1412-1417
573. Wrzolek MA: The effect of zinc on vitamin D-induced cardiac necrosis. *J Mol Cell Cardiol* 1985, 17:109-117
574. Wrzolkowa T, Zydowo M: Ultrastructural studies on the vitamin D-induced heart lesions in the rat. *J Mol Cell Cardiol* 1980, 12:1117-1133
575. Schoeb TR, Panciera RJ: Pathology of blister beetle (*Epicauda*) poisoning in horses. *Vet Pathol* 1979, 16:18-31
576. Abdellatif AMM, Vles RO: Pathological effects of dietary rapeseed oils with high or low erucic acid content in ducklings. *Poult Sci* 1973, 52:1932-1936
577. Beare-Rogers JL, Nera EA: Cardiac fatty acids and histopathology of rats, pigs, monkeys and gerbils fed rapeseed oil. *Comp Biochem Physiol* 1972, 41B:793-800
578. Charlton KM, Corner AH, Davey K, Kramer JKG, Mahadevan S, Sauer FD: Cardiac lesions in rats fed rapeseed oils. *Can J Comp Med* 1975, 39:261-269
579. Chien KR, Bellary A, Nicar M, Mukherjee A, Buja LM: Induction of a reversible cardiac lipidosis by a dietary long-chain fatty acid (erucic acid). Relationship to lipid accumulation in border zones of myocardial infarcts. *Am J Pathol* 1983, 112:68-77
580. Clandinin MT, Yamashiro S: Effect of dietary supplementation with stearic acid on the severity of myocardial lesions. *Res Vet Sci* 1983, 35:306-309
581. Ratanasethkul C, Riddell C, Salmon RE, O'Neil JB: Pathological changes in chickens, ducks and turkeys fed high levels of rapeseed oil. *Can J Comp Med* 1976, 40:360-369
582. Sauer FD, Kramer JKG: The metabolism of long-chain monoenoic fatty acids in heart muscle and their cardiopathogenic implications. *Adv Nutr Res* 1980, 3:207-230
583. Umemura T, Slinger SJ, Bhatnager MK, Yamashiro S: Histopathology of the heart from rats fed rapeseed oils. *Res Vet Sci* 1978, 25:318-322
584. Yamashiro S, Clandinin MT: Myocardial ultrastructure of rats fed high and low erucic rapeseed oils. *Exp Mol Pathol* 1980, 33:55-64
585. Gaunt IF, Grasso P, Gangolli SD: Brominated maize oil: I. Short-term toxicity and bromine-storage studies in rats fed brominated maize oil. *Food Cosmet Toxicol* 1971, 9:1-11
586. Grice HC, Wiberg GS, Heggveit HA: Studies in food additives cardiomyopathies.³³³ pp 189-201
587. Munro IC, Hand B, Middleton EJ, Heggveit HA, Grice HC: Toxic effects of brominated vegetable oils in rats. *Toxicol Appl Pharmacol* 1972, 22:432-439
588. Munro IC, Hasnain S, Salem FA, Goodman T, Grice HC, Heggveit HA: Cardiotoxicity of brominated vegetable oils. *Recent Adv Stud Card Struct Metab* 1972, 1:588-595
589. Munro IC, Middleton EJ, Grice HC: Biochemical and pathological changes in rats fed brominated cottonseed oil for 80 days. *Food Cosmet Toxicol* 1969, 7:25-33
590. Munro IC, Salem FA, Goodman T, Hasnain SH: Biochemical and pathological changes in the heart and liver of rats given brominated cottonseed oil. *Toxicol Appl Pharmacol* 1969, 19:62-70
591. Kusewitt DF, Wagner JE, Dixon LW, Anderson PA: Fatal myocarditis in mice fed rancid purified feed. *Lab Anim Sci* 1984, 34:70-74
592. Smith HA: The pathology of gossypol poisoning. *Am J Pathol* 1957, 33:353-365
593. Patton CS, Legendre AM, Gompf RE, Walker MA: Heart failure caused by gossypol poisoning in two dogs. *J Am Vet Med Assoc* 1985, 187:625-627
594. West JL: Lesions of gossypol poisoning in the dog. *J Am Vet Med Assoc* 1940, 96:74-76
595. Hendy RJ, Abraham R, Grasso P: The effect of chloroquine on rat heart lysosomes. *J Ultrastruct Res* 1969, 29:485-495
596. Ridout RM, Decker RS, Wildenthal K: Chloroquine-induced lysosomal abnormalities in cultured foetal mouse hearts. *J Mol Cell Cardiol* 1978, 10:175-183
597. Smith B, O'Grady F: Experimental chloroquine myopathy. *J Neurol Neurosurg Psychiatr* 1966, 29:255-258
598. Ehrich WE, Bellet S, Lewey FH: Cardiac changes from CO poisoning. *Am J Med Sci* 1944, 208:511-523
599. Kjeldsen K, Thomsen HK, Astrup P: Effects of carbon monoxide on myocardium: Ultrastructural changes in rabbits after moderate, chronic exposure. *Circ Res* 1974, 34:339-348
600. Lough J: Cardiomyopathy produced by cigarette smoke: Ultrastructural observations in guinea pigs. *Arch Pathol Lab Med* 1978, 102:377-380
601. Suzuki T: Effects of carbon monoxide inhalation on the fine structure of the rat heart muscle. *Tohoku J Exp Med* 1969, 97:197-211
602. Thomsen HK, Kjeldsen K: Threshold limit for carbon monoxide-induced myocardial damage. *Arch Environ Health* 1974, 29:73-78
603. Yarom R, More R, Sherman Y, Yagen G: T-2 toxin-induced pathology in the hearts of rats. *Br J Exp Pathol* 1983, 64:570-577
604. Kellner A, Robertson T: Selective necrosis of cardiac and skeletal muscle induced experimentally by means of proteolytic enzyme solutions given intravenously. *J Exp Med* 1954, 99:387-404
605. Ruffolo PR: The pathogenesis of necrosis: I. Correlated light and electron microscopic observations of the myocardial necrosis induced by the intravenous injection of papain. *Am J Pathol* 1964, 45:741-756
606. Jasmin G: Toxic action of paraphenylenediamine in the rat and various other rodents. *Rev Canad Biol* 1961, 20:37-46
607. Jasmin G, Gareau R: Histopathological study of mus-

- cle lesions produced by paraphenylenediamine in rats. *Br J Exp Pathol* 1961, 42:592-596
608. Grasso P, Muir A, Golberg L, Batstone E: Studies on Brown FK: IV. Cytopathic effects of Brown FK on cardiac and skeletal muscle in the rat. *Food Cosmet Toxicol* 1968, 6:13-24
 609. Boor PJ, Ferrans VJ: Ultrastructural alterations in allylamine-induced cardiomyopathy: Early lesions. *Lab Invest* 1982, 47:76-86
 610. Boor PJ, Moslen MT, Reynolds ES: Allylamine cardiotoxicity: I. Sequence of pathologic events. *Toxicol Appl Pharmacol* 1979, 50:581-592
 611. Boor PJ, Nelson TJ, Chieco P: Allylamine cardiotoxicity: II. Histopathology and histochemistry. *Am J Pathol* 1980, 100:739-764
 612. Lalich JJ, Allen JR, Paik WCW: Myocardial fibrosis and smooth muscle cell hyperplasia in coronary arteries of allylamine-fed rats. *Am J Pathol* 1972, 66:225-234
 613. Will JA, Rowe GG, Olson L, Crampton CW: A chemically induced acute model of myocardial damage in intact calves. *Res Commun Chem Pathol Pharmacol* 1971, 2:61-66
 614. Berger JM, Bencosme SA: Divergence in patterns of atrial and ventricular cardiocyte degeneration: Studies with plasmocid. *J Mol Cell Cardiol* 1971, 2:41-49
 615. D'Agostino AN: An electron microscopic study of skeletal and cardiac muscle of the rat poisoned by plasmocid. *Lab Invest* 1963, 12:1060-1071
 616. Hicks SP: Brain metabolism in vivo: II. The distribution of lesions caused by azide, malonitrile, plasmocid and dinitrophenol poisoning in rats. *Arch Pathol* 1950, 50:545-561
 617. Balentine JD: Cardiovascular system and skeletal muscle. *Pathology of Oxygen Toxicity*. New York, Academic Press, 1982, pp 214-348
 618. Busing CM, Kreinsen U, Buhler F, Bleyl U: Light and electron microscopic examinations of experimentally produced heart muscle necroses following normobaric hyperoxia. *Virchows Arch [Pathol Anat]* 1975, 366:137-147
 619. Hughson M, Balentine JD, Daniell HB: The ultrastructural pathology of hyperbaric oxygen exposure: Observations on the heart. *Lab Invest* 1977, 37:516-525
 620. Alexander CS, Sekhri KK, Nagasawa HT: Alcoholic cardiomyopathy in mice: Electron microscopic observations. *J Mol Cell Cardiol* 1977, 9:247-254
 621. Hall JL, Rowlands DT: Cardiotoxicity of alcohol: An electron microscopic study in the rat. *Am J Pathol* 1970, 60:153-164
 622. Noren GR, Staley NA, Einzig S, Mikell FL, Asinger RW: Alcohol-induced congestive cardiomyopathy: An animal model. *Cardiovasc Res* 1983, 17:81-87
 623. Regan TJ: Alcoholic cardiomyopathy. *Prog Cardiovasc Dis* 1984, 27:141-152
 624. Rossi MA: Alcohol and malnutrition in the pathogenesis of experimental alcoholic cardiomyopathy. *J Pathol* 1980, 130:105-116
 625. Rossi MA, Olivera JSM, Zucoloto S, Becker PFL: Norepinephrine levels and morphologic alterations of myocardium in chronic alcoholic rats. *Beitr Pathol* 1976, 159:51-60
 626. Kino M: Chronic effects of ethanol under partial inhibition of catalase activity in the rat heart: Light and electron microscopic observations. *J Mol Cell Cardiol* 1981, 13:5-21
 627. Mattfeldt T, Mall G, Volk B: Morphometric analysis of rat heart mitochondria after chronic ethanol treatment. *J Mol Cell Cardiol* 1980, 12:1311-1319
 628. Polimeni PI, Otten MD, Hoeschen LE: In vivo effects of ethanol on the rat myocardium: Evidence for a reversible, non-specific increase of sarcolemmal permeability. *J Mol Cell Cardiol* 1983, 15:113-122
 629. Regan TJ, Ettinger PO, Haider B, Oldewurtel HA, Lyons MM: The role of ethanol in cardiac disease. *Annu Rev Med* 1977, 28:393-409
 630. Sarma JSM, Ikeda S, Fischer R, Maruyama Y, Weishaar R, Bing RJ: Biochemistry and contractility properties of heart muscle after prolonged ethanol administration. *J Mol Cell Cardiol* 1976, 8:951-972
 631. Schreiber S, Brinden K, Oratz M, Rothschild MA: Ethanol, acetaldehyde and myocardial protein synthesis. *J Clin Invest* 1972, 51:2820-2826
 632. Segal LD, Rending SV, Choquet V, Chacko K, Amsterdam EA, Mason DT: Effects of chronic graded ethanol consumption in the metabolism, ultrastructure, and mechanical function of the rat heart. *Cardiovasc Res* 1975, 9:649-663
 633. Segal LD, Rendig SV, Mason DT: Alcohol-induced cardiac hemodynamic and Ca flux dysfunctions are reversible. *J Mol Cell Cardiol* 1981, 13:443-445
 634. Whitman V, Schuler HG, Musselman J: Effects of chronic ethanol consumption on the myocardial hypertrophic response to a pressure overload in the rat. *J Mol Cell Cardiol* 1980, 12:519-525
 635. Miller H, Abelmann WH: Effects of dietary ethanol upon experimental trypanosomal (*T cruzi*) myocarditis. *Proc Soc Exp Biol Med* 1967, 126:193-198
 636. Morin Y, Roy PE, Mohiuddin SM, Taskar PK: The influence of alcohol on viral and isoproterenol cardiomyopathy. *Cardiovasc Res* 1967, 3:363-368
 637. Anderson HH, Leake CD: The oral toxicity of emetine hydrochloride and certain related compounds in rabbits and cats. *Am J Trop Med* 1930, 10:249-259
 638. Khan MY, Haider B, Thind IS: Emetine-induced cardiomyopathy in rabbits. *J Submicrosc Cytol* 1983, 15:495-507
 639. Pierce MB, Bulloch RT, Murphy ML: Selective damage of myocardial mitochondria due to emetine hydrochloride. *Arch Pathol* 1971, 91:8-18
 640. Rinehart JF, Anderson HH: Effect of emetine on cardiac muscle. *Arch Pathol* 1931, 11:546-553
 641. Zbinden G, Kleinert R, Rageth B: Assessment of emetine cardiotoxicity in a subacute toxicity experiment in rats. *J Cardiovasc Pharmacol* 1980, 2:155-164
 642. Cohrs P: Circulatory system. *Textbook of the Special Pathological Anatomy of Domestic Animals*. New York, Pergamon Press, 1967, pp 1-72
 643. Fernandez LA, Downing SE: Cardiomyopathy produced in rats with acute renal hypertension. *J Lab Clin Med* 1980, 95:159-167
 644. Gavras H, Kremer D, Brown JJ, Gray B, Lever AF, MacAdam RF, Medina A, Morton JJ, Robertson JIS: Angiotensin- and norepinephrine-induced myocardial lesions: Experimental and clinical studies in rabbits and man. *Am Heart J* 1975, 89:321-332
 645. Giacomelli F, Anversa P, Weiner J: Effect of angiotensin-induced hypertension on rat coronary arteries and myocardium. *Am J Pathol* 1976, 86:111-138
 646. Holman RL: Acute necrotizing arteritis, aortitis, and auriculitis following uranium nitrate injury in dogs with altered plasma proteins. *Am J Pathol* 1941, 17:359-381
 647. Morioka S, Simon G: Echocardiographic evidence for early left ventricular hypertrophy in dogs with renal hypertension. *Am J Cardiol* 1982, 49:1890-1895
 648. Muirhead EE: Renal tissue and extracts vs cardiovascular injury. *Arch Pathol* 1963, 76:613-619
 649. Platt H: Morphological changes in the cardiovascular system associated with nephritis in dogs. *J Pathol Bacteriol* 1952, 64:539-549
 650. Winternitz MC, Mylon E, Waters LL, Katzenstein R: Studies on the relation of the kidney to cardiovascular disease. *Yale J Biol Med* 1940, 12:623-687
 651. King JM, Roth L, Haschek WM: Myocardial necrosis secondary to neural lesions in domestic animals. *J Am Vet Med Assoc* 1982, 180:144-148
 652. Burch GE, Sohal RS, Sun SC, Colcolough HL: Effects

- of experimental intracranial hemorrhage on the ultrastructure of the myocardium of mice. *Am Heart J* 1969, 77:427-429
653. Burch GE, Sun SC, Colcolough HL, DePasquale NP, Sohal RS: Acute myocardial lesions following experimentally-induced intracranial hemorrhage in mice: A histological and histochemical study. *Arch Pathol* 1967, 84:517-521
 654. Hawkins WE, Clower BR: Myocardial damage after head trauma and simulated intracranial hemorrhage in mice: The role of the autonomic nervous system. *Cardiovasc Res* 1971, 5:524-529
 655. Hunt D, Gore I: Myocardial lesions following experimental intracranial hemorrhage. Prevention with propranolol. *Am Heart J* 1972, 83:232-236
 656. Jacob WA, Van Bogaert A, de Groodt-Lasseal MHA: Myocardial ultrastructure and haemodynamic reactions during experimental subarachnoid hemorrhage. *J Mol Cell Cardiol* 1972, 4:287-298
 657. Kaye MP, McDonald RH, Randall WC: Systolic hypertension and subendocardial hemorrhages produced by electrical stimulation of the stellate ganglion. *Circulation* 1961, 9:1164-1170
 658. Klouda MA, Brynjolfsson G: Cardiotoxic effects of electrical stimulation of the stellate ganglia. *Ann NY Acad Sci* 1969, 156:271-280
 659. Greenhoot JH, Reichenbach DD: Cardiac injury and subarachnoid hemorrhage: A clinical, pathological, and physiological correlation. *J Neurosurg* 1969, 30:521-531
 660. Groover ME, Stout C: Neurogenic myocardial necrosis. *Angiology* 1965, 16:180-186
 661. Manning GW, Hall GE, Banting FG: Vagus stimulation and the production of myocardial damage. *Can Med Assoc J* 1937, 37:314-318
 662. Afanassiev YI, Trepilets VY: Histostructural changes in the rabbit myocardium after stimulation of some of the hypothalamic nuclei. *Folia Morphol (Praha)* 1977, 25:260-265
 663. Melville KI, Blum B, Shister H, Silver MD: Cardiac ischemic changes and arrhythmias induced by hypothalamic stimulation. *Am J Cardiol* 1963, 12:781-791
 664. Melville KI, Garvey HL, Gillis RA: Neurogenic lesions of heart muscle. *Recent Adv Stud Card Struct Metab* 1973, 2:443-447
 665. Melville KI, Garvey HL, Shister HE, Knaack J: Central nervous system stimulation and cardiac ischemic changes in monkeys. *Ann NY Acad Sci* 1969, 156:241-260
 666. Macintire DK, Snider TG: Cardiac arrhythmias associated with multiple trauma in dogs. *J Am Vet Med Assoc* 1984, 184:541-545
 667. Reichenbach DD, Benditt EP: Catecholamine and cardiomyopathy: The pathogenesis and potential importance of myofibrillar degeneration. *Hum Pathol* 1970, 1:125-150
 668. Sharma VN, Barar FS: Restraint stress as it influences the myocardium of rat. *Indian J Med Res* 1966, 54:1102-1107
 669. Fani K, Jimenez FA, De Soto F: Heart morphological changes in rats placed in a crowded environment. *J Toxicol Environ Health* 1977, 3:421-429
 670. Weber HW, Van der Walt JJ: Cardiomyopathy in crowded rabbits: A preliminary report. *S Afr Med J* 1973, 47:1591-1595
 671. Weber HW, Van der Walt JJ: Cardiomyopathy in crowded rabbits. *Recent Adv Stud Card Struct Metab* 1975, 6:471-477
 672. Lauria P, Sharma VN, Vanjani S: Effect of prolonged stress of repeated electric shock on rat myocardium. *Indian J Physiol Pharmacol* 1972, 16:315-318
 673. Corley KC, Mauck HP, Shiel F: Cardiac responses associated with "yoked-chair" shock avoidance in squirrel monkeys. *Psychobiology* 1975, 12:439-444
 674. Corley KC, Shiel FO, Mauck HP, Clark LS, Barber JH: Myocardial degeneration and cardiac arrest in squirrel monkey: Physiological and psychological correlates. *Psychophysiology* 1977, 14:322-328
 675. Corley KC, Shiel FO, Mauck HP, Greenhoot J: Electrocardiographic and cardiac morphological changes associated with environmental stress in squirrel monkeys. *Psychosom Med* 1973, 35:361-364
 676. Babero BB, Yousef MK, Wawerna JC: Histo-pathological changes in cold-exposed kangaroo rats, *Dipodomys merriami*. *Comp Biochem Physiol* 1971, 39:361-366
 677. Lin MT, Chai CY, Sun SC, Kau SL: Myocardial lesions produced by external heat or cold exposure in rats. *Chin J Physiol* 1977, 22:115-125
 678. Tanaka M: Electron microscopic study of cardiac lesions induced in rats by isoproterenol and by repeated stress: With suggestion that idiopathic cardiomyopathy may be a "disease of adaptation." *Jpn Circ J* 1981, 45:1342-1354
 679. Tanaka M, Tsuchihashi Y, Katsume H, Ijichi H, Iyata Y: Comparison of cardiac lesions induced in rats by isoproterenol and by repeated stress of restraint and water immersion with special reference to etiology of cardiomyopathy. *Jpn Circ J* 1980, 44:971-980
 680. Kleimenova NN, Arefolov VA, Bondarenko NA: [Effect of chronic stress on the ultrastructure of the myocardium and hypothalamus of "emotional" and "unemotional" rats]. *Biull Eksp Biol Med* 1983, 95:1:18-21
 681. Meerson FZ: Pathogenesis and prophylaxis of cardiac lesions in stress. *Adv Myocardiol* 1983, 4:3-21
 682. Meerson FZ, Samosudova NV, Glagoleva EV, Shimkovich MV, Belkina LM: [Disorders of myocardial contraction and cardiomyocyte ultrastructure after emotional stress]. *Arkh Anat Gistol Embriol* 1983, 84:2:43-49
 683. Raab W: Emotional and sensory stress factors in myocardial pathology: Neurogenic and hormonal mechanisms in pathogenesis, therapy, and prevention. *Am Heart J* 1966, 72:538-564
 684. Lawler JE, Barker GF, Hubbard JW, Schaub RG: Effects of stress on blood pressure and cardiac pathology of rats with borderline hypertension. *Hypertension* 1981, 3:496-505
 685. Burns JW, Laughlin H, Witt WM, Young JT, Ellis JP Jr: Pathophysiologic effects of acceleration stress in the miniature swine. *Aviat Space Environ Med* 1983, 54:881-893
 686. Raab W, Chaplin JP, Bajusz E: Myocardial necroses produced in domesticated rats and in wild rats by sensory and emotional stresses. *Proc Soc Exp Biol Med* 1964, 116:665-669
 687. Horne WA, Gilmore DR, Dietze AE, Freden CO, Short CE: Effects of gastric distention-volvulus on coronary blood flow and myocardial oxygen consumption in the dog. *Am J Vet Res* 1984, 46:98-104
 688. Muir WW: Gastric dilatation/volvulus in the dog, with emphasis on cardiac arrhythmias. *J Am Vet Med Assoc* 1982, 180:739-742
 689. Muir WW, Weisbrode SE: Myocardial ischemia in dogs with gastric dilatation/volvulus. *J Am Vet Med Assoc* 1982, 181:363-366
 690. Bradley R, Markson LM, Bailey J: Sudden death and myocardial necrosis in cattle. *J Pathol* 1981, 135:19-38
 691. Jones TO: Sudden death in calves at feeding time. *Vet Rec* 1979, 104:414
 692. Schofield FW: Sudden death in calves associated with myocardial degeneration. *Can J Comp Med* 1947, 11:324-329

693. Raab W, Bajusz E, Kimura H, Herrlich HC: Isolation, stress, myocardial electrolytes, and epinephrine cardiotoxicity in rats. *Proc Soc Exp Biol Med* 1968, 127:142-147
694. Balazs R, Murphy JB, Grice HC: The influence of environmental changes on the cardiotoxicity of isoprenaline in rats. *J Pharm Pharmacol* 1962, 14:750-755
695. Hatch A, Balazs T, Wiberg GS, Grice HC: Long-term isolation stress in rats. *Science* 1963, 142:507
696. Welch BL, Welch AS: Graded effect of social stimulation upon d-amphetamine toxicity, aggressiveness and heart and adrenal weight. *J Pharmacol Exp Ther* 1966, 151:331-338
697. Perret M: Stress-effects on *Microcebus murinus*. *Folia Primatol (Basel)* 1982, 39:63-114
698. Bartsch RC, McConnell EE, Imes GD, Schmidt JM: A review of exertional rhabdomyolysis in wild and domestic animals and man. *Vet Pathol* 1977, 14:314-324
699. McConnell EE, Basson PA, DeVos V, Myers BJ, Kuntz RE: A survey of diseases among 100 free-ranging baboons (*Papio ursinus*) from the Kruger National Park. *Onderstepoort J Vet Res* 1974, 41:97-168
700. Mugeru GM, Wandera JG: Degenerative polymyopathies in East African domestic and wild animals. *Vet Rec* 1967, 80:410-413
701. Groover ME Jr, Seljeskos EL, Haglin JJ, Hitchcock CR: Myocardial infarction in the Kenya baboon without demonstrable atherosclerosis. *Angiology* 1963, 14:408-416
702. Weber HW, Van der Welt JJ, Greeff MJ: Spontaneous cardiomyopathies in Chacma baboons. *Recent Adv Stud Card Struct Metab* 1973, 2:361-375
703. Lindholm A, Johansson H, Kjaersgaard P: Acute rhabdomyolysis ("tying-up") in standardbred horses: A morphological and biochemical study. *Acta Vet Scand* 1974, 15:325-339
704. Cowan MJ, Giddens WE, Reichenbach DD: Selective myocardial cell necrosis in nonhuman primates. *Arch Pathol Lab Med* 1983, 107:34-39
705. Cawley GD, Bradley R: Sudden death in calves associated with acute myocardial degeneration and selenium deficiency. *Vet Rec* 1978, 103:239-240
706. Rogers PAM, Poole DBR: Sudden death in calves. *Vet Rec* 1978, 103:366
707. Bergmann V: Changes of cardiac and skeletal muscle in pigs following transport stress: An electron microscopic study. *Exp Pathol* 1979, 17:243-248
708. Johansson G, Jönsson L: Myocardial cell damage in the porcine stress syndrome. *J Comp Pathol* 1977, 87:67-74
709. Johansson G, Jönsson L, Lannek N, Blomgren L, Lindberg P, Poupa O: Severe stress-cardiopathy in pigs. *Am Heart J* 1974, 87:451-457
710. Johansson G, Olsson K, Häggendal J, Jönsson L, Thorén-Tolling K: Effect of stress on myocardial cells and blood levels of catecholamines in normal and amygdalotomized pigs. *Can J Comp Med* 1982, 46:176-182
711. Jönsson L, Johansson G: Cardiac muscle cell damage induced by restraint stress. *Virchows Arch Cell Pathol B* 1974, 17:1-12
712. Topel DG, Christian LL: Porcine stress syndrome. *Diseases of Swine*. 5th edition. Edited by AD Leman, RD Glock, WL Mengeling, RHC Penny, E Scholl, B Straw. Ames, Iowa, Iowa State University Press, 1981, pp 647-655
713. Häggendal J, Johansson G, Jönsson L, Thorén-Tolling K: Effect of propranolol on myocardial cell necroses and blood levels of catecholamines in pigs subjected to stress. *Acta Pharmacol Toxicol (Copenh)* 1982, 50:58-66
714. Thorén-Tolling K, Jönsson L: Creatine kinase isoenzymes in serum of pigs having myocardial and skeletal muscle necrosis. *Can J Comp Med* 1983, 47:207-216
715. Thielscher HH: Zur Pathogenese des akuten Herzversagens beim Schwein. *Tierärztl Umschau* 1984, 39: 692-694
716. Gronert GA: Malignant hyperthermia. *Anesthesiology* 1980, 53:395-423
717. Fenoglio JJ Jr, Irely NS: Myocardial changes in malignant hyperthermia. *Am J Pathol* 1977, 89:51-58
718. Mambo NC, Silver MD, McLaughlin PR, Huckell VF, McEwan PM, Britt BA, Morch JE: Malignant hyperthermia susceptibility: A light and electron microscopic study of endomyocardial biopsy specimens from nine patients. *Hum Pathol* 1980, 11:381-388
719. Fajardo LF, Eltringham JR, Stewart JR: Combined cardiotoxicity of adriamycin and X-radiation. *Lab Invest* 1976, 34:86-96
720. Fajardo LF, Stewart JR: Pathogenesis of radiation-induced myocardial fibrosis. *Lab Invest* 1973, 29:244-257
721. Fajardo LF, Stewart JR: Experimental radiation-induced heart disease: I. Light microscopic studies. *Am J Pathol* 1970, 59:299-315
722. Fajardo LF, Stewart JR, Cohn KE: Morphology of radiation-induced heart disease. *Arch Pathol* 1968, 86:512-519
723. Khan MY: Radiation-induced cardiomyopathy: I. An electron microscopic study of cardiac muscle cells. *Am J Pathol* 1973, 73:131-146
724. Khan MY: Radiation-induced cardiomyopathy: II. An electron microscopic study of myocardial microvasculature. *Am J Pathol* 1974, 74:125-136
725. Lauk S, Kizel Z, Buschmann J, Trott K-R: Radiation-induced heart disease in rats. *Int J Radiat Oncol Biol Phys* 1985, 11:801-808
726. Maeda S: Pathology of experimental radiation pancarditis: I. Observation on radiation-induced heart injuries following a single dose of X-ray irradiation to rabbit heart with special reference to its pathogenesis. *Acta Pathol Jpn* 1980, 30:59-78
727. Selwyn AP: The cardiovascular system and radiation. *Lancet* 1983, 2:152-154
728. Stewart JR, Fajardo LF: Radiation-induced heart disease: An update. *Prog Cardiovasc Dis* 1984, 27:173-194
729. Tajuddin MR, Johri SK, Tarig M, Ram V: Effects of propranolol and hydrocortisone pretreatment on radiation-induced myocardial injury in rats. *Adv Myocardial* 1983, 4:255-262
730. Gavin PR, Gillette EL: Radiation response of the canine cardiovascular system. *Radiat Res* 1982, 90:489-500
731. Moss AJ, Smith DW, Michaelson S, Schreiner BF Jr: Radiation technique for production of localized myocardial necrosis in the intact dog. *Proc Soc Exp Biol Med* 1963, 112:903-905
732. Zook BC, Bradley EW, Casarett GW, Rogers CC: Pathologic changes in the hearts of beagles irradiated with fractionated fast neutrons or photons. *Radiat Res* 1981, 88:607-618
733. Stryker JA, Lee KJ, Abt AB: The effects of X radiation on the canine heart. *Radiat Res* 1980, 82:200-210
734. Barker-Voelz MA, Van Vleet JF, Tacker WA Jr, Bourland JD, Geddes LA, Schollmeyer MP: Alterations induced by a single defibrillating shock applied through a chronically implanted catheter electrode. *J Electrocardiol* 1983, 16:167-180
735. Dahl CF, Ewy GA, Warner ED, Thomas ED: Myocardial necrosis from direct current countershock. *Circulation* 1974, 50:956-961
736. Doherty PW, McLaughlin PR, Billingham ME, Kernoff R, Goris ML, Harrison DC: Cardiac damage produced by direct current countershock applied to the heart. *Am J Cardiol* 1979, 43:225-231
737. Lerman BB, Weiss JL, Bulkley BH, Becker LC, Weisfeldt ML: Myocardial injury and induction of arrhythm-

- mia by direct current shock delivered via endocardial catheters in dogs. *Circulation* 1984, 69:357-368
738. Patton JN, Allen JD, Pantridge JF: The effects of shock energy, propranolol, and verapamil on cardiac damage caused by transthoracic countershock. *Circulation* 1984, 69:357-368
 739. Reichenbach D, Benditt EP: Myofibrillar degeneration: A common form of cardiac muscle injury. *Ann NY Acad Sci* 1969, 156:164-176
 740. Tacker WA Jr, Van Vleet JF: Cardiac damage produced by defibrillation, *Electrical Defibrillation*. Edited by WA Tacker Jr, LA Geddes. Boca Raton, Florida, CRC Press, 1980, pp 137-153
 741. Van Vleet JF, Ferrans VJ, Barker MA, Tacker WA Jr, Bourland JD, Schollmeyer MP: Ultrastructural alterations in the fibrous sheath, endocardium and myocardium of dogs with chronically implanted automatic defibrillator electrode catheters and given single defibrillating shocks terminally. *Am J Vet Res* 1982, 43:909-915
 742. Van Vleet JF, Tacker WA Jr, Bourland JD, Kallok MJ, Schollmeyer MP: Cardiac damage in dogs with chronically implanted automatic defibrillator electrode catheters and given four episodes of multiple shocks. *Am Heart J* 1983, 106:300-307
 743. Van Vleet JF, Tacker WA Jr, Cechner PE, Bright RM, Greene JA, Raffie MR, Geddes LA, Ferrans VJ: Effect of shock strength survival and acute cardiac damage induced by open-thorax defibrillation of dogs. *Am J Vet Res* 1978, 39:981-987
 744. Van Vleet JF, Tacker WA Jr, Geddes LA, Ferrans VJ: Sequential cardiac morphologic alterations induced in dogs by single transthoracic damped sinusoidal waveform defibrillator shocks. *Am J Vet Res* 1978, 39:271-278
 745. Van Vleet JF, Tacker WA Jr, Geddes LA, Ferrans VJ: Acute cardiac damage in dogs given multiple transthoracic shocks with a trapezoidal waveform defibrillator. *Am J Vet Res* 1977, 38:617-626
 746. Van Vleet JF, Tacker WA Jr, Geddes LA, Ferrans VJ: Sequential ultrastructural alterations in ventricular myocardium of dogs given large single transthoracic damped sinusoidal waveform defibrillator shocks. *Am J Vet Res* 1980, 41:493-501
 747. Warner ED, Dahl C, Ewy CA: Myocardial injury from transthoracic defibrillator countershock. *Arch Pathol Lab Med* 1975, 99:55-59
 748. Burton RR, MacKenzie WF: Cardiac pathology associated with high sustained +Gz: I. Subendocardial hemorrhage. *Aviat Space Environ Med* 1976, 47:711-717
 749. Burton RR, MacKenzie NF: II. Heart pathology associated with exposure to high sustained +Gz. *Aviat Space Environ Med* 1975, 46:1251-1253
 750. Lindsey JN, Dowell RT, Sordahl LA, Erickson HH, Stone HL: Ultrastructural effects of +Gz stress on swine cardiac muscle. *Aviat Space Environ Med* 1976, 47:505-511
 751. MacKenzie WF, Burton RR, Butcher WI: Cardiac pathology associated with high sustained +Gz: II. Stress cardiomyopathy. *Aviat Space Environ Med* 1976, 47:718-725
 752. Burns JW, Laughlin MH, Witt WM, Young JT, Ellis JP Jr: Pathophysiologic effects of acceleration stress in the miniature swine. *Aviat Space Environ Med* 1983, 54:881-893
 753. Ranga V, Laky D, Budai M, Gadariu S: Experimental study on the effects of +Gz acceleration under gestational conditions: I. Ultrastructural myocardial lesions. *Morphol Embryol* 1982, 28:303-306
 754. Smith AH, Spangler WL, Burton RR, Rhode EA: Responses of domestic fowl to repeated +Gz acceleration. *Aviat Space Environ Med* 1979, 50:1134-1138
 755. Chang J, Hackel DB: Comparative study of myocardial lesions in hemorrhagic shock. *Lab Invest* 1973, 28:641-647
 756. Hackel DB, Goodale WT: Effects of hemorrhagic shock on the heart and circulation of intact dogs. *Circulation* 1955, 11:628-634
 757. Kajihara H, Hara H, Seyama S, Iijima S, Yoshida M: Light and electron microscopic observations of the myocardium of dogs in hemorrhagic shock. *Acta Pathol Jap* 1973, 23:315-333
 758. Martin AM Jr, Hackel DB: An electron microscopic study of the progression of myocardial lesions in the dog after hemorrhagic shock. *Lab Invest* 1966, 15:243-260
 759. Martin AM Jr, Hackel DB, Entman ML, Capp MP, Spach MS: Mechanisms in the development of myocardial lesions in hemorrhagic shock. *Ann NY Acad Sci* 1969, 156:79-90
 760. Martin AM Jr, Hackel DB, Kurtz SM: The ultrastructure of zonal lesions of the myocardium in hemorrhagic shock. *Am J Pathol* 1964, 44:127-140
 761. Ratliff NB, Hackel DB, Mikat E: The effect of hyperbaric oxygen on the myocardial lesions of hemorrhagic shock in dogs. *Am J Pathol* 1967, 51:341-349
 762. Ratliff NB, Kopelman RI, Goldner RD, Cruz PT, Hackel DB: Formation of myocardial zonal lesions. *Am J Pathol* 1975, 79:321-334
 763. Clark AF, Tandler B, Vignos PJ Jr: Glucocorticoid-induced alterations in the rabbit heart. *Lab Invest* 1982, 47:603-610
 764. Gupta RK: Cortisone induced cardiac lesions. *Indian J Exp Biol* 1977, 15:314-316
 765. Ito T, Murata M, Kamiyama A: Experimental study of cardiomyopathy induced by glucocorticoids. *Jpn Circ J* 1979, 43:1043-1047
 766. Ketelsen U-P, Freund-Molbert E, Struck E: Pathomorphological changes in steroid myopathy: Ultrastructural changes within the plasmalemma of skeletal and cardiac muscle cells as compared to the intracellular reaction. *Beitr Pathol* 1974, 153:133-164
 767. Lie RK, Jodal HG, Rotevatn S: Accumulation of myocardial lipid droplets in dexamethasone-treated mice. *Cell Tissue Res* 1981, 216:661-663
 768. Mall G, Reinhard H, Stopp D, Rossner JA: Morphometric observations on the rat heart after high-dose treatment with cortisol. *Virchows Arch [Pathol Anat]* 1980, 385:169-180
 769. Bajusz E: The role of some essential nutrients in the pathogenesis of cardiac necroses (studies on K-, Mg-, Na- and Cl- deficiencies). *Rev Canad Biol* 1961, 20:713-766
 770. Bajusz E: Primary (nutritional and/or metabolic) and secondary cardiomyopathies in man and laboratory animals and methods for their analysis, *Nutritional Aspects of Cardiovascular Diseases*. Philadelphia, J B Lippincott, 1965, pp 72-126
 771. D'Agostino AN: An electron microscopic study of cardiac necrosis produced by 9-fluorocortisol and sodium phosphate. *Am J Pathol* 1964, 45:633-644
 772. Lehr D: Tissue electrolyte alteration in disseminated myocardial necrosis. *Ann NY Acad Sci* 1969, 156:344-378
 773. Lehr D, Krukowski M: About the mechanism of myocardial necrosis induced by sodium phosphate and adrenal corticoid overdosage. *Ann NY Acad Sci* 1963, 105:137-182
 774. Nienhaus H, Poche R, Reimold E: Elektrolytverschiebungen, histologische Veränderungen der Organe und Ultrastruktur des Herzmuskels nach Belastung mit Cortisol, Aldosteron und primärem Natriumphosphat bei der Ratte. *Virchows Arch [Pathol Anat]* 1963, 337:245-269

775. Selye H: The Chemical Prevention of Cardiac Necroses. New York, Ronald Press, 1958, pp 3-194
776. Selye H: The pluricausal cardiopathies. *Ann NY Acad Sci* 1969, 156:195-206
777. Selye H: Experimental Cardiovascular Diseases. Parts 1 and 2, New York, Springer-Verlag, 1970, pp 1-1099
778. Selye H, Gabbiani G: The role of electrolytes in the pathogenesis of experimental cardiopathies without vascular involvement.³⁰⁰ pp 135-160
779. Howard EB, Nielsen SW: Pheochromocytomas associated with hypertensive lesions in dogs. *J Am Vet Med Assoc* 1965, 147:245-252
780. McAllister HA Jr: Endocrine diseases and the cardiovascular system.³⁴¹ pp 1035-1057
781. Dahme E, Schlemmer W: Endokrin-aktive Nebennierenmarktumoren des Hundes und ihre Auswirkungen auf die arterielle Blutstrombahn: Eine morphologische und pharmakologisch-chemische-Studie. *Zentralbl Vet Med* 1959, 6:249-259
782. Müller B, Werle E, Sell J: Innersekretorisch Wirksame Nebennierenmarksgeschwulst (Phäochromozytom) bei einem Hund. *Zentralbl Vet Med* 1955, 2:289-300
783. Fein FS, Sonnenblick EH: Diabetic cardiomyopathy. *Prog Cardiovasc Dis* 1985, 27:255-270
784. Chobanian AV, Arquilla ER, Clarkson TB, Eder HA, Howard CF Jr, Regan TJ, Williamson JR: Cardiovascular complications. *Diabetes (Suppl 1)* 1982, 31:54-64
785. Factor SM, Bhan R, Minase T, Wolinsky H, Sonnenblick EH: Hypertensive-diabetic cardiomyopathy in the rat: An experimental model of human disease. *Am J Pathol* 1981, 102:219-228
786. Factor SM, Minase T, Bhan R, Wolinsky H, Sonnenblick EH: Hypertensive diabetic cardiomyopathy in the rat: Ultrastructural features. *Virchows Arch [Pathol Anat]* 1983, 398:305-317
787. Factor SM, Minase T, Cho S, Fein F, Capasso JM, Sonnenblick EH: Coronary microvascular abnormalities in the hypertensive-diabetic rat: A primary case of cardiomyopathy? *Am J Pathol* 1984, 116:9-20
788. Fein FS, Capasso JM, Aronson RS, Cho S, Nordin C, Miller-Green B, Sonnenblick EH, Factor SM: Combined renovascular hypertension and diabetes in rats: A new preparation of congestive cardiomyopathy. *Circulation* 1984, 70:318-330
789. Fluckiger W, Perrin IV, Ross GL: Morphometric studies on retinal microangiopathy and myocardiopathy in hypertensive rats (SHR) with induced diabetes. *Virchows Arch [Cell Pathol]* 1984, 47:79-94
790. Giacomelli F, Wiener J: Primary myocardial disease in the diabetic mouse: An ultrastructural study. *Lab Invest* 1979, 40:460-473
791. Murthy VK, Shipp JC: Accumulation of myocardial triglycerides in ketotic diabetes: Evidence for increased biosynthesis. *Diabetes* 1977, 26:222-229
792. Regan TJ, Ettinger PO, Khan MI, Jesrani MU, Lyons MM, Oldewurtel HA, Weber M: Altered myocardial function and metabolism in chronic diabetes mellitus without ischemia in dogs. *Circ Res* 1974, 35:222-237
793. Schaffner SW, Tan BH, Wilson GL: Development of a cardiomyopathy in a model of noninsulin-dependent diabetes. *Am J Physiol* 1985, 248:179-185
794. Seager MJ, Singal PK, Orchard R, Pierce GN, Dhalla NS: Cardiac cell damage: A primary myocardial disease in streptozotocin-induced chronic diabetes. *Br J Exp Pathol* 1984, 65:613-623
795. Volk BW, Wellmann KF: Experimental atherosclerosis in normal and subdiabetic rabbits: II. Longterm studies. *Atherosclerosis* 1971, 14:331-339
796. Callas G, Hayes JR: Alterations in the fine structure of cardiac muscle mitochondria induced by hyperthyroidism. *Anat Rec* 1974, 178:539-550
797. Hawkey CM, Olsen EGJ, Symons C: Production of cardiac muscle abnormalities in offspring of rats receiving triiodothyroacetic acid (triac) and the effect of beta adrenergic blockade. *Cardiovasc Res* 1981, 15:196-205
798. Hoenig M, Goldschmidt MH, Ferguson DC, Koch K, Eymontt MJ: Toxic nodular goiter in the cat. *J Small Anim Pract* 1982, 23:1-12
799. Holzworth J, Theran P, Carpenter JL, Harpster NK, Todoroff RJ: Hyperthyroidism in the cat: Ten cases. *J Am Vet Med Assoc* 1980, 176:345-353
800. Liu S-K, Peterson ME, Fox PR: Hypertrophic cardiomyopathy and hyperthyroidism in the cat. *J Am Vet Med Assoc* 1984, 185:52-57
801. McCallister LP, Page E: Effects of thyroxine on ultrastructure of rat myocardial cells: A stereological study. *J Ultrastruct Res* 1973, 42:136-155
802. Page E, McCallister LP: Quantitative electron microscopic description of heart muscle cells: Application to normal, hypertrophied and thyroxine-stimulated hearts. *Am J Cardiol* 1973, 31:172-181
803. Pearce PC, Hawkey CM, Symons C, Olsen EGJ: Effect of triac and β -adrenergic blocking agents on the myocardium of developing rats. *Cardiovasc Res* 1983, 17:7-14
804. Peterson ME, Keene B, Ferguson DC, Pipers FS: Electrocardiographic findings in 45 cats with hyperthyroidism. *J Am Vet Med Assoc* 1982, 180:934-937
805. Peterson ME, Kintzer PP, Cavanagh PG, Fox PR, Ferguson DC, Johnson GF, Becker DV: Feline hyperthyroidism: Pretreatment clinical and laboratory evaluation of 131 cases. *J Am Vet Med Assoc* 1983, 183:103-110
806. Piatnek DA, Olson RE: Experimental hyperthyroidism in dogs and effect of salivariectomy. *Am J Physiol* 1961, 201:723-728
807. Piatnek-Leunissen D, Olsen RE: Cardiac failure in the dog as a consequence of exogenous hyperthyroidism. *Circ Res* 1967, 20:242-252
808. Poche R: Das submikroskopische Bild der Herzmuskelveränderungen nach Überdosierung von Schilddrüsenhormon. *Beitr Pathol* 1957, 118:407-420
809. Poche R: Über den Einfluss von Dinitrophenol und Thyroxin auf die Ultrastruktur des Herzmuskels bei der Ratte. *Virchows Arch [Pathol Anat]* 1962, 335:282-297
810. Reith A, Fuchs S: The heart muscle of the rat under influence of triiodothyronine and riboflavin deficiency with special reference to mitochondria: A morphologic and morphometric study by electron microscopy. *Lab Invest* 1973, 29:229-235
811. Sanford CF, Griffin EE, Wildenthal K: Synthesis and degradation of myocardial protein during the development and regression of thyroxine-induced cardiac hypertrophy in rats. *Circ Res* 1978, 43:688-694
812. Skelton CL, Sonnenblick EH: Heterogeneity of contractile function in cardiac hypertrophy. *Circ Res (Suppl II)* 1974, 34 and 35:83-96
813. Smitherman TC, Johnson RS, Taubert K, Decker RS, Wildenthal K, Shapiro W, Butsch R, Richards EG: Acute thyrotoxicosis in the rabbit: Changes in cardiac myosin, contractility, and ultrastructure. *Biochem Med* 1979, 21:277-298
814. Stauer BE, Scherpe A: Experimental hyperthyroidism: I. Hemodynamics and contractility in situ. *Basic Res Cardiol* 1975, 70:115-129
815. Symons C, Olsen EGJ, Hawkey CM: The production of cardiac hypertrophy by triiodothyroacetic acid. *J Endocr* 1975, 65:341-346
816. McFadden PM, Berenson GS: Basement membrane changes in myocardial and skeletal muscle capillaries in myxedema. *Circulation* 1972, 45:808-814
817. Belshaw BE: Thyroid diseases.²³⁰ Vol II, pp 1592-1614
818. Gilbert PL, Siegal RJ, Melmed S, Sherman CT, Fish-

- bein MC: Cardiac morphology in rats with growth hormone-producing tumors. *J Mol Cell Cardiol* 1985, 17:805-811
819. Penney DG, Dunbar JC Jr, Baylerian MS: Cardiomegaly and haemodynamics in rats with a transplantable growth hormone-secreting tumor. *Cardiovasc Res* 1985, 19:270-277
 820. Gainer JH: Viral myocarditis in animals. *Adv Cardiol* 1974, 13:94-105
 821. Lansdown ABG: Viral infection and disease of the heart. *Prog Med Virol* 1978, 24:70-113
 822. Lerner AM, Wilson FM: Virus myocardiopathy. *Prog Med Virol* 1973, 15:63-91
 823. Matsumori A, Kawai C: Animal models of cardiomyopathy. *Int J Cardiol* 1983, 3:368-373
 824. Rabin ER, Melnick JL: Experimental acute myocarditis. *Prog Cardiovasc Dis* 1964, 7:65-72
 825. Rabin ER, Jensen AB: Electron microscopic studies of animal viruses with emphasis on in vivo infections. *Prog Med Virol* 1967, 9:392-450
 826. Reyes MP, Lerner AM: Cocksackievirus myocarditis with special reference to acute and chronic effects. *Prog Cardiovasc Dis* 1985, 27:373-394
 827. Woodruff JF: Viral myocarditis. *Am J Pathol* 1980, 101:427-484
 828. Deguchi H: Ultrastructural alterations of the myocardium in Cocksackie B3 virus myocarditis in mice: 18 Month follow-up study by transmission and analytical electron microscopy. *Jpn Circ J* 1981, 45:695-712
 829. Burch GE: Ultrastructural myocardial changes produced by viruses. *Recent Adv Stud Card Struct Metab* 1975, 6:501-523
 830. Kawai C, Matsumori A, Kamagai N, Tokuda M: Experimental Cocksackie virus B-3 and B-4 myocarditis in mice. *Jpn Circ J* 1978, 42:43-47
 831. Matsumori A, Kawai C: Cocksackie virus B3 perimyocarditis in BALB/c mice: Experimental model of chronic perimyocarditis in the right ventricle. *J Pathol* 1980, 131:97-106
 832. Morita H: Experimental Cocksackie B3 virus myocarditis in golden hamsters: Light and electron microscopic findings in a long-term follow-up study. *Jpn Circ J* 1981, 45:713-729
 833. Rabin ER, Hassan SA, Jensen AB, Melnick JL: Cocksackie virus B3 myocarditis in mice: An electron microscopic, immunofluorescent and virus-assay study. *Am J Pathol* 1964, 44:795-797
 834. Miranda QR, Kirk RS, Beswick TSL: The long-term effects of neonatal Cocksackie-B infection in mice: Reduced fecundity of recovered females. *J Pathol* 1973, 109:183-193
 835. Miranda QR, Kirk RS, Beswick TSL, Campbell ACP: Experimental Cocksackie-B myocarditis in mice. *J Pathol* 1973, 109:175-182
 836. Reyes MP, Ho K-L, Smith F, Lerner AM: A mouse model of dilated-type cardiomyopathy due to Cocksackievirus B3. *J Infect Dis* 1981, 144:232-236
 837. Wilson FM, Miranda QR, Chason JL, Lerner AM: Residual pathological changes following murine Cocksackie A and B myocarditis. *Am J Pathol* 1969, 55:253-265
 838. El-Khatib MR, Chason JL, Lerner AM: Ventricular aneurysms complicating Cocksackie virus group B, types 1 and 4 murine myocarditis. *Circulation* 1979, 59:412-416
 839. Hoshino T, Matsumori A, Kawai C, Imai J: Ventricular aneurysms and ventricular arrhythmias complicating Cocksackie virus B1 myocarditis of Syrian golden hamsters. *Cardiovasc Res* 1984, 18:24-29
 840. Khatib R, Chason JL, Lerner AM: A mouse model of transmural myocardial necrosis due to Cocksackie virus B4: Observations over 12 months. *Intervirology* 1982, 18:197-202
 841. Saffitz JE, Schwartz DJ, Southworth W, Murphree S, Rodriguez ER, Ferrans VJ, Roberts WC: Cocksackie viral myocarditis causing transmural right and left ventricular infarction without coronary narrowing. *Am J Cardiol* 1983, 52:644-647
 842. Huber SA, Job LP: Differences in cytolytic T cell response of Balb/c mice infected with myocarditis and non-myocarditic strains of Cocksackievirus Group B, Type 3. *Infect Immun* 1983, 39:1419-1427
 843. Huber SA, Job LP: Cellular immune mechanisms in Cocksackievirus Group B, Type 3 induced myocarditis in Balb/c mice. *Myocardial Injury*. Edited by JJ Spitzer. New York, Plenum Publishing, 1983, pp 491-508
 844. Huber SA, Job LP, Auld KR, Woodruff JF: Sex-related differences in the rapid production of cytotoxic spleen cells active against uninfected myofibers during Cocksackie virus B-3 infection. *J Immunol* 1981, 126:1336-1340
 845. Huber SA, Job LP, Woodruff JF: Lysis of infected myofibers by Cocksackievirus B-3 immune T lymphocytes. *Am J Pathol* 1980, 98:681-694
 846. Huber SA, Lodge PA: Cocksackievirus B-3 myocarditis in Balb/c mice: Evidence for autoimmunity to myocyte antigens. *Am J Pathol* 1984, 116:21-29
 847. Woodruff JF, Woodruff JJ: Involvement of T lymphocytes in the pathogenesis of Cocksackie virus B3 heart disease. *J Immunol* 1974, 113:1726-1734
 848. Wong CY, Woodruff JJ, Woodruff JF: Generation of cytotoxic lymphocytes during Cocksackievirus B-3 infection: I. Model and viral specificity. *J Immunol* 1977, 118:1159-1164
 849. Acland HM, Littlejohns IR: Encephalomyocarditis virus infection of pigs: I. An outbreak in New South Wales. *Aust Vet J* 1975, 51:409-415
 850. Acland HM, Littlejohns IR: Encephalomyocarditis,⁷¹² pp 339-343
 851. Gainer JH: Encephalomyocarditis virus infections in Florida, 1960-1966. *J Am Vet Med Assoc* 1967, 151:421-425
 852. Gainer JH, Sandefur JR, Bigler WJ: High mortality in a Florida swine herd infected with the encephalomyocarditis virus: An accompanying epizootologic survey. *Cornell Vet* 1968, 58:31-47
 853. Helwig FC, Schmidt ECH: A filter passing agent producing interstitial myocarditis in anthropoid apes and small animals. *Science* 1945, 102:31-33
 854. Matsumori A, Kawai C: An animal model of congestive (dilated) cardiomyopathy: Dilatation and hypertrophy of the heart in the chronic stage in DBA/2 mice with myocarditis caused by encephalomyocarditis virus. *Circulation* 1982, 66:355-360
 855. Matsumori A, Kawai C: An experimental model for congestive heart failure after encephalomyocarditis virus myocarditis in mice. *Circulation* 1982, 65:1230-1235
 856. Matsumori A, Kawai C, Sawada S: Encephalomyocarditis (EMC) virus myocarditis in DBA/2 mice: I. Acute stage. *Jpn Circ J* 1981, 45:1403-1408
 857. Meessen H, Muntefering H, Schmidt WAK, Muller-Rachholtz ER, Kieker W-R: Virus-induced damage of the myocardial cell. *Recent Adv Stud Card Struct Metab* 1975, 6:525-533
 858. Burch GE, Harb MJ: Lesions induced by encephalomyocarditis virus and Cocksackie virus B in newborn mice. *Arch Pathol Lab Med* 1979, 103:348-354
 859. Harb JM, Burch GE: Ultrastructural cytopathology of mouse myocardium associated with EMC virus infection. *J Mol Cell Cardiol* 1973, 5:55-62
 860. Matsumori A, Kawai C, Sawada S: Encephalomyocarditis virus myocarditis in inbred strains of mice: Chronic stage. *Jpn Circ J* 1982, 46:1192-1196
 861. Matsumori A, Kishimoto C, Kawai C, Sawada S: Right

- ventricular aneurysms complicating encephalomyocarditis virus myocarditis in mice. *Jpn Circ J* 1983, 47:1322-1324
862. Lenghaus C, Studdert MJ: Acute and chronic viral myocarditis: Acute diffuse nonsuppurative myocarditis and residual myocardial scarring following infection with canine parvovirus. *Am J Pathol* 1984, 115:316-319
 863. Atwell RB, Kelly WR: Canine parvovirus: A cause of chronic myocardial fibrosis and adolescent congestive heart failure. *J Small Anim Pract* 1980, 21:609-620
 864. Bastianello SS: Canine parvovirus myocarditis: Clinical signs and pathological lesions encountered in natural cases. *J S Afr Vet Assoc* 1981, 52:105-108
 865. Carpenter JL, Roberts RM, Harpster NK, King NW Jr: Intestinal and cardiopulmonary forms of parvovirus infection in a litter of pups. *J Am Vet Med Assoc* 1980, 176:1269-1273
 866. Hayes MA, Russell RG, Babiuk LA: Sudden death in young dogs with myocarditis caused by parvovirus. *J Am Vet Med Assoc* 1979, 174:1197-1203
 867. Jezyk PF, Haskins ME, Jones CL: Myocarditis of probable viral origin in pups of weaning age. *J Am Vet Med Assoc* 1979, 174:1204-1207
 868. Kramer JM, Meunier PC, Pollock RVH: Canine parvovirus: Update. *Vet Med Small Anim Clin* 1980, 175:1541-1555
 869. Parrish CR, Oliver RE, Julian AF, Smith BF, Kyle BH: Pathological and virological observations on canine parvoviral enteritis and myocarditis in the Wellington region. *NZ Vet J* 1980, 28:238-241
 870. Robinson WF, Huxtable CR, Pass DA: Canine parvoviral myocarditis: A morphologic description of the natural disease. *Vet Pathol* 1980, 17:282-293
 871. Robinson WF, Huxtable CRR, Pass DA, Howell J McC: Clinical and electrocardiographic findings in suspected viral myocarditis of pups. *Aust Vet J* 1979, 55:351-355
 872. Thiel W: Myocarditis bei hundewelpen (Myocarditis in puppies). *Berl Münch Tierarztl Wschr* 1980, 93:271-273
 873. Lenghaus C, Studdert MJ, Finnie JW: Acute and chronic canine parvovirus myocarditis following intrauterine inoculation. *Aust Vet J* 1980, 56:465-468
 874. Cimprich RE, Robertson JL, Kutz SA, Struve PS, Detweiler DK, DeBaecke PJ, Streett CS: Degenerative cardiomyopathy in experimental Beagles following parvovirus exposure. *Toxicol Pathol* 1981, 9:19-21
 875. Meunier PC, Cooper BJ, Appel MJG, Slauson DO: Experimental viral myocarditis: Parvoviral infection of neonatal pups. *Vet Pathol* 1984, 21:509-515
 876. Ilgen BE, Conroy JD: Fatal cardiomyopathy in an adult dog resembling parvovirus-induced myocarditis: A case report. *J Am Anim Hosp Assoc* 1982, 18:613-617
 877. Higgins RJ, Krakowka S, Metzler AE, Koestner A: Canine distemper virus-associated cardiac necrosis in the dog. *Vet Pathol* 1981, 18:472-486
 878. Hashimoto A, Hirai K, Suzuki Y, Fujimoto Y: Experimental transplacental transmission of canine herpes virus in pregnant bitches during the second trimester of gestation. *Am J Vet Res* 1983, 44:610-614
 879. Flir K: Zur Pathologie des Morbus Aujeszky beim Hund. *Arch Exp Vet Med* 1955, 9:949-956
 880. Callis JJ, McKercher PD: Foot-and-mouth disease,⁷¹² pp 278-287
 881. Blailock ZR, Rabin ER, Melnick JL: Adenovirus myocarditis in mice: An electron microscopic study. *Exp Mol Pathol* 1968, 9:84-96
 882. Grodums EI, Zbitnew A: Experimental herpes simplex virus carditis in mice. *Infect Immun* 1976, 14:1322-1331
 883. Hassan SA, Rabin ER, Melnick JL: Reovirus myocarditis in mice: An electron microscopic, immunofluorescent, and virus assay study. *Exp Mol Pathol* 1965, 4:66-80
 884. Rabin ER, Phillips CA, Jenson AB, Melnick JL: Vacinia virus myocarditis in mice: An electron microscopic and virus assay study. *Exp Mol Pathol* 1965, 4:98-111
 885. Harrison AK, Murphy FA, Gardner JJ, Bauer SP: Myocardial and pancreatic necrosis induced by Rocio virus, a new flavivirus. *Exp Mol Pathol* 1980, 32:102-113
 886. Harrison AK, Murphy FA, Gardner JJ: Visceral target organs in systemic St. Louis encephalitis virus infection of hamsters. *Exp Mol Pathol* 1982, 37:292-304
 887. Garcia-Tamayo J: Venezuelan equine encephalomyelitis virus in the heart of newborn mice. *Arch Pathol* 1973, 96:294-297
 888. Small JD, Aurelian L, Squire RA, Strandberg JD, Melby EC Jr, Turner TB, Newman B: Rabbit cardiomyopathy associated with a virus antigenically related to human coronavirus strain 229E. *Am J Pathol* 1979, 95:709-730
 889. Nagy Z, Derzsy D: A viral disease of goslings: II. Microscopic findings. *Acta Vet Acad Sci Hung* 1968, 18:3-18
 890. Parker GA, Stedham MA, Van Dellan A: Myocarditis of probable viral origin in chickens. *Avian Dis* 1977, 21:123-132
 891. Springer WT, Schmittle SC: Avian encephalomyelitis: A chronological study of the histopathogenesis in selected tissues. *Avian Dis* 1968, 12:229-239
 892. Kerr KM, Olson NO: Cardiac pathology associated with viral and mycoplasmal arthritis in chickens. *Ann NY Acad Sci* 1967, 143:204-217
 893. Chevillat NF, Beard CW: Cytopathology of Newcastle disease: The influence of basal and thymic lymphoid systems in the chicken. *Lab Invest* 1972, 27:129-143
 894. Ranck FM Jr, Gainer JH, Hanley JE, Nelson SL: Natural outbreak of Eastern and Western encephalitis in pen-raised chukars in Florida. *Avian Dis* 1965, 9:8-20
 895. McKenzie BE, Easterday BC, Will JA: Light and electron microscopic changes in the myocardium of influenza-infected turkeys. *Am J Pathol* 1972, 69:239-254
 896. Allen AM, Ganaway JR, Moore TD, Kinard RF: Tyzzer's disease syndrome in laboratory rabbits. *Am J Pathol* 1965, 46:859-882
 897. Fujiwara K, Takagaki Y, Maejima K, Kato K, Naiki M, Tajima Y: Tyzzer's disease in mice: Pathologic studies on experimentally infected animals. *Jpn J Exp Med* 1963, 33:183-202
 898. Jonas AM, Percy DH, Craft J: Tyzzer's disease in the rat: Its possible relationship with megaloleitis. *Arch Pathol* 1970, 90:516-528
 899. Tsuchitani M, Umemura T, Narama I, Yanabe M: Naturally occurring Tyzzer's disease in a clean mouse colony: High mortality with coincidental cardiac lesions. *J Comp Pathol* 1983, 93:499-507
 900. Zook BC, Huang K, Rhorer RG: Tyzzer's disease in Syrian hamsters. *J Am Vet Med Assoc* 1977, 171:833-836
 901. Jubb KVF, Kennedy PC, Palmer N,⁹⁷ pp 197-199
 902. Henry L, Beverley JKA: Experimental toxoplasmic myocarditis and myositis in mice. *Br J Exp Pathol* 1969, 50:230-238
 903. Castagnino HE, Thompson AC: Cardiopatía chagásica experimental. *Cardiopatía Chagásica*. Buenos Aires, Editorial Kapelusz, 1980, pp 299-308
 904. Acosta AM, Santos-Buch CA: Autoimmune myocarditis induced by *Trypanosoma cruzi*. *Circulation* 1985, 71:1255-1261
 905. Andrade ZA, Andrade SG, Sadigursky M: Damage and healing in the conducting tissue of the heart (an experimental study in dogs infected with *Trypanosoma cruzi*). *J Pathol* 1984, 143:93-101
 906. Andrade ZA, Andrade SG, Sadigursky M, Maguire JH: Experimental Chagas' disease in dogs: A pathologic and ECG study of the chronic indeterminate phase of the infection. *Arch Pathol Lab Med* 1981, 105:460-464
 907. Federici EE, Abelman WH, Nova FA: Chronic and progressive myocarditis and myositis in C3H mice in-

- fectured with *Trypanosoma cruzi*. Am J Tryp Hyg 1964, 13:272-286
908. Johnson CM: Cardiac changes in dogs experimentally infected with *Trypanosoma cruzi*. Am J Trop Med 1938, 18:197-206
909. Kumar R, Kline IK, Abelman WH: Experimental *Trypanosoma cruzi* myocarditis: Relative effects upon the right and left ventricles. Am J Pathol 1969, 57:31-48
910. MacClure E, Poche R: Die experimentelle Chagas-Myocarditis der weissen Maus im electronenmikroskopischen Bild. Virchows Arch [Pathol Anat] 1960, 333:405-420
911. Rossi MA, Goncalves S, Ribeiro-dos-Santos R: Experimental *Trypanosoma cruzi* cardiomyopathy in BALB/c mice: The potential role of intravascular platelet aggregation in its genesis. Am J Pathol 1984, 114:209-216
912. Santos-Buch CA: American trypanosomiasis: Chagas' disease. Int Rev Exp Pathol 1979, 19:63-100
913. Teixeira ARL, Teixeira ML, Santos-Buch CA: The immunology of experimental Chagas' disease: IV. Production of lesions in rabbits similar to those of chronic Chagas' disease in man. Am J Pathol 1975, 80:163-180
914. Williams GD, Adams LG, Yaeger RG, McGrath RK, Read WK, Bilderback WR: Naturally occurring trypanosomiasis (Chagas' disease) in dogs. J Am Vet Med Assoc 1977, 171:171-177
915. Rossi MA, Carobrea SG: Experimental *Trypanosoma cruzi* cardiomyopathy in BALB/c mice: Histochemical evidence of hypoxic changes in the myocardium. Br J Exp Pathol 1985, 66:155-160

From: Jones, Jennifer L
To: Nemser, Sarah
Subject: RE: 800.261-Zignature Kangaroo Formula: (b) (6) - EON-350158
Date: Wednesday, April 04, 2018 2:06:00 PM
Attachments: image001.png
image004.png
image005.png
image006.png
image007.png
image011.png

Sometimes, I'm the only one on the emails.

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Nemser, Sarah
Sent: Wednesday, April 04, 2018 9:42 AM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: FW: 800.261-Zignature Kangaroo Formula: (b) (6) - EON-350158

I am not getting original emails about cases. Am I not on the emails?

S

Sarah Nemser M.S.

Vet-LIRN Network Coordinator

tel: 240-402-0892

fax: 301-210-4685
sarah.nemser@fda.hhs.gov

From: Jones, Jennifer L
Sent: Wednesday, April 04, 2018 9:32 AM
To: Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Cc: Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>
Subject: RE: 800.261-Zignature Kangaroo Formula: (b) (6) - EON-350158

MRx summary below. We are purchasing store-bought product for Tau, Met, Cys testing. A previous case without food had a Cocker Spaniel-same Zignature Essentials Food, low Tau on labwork. If the Food results are negative, we may need to consider Tau/Cys/Met inhibitors in the food or breed-related AA handling deficiencies causing the DCM

MRx summary:

Presenting complaint 10/27 to rDVM: developed a cough on 10/25, cough for 3-4 days, not lethargic, normal eating/drinking, no vomiting or diarrhea, worse when lying down, dog didn't cough while in clinic except for a tracheal cough when pulling on the leash → treated with hydroxyzine, doxycycline, hydrocodone → stopped all 3 drugs Monday b/c cough worsened → to ER on (b) (6) after coughing up pink tinged foam; no lethargy, continues to eat and drink; UTD on vaccines and HWP, no drugs → treat with Lasix, benazepril, vetmedin, spironolactone, Tau, L-carnitine and **vet recommended a diet change** → labwork done 11/14 → to rDVM 11/16: doing well → recheck 2/26/18: intermittent cough, related to excitement, change diet to RC Early Cardiac → on recheck improved → suspect Tau responsive DCM-mild, suspect cough secondary to bronchial or primary respiratory disease → recheck 3/13: resting RR 16 rpm, minimal coughing only when excited, since switching to cardiac food BMs are dense and tenesmus, owner is weaning dog off lasix

PE 10/27 @ rDVM: numerous lipomatous & dermal masses, no audible murmur or arrhythmia, shallow breathing

PE (b) (6) @ specialist: LS-OU, HR 100 bpm, mild periodontal disease, Gr II/VI, left apical protosystolic murmur, questionable mild inc bronchovesicular sounds bilaterally, SC mass left ventrum, mildly tense cranial abdominal palpation

PE 11/16 @ rDVM: mild underbite, H/L wnl

PE 2/26: Gr III/VI pansystolic, PMI MV, reg rhythm with S3 gallop, HR 130, BCS 6/9, hepatomegaly

PE 3/13: T 99.9F, RR 56, HR 124 bpm, Gr III/VI murmur, rest nsf

Labs: 10/27 CBC: Lym 1.01 (1.05-5.1)

-3/13: Lym 1044 (1060-4950), Plt 615 (143-448), Plt inc on direct

10/27 Chem: ALP 440 (23-212), GGT 30 (0-11), rest nsf

-11/14: Glu 51 (70-143), Glob 4.7 (2.5-4.5), ALP 621, GGT 31

-3/13: Na:K 27, ALP 2243 (5-180), GGT 117 (0-13)

(b) (6) BP 100 (based on Echo)

-2/26: 155 mg Hg, direct measurement

-3/13: 130-140 mmHg, direct measurement

11/3 Tau-blood: 168 (200-350)

3/13 UA: 1 010, pH 5

3/13 TT4: 0.8 (1-4)

Rads 10/27: generalized cardiomegaly, left atrial enlargement, slight left auricular bulge, increased sternal contact & rounded heart, dorsal tracheal deviation, prominent pulmonary vasculature with questionably mild inc interstitial opacity in caudal-dorsal lungs, suggesting early CHF/PE

(b) (6) **Echo:** severe LV hypertrophy, mild-mod MV regurgitation, mod-sev LA dilation,

mild TV regurg, mild RV & RA dilation, mod-sev lower systolic function values

-2/26: mild LV dilation, mild MV regurg, normal LA, mild TV regurg, normal RV & RA, low normal systolic functional indices of LV

(b) (6) **ECG:** normal sinus rhythm

Prior MHx: 7/2017: doing well at home-occasionally coughs several SQ masses, no murmur or cough on tracheal palpation; 10/23/2017-vaccines, doing well per O, no murmur ausculted, not been getting HWP consistently,

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Jones, Jennifer L
Sent: Tuesday, March 27, 2018 3:40 PM
To: Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>
Cc: Rotstein, David <David.Rotstein@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Subject: RE: Zignature Kangaroo Formula: (b) (6) - EON-350158

Yes-let's take a look! I think we should check taurine, cysteine, methionine, and beta-alanine. I'm curious if those aminoacid levels are normal if there is some underlying renal disease causing whole body taurine depletion.
<https://academic.oup.com/ajcal/article/36/1/29/138000>

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Palmer, Lee Anne
Sent: Tuesday, March 27, 2018 3:25 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Cc: Rotstein, David <David.Rotstein@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Subject: FW: Zignature Kangaroo Formula (b) (6) - EON-350158

In case of interest – taurine level low?

From: PFR Event [<mailto:pfreventcreation@fda.hhs.gov>]
Sent: Tuesday, March 27, 2018 3:20 PM
To: Cleary, Michael * <Michael.Cleary@fda.hhs.gov>; HQ Pet Food Report Notification <HQPetFoodReportNotification@fda.hhs.gov> (b) (6)
Subject: Zignature Kangaroo Formula: (b) (6) - EON-350158

A PFR Report has been received and PFR Event [EON-350158] has been created in the EON System

A "PDF" report by name "2044632-report pdf" is attached to this email notification for your reference. Please note that all documents received in the report are compressed into a zip file by name "2044632-attachments zip" and is attached to this email notification

Below is the summary of the report:

EON Key: EON-350158
ICSR #: 2044632
EON Title: PFR Event created for Zignature Kangaroo Formula; 2044632

AE Date	(b) (6)	Number Fed/Exposed	1
Best By Date		Number Reacted	1
Animal Species	Dog	Outcome to Date	Better/Improved/Recovering
Breed	Retriever - Labrador		
Age	13 Years		
District Involved	PFR (b) (6) DO		

Product information

Individual Case Safety Report Number: 2044632

Product Group: Pet Food

Product Name: Zignature Kangaroo Formula

Description: At the time of diagnosis (b) (6), (b) (6) was a 13 year old female spayed Labrador retriever who had been maintained on a Zignature Kangaroo formula. She presented with a history of a progressive cough which, prior to presentation, became productive and she coughed up a small volume of pink foam (possible pulmonary edema). On examination she had a 2/6 left apical systolic heart murmur and on echo diagnosed with advanced dilated cardiomyopathy with severe left ventricular dilation, moderate to severe left ventricular systolic dysfunction, and moderate to severe left atrial dilation. Thoracic radiographs were suspicious for early congestive heart failure. A whole blood taurine level was submitted and was low at 168. She was treated with furosemide, benazepril, pimobendan, spironolactone, taurine and L-carnitine and her diet was changed to Royal Canin Early Cardiac. At her recheck in 2/26/18, (b) (6) heart had improved significantly with now mild dilated cardiomyopathy with normalized left atrial dimensions, mild left ventricular dilation and low normal left ventricular systolic function. The furosemide was able to be discontinued at this time.

Submission Type: Initial

Report Type: Adverse Event (a symptom, reaction or disease associated with the product)

Outcome of reaction/event at the time of last observation: Better/Improved/Recovering

Number of Animals Treated With Product: 1

Number of Animals Reacted With Product: 1

Product Name	Lot Number or ID	Best By Date
Zignature Kangaroo Formula		

Sender information

(b) (6)

Owner information

(b) (6)

To view this PFR Event, please click the link below:

<https://eon.fda.gov/eon/> (b) (6)

To view the PFR Event Report, please click the link below:

<https://eon.fda.gov/eon/> (b) (6)

=====

This email and attached document are being provided to you in your capacity as a Commissioned Official with the U.S. Department of Health and Human Services as authorized by law. You are being provided with this information pursuant to your signed Acceptance of Commission.

This email message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential. Any dissemination, distribution, or copying is strictly prohibited.

The information is provided as part of the Federal-State Integration initiative. As a Commissioned Official and state government official, you are reminded of your obligation to protect non-public information, including trade secret and confidential commercial information that you receive from the U.S. Food and Drug Administration from further disclosure. The information in the report is intended for situational awareness and should not be shared or acted upon independently. Any and all actions regarding this information should be coordinated through your local district FDA office.

Failure to adhere to the above provisions could result in removal from the approved distribution list. If you think you received this email in error, please send an email to FDAREportableFoods@fda.hhs.gov immediately.

From: Jones, Jennifer L
To: Palmer, Lee Anne; Rotstein, David; Carey, Lauren
Cc: Ceric, Olga; Nemser, Sarah; "Reimschuessel, Renate (Renate.Reimschuessel@fda.hhs.gov)"
Subject: RE: 800.261-Zignature Kangaroo Formula: (b) (6) - EON-350158
Date: Wednesday, April 04, 2018 9:32:00 AM
Attachments: EON-350158 (b) (6) -case summary-4.4.2018.doc
image001.png
image002.png
image003.png

MRx summary below. We are purchasing store-bought product for Tau, Met, Cys testing. A previous case without food had a Cocker Spaniel-same Zignature Essentials Food, low Tau on labwork. If the Food results are negative, we may need to consider Tau/Cys/Met inhibitors in the food or breed-related AA handling deficiencies causing the DCM

MRx summary:

Presenting complaint 10/27 to rDVM: developed a cough on 10/25, cough for 3-4 days, not lethargic, normal eating/drinking, no vomiting or diarrhea, worse when lying down, dog didn't cough while in clinic except for a tracheal cough when pulling on the leash → treated with hydroxyzine, doxycycline, hydrocodone → stopped all 3 drugs Monday b/c cough worsened → to ER on (b) (6) after coughing up pink tinged foam; no lethargy, continues to eat and drink; UTD on vaccines and HWP, no drugs → treat with Lasix, benazepril, vetmedin, spironolactone, Tau, L-carnitine and **vet recommended a diet change** → labwork done 11/14 → to rDVM 11/16: doing well → recheck 2/26/18: intermittent cough, related to excitement, change diet to RC Early Cardiac → on recheck improved → suspect Tau responsive DCM-mild, suspect cough secondary to bronchial or primary respiratory disease → recheck 3/13: resting RR 16 rpm, minimal coughing only when excited, since switching to cardiac food BMs are dense and tenesmus, owner is weaning dog off lasix

PE 10/27 @ rDVM: numerous lipomatous & dermal masses, no audible murmur or arrhythmia, shallow breathing

PE (b) (6) @ specialist: LS-OU, HR 100 bpm, mild periodontal disease, Gr II/VI, left apical protosystolic murmur, questionable mild inc bronchovesicular sounds bilaterally, SC mass left ventrum, mildly tense cranial abdominal palpation

PE 11/16 @ rDVM: mild underbite, H/L wnl

PE 2/26: Gr III/VI pansystolic, PMI MV, reg rhythm with S3 gallop, HR 130, BCS 6/9, hepatomegaly

PE 3/13: T 99.9F, RR 56, HR 124 bpm, Gr III/VI murmur, rest nsf

Labs: 10/27 CBC: Lym 1.01 (1.05-5.1)

-3/13: Lym 1044 (1060-4950), Plt 615 (143-448), Plt inc on direct

10/27 Chem: ALP 440 (23-212), GGT 30 (0-11), rest nsf

-11/14: Glu 51 (70-143), Glob 4.7 (2.5-4.5), ALP 621, GGT 31

-3/13: Na:K 27, ALP 2243 (5-180), GGT 117 (0-13)

(b) (6) BP 100 (based on Echo)

-2/26: 155 mg Hg, direct measurement

-3/13: 130-140 mmHg, direct measurement

11/3 Tau-blood: 168 (200-350)

3/13 UA: 1.010, pH 5

3/13 TT4: 0.8 (1-4)

Rads 10/27: generalized cardiomegaly, left atrial enlargement, slight left auricular bulge, increased sternal contact & rounded heart, dorsal tracheal deviation, prominent pulmonary vasculature with questionably mild inc interstitial opacity in caudal-dorsal lungs, suggesting early CHF/PE

(b) (6) **Echo:** severe LV hypertrophy, mild-mod MV regurgitation, mod-sev LA dilation, mild TV regurg, mild RV & RA dilation, mod-sev lower systolic function values

-2/26: mild LV dilation, mild MV regurg, normal LA, mild TV regurg, normal RV & RA, low normal systolic functional indices of LV

(b) (6) **ECG:** normal sinus rhythm

Prior MHx: 7/2017: doing well at home-occasionally coughs several SQ masses, no murmur or cough on tracheal palpation; 10/23/2017-vaccines, doing well per O, no murmur ausculted, not been getting HWP consistently,

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Jones, Jennifer L
Sent: Tuesday, March 27, 2018 3:40 PM
To: Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>
Cc: Rotstein, David <David.Rotstein@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Subject: RE: Zignature Kangaroo Formula: (b) (6) - EON-350158

Yes-let's take a look! I think we should check taurine, cysteine, methionine, and beta-alanine. I'm curious if those aminoacid levels are normal if there is some underlying renal disease causing whole body taurine depletion.

<https://academic.oup.com/ajcal/article/36/1/29/138000>

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Palmer, Lee Anne
Sent: Tuesday, March 27, 2018 3:25 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Cc: Rotstein, David <David.Rotstein@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Subject: FW: Zignature Kangaroo Formula: (b) (6) - EON-350158

In case of interest – taurine level low?

From: PFR Event [mailto:pfreventcreation@fda.hhs.gov]

Sent: Tuesday, March 27, 2018 3:20 PM

To: Cleary, Michael * <Michael.Cleary@fda.hhs.gov>; HQ Pet Food Report Notification <HQPetFoodReportNotification@fda.hhs.gov>; (b) (6)

Subject: Zignature Kangaroo Formula: (b) (6) - EON-350158

A PFR Report has been received and PFR Event [EON-350158] has been created in the EON System

A "PDF" report by name "2044632-report pdf" is attached to this email notification for your reference. Please note that all documents received in the report are compressed into a zip file by name "2044632-attachments zip" and is attached to this email notification

Below is the summary of the report:

EON Key: EON-350158

ICSR #: 2044632

EON Title: PFR Event created for Zignature Kangaroo Formula; 2044632

AE Date	(b) (6)	Number Fed/Exposed	1
Best By Date		Number Reacted	1
Animal Species	Dog	Outcome to Date	Better/Improved/Recovering
Breed	Retriever - Labrador		
Age	13 Years		
District Involved	PFR (b) (6) DO		

Product information

Individual Case Safety Report Number: 2044632

Product Group: Pet Food

Product Name: Zignature Kangaroo Formula

Description: At the time of diagnosis (b) (6), (b) (6) was a 13 year old female spayed Labrador retriever who had been maintained on a Zignature Kangaroo formula. She presented with a history of a progressive cough which, prior to presentation, became productive and she coughed up a small volume of pink foam (possible pulmonary edema). On examination she had a 2/6 left apical systolic heart murmur and on echo diagnosed with advanced dilated cardiomyopathy with severe left ventricular dilation, moderate to severe left ventricular systolic dysfunction, and moderate to severe left atrial dilation. Thoracic radiographs were suspicious for early congestive heart failure. A whole blood taurine level was submitted and was low at 168. She was treated with furosemide, benazepril, pimobendan, spironolactone, taurine and L-carnitine and her diet was changed to Royal Canin Early Cardiac. At her recheck in 2/26/18, (b) (6) heart had improved significantly with now mild dilated cardiomyopathy with normalized left atrial dimensions, mild left ventricular dilation and low normal left ventricular systolic function. The furosemide was able to be discontinued at this time.

Submission Type: Initial

Report Type: Adverse Event (a symptom, reaction or disease associated with the product)

Outcome of reaction/event at the time of last observation: Better/Improved/Recovering

Number of Animals Treated With Product: 1

Number of Animals Reacted With Product: 1

Product Name	Lot Number or ID	Best By Date
Zignature Kangaroo Formula		

Sender information

(b) (6)

Owner information

(b) (6)

To view this PFR Event, please click the link below:

<https://eon.fda.gov> (b) (6)

To view the PFR Event Report, please click the link below:

<https://eon.fda.gov/eon/> (b) (6) (b) (6)

This email and attached document are being provided to you in your capacity as a Commissioned Official with the U.S. Department of Health and Human Services as authorized by law. You are being provided with this information pursuant to your signed Acceptance of Commission.

This email message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential. Any

dissemination, distribution, or copying is strictly prohibited

The information is provided as part of the Federal-State Integration initiative. As a Commissioned Official and state government official, you are reminded of your obligation to protect non-public information, including trade secret and confidential commercial information that you receive from the U.S. Food and Drug Administration from further disclosure. The information in the report is intended for situational awareness and should not be shared or acted upon independently. Any and all actions regarding this information should be coordinated through your local district FDA office.

Failure to adhere to the above provisions could result in removal from the approved distribution list. If you think you received this email in error, please send an email to FDAREportableFoods@fda.hhs.gov immediately.

Vet-LIRN Case Summary Document

Vet-LIRN Case Number:	
EON/CC #:	EON-350158
Owner LAST Name:	(b) (6)
Vet LAST Name:	(b) (6)
Vet-LIRN Initiation Date:	3/28/2018
MedRec: Requested:	Received with Complaint
MedRec: Received:	
MedRec: Significant finding:	
Vet-LIRN Tests (planned):	
Vet-LIRN Test Results:	
Result Interpretation:	
IF NFA, justification:	

COMPLAINT Narrative: At the time of diagnosis (b) (6), (b) (6) was a 13 year old female spayed Labrador retriever who had been maintained on a Zignature Kangaroo formula. She presented with a history of a progressive cough which, prior to presentation, became productive and she coughed up a small volume of pink foam (possible pulmonary edema). On examination she had a 2/6 left apical systolic heart murmur and on echo diagnosed with advanced dilated cardiomyopathy with severe left ventricular dilation, moderate to severe left ventricular systolic dysfunction, and moderate to severe left atrial dilation. Thoracic radiographs were suspicious for early congestive heart failure. A whole blood taurine level was submitted and was low at 168. She was treatment with furosemide, benazepril, pimobendan, spironolactone, taurine and L-carnitine and her diet was changed to Royal Canin Early Cardiac. At her recheck in 2/26/18, (b) (6) heart had improved significantly with now mild dilated cardiomyopathy with normalized left atrial dimensions, mild left ventricular dilation and low normal left ventricular systolic function. The furosemide was able to be discontinued at this time.

Signalment: (b) (6) -13 yr FS Lab

Signs: productive, progressive cough

Food Product: Zignature Kangaroo Formula

Plan:

- MRx
- Open product for Tau, Cysteine, Methionine, +/- Beta-Alanine

MRx summary:

Presenting complaint 10/27 to rDVM: developed a cough on 10/25, cough for 3-4 days, not lethargic, normal eating/drinking, no vomiting or diarrhea, worse when lying down, dog didn't cough while in clinic except for a tracheal cough when pulling on the leash → treated with hydroxyzine, doxycycline, hydrocodone → stopped all 3 drugs Monday b/c cough worsened → to ER on (b) (6) after coughing up pink tinged foam; no lethargy, continues to eat and drink; UTD on vaccines and HWP, no drugs → treat with Lasix, benazepril, vetmedin, spironolactone, Tau, L-carnitine and **vet recommended a diet change** → labwork done 11/14 → to rDVM 11/16: doing well → recheck 2/26/18: intermittent cough, related to

excitement, change diet to RC Early Cardiac → on recheck improved → suspect Tau responsive DCM-mild, suspect cough secondary to bronchial or primary respiratory disease → recheck 3/13: resting RR 16 rpm, minimal coughing only when excited, since switching to cardiac food BMs are dense and tenesmus, owner is weaning dog off lasix

PE 10/27 @ rDVM: numerous lipomatous & dermal masses, no audible murmur or arrhythmia, shallow breathing

PE (b) (6) @ specialist: LS-OU, HR 100 bpm, mild periodontal disease, Gr II/VI, left apical protosystolic murmur, questionable mild inc bronchovesicular sounds bilaterally, SC mass left ventrum, mildly tense cranial abdominal palpation

PE 11/16 @ rDVM: mild underbite, H/L wnl

PE 2/26: Gr III/VI pansystolic, PMI MV, reg rhythm with S3 gallop, HR 130, BCS 6/9, hepatomegaly

PE 3/13: T 99.9F, RR 56, HR 124 bpm, Gr III/VI murmur, rest nsf

Labs: 10/27 CBC: Lym 1.01 (1.05-5.1)

-3/13: Lym 1044 (1060-4950), Plt 615 (143-448), Plt inc on direct

10/27 Chem: ALP 440 (23-212), GGT 30 (0-11), rest nsf

-11/14: Glu 51 (70-143), Glob 4.7 (2.5-4.5), ALP 621, GGT 31

-3/13: Na:K 27, ALP 2243 (5-180), GGT 117 (0-13)

(b) (6) BP 100 (based on Echo)

-2/26: 155 mg Hg, direct measurement

-3/13: 130-140 mmHg, direct measurement

11/3 Tau-blood: 168 (200-350)

3/13 UA: 1.010, pH 5

3/13 TT4: 0.8 (1-4)

Rads 10/27: generalized cardiomegaly, left atrial enlargement, slight left auricular bulge, increased sternal contact & rounded heart, dorsal tracheal deviation, prominent pulmonary vasculature with questionably mild inc interstitial opacity in caudal-dorsal lungs, suggesting early CHF/PE

(b) (6) **Echo:** severe LV hypertrophy, mild-mod MV regurgitation, mod-sev LA dilation, mild TV regurg, mild RV & RA dilation, mod-sev lower systolic function values

-2/26: mild LV dilation, mild MV regurg, normal LA, mild TV regurg, normal RV & RA, low normal systolic functional indices of LV

(b) (6) **ECG:** normal sinus rhythm

Prior MHx: 7/2017: doing well at home-occasionally coughs, several SQ masses, no murmur or cough on tracheal palpation; 10/23/2017-vaccines, doing well per O, no murmur ausculted, not been getting HWP consistently,

An article about beta-alanine: <https://academic.oup.com/alcalc/article/36/1/29/138000>

If Tau & Cys/Met are normal, we may need to reconsider other MOA's causing this, unrelated to the food.

I emailed the vet to request the full MRx and see if lot/best by information available for the leftover food.

4/4/2018

JJ-Vet sent the full MRx available and does not have any leftover food. We will purchase the food for testing. A dog from a previous case without food (800.218- (b) (6)), Cocker Spaniel with Low Tau and also eating Zignature Essentials Kangaroo.

MRx added to above summary.

From: Jones, Jennifer L
To: Carey, Lauren; Hartogensis, Martine; Nemser, Sarah; Palmer, Lee Anne; Rotstein, David
Subject: RE: DCM Comms Going Live Today
Date: Thursday, July 19, 2018 9:32:00 AM
Attachments: PFI-VetLIRN DCM-7.19.2018.pptx
image001.png
image003.png

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Carey, Lauren
Sent: Thursday, July 19, 2018 9:28 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Hi Martine,

Slides attached. I'm willing to make any changes. Just let me know.

Thanks,
Lauren

From: Hartogensis, Martine
Sent: Thursday, July 19, 2018 9:23 AM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: FW: DCM Comms Going Live Today

Hi!

If you are comfortable and want to send me slides for the webinar today, that would be great. PFI can put them on the shared screen.

Thanks!!
Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 19, 2018 9:11 AM

To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Subject: RE: DCM Comms Going Live Today

Good morning, Martine. Will you/your FDA colleagues want to present anything on the screen? I recall during our last webinar with you that we could not give you presenter privileges in GoToMeeting – something to do with your IT/firewall, I think. If you want me to put anything on the screen, please send it to me. I have the redacted version of your presentation from June and the public announcement. Thanks.

Regards,

Peter

O: + (b) (6)

M: (b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Sent: Thursday, July 19, 2018 6:57 AM

To: Tabor, Peter <peter@petfoodinstitute.org>

Subject: Re: DCM Comms Going Live Today

Ok, sounds good and thank you!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>

Date: July 18, 2018 at 10:40:10 PM EDT

To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Subject: Re: DCM Comms Going Live Today

Thanks, Martine. Most participants PFI producer members participants are SMEs, with a few corporate/legal reps in the mix. I really want this webinar to focus on the science behind FDA's notice and got broad agreement from members during our prep for this meeting today.

Sent using OWA for iPhone

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Sent: Wednesday, July 18, 2018 7:16:01 PM

To: Tabor, Peter

Subject: RE: DCM Comms Going Live Today

Hi Peter,

Thank you so much for the list. Here are the folks invited from CVM:

Bill Burkholder
Siobhan DeLancey
Dave Rotstein
Pat McDermott
Jennifer Jones
Lauren Carey
Anne Norris
Lee Anne Palmer
David Edwards
Sarah Nemser
Janice Steinschneider
John Baker
Eric Nelson
Neal Bataller

Also, I recognize a few names on your list, but can you tell me (in general) if the PFI participants are mainly SMEs or leadership? We just want to get an idea of our audience.

Thanks very much in advance!

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Wednesday, July 18, 2018 4:58 PM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Attached is a list of PFI member participants in tomorrow's webinar. Also attached is the proposed agenda and the questions we sent you earlier, just for reference.

Did you already send us a list of FDA participants in the webinar? If not, can you send it this afternoon/evening?

Thanks and we look forward to the call.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Sent: Monday, July 16, 2018 9:29 PM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter!

Looks great! Looking forward to our meeting Thursday!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 16, 2018 at 2:17:16 PM EDT
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Not sure if you're still in Denver or on your way home – I hope the AVMA meeting went well. I wanted to get your input on a draft agenda for the Thu webinar, to make the most of everyone's time.

Proposed Agenda

- Welcome, introductions and PFI anti-trust policy reminder – PFI, FDA (10 minutes)
- Overview of the issue, including the FDA notice and the data FDA presented to PFI in June – FDA (30 minutes, including Qs from PFI)
- Review of questions PFI sent to FDA for the webinar – PFI, FDA (50 minutes)
- Open Q&A – PFI, FDA (20 minutes)
- Conclusion and adjourn (10 minutes)

Please take a look and reply to me at your earliest convenience (today if possible) with thoughts or suggested tweaks. Thanks and safe travels home.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 12, 2018 11:11 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Yes, let's touch base. I am in a meeting until 12 and can call you then. Does that work for you?

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 12, 2018 10:45 AM
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Subject: Re: DCM Comms Going Live Today

Thanks for the heads-up, Martine. Very kind of you. My colleagues and I will review the info and I'll be in touch this afternoon.

I was under the impression that our webinar next week would inform FDA's and pet food makers' understanding of the issue, perhaps before any public messaging was issued. So this is a little concerning. I imagine the public reaction might be quite severe and impact products that aren't implicated by FDA. Hopefully we can chat this afternoon.

Thanks again for reaching out.

Sent using OWA for iPhone

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Sent: Thursday, July 12, 2018 10:34:41 AM
To: Tabor, Peter
Subject: DCM Comms Going Live Today

Hi Peter,

I just left you a VM. I am attaching the DCM comms materials that will be going live today. Please feel free to share them with your members and let me know if you have any questions.

Martine

Martine Hartogenesis, DVM
FDA Center for Veterinary Medicine
Deputy Director, Office of Surveillance & Compliance
(240) 402-7178

From: Carey, Lauren
To: Hartogensis, Martine; Jones, Jennifer L; Nemser, Sarah; Palmer, Lee Anne; Rotstein, David
Subject: RE: DCM Comms Going Live Today
Date: Thursday, July 19, 2018 9:46:11 AM
Attachments: PFI - 7-18-2018 DCM Presentation - lc.ppt

Hi Martine,

How's this?

Thanks,
Lauren

From: Hartogensis, Martine
Sent: Thursday, July 19, 2018 9:39 AM
To: Carey, Lauren <Lauren.Carey@fda.hhs.gov>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Hi Lauren,

I had some edits and questions on slide 4. Also, are the last 2 slides showing the same material (brands)? Maybe it will be more clear when you present.

(b) (5)

Thanks!!

Martine

From: Carey, Lauren
Sent: Thursday, July 19, 2018 9:28 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Hi Martine,

Slides attached. I'm willing to make any changes. Just let me know.

Thanks,
Lauren

From: Hartogensis, Martine

Sent: Thursday, July 19, 2018 9:23 AM

To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>

Subject: FW: DCM Comms Going Live Today

Hi!

If you are comfortable and want to send me slides for the webinar today, that would be great. PFI can put them on the shared screen.

Thanks!!

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]

Sent: Thursday, July 19, 2018 9:11 AM

To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Subject: RE: DCM Comms Going Live Today

Good morning, Martine. Will you/your FDA colleagues want to present anything on the screen? I recall during our last webinar with you that we could not give you presenter privileges in GoToMeeting – something to do with your IT/firewall, I think. If you want me to put anything on the screen, please send it to me. I have the redacted version of your presentation from June and the public announcement. Thanks.

Regards,

Peter

O: + (b) (6)

M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Sent: Thursday, July 19, 2018 6:57 AM

To: Tabor, Peter <peter@petfoodinstitute.org>

Subject: Re: DCM Comms Going Live Today

Ok, sounds good and thank you!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>

Date: July 18, 2018 at 10:40:10 PM EDT

To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Subject: Re: DCM Comms Going Live Today

Thanks, Martine. Most participants PFI producer members participants are SMEs, with a few corporate/legal reps in the mix. I really want this webinar to focus on the science behind FDA's notice and got broad agreement from members during our prep for this meeting today.

Sent using OWA for iPhone

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Sent: Wednesday, July 18, 2018 7:16:01 PM

To: Tabor, Peter

Subject: RE: DCM Comms Going Live Today

Hi Peter,

Thank you so much for the list. Here are the folks invited from CVM:

Bill Burkholder
Siobhan DeLancey
Dave Rotstein
Pat McDermott
Jennifer Jones
Lauren Carey
Anne Norris
Lee Anne Palmer
David Edwards
Sarah Nemser
Janice Steinschneider
John Baker
Eric Nelson
Neal Bataller

Also, I recognize a few names on your list, but can you tell me (in general) if the PFI participants are mainly SMEs or leadership? We just want to get an idea of our audience.

Thanks very much in advance!

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]

Sent: Wednesday, July 18, 2018 4:58 PM

To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Attached is a list of PFI member participants in tomorrow's webinar. Also attached is the proposed agenda and the questions we sent you earlier, just for reference.

Did you already send us a list of FDA participants in the webinar? If not, can you send it this afternoon/evening?

Thanks and we look forward to the call.

Regards,

Peter

O: + (b) (6)

M: (b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Sent: Monday, July 16, 2018 9:29 PM

To: Tabor, Peter <peter@petfoodinstitute.org>

Subject: RE: DCM Comms Going Live Today

Hi Peter!

Looks great! Looking forward to our meeting Thursday!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>

Date: July 16, 2018 at 2:17:16 PM EDT

To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Not sure if you're still in Denver or on your way home – I hope the AVMA meeting went well. I wanted to get your input on a draft agenda for the Thu webinar, to make the most of everyone's time.

Proposed Agenda

- Welcome, introductions and PFI anti-trust policy reminder – PFI, FDA (10 minutes)
- Overview of the issue, including the FDA notice and the data FDA presented to PFI in June – FDA (30 minutes, including Qs from PFI)
- Review of questions PFI sent to FDA for the webinar – PFI, FDA (50 minutes)
- Open Q&A – PFI, FDA (20 minutes)

- Conclusion and adjourn (10 minutes)

Please take a look and reply to me at your earliest convenience (today if possible) with thoughts or suggested tweaks. Thanks and safe travels home.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 12, 2018 11:11 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Yes, let's touch base. I am in a meeting until 12 and can call you then. Does that work for you?

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 12, 2018 10:45 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: Re: DCM Comms Going Live Today

Thanks for the heads-up, Martine. Very kind of you. My colleagues and I will review the info and I'll be in touch this afternoon.

I was under the impression that our webinar next week would inform FDA's and pet food makers' understanding of the issue, perhaps before any public messaging was issued. So this is a little concerning. I imagine the public reaction might be quite severe and impact products that aren't implicated by FDA. Hopefully we can chat this afternoon.
Thanks again for reaching out.

Sent using OWA for iPhone

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 12, 2018 10:34:41 AM
To: Tabor, Peter
Subject: DCM Comms Going Live Today

Hi Peter,

I just left you a VM. I am attaching the DCM comms materials that will be going live today. Please

feel free to share them with your members and let me know if you have any questions.

Martine

Martine Hartogensis, DVM
FDA Center for Veterinary Medicine
Deputy Director, Office of Surveillance & Compliance
(240) 402-7178

7 Page(s) of Drafts have been Withheld in Full as (b)(5) immediately following this page.



From: Jones, Jennifer L
To: Hartogenesis, Martine; Palmer, Lee Anne; Rotstein, David; Burkholder, William; Norris, Anne; DeLancey, Siobhan
Cc: McDermott, Patrick
Subject: RE: DCM Comms Going Live Today
Date: Friday, July 27, 2018 7:54:00 AM
Attachments: [image002.png](#)
[image004.png](#)
[image006.jpg](#)

Good morning,

Here is the follow-up I had for PFI after yesterday's call about the dog that recovered after veterinary treatment, diet change, and supplementation.

13 year old Female Spayed Labrador Retriever

Diagnosed with DCM by echo at the end of October 2017.

Echo: severe eccentric left ventricular dilation, mild-moderate Mitral Valve regurgitation, mod-sev LA dilation, mild Tricuspid Valve regurgitation, mild Right Ventricular and right atrial dilation, moderate-severe decrease in contractility/heart muscle function

Eating a Grain free diet with the following parameters according to the label: Crude protein (min) 26%, Crude fat (min) 14%, Crude fiber (4.5%), Moisture (max) 10%, *actual* product Taurine level 0.05%

The vet treated with Lasix, benazepril, vetmedin, spironolactone, Taurine (1500 mg BID), L-carnitine (1500 mg TID) and **vet recommended a diet change**

At the end of Feb 2018-recheck echo was improved: mild, improved eccentric Left Ventricular chamber dilation, mild, improved Mitral and very mild tricuspid valve regurgitation, normal/improved Left Atrial chamber dilation, subjectively normal Right Ventricular & Right Atrial dimensions, low normal improved left ventricular contractility/heart muscle function

The new diet had the following parameters according to the label: Crude protein (min) 22%, Crude fat (min) 14%, Crude fiber (max) 5.3%, Moisture (max) 10%, Taurine (min) 0.18%

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Hartogenesis, Martine

Sent: Thursday, July 26, 2018 11:59 AM

To: Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>; Burkholder, William <William.Burkholder@fda.hhs.gov>; Norris, Anne <Anne.Norris@fda.hhs.gov>; DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>

Cc: McDermott, Patrick <Patrick.McDermott@fda.hhs.gov>

Subject: FW: DCM Comms Going Live Today

Just a few points from PFI before our webinar today.

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 26, 2018 11:38 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good morning, Martine. First, thanks for this opportunity to engage with FDA on this issue. As difficult as it can be at times, I think this is positive and consistent with PFI members' commitment to product safety and pet health. The more we can work together and the sooner in the process, the better.

We have a good game of phone tag going so just wanted to send a quick note in case we don't speak before the webinar at 2:00pm.

- Per our conversation, we'll pick up where we left off. I'll start posing the questions we sent o FDA in advance of the 19 July webinar.
- I know we're scheduled for one hour but I imagine there will be a lot of interest, so please advise if you/your colleagues are ok with going longer if necessary – hopefully no more than 10-15 minutes past our allotted time.
- One question I'll pose if others don't, perhaps near the end of the webinar, relates to FDA's messaging going forward on this issue. There's a lot of concern among pet food makers that an entire sector (grain-free) and a few ingredients (peas, lentils, legumes and potatoes) have been indicted when it appears that the issue is really about formulation by certain pet food makers since many grain-free diets and/or diets containing the aforementioned ingredients are not implicated. Also, any FDA messaging usually leads to a spike in calls to pet food makers' call centers, even if they don't make the products FDA may be investigating – the jerky treats investigation is a perfect example.

That's all for now. I am unavailable until around 1:00pm but feel free to call after that if we need to speak before the webinar at 2:00pm.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 7:15 PM
To: Tabor, Peter <peter@petfoodinstitute.org>
Cc: (b) (6) <(b) (6)@petfoodinstitute.org>; Milton, Nanette <Nanette.Milton@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Ok, thanks Peter!

Nanette, can you work with (b) (6) to schedule an hour continuation of the PFI webinar? We got cut

off after the first hour...

Looks like Tuesday around 11 might work.

Thanks in advance!!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 19, 2018 at 4:40:25 PM EDT
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Cc: (b) (6) <(b) (6)@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi, Martine. Sorry this message is coming to you later than expected. If you could let us know whether Tuesday, 24 July in the morning (11:00am ET start time) works for you, I can notify our participants and get it on everyone's calendar.

Thanks again and we'll be in touch.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 11:30 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

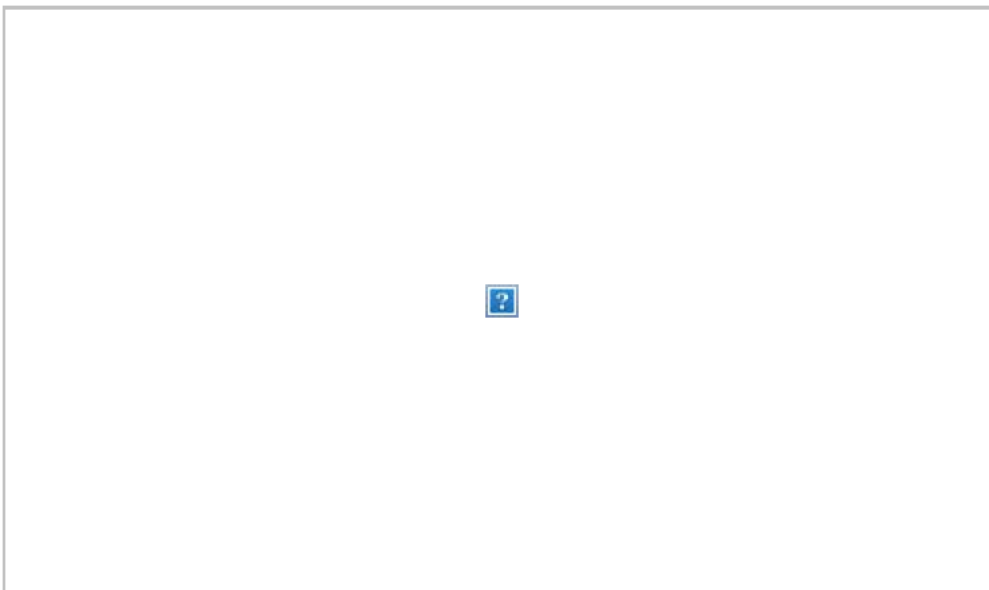
Hi Peter,

No worries and I am available now. (b) (6)

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 19, 2018 11:29 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Sorry about the technical difficulties. GoToMeeting is down around the country, apparently – see below.



Please let me know when you're free to chat. Hopefully we can find time in the next few days to reschedule.

Regards,

Peter

O: + (b) (6)

M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Sent: Thursday, July 19, 2018 9:50 AM

To: Tabor, Peter <peter@petfoodinstitute.org>

Subject: RE: DCM Comms Going Live Today

Welcome, and the epi slides...

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]

Sent: Thursday, July 19, 2018 9:42 AM

To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Subject: RE: DCM Comms Going Live Today

Great – thanks.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 9:40 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Here are the Vet-LIRN slides. I will be sending the epi slides in a bit.

Thanks!!

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 19, 2018 9:11 AM
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good morning, Martine. Will you/your FDA colleagues want to present anything on the screen? I recall during our last webinar with you that we could not give you presenter privileges in GoToMeeting – something to do with your IT/firewall, I think. If you want me to put anything on the screen, please send it to me. I have the redacted version of your presentation from June and the public announcement. Thanks.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 6:57 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: Re: DCM Comms Going Live Today

Ok, sounds good and thank you!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 18, 2018 at 10:40:10 PM EDT
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: Re: DCM Comms Going Live Today

Thanks, Martine. Most participants PFI producer members participants are SMEs, with a few corporate/legal reps in the mix. I really want this webinar to focus on the science behind FDA's notice and got broad agreement from members during our prep for this meeting today.

Sent using OWA for iPhone

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Wednesday, July 18, 2018 7:16:01 PM
To: Tabor, Peter
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Thank you so much for the list. Here are the folks invited from CVM:

Bill Burkholder
Siobhan DeLancey
Dave Rotstein
Pat McDermott
Jennifer Jones
Lauren Carey
Anne Norris
Lee Anne Palmer
David Edwards
Sarah Nemser
Janice Steinschneider
John Baker
Eric Nelson
Neal Bataller

Also, I recognize a few names on your list, but can you tell me (in general) if the PFI participants are mainly SMEs or leadership? We just want to get an idea of our audience.

Thanks very much in advance!

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]

Sent: Wednesday, July 18, 2018 4:58 PM
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Attached is a list of PFI member participants in tomorrow's webinar. Also attached is the proposed agenda and the questions we sent you earlier, just for reference.

Did you already send us a list of FDA participants in the webinar? If not, can you send it this afternoon/evening?

Thanks and we look forward to the call.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Sent: Monday, July 16, 2018 9:29 PM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter!

Looks great! Looking forward to our meeting Thursday!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 16, 2018 at 2:17:16 PM EDT
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Not sure if you're still in Denver or on your way home – I hope the AVMA meeting went well. I wanted to get your input on a draft agenda for the Thu webinar, to make the most of everyone's time.

Proposed Agenda

- Welcome, introductions and PFI anti-trust policy reminder – PFI, FDA (10 minutes)
- Overview of the issue, including the FDA notice and the data FDA presented to PFI in June –

- FDA (30 minutes, including Qs from PFI)
- Review of questions PFI sent to FDA for the webinar – PFI, FDA (50 minutes)
- Open Q&A – PFI, FDA (20 minutes)
- Conclusion and adjourn (10 minutes)

Please take a look and reply to me at your earliest convenience (today if possible) with thoughts or suggested tweaks. Thanks and safe travels home.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Sent: Thursday, July 12, 2018 11:11 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Yes, let's touch base. I am in a meeting until 12 and can call you then. Does that work for you?

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 12, 2018 10:45 AM
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Subject: Re: DCM Comms Going Live Today

Thanks for the heads-up, Martine. Very kind of you. My colleagues and I will review the info and I'll be in touch this afternoon.

I was under the impression that our webinar next week would inform FDA's and pet food makers' understanding of the issue, perhaps before any public messaging was issued. So this is a little concerning. I imagine the public reaction might be quite severe and impact products that aren't implicated by FDA. Hopefully we can chat this afternoon.

Thanks again for reaching out.

Sent using OWA for iPhone

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Sent: Thursday, July 12, 2018 10:34:41 AM
To: Tabor, Peter
Subject: DCM Comms Going Live Today

Hi Peter,

I just left you a VM. I am attaching the DCM comms materials that will be going live today. Please feel free to share them with your members and let me know if you have any questions.

Martine

Martine Hartogenesis, DVM
FDA Center for Veterinary Medicine
Deputy Director, Office of Surveillance & Compliance
(240) 402-7178

From: (b) (6)
To: [Jones, Jennifer L](#)
Subject: RE: FDA case investigation for (b) (6) (800.261)
Date: Thursday, April 19, 2018 11:13:46 AM
Attachments: [image002.png](#)
[image006.png](#)

Hi Dr. Jones,

I will work on getting this record to you.

(b) (6)

From: Jones, Jennifer L [mailto:Jennifer.Jones@fda.hhs.gov]
Sent: Thursday, April 19, 2018 7:41 AM
To: (b) (6)
Subject: FDA case investigation for (b) (6) (800.261)

Good morning (b) (6)

Thank you for submitting your consumer complaint to FDA. I'm sorry to hear about (b) (6) illness. As part of our investigation, we'd like to request:

- **Full Medical Records**
 - Please email (preferred) or fax (301-210-4685) a copy of (b) (6) **entire** medical history (not just this event).

I attached a copy of our Vet-LIRN network procedures. The procedures describe how Vet-LIRN operates and how veterinarians help with our case investigations.

Please respond to this email so that we can initiate our investigation.

Thank you kindly,
Dr. Jones

Jennifer L. A. Jones, DVM

Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
new tel: 240-402-5421
fax: 301-210-4685
e-mail: jennifer.jones@fda.hhs.gov
Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm>



From: CVCA - Cardiac Care for Pets (b) (6)
To: Jones, Jennifer L
Subject: Re: FDA Case investigation for (b) (6) (EON-350158)
Date: Wednesday, March 28, 2018 6:28:29 PM
Attachments: [image002.png](#)
[image001.png](#)
(b) (6) [echo report 1.pdf](#)
[cho 2.pdf](#)
[ecal.pdf](#)
[ix2.pdf](#)
[abs3.pdf](#)
[ix44.pdf](#)
[onsult.pdf](#)
[r.pdf](#)
[aurine.pdf](#)
[3W.pdf](#)
[3W.pdf](#)
[ix.pdf](#)
[abs38.pdf](#)
[cho_data.pdf](#)
[echo_adata.pdf](#)

Attached is entire medical records for (b) (6)..Please let us know if you need anything else-
Thank-

On Wed, Mar 28, 2018 at 6:08 PM, CVCA - Cardiac Care for Pets (b) (6) <(b) (6)@cvcavets.com> wrote:

Dear Dr. Jones,

Thank you for following up on our patient, (b) (6). We will be sending you our complete records for (b) (6) including the primary veterinarian history that we have and the history from her previous emergency room visit. Unfortunately, the diagnosis was made in October and the client has disposed of the diet. We will certainly keep this in mind for future patients with dilated cardiomyopathy which could potentially be diet-related and have those owners keep a sample and record the lot number for future testing/tracking. Thank you again for looking into this issue for our patients.

Sincerely,

(b) (6) - Cardiology

On Wed, Mar 28, 2018 at 2:40 PM, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov> wrote:

Good afternoon (b) (6),

Thank you for submitting your consumer complaint to FDA. I'm sorry to hear about (b) (6) illness.

As part of our investigation, we'd like to request:

- **Full Medical Records**
 - Please email (preferred) or fax ([301-210-4685](tel:301-210-4685)) a copy of (b) (6) entire medical history (not just this event).
 - Do you have records from her referring veterinarian?
- **Potentially Test Remaining OPEN product**
 - Do you have any remaining product left?
 - Is there a lot number or best by date for the leftover food?

Hold any remaining UNOPENED product for potential collection.

I attached a copy of our Vet-LIRN network procedures. The procedures describe how Vet-LIRN operates and how veterinarians help with our case investigations.

Please respond to this email so that we can initiate our investigation.

Thank you kindly,

Dr. Jones

Jennifer L. A. Jones, DVM

Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
new tel: [240-402-5421](tel:240-402-5421)

fax: [301-210-4685](tel:301-210-4685)

e-mail: jennifer.jones@fda.hhs.gov

Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ncm?47334.htm>



CVCA - Cardiac Care for Pets

(b) (6)

Phone: (b) (6)

Fax: (b) (6)

Email: (b) (6)@cvcavets.com

Visit our website at: www.cvcavets.com

"Like" us on Facebook at: www.facebook.com/CVCAVETS

"Follow" us on Instagram at: www.instagram.com/CVCAVETS

We want to hear from you! Access our online survey by clicking [here](#).

If there is anything that we can do to improve our service for you, please do not hesitate to contact us directly. We would greatly appreciate your feedback and invite you to fill out a survey based on your experience with CVCA.

Share your photos with us!

If you have a photo that you would like to share, we would love to post it on our Facebook page. Like us on [Facebook](#) and post to our wall or you can email the image with a fun fact to cvcainfo@cvcavets.com and we will forward it to our Facebook administrator.

Please note -- Images are usually posted within 1 month of submission.

CVCA - Cardiac Care for Pets

(b) (6)

Phone:

(b) (6)

Fax:

(b) (6)

• **Email:** (b) (6)@cvcavets.com

Visit our website at: www.cvcavets.com

"Like" us on Facebook at: www.facebook.com/CVCAVETS

"Follow" us on Instagram at: www.instagram.com/CVCAVETS

We want to hear from you! Access our online survey by clicking [here](#).

If there is anything that we can do to improve our service for you, please do not hesitate to contact us directly. We would greatly appreciate your feedback and invite you to fill out a survey based on your experience with CVCA.

Share your photos with us!

If you have a photo that you would like to share, we would love to post it on our Facebook page. Like us on [Facebook](#) and post to our wall or you can email the image with a fun fact to cvcainfo@cvcavets.com and we will forward it to our Facebook administrator.

Please note -- Images are usually posted within 1 month of submission.

Client: (b) (6)
Patient Name: (b) (6)
Species: Canine
Breed: Labrador Retriever

Gender: Female/Spayed
Weight: 67.60 lbs
Age: 11 Years
Doctor: (b) (6) DVM

(b) (6)

Test	Results	Reference Interval	LOW	NORMAL	HIGH
Catalyst Dx (November 14, 2017 4:20 PM)					
					11/27/2017 10:05 AM
GLU	51 mg/dL	70 - 143	LOW		93 mg/dL
CREA	1.5 mg/dL	0.5 - 1.8			1.1 mg/dL
BUN	26 mg/dL	7 - 27			21 mg/dL
BUN/CREA	17				19
PHOS	4.3 mg/dL	2.5 - 6.8			4.1 mg/dL
CA	10.8 mg/dL	7.9 - 12.0			10.5 mg/dL
TP	8.0 g/dL	5.2 - 8.2			7.2 g/dL
ALB	3.3 g/dL	2.2 - 3.9			3.4 g/dL
GLOB	4.7 g/dL	2.5 - 4.5	HIGH		3.8 g/dL
ALB/GLOB	0.7				0.9
ALT	81 U/L	10 - 125			61 U/L
ALKP	521 U/L	23 - 212	HIGH		440 U/L
GGT	31 U/L	0 - 11	HIGH		30 U/L
TBIL	< 0.1 mg/dL	0.0 - 0.9			0.1 mg/dL
CHOL	301 mg/dL	110 - 320			210 mg/dL
AMYL	708 U/L	500 - 1500			726 U/L
LIPA	640 U/L	200 - 1800			856 U/L
Na	149 mmol/L	144 - 160			153 mmol/L
K	4.7 mmol/L	3.5 - 5.8			5.3 mmol/L
Na/K	32				29
Cl	109 mmol/L	109 - 122			117 mmol/L
Osm Calc	298 mmol/kg				307 mmol/kg

(b) (6)

Patient Demographics

(b) (6)		Study Date: 11/01/2017	
Patient ID: (b) (6)	Accession #:	Alt ID:	
DOB:	Age:	Gender:	Ht: Wt: 67lb 4oz BSA:
Institution: CVCA (b) (6)			
Referring Physician:			
Physician of Record:		Performed By:	
Comments:			

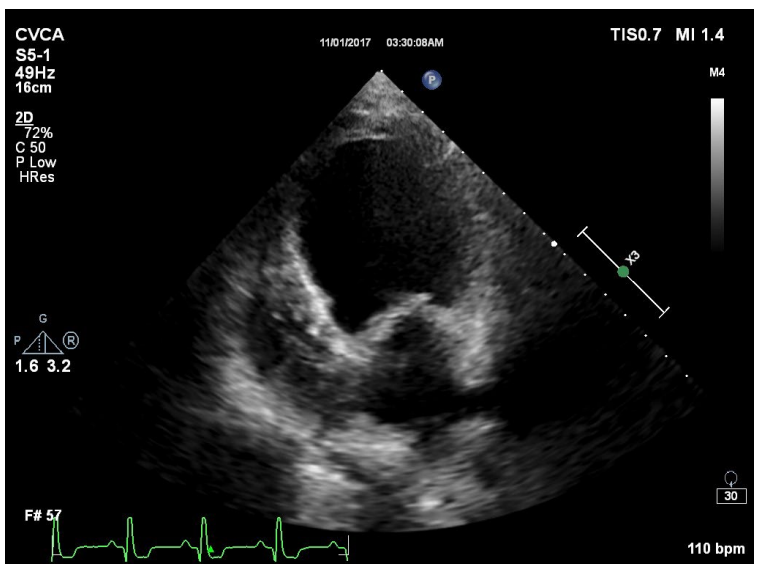
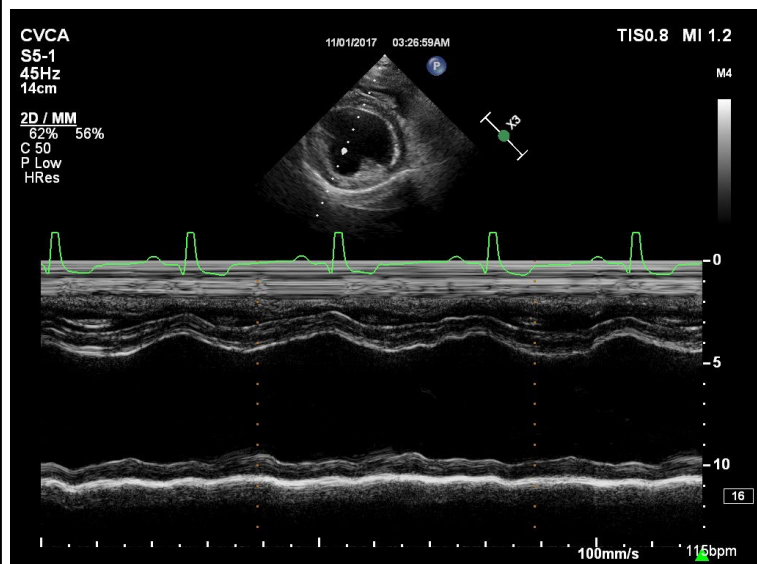
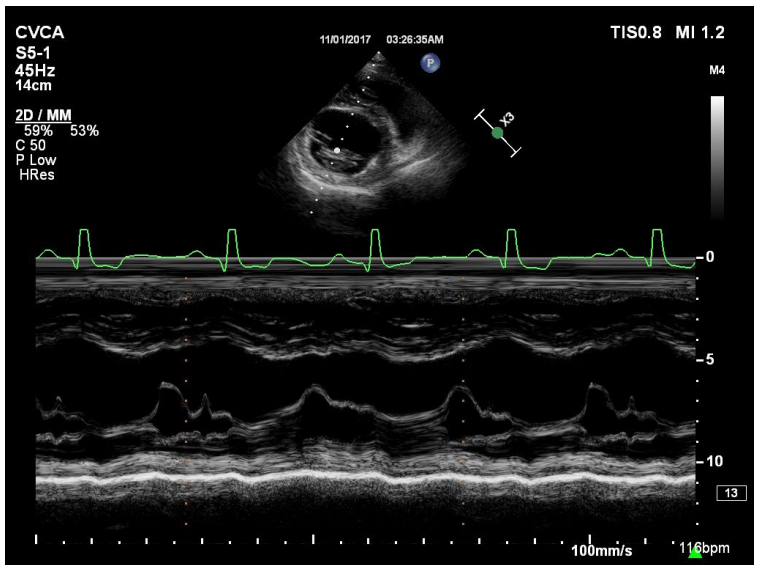
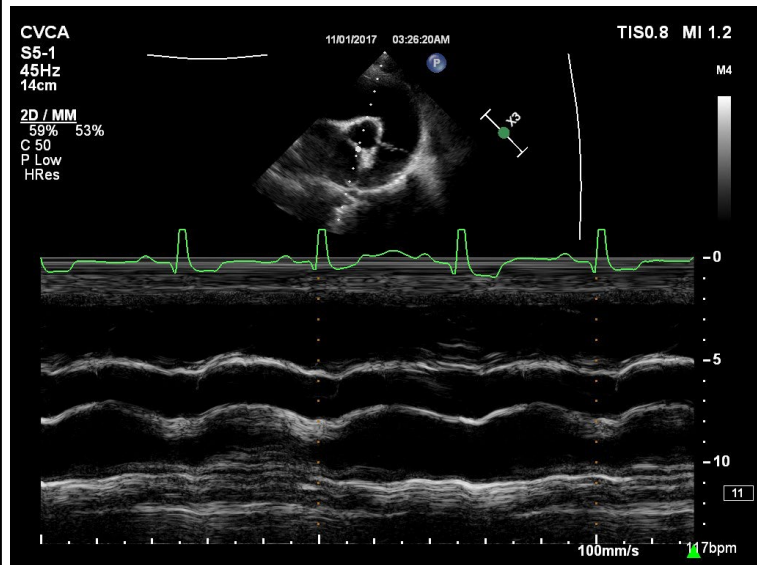
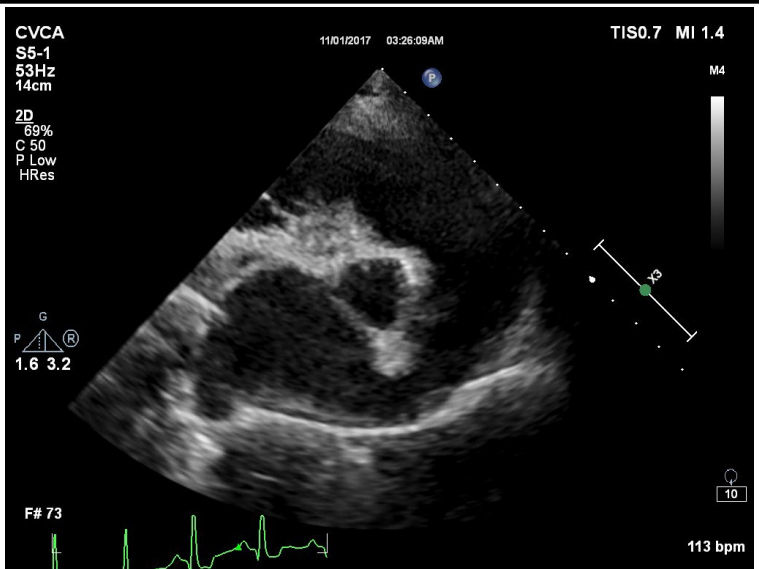
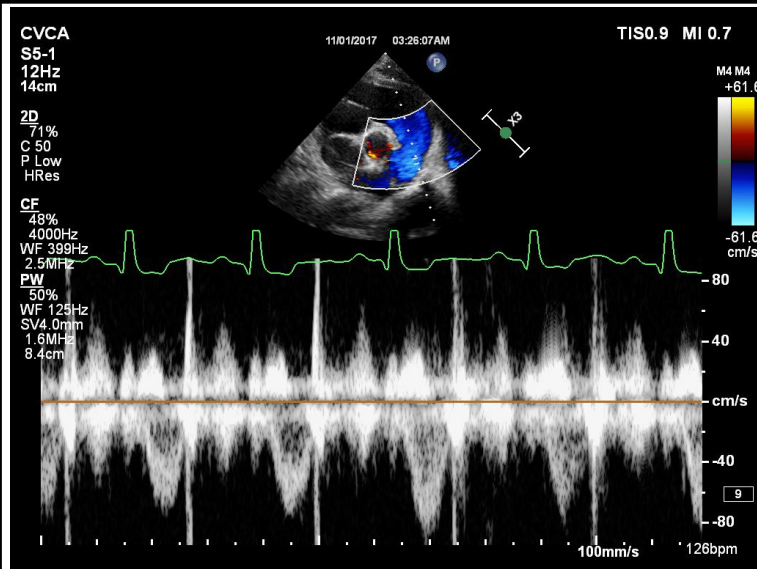
Adult Echo: Measurements and Calculations

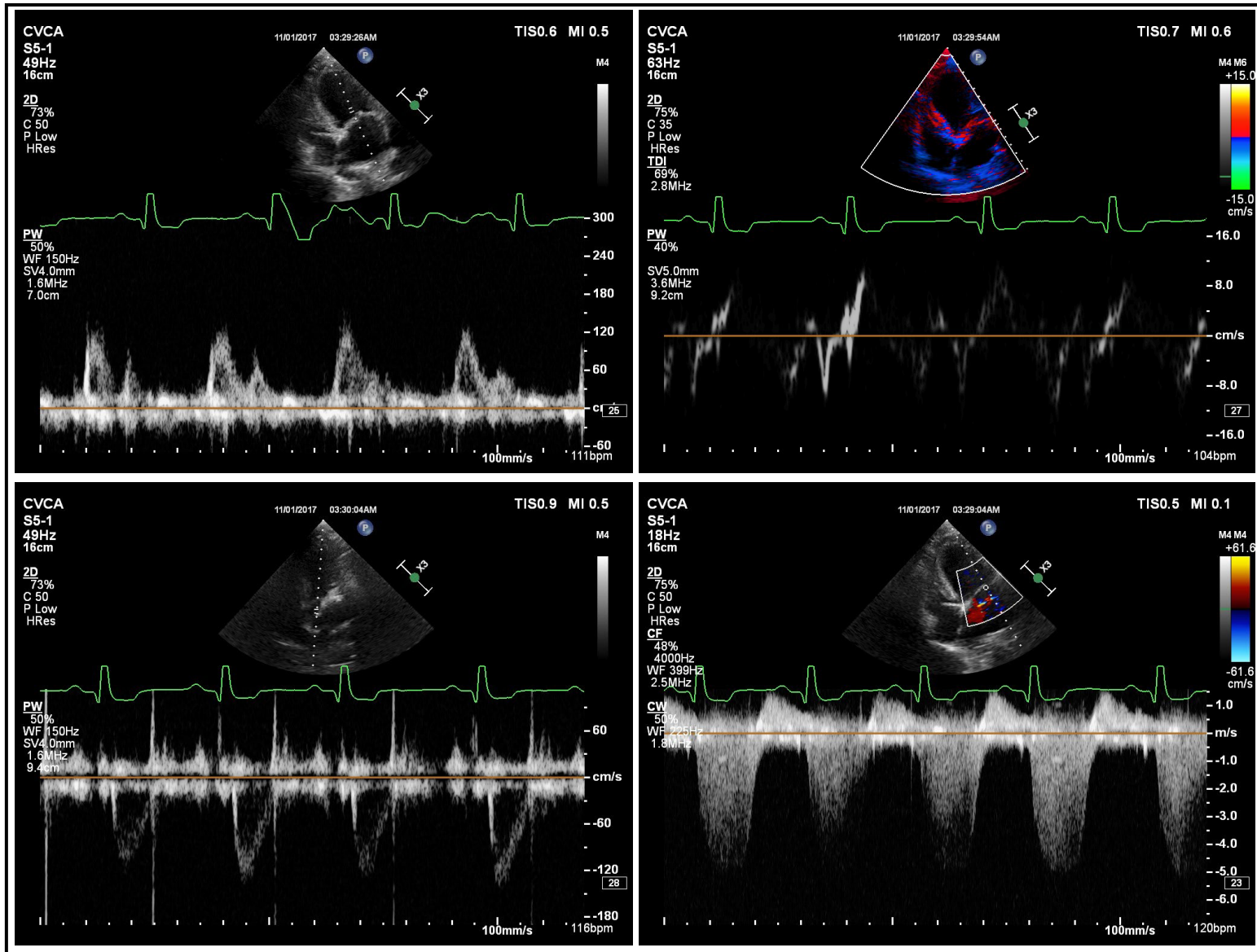
2D

LVIDd (2D)	6.23 cm	LVAd (A4C)	34.40 cm ²	IVSd (2D)	0.932 cm
LVPWd (2D)	0.791 cm	LVA _s (A4C)	25.70 cm ²	RVIDd/LVIDd	0.139
EDV (2D-Teich)	196 ml	EDV (A4C)	141 ml	RVIDd (2D)	0.866 cm
EDV (2D-Cubed)	242 ml	ESV (A4C)	88.8 ml	LA Area	24.1 cm ²
A4Cd		LV Mass (Cubed)	239 g	LA Dimen (2D)	4.2 cm
LV Vol	141 ml				
LV Length	6.89 cm				
LV Area	34.4 cm ²				
A4Cs		IVS/LVPW (2D)	1.18	LA/Ao (2D)	1.75
LV Vol	88.8 ml				
LV Length	6.13 cm				
LV Area	25.7 cm ²				
LVLd (A4C)	6.9 cm	SV (A4C)	52.2 ml	AoR Diam (2D)	2.4 cm
LVLs (A4C)	6.1 cm	EF (A4C)	37.0 %		

MMode

IVSd (MM)	0.966 cm	SV (MM-Teich)	78.0 ml	LVPW % (MM)	21.1 %
LVIDd (MM)	6.30 cm	FS (MM-Teich)	19.4 %	RVIDd (MM)	0.322 cm
LVPWd (MM)	0.859 cm	EF (MM-Teich)	38.8 %	LA Dimen (MM)	3.7 cm
IVSs (MM)	1.11 cm	EDV (MM-Cubed)	250 ml	AoR Diam (MM)	2.3 cm
LVIDs (MM)	5.08 cm	ESV (MM-Cubed)	131 ml	LA/Ao (MM)	1.61
LVPWs (MM)	1.04 cm	SV (MM-Cubed)	119 ml	MV D-E Exc Dist	1.4 cm
IVS/LVPW (MM)	1.12	EF (MM-Cubed)	47.6 %	MV D-E Slope	43.6 cm/s





Signature

Signature:

Name(Print):

Date:

Patient Chart for (b) (6)
Date: 03-14-18, Time: 5:05p

Client: (b) (6)
Page: 2

11-25-13	64.00
09-16-13	69.00
07-10-13	59.30
07-25-12	68.30
01-09-12	71.00

MEDICAL HISTORY

Date	By	Code	Description	Qty (Variance)	Photo
------	----	------	-------------	----------------	-------

03-13-18	(b) (6)	(b) (6)	(b) (6) Requisition #33171286-9910		
		865	Senior Screen		
			Attachments\8546'	(b) (6)	3.14.18 Lab.pdf
		C153	Office Visit - Recheck		
		P163	Blood Pressure		
			CHECK-IN Patient check-in		
			SMT: 11-14-17 at 10:51a: recheck blood chemistry profile w/ electrolytes O wants AB		
			CMO: 02-12-18 at 4:59p: called o to r/s - ok with (b) (6)		
			AB2: 02-27-18 at 11:15a: exam, BP, sr screen per last CVCA report		
			SMT: 03-12-18 at 2:09p: LMOM		

Age: 12y Weight: 71.50 Temp: 99.90 Respiration: 56.00 Pulse: 124.00
CRT: pink 1-2 secs.

SUBJECTIVE SECTION

exam, BP, sr screen per last CVCA report

resting resp around 16 per mom, doing well at home, eating/drinking normal, bathroom normal, minimal coughing only when excited, since o switched to cardiac food BMs are very dense and sometimes has trouble passing stool, no vomiting, no other concerns, per o is weaning p off lasix

OBJECTIVE SECTION

ABNORMALITIES

Oral Cavity
mm pink

Cardiovascular
III/VI murmur as previously described

Respiratory
Respiratory rate normal; lungs eupneic

Lymphatic
All palpable LN's WNL

Other
euhydrated, BAR

PLAN SECTION

NOTES

BP 130-140 (LHL, size 5 cuff)

Patient Chart for (b) (6)
Date: 03-14-18, Time: 5:05p

Client: (b) (6)
Page: 3

Date	By	Code	Description	Qty (Variance)	Photo
------	----	------	-------------	----------------	-------

			Senior screen to (b) (6) UA free catch		
--	--	--	--	--	--

			Disc firm stools and mild tenesmus- adv can trial metamucil but rec confirm with cardiologist ok to add in.		
--	--	--	---	--	--

(b) (6)

(b) (6)

CVCA CONSULTATION REQUEST FORM

Date: Tuesday, (b) (6)

Client Id #: (b) (6) Client Name: (b) (6)

Address: (b) (6) City: (b) (6) State: (b) (6) Zip: (b) (6)

Telephone:

Cellular:	:	(b) (6)
Cellular:	:	(b) (6)

Animal Name: (b) (6) Species: Canine Breed: Labrador Retriever

Color: Yellow Sex: spayed female Weight: 0Kg.

Date of Birth: (b) (6) Age: 13 Yrs. 0 Mos.

Referring Veterinary Hospital: No Vet
Doctor's Name: No Vet
Referring Veterinary Hospital Phone #: (b) (6) 000-0000

(b) (6) Doctor Requesting Consult: (b) (6) DVM

Relevant History / Physical Findings:
Cough started last Wednesday. Radiographs and blood work were performed. Radiographs revealed suspected cardiomegaly. Blood work showed mild ALP and GGT elevations. The owner made cardio-consultation on Friday however her cough got worse with pink tinged foam so (b) (6) was brought to (b) (6) for a cardiology consultation. (b) (6) has been a healthy dog with no current medications. She is up to date on vaccination and heartworm preventative.

Current Medications:
Hydroxyzine, Doxycycline, and hydrocodone, which was stopped because her coughing got worse with those medications.

Radiographs performed at:

- ☒ RDVM
- ☐ (b) (6)

Consulting Cardiologist:

10/31/2017 CVCA Consult 2013
(b) (6) DVM, (b) (6)

Patient Demographics

(b) (6)				Study Date: 02/26/2018	
Patient ID:	(b) (6)	Accession #:		Alt ID:	
DOB:		Age:		Gender:	
		Ht:		Wt:	73lb 0oz
Institution:	(b) (6)			BSA:	
Referring Physician:					
Physician of Record:					
Comments:	Performed By: (b) (6)				

Adult Echo: Measurements and Calculations

2D

LVIDd (2D)	5.01 cm	LVAd (A4C)	21.30 cm²	IVSd (2D)	1.24 cm
LVPWd (2D)	1.20 cm	LVAAs (A4C)	13.90 cm²	RVIDd/LVIDd	0.139
EDV (2D-Teich)	119 ml	EDV (A4C)	61.9 ml	RVIDd (2D)	0.695 cm
EDV (2D-Cubed)	126 ml	ESV (A4C)	33.3 ml	LA Area	15.8 cm²
A4Cd		LV Mass (Cubed)	186 g	LA Dimen (2D)	2.9 cm
LV Vol	61.9 ml				
LV Length	5.90 cm				
LV Area	21.3 cm²				
A4Cs		IVS/LVPW (2D)	1.03	LA/Ao (2D)	1.21
LV Vol	33.3 ml				
LV Length	4.79 cm				
LV Area	13.9 cm²				
LVLd (A4C)	5.9 cm	SV (A4C)	28.6 ml	AoR Diam (2D)	2.4 cm
LVLs (A4C)	4.8 cm	EF (A4C)	46.2 %	HR - AV	82 bpm

MMode

IVSd (MM)	1.09 cm	SV (MM-Teich)	52.1 ml	LVPW % (MM)	40.9 %
LVIDd (MM)	4.96 cm	FS (MM-Teich)	22.4 %	RVIDd (MM)	0.806 cm
LVPWd (MM)	0.965 cm	EF (MM-Teich)	44.9 %	LA Dimen (MM)	3.1 cm
IVSs (MM)	1.58 cm	EDV (MM-Cubed)	122 ml	AoR Diam (MM)	2.4 cm
LVIDs (MM)	3.85 cm	ESV (MM-Cubed)	57.1 ml	LA/Ao (MM)	1.29
LVPWs (MM)	1.36 cm	SV (MM-Cubed)	64.9 ml	MV D-E Slope	25.7 cm/s
IVS/LVPW (MM)	1.13	EF (MM-Cubed)	53.2 %	MV E-F Slope	13.6 cm/s

EDV (MM-Teich)	116 ml	FS (MM-Cubed)	22.4 %	MV EPSS	0.3 cm
ESV (MM-Teich)	63.9 ml	IVS % (MM)	45.0 %		

Doppler

LVOT Vmax		MV E/A	1.6	E`/A` Medial	1.3
Max PG	18 mmHg				
Vmax	211 cm/s				
RVOT Vmax		Med E` Vel	5.71 cm/s	TR Vmax	
Max PG	3 mmHg			Max PG	6 mmHg
Vmax	91.2 cm/s			Vmax	125 cm/s
MV Peak E Vel		E/Med E`	8.5		
Vel	0.488 m/s				
PG	1 mmHg				
MV Peak A Vel		Med A` Vel	4.54 cm/s		
Vel	30.8 cm/s				
PG	0 mmHg				

Other Measurements

Dimensions: Diameters

LVID/Ao (2D)	2.09
EDVI	57.4 ml/m²
ESVI	30.9 ml/m²

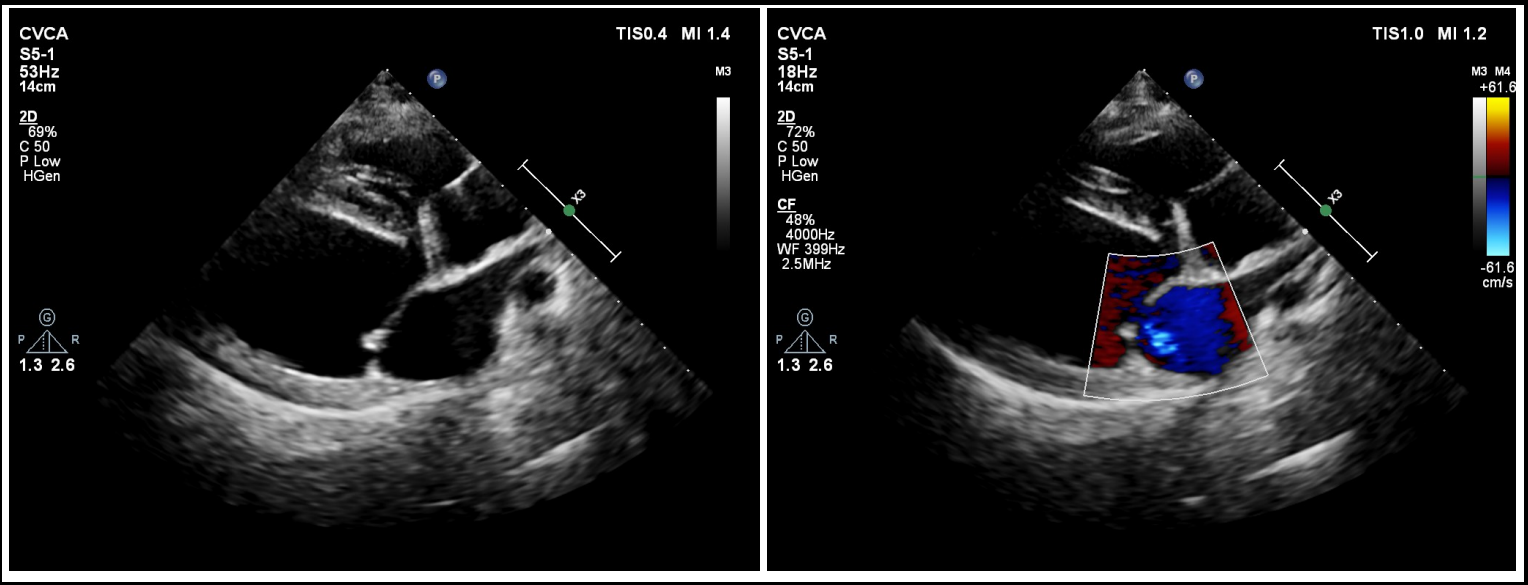
EF & Volume: Simpson's

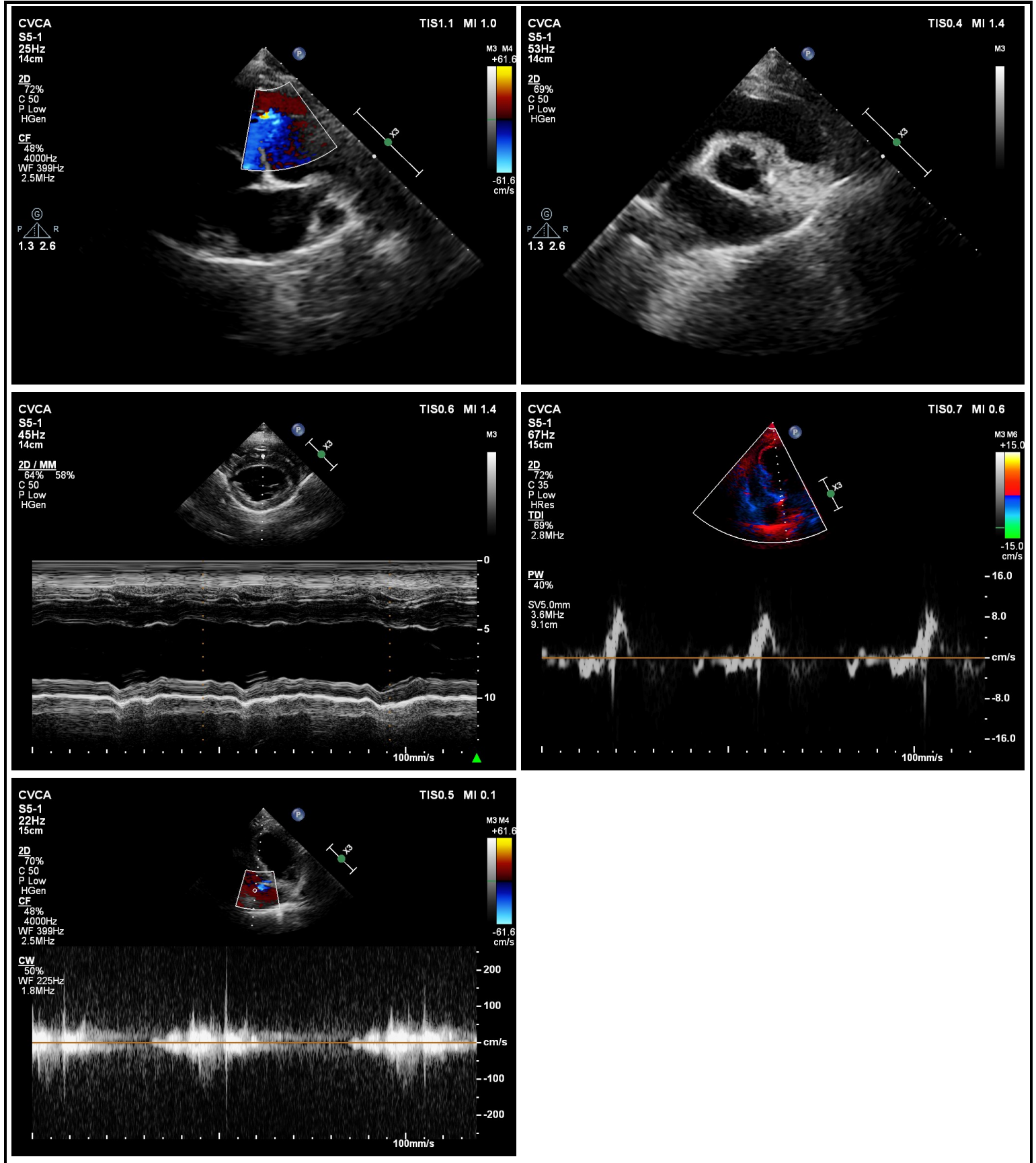
Sphericity Id	1.2
---------------	-----

Dimensions: Diameters

LVEDDN	1.77
LVID/Ao (2D)	2.09

Images





Signature

Signature:
 Name(Print):

Date:

CVCA, Cardiac Care for Pets

(b) (6)

Phone: (b) (6) Fax (b) (6)
Email: (b) (6) @cvcavets.com
www.cvcavets.com



Client: (b) (6)
Co-owner:
Patient name: (b) (6)
Species: Canine
Breed: Labrador Retriever
Sex: FS
Age: 13 years and 5 months old
Weight: 33.18kg. / 73.15 lbs

Primary Care Veterinarian: (b) (6)
Primary Care Hospital: (b) (6)
Phone: (b) (6) ext: (b) (6)
Fax: (b) (6) Email:

Cardiac Evaluation Report

Exam Date: (b) (6)

Diagnosis

- Advanced dilated cardiomyopathy - rule out idiopathic vs. taurine-responsive
- Mild to moderate mitral valve regurgitation as cause of heart murmur
- Trace tricuspid valve regurgitation
- Moderate to severe left atrial chamber dilation
- Severe eccentric left ventricular chamber dilation
- Moderate to severe decrease in contractility/heart muscle function
- Mild left ventricular wall thinning
- Mild right atrial and right ventricular chamber dilation
- Progressive cough - rule out: early left sided congestive heart failure vs. mainstem bronchial compression

Medications

- Begin Lasix/Furosemide 40 mg tablets - Give 1 tablet twice daily.
 - > For mild increases in respiratory rate/effort, you may give an additional dose of Lasix.
 - > If you are consistently giving an additional dose of Lasix, please contact our office so we may help adjust medications long-term.
 - > We may increase this dose in the future based on at home monitoring of breathing and recheck blood work.
- Begin Benazapril 10 mg tablets - Give 1 tablet twice daily for 4 days then increase to 1 and 1/2 tablet twice daily thereafter
- Begin Vetmedin/Pimobendan 5mg tablets - Give 1 and 1/2 tablets twice daily. Will switch to 7.5 mg EZ tablets at 1 tablet twice daily. The 7.5mg tablet will be compounded through (b) (6) pharmacy, please call them to set up shipping and billing (b) (6)
- Please call if you notice a decrease in appetite, vomiting, lethargy, weakness or any other signs of illness while beginning/adjusting the medications.
- Continue with monthly heartworm and flea/tick control as prescribed by (b) (6).

In 2 weeks, if (b) (6) is eating and feeling well:

- Begin Spironolactone 25 mg tablets - Give 1 tablet once daily for 4 days then increase to 1 tablet twice daily thereafter

- Begin Taurine 1500 mg twice daily.
- Begin L-carnitine 1500 mg three times daily.
- You may purchase the taurine and L-carnitine at any health food or nutrition store or www.puritanspride.com. You may also obtain the L-carnitine in bulk powder form from North Carolina State University by calling (b) (6).

Please allow 24-48 hours for CVCA to process prescription refill requests.

Refill all medications indefinitely unless directed by CVCA or your primary care veterinarian.

- **Please check all medications and dosages on your discharge report against the pharmacy labels.**

Please Note

- Please see our website www.cvcavets.com for more information about (b) (6) dilated cardiomyopathy.

Nutrition Recommendations:

- (b) (6) is on a specialized diet which could be contributing to taurine deficiency. Please change her to a new diet, as her housemate is on a novel protein diet - consider prescription diets such as Royal Canin or Science Diet. Please discuss diet options with (b) (6).
 - In patients with early/mild heart failure, CVCA recommends feeding a diet with less than 80 mg of sodium per 100 kCal of food (50-80 mg/100 kCal). In patients with refractory heart failure signs, further sodium restriction may be beneficial.
 - For more information about sodium content of various foods, please visit:
 - Dog: http://vet.tufts.edu/wp-content/uploads/reduced_sodium_diet_for_dogs.pdf
 - Treats: http://vet.tufts.edu/wp-content/uploads/treats_for_dogs_with_heart_disease.pdf
 - CVCA recommends avoiding kidney diets unless (b) (6) has kidney disease that warrants protein restriction.
 - Diet changes should be done gradually (ie. over ~1 month) to avoid GI upset and avoided until (b) (6) is stable and eating well on the cardiac medications, usually about 2 weeks after starting or adjusting therapy.
 - If you are interested in a consultation with a veterinary nutritionist, please visit <http://vetnutrition.tufts.edu/make-an-appointment/>
 - CVCA recommends fish oil supplements (omega-3 fatty acids) in many dogs with cardiac disease. Her dose should be approximately EPA 1220 mg and DHA 760 mg total per day. Please start at 1/2 the dose for one week, then increase to the full dose if tolerating well thereafter. Please avoid Cod liver oil and flax seed as well as products with Vit A and/or D.
- For more information about fish oils, please visit --<http://vet.tufts.edu/heartsmart/diet/important-nutrients-for-pets-with-heart-disease/>
- In addition to the supplements approved by Tuft's Veterinary Nutrition Service, other reputable brands include Welactin and Nordic Naturals. (b) (6) may have additional brand recommendations.

Activity Recommendations

- Keep (b) (6) very quiet for the next 3-4 days with only brief leash walks to eliminate.
- Once her coughing has resolved, (b) (6) may gradually resume activity as she wants and is able to do. Please allow (b) (6) to take more breaks and rest during activity.
- Please try avoid burst type activity, as this increases the arrhythmia risk and avoid exercise in the hot/humid weather.
- Please try to warm (b) (6) up for 5-10 minutes with walking prior to moderate activity and take more rests during more vigorous activity.

At Home Monitoring:

- Monitor for signs of cough, respiratory difficulty, exercise intolerance, abdominal swelling, weakness, lethargy, etc. If you note any of these symptoms, please notify CVCA or (b) (6) as these symptoms may indicate recurrent congestive heart failure. If you note an increase in cough, respiratory rate or effort, please feel free to give an additional dose of Lasix/Furosemide, while contacting CVCA.
- In order to monitor for the development of early congestive heart failure in the out-patient setting, we recommend monitoring your pet's resting respiratory rate several times a week. Normal resting respiratory rates should be less than 30 breaths per minute. Consider using a respiratory rate monitoring application to track (b) (6) respiratory rate - Cardalis or BI Pharma have reliable phone applications. Please contact us if you note a persistent or progressive increase.
- In addition, (b) (6) is sadly at increased risk for sudden cardiac death due to her cardiac disease. Dobermans are particularly at risk for development of severe, sudden malignant arrhythmias that sadly may result in sudden death. However, we hope to minimize these risks with our treatment plan.

Future Anesthesia/Fluid Recommendations

- Avoid intravenous or subcutaneous fluid therapy in the future, if possible. If fluid therapy is indicated, please contact CVCA.
- (b) (6) should not receive corticosteroids (prednisone) in the future please contact CVCA for recommendations, if corticosteroids are indicated.
- Avoid elective anesthesia, as (b) (6) is at high risk for complications due to the degree of cardiac disease. If anesthesia is necessary in the future, please contact CVCA for recommendations for monitoring and anesthetics.

Reevaluation

- Please recheck with (b) (6) in the next day or two to obtain taurine levels. Please forward these results when available.
- Please recheck with (b) (6) in 2 weeks for a follow up examination and blood chemistry profile with electrolytes and as recommended by (b) (6). Please forward these results when available.
- Please recheck with (b) (6) every 4-6 months for a follow up examination and blood chemistry profile with electrolytes and as recommended by (b) (6). Please forward these results when available.
- Please recheck with CVCA in 5 months for a follow up consultation/examination, blood pressure, and echocardiogram. Please contact us or schedule an earlier appointment if (b) (6) has any problems or symptoms indicative of worsening heart disease or if recommended by (b) (6).

Visit Summary

Heart Rate: 132 bpm

BP: 100mmHg (based on MR gradient)

History:

(b) (6) developed a cough last Wednesday (10/25/17). Radiographs and blood work were performed by (b) (6). The lab work (which is unavailable for review) reportedly showed an elevated ALP 440 and GGT 30 and mild lymphopenia. Thoracic radiographs were performed which revealed cardiomegaly. (b) (6) was treated with hydroxyzine 50mg BID, doxycycline 200mg AM and 100mg PM, and hydrocodone 5mg q8-12h. All medications were stopped on Monday as her cough had worsened and she was presented to the (b) (6) for a cardiac evaluation as her coughing had worsened and she had brought up a small volume of pink-tinged foam after a coughing fit. During this time there has been no evidence of lethargy and she continues to eat and drink normally at home.

PPHx: None

Meds: None

Other: UTD on vaccinations, On HW preventative

Diet: Zignature (Kangaroo)

Physical Exam Findings:

BAR, sweet but nervous

OP/EENT: Pink, moist mucous membranes, CRT <2s, mild periodontal disease, LS OU, clear AU, No nasal or ocular discharge, no cough on tracheal palpation

PLN: WNL

H/L: Grade 2/6 left apical protosystolic heart murmur, regular rhythm, strong synchronous femoral pulses, RR: 36 breaths/min, questionable mild increase in bronchovesicular sounds bilaterally, no crackles or wheezes ausculted, eupneic

Abd: Soft non-painful abdominal palpation, no palpable masses or fluid wave

MS/Neuro: BCS 5/9, Amb x 4, Mentally alert and appropriate

Integ: Normal turgor, subcutaneous mass left ventrum

Other Diagnostics:

10/27/17 pDVM CXR: Generalized cardiomegaly characterized by widening of the cardiac silhouette and loss of the caudal cardiac waist consistent with left atrial enlargement. Slight left auricular bulge. Increased sternal contact and rounding of the right heart on the VD radiograph. Dorsal deviation of the trachea. Prominent pulmonary vasculature with a questionable mild increase in interstitial opacity in the caudodorsal lung fields which may suggest early congestive heart failure/pulmonary edema.

Echocardiographic Findings

Severe left ventricular eccentric hypertrophy with apical rounding and increased sphericity, mild-moderate centrally

FDA-CVM-FOIA-2019-1704-000853

located mitral regurgitant jet, moderate-severe secondary left atrial dilation on 2D imaging and moderately-severely increased LA:Ao ratio on M-mode imaging, mild eccentric low velocity tricuspid regurgitation with mildly elevated estimated right ventricular pressures consistent with mild pulmonary hypertension, mild right ventricular and right atrial dilation, normal left and right ventricular outflow velocities, moderately to severely depressed indices of systolic function (FS% and EF% by modified Simpson's - LVDI 144ml/m², LVSI 90ml/m²), increased EPSS, elevated transmitral inflow velocities and E:A wave ratio on spectral Doppler tracings, normal TDI E':A' ratio of the lateral mitral annulus, no masses, effusions or heartworms observed.
ECG during echocardiogram: Normal sinus rhythm. No ventricular ectopy noted.

Comments

Dear (b) (6),

Thank you for sending (b) (6) to see us with (b) (6) today. Sadly, (b) (6) has dilated cardiomyopathy with moderate to severe systolic dysfunction and moderate to severe left atrial dilation. This places her at a high risk of developing congestive heart failure and with the progression in her cough I am concerned that we may be dealing with congestive heart failure at this time. We have begun therapy to control congestive heart failure, support cardiac function, slow down the progression of the heart disease and improve survival. We are now seeing more dogs on specialized diets that are developing taurine deficiency and we have discussed submission of taurine levels to evaluate whether this may be a contributing factor to (b) (6) condition. (b) (7)(A) is interested in pursuing this test at your clinic, taurine levels should be drawn and placed in a heparinized tube (green top) and should be frozen and submitted to (b) (6) (who sends it to UC Davis). It will be interesting to see if this is a contributing factor to (b) (6) condition.

We will continue to closely monitor (b) (6) heart disease via serial echocardiography and institute further therapy when progression is noted. While on this course of medication, it is important to monitor the chemistry profiles and blood pressures. Dogs with dilated cardiomyopathy are at a higher risk of developing ventricular arrhythmias. None were noted today; however, it will be important to monitor for arrhythmias periodically in the future. Unfortunately, the prognosis is guarded after the onset of congestive heart failure, and we discussed with the (b) (6) family that the average survival is ~ 6-12 months.^{1,2} Survival time is highly individually variable depending on response to therapy.

We appreciate your continued referrals and the trust you place in CVCA to co-manage your cardiac patients. We look forward to working with you on this case and others. In an effort to continue to improve CVCA's service to both you and your clients, please visit our website at www.cvcavets.com and complete our online referring veterinarian survey.

Sincerely,

(b) (6) - Cardiology

(b) (6)

Case Summary:

(b) (6) a 13 Yrs. 0 Mos. old, spayed female, Labrador Retriever presented on Tuesday, (b) (6) to the (b) (6) for a coughing.

History: (b) (6) started coughing last Wednesday. She was brought to a primary veterinarian. Radiographs and blood work were performed. Radiographs revealed suspected cardiomegaly. Blood work showed mild ALP and GGT elevations. Prescribed hydroxyzine, doxycycline, and hydrocodone, which was stopped on Monday because her coughing got worse with those medications. The owner made an appointment with a CVCA on Friday(11-1-2017). However her cough got worse with pink tinged foam so (b) (6) was brought to (b) (6) for a cardiology consultation. (b) (6) has been a healthy dog with no current medications. She is up to date on vaccination and heartworm preventative.

CBC (10-27-2017) WNL
Chem (10-27-2017) ALP 440, GGT 30, other values were WNL
OVA & Parasites (7-17-2017) Negative

Physical Exam:

(b) (6)
1:47 PM
Vital Sign 656
Weight 30.5 kilograms
Temp 100.5
HR 100
Resp 42
Muc_Me Pink/Healthy
mb
CRT <2 sec
Mentation QAR
Pain 0 - No visible Pain
Scale

BCS: 5/9

EENT: MM- pink, mild calculus and gingivitis, CRT <2 sec. Oral exam- no significant findings (NSF), Lenticular sclerosis on OU, throat -NSF.

Hydration appears: within normal limits (WNL)

Peripheral lymph nodes: Palpate WNL

Airway: RR= 30 BPM, no upper respiratory noise, airway not compromised.

Respiration: RR= 24 RPM, Eupneic with no crackles or wheezes. Bilateral breath sounds ausculted, normal bronchovesicular sounds.

Cardiovascular: HR = 100 BPM, Heart auscults with NSF. No murmurs noted. Femoral pulses are adequate and synchronous.

Abdomen: Mildly tensed cranial abdomen on palpation, no organomegaly was noticed,

Neurologic: Alert and responsive. Ambulatory with no CP deficits noted. Full neurologic examination was not performed.

Integument: Hair coat has NSF. A 3cm x 3 cm soft subcutaneous mass was palpated on left caudal abdomen.
Musculoskeletal: Musculature is WNL.No obvious lameness or gait disturbance.
Urogenital: WNL.
Rectal: Normal stool was palpated on rectal examination.

Initial Diagnostics:
Echocardiogram

Differential Diagnosis:
Coughs -R/O heart vs lung

Client Communication:

Plan:

Please call if you have any questions or concerns.

Thank you,

(b) (6) DVM

(b) (6) DVM
10/31/2017 Initial (b) (6)
(b) (6) DVM, (b) (6)

(b) (6)

(b) (6)

Owner: (b) (6)
Patient: (b) (6)
Species: CANINE
Breed: LABRADOR RETRIE
Age: 11Y
Gender: FS

(b) (6)

Account: 21467

Requisition #: (b) (6)
Accession #: (b) (6)
Order recvd: 07/11/2017
Ordered by: (b) (6)
Reported: 07/11/2017




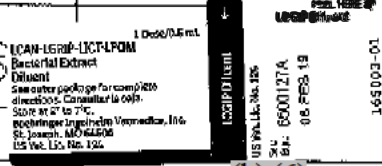
OVA AND PARASITES 3 OR MORE	
OVA & PARASITES	
NO OVA OR PARASITES SEEN	
In cases of acute or chronic diarrhea in addition to a fecal floatation and antigen testing for ova and parasites consider testing for viral, bacterial and protozoal infectious agents using RealPCR (canine diarrhea panel: test code 2625; feline diarrhea panel: test code 2627).	

(b) (6)
07/11/2017

FINAL REPORT

PAGE 1 OF 1

(b) (6)

(b) (6)	Name: (b) (6)	Species: Canine	Breed: Lab/Ret	Color: B/K	DOB: (b) (6)	SEX: F(S)
Date: 10/23/17	42.0 lbs. Imrab 3TF 3yr dog # 3021	(b) (6)				
	<u>Naramune II</u>					
	Dog well per O PE - B/RH, mm pink, H/L WWL, abd palpates NSF, BCS 5/9. Looks good!					
	Re HA + NA monthly Hw/ave 3/2018, DHC due next month Has been receiving HA, but not consistently per O - disc'd importance of giving monthly! Disp HA @ green 12m NA 34-600* (cont)	(b) (6)				
11/16/17	42.0 lbs. Duramune DIAZP/L Ultra	(b) (6)				
P: 160 R: part mm: P/I	Dog well per O PE - B/RH, mm pink. V. mild underbite, teeth clean H/L WWL, abd palpates NSF, BCS 5/9. Hw/ave 3/18					
	(b) (6)					
	# 324887	(b) (6)				

FDA CVM FOIA 2019-1704-000858

(b) (6)

(b) (6)	Name:	Species:	Breed:	Color:	DOB:	SEX:
	(b) (6)	Canine	Lab Ret.	Yellow	(b) (6)	F(s)
Date: 7/10/17	72 lbs Imrab 3TF, 3V, Tap #1520 (b) (6)					
	SATAP HW (Thyme) (John) (Kra)					
	Fecal to (b) (6) (W) NPS					
	DW @ home, occasionally coughs. Several SQ masses - no changes noted per S.					
	PE: BAR. H/L NSF - no audible murmur, no cough elicited on tracheal palp. Abd NSF on palp. Min tartar. Several SQ masses - palpate upomatoid P. Due 10/12/17 Lyme & HL vacu (b) (6)					
	#30558/ 226 ⁵⁰ 226 ⁵⁰ (b) (6)					
7/12/17	Disp: Advantix II Navy (>55 lbs (#1) + 2 free doses					
	Heartgard @ Brown Lpk (#1)					
	#305994 286 ⁷⁴ 286 ⁷⁴ (b) (6)					
10/23/17	Disp: Advantix II Navy (>55 lb) 6pk (#1)					
	H/G to share w/ Bon #321280 (b) (6)					
10/27/17	65.5 lbs ✓ cough = x3-4d, not lethargic					
T 100.7°	eld N, no V/D, worse when laying down					
	PE: BAR. Numerous lipomatous & dermal masses.					
	MM pink, euhdrated, min tartar. Abd					
	nonpainful on palp. H/L - no audible					
	murmur or arrhythmias, no skin lung					
	sounds. Breathing very shallow - thorax doesn't					
	expand fully/normally - not dyspneic, no					
	visible abd component to breathing	P: CRP ALP 440, GGT 30, lymphs very h, N-E test				
		P Lat thorax xray. heart appears sl large				

(b) (6)

(b) (6)	Name: (b) (6)	Species: Canine	Breed: Lab Ret	Color: Yellow	DOB: (b) (6)	SEX: F(S)
Date: 10/27/17	Some ↑ opacity in cd-dorsal lung fields					
<u>CONT:</u>	Trachea NSF. VHS N 13					
VD thorax xray: R side of heart rounded, lung pattern less prominent in this view.						
Reviewed xrays w/ 5-disc bronchitis, lung fibrosis at age, cardiac, open.						
Disc R side of heart looks ↑, disc HWDz (test 3 mos ago & on HUP), DCM (heart not dilated), pericardial effusion (heart not globoid), etc						
Rec await lab results, consider tx for allergic bronchitis, but re cardiac workup of not improving.						
Dog did not cough while in clinic except for tracheal cough when pulling on leash.						
called 5-disc GIHP1, mild TAP - not likely a concern at this time.						
Rec meds below, call in 3-5 d w/ update.						
<u>Disp:</u> Hydroxyzine 50mg #30, 1 PO BID						
Hydrocodone 5mg #30, 1 PO Q8-12h PRN cough						
Doxycycline 100mg #40, 2 PO BID, 1 PO PM						
#322079 (b) (6)						
#321899 (b) (6)						

Client:

(b) (6)

Patient Name: (b) (6)

Species: Canine

Breed: Labrador Retriever

Gender: Female/Spayed

Weight: 72.00 lbs

Age: 11 Years

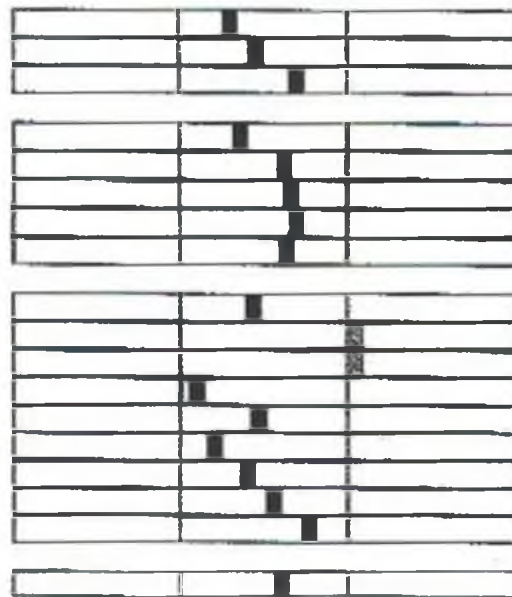
Doctor: (b) (6) DVM

(b) (6)

Test	Results	Reference Interval	LOW	NORMAL	HIGH
------	---------	--------------------	-----	--------	------

Catalyst Dx (October 27, 2017 10:05 AM)

GLU	93 mg/dL	70 - 143			
CREA	1.1 mg/dL	0.5 - 1.8			
BUN	21 mg/dL	7 - 27			
BUN/CREA	19				
PHOS	4.1 mg/dL	2.5 - 5.8			
CA	10.5 mg/dL	7.9 - 12.0			
TP	7.2 g/dL	5.2 - 8.2			
ALB	3.4 g/dL	2.2 - 3.9			
GLOB	3.8 g/dL	2.5 - 4.5			
ALB/GLOB	0.9				
ALT	61 U/L	10 - 125			
ALKP	440 U/L	23 - 212			HIGH
GGT	30 U/L	0 - 11			HIGH
TBIL	< 0.1 mg/dL	0.0 - 0.9			
CHOL	210 mg/dL	110 - 320			
AMYL	726 U/L	500 - 1500			
LIPA	856 U/L	200 - 1800			
Na	163 mmol/L	144 - 160			
K	5.3 mmol/L	3.5 - 5.8			
Na/K	29				
Cl	117 mmol/L	109 - 122			
Osm Calc	307 mmol/kg				



Printed: October 27, 2017 10:05 AM

Page 2 of 2

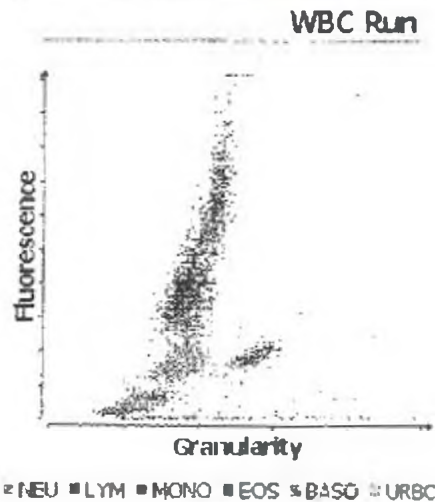
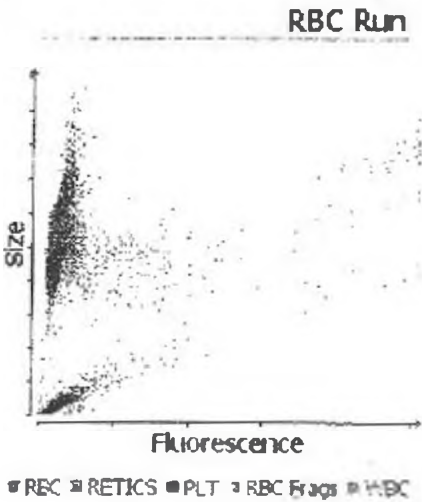
(b) (6)

Client: (b) (6)
Patient Name: (b) (6)
Species: Canine
Breed: Labrador Retriever

Gender: Female/Spayed
Weight: 72.00 lbs
Age: 11 Years
Doctor: (b) (6) DVM

(b) (6)

Test	Results	Reference Interval	LOW	NORMAL	HIGH
ProCyt Dx (October 27, 2017 9:57 AM)					
RBC	7.24 M/ μ L	5.66 - 8.87			
HCT	44.6 %	37.3 - 61.7			
HGB	15.6 g/dL	13.1 - 20.5			
MCV	61.6 fL	61.6 - 73.5			
MCH	21.5 pg	21.2 - 25.9			
MCHC	35.0 g/dL	32.0 - 37.9			
RDW	19.5 %	13.6 - 21.7			
%RETIC	0.8 %				
RETIC	59.4 K/ μ L	10.0 - 110.0			
WBC	6.94 K/ μ L	5.05 - 16.76			
%NEU	71.9 %				
%LYM	14.6 %				
%MONO	9.9 %				
%EOS	2.6 %				
%BASO	1.0 %				
NEU	4.99 K/ μ L	2.95 - 11.64			
LYM	1.01 K/ μ L	1.05 - 5.10	LOW		
MONO	0.69 K/ μ L	0.16 - 1.12			
EOS	0.18 K/ μ L	0.06 - 1.23			
BASO	0.07 K/ μ L	0.00 - 0.10			
PLT	318 K/ μ L	148 - 484			
MPV	11.9 fL	8.7 - 13.2			
PDW	16.2 fL	9.1 - 18.4			
PCT	0.38 %	0.14 - 0.46			



(b) (6)

(b) (6)

(b) (6)

(b) (6)



(b) (6)

PEY OWNER: (b) (6)

(b) (6)

SPECIES: CANINE
BREED: LABRADOR RETRIEVER
GENDER: FEMALE SPAYED
AGE: 12Y

ACQUAINTANCE: 2/14/87
OWNER HISTORY: (b) (6)

ACCESSION #: (b) (6)
REGISTRATION #: 38377288C
DATE OF COLLECTION: 03/14/2018
DATE OF RECEIPT: 03/14/2018
DATE OF REPORT: 03/14/2018

(b) (6) 885 SENIOR SENIOR

HEMATOLOGY

TEST	RESULT	REF. RANGE
RBC	7.06	(5.38 - 8.70) $\mu\text{mol/L}$
Hematocrit	43.3	(38.3 - 55.5) %
Hemoglobin	14.2	(13.4 - 20.7) g/dL
MCV	62	(58 - 75) fL
L MCH	20.3	(21.6 - 28.1) pg
MCHC	32.8	(32.6 - 38.2) g/dL
% Reticulocyte	0.3	%
Reticulocyte	21	(10 - 110) K/L
WBC	7.3	(4.8 - 17.6) K/L
% Neutrophil	78.1	%
% Lymphocyte	14.3	%
% Monocyte	7.0	%
% Eosinophil	2.5	%
% Basophil	0.0	%
Neutrophil	5656	(2840 - 12870)
L Lymphocyte	1044	(1080 - 4880) /L
Monocyte	511	(130 - 1150) /L
Eosinophil	130	(70 - 1400) /L
Basophil	0	(0 - 100) /L
H Platelet	615	(143 - 445) K/L
Platelet Comments	PLATELETS APPEAR INCREASED ON THE BLOOD FILM.	
Remarks	SLIDE REVIEWED MICROSCOPICALLY. NO PARASITES SEEN.	

CHEMISTRY

TEST	RESULT	REF. RANGE
Glucose	86	(80 - 174) mg/dL
DEKX-BMA ³	3	(0 - 144) U/L
Creatinine	1.90	(0.3 - 1.59) mg/dL
BUN	17	(8 - 38) mg/dL
BUN/Creatinine Ratio	17.90	
Phosphorus	3.7	(2.5 - 5.7) mg/dL
Calcium	14.88	(9.4 - 14.99) mg/dL
Sodium	147	(142 - 152)
Potassium	5.4	(4.0 - 5.4) mmol/L
LiNa/K Ratio	2.7	(2.8 - 3.7)

CHloride	108	(105 - 115)
TCO2 (Bicarbonate)	23	(18 - 27) mmol/L
Ammonia	20	(14 - 25) mmol/L
Total Protein	6.8	(5.5 - 7.5) g/dL
Albumin	3.4	(2.7 - 3.5) g/dL
Globulin	3.4	(2.4 - 4.0) g/dL
Alb/Glob Ratio	1.0	(0.7 - 1.5)
ALT	185	(18 - 121) U/L
AST	26	(16 - 55) U/L
HALP	2243	(5 - 188) U/L
HGGT ^b	117	(8 - 13) U/L
Bilirubin - Total	0.1	(0.0 - 0.3) mg/dL
Bilirubin - Unconjugated	0.0	(0.0 - 0.2) mg/dL
Bilirubin - Conjugated	0.1	(0.0 - 0.1) mg/dL
Cholesterol	328	(191 - 345) mg/dL
Creatine Kinase	130	(10 - 280) U/L
Hemolysis Index ^c	1+	
Lipemia Index ^d	N	

URINALYSIS

TEST	RESULT	REF. RANGE
Collection	FREE-CATCH	
Color	YELLOW	
Clarity	CLEAR	
Specific Gravity	1.010	
pH	6.0	
Urine Protein ^a	NEGATIVE	
Glucose	NEGATIVE	
Ketones	NEGATIVE	
Blood // Hemoglobin	NEGATIVE	
Bilirubin	NEGATIVE	
Urobilinogen	NORMAL	
White Blood Cells	0-2	(0 - 5) HPF
Red Blood Cells	NONE	HPF
Bacteria	NONE SEEN	
Epithelial Cells	FREE (0-1)	
Mucus	NONE SEEN	
Casts	NONE SEEN	

See drop images for complete access to this patient's diagnostic results, including historical assays and images. Log in to www.fedacv.com
Final report generated March 14, 2018

(b) (6)
PAGE 1 of 2

(b) (6)

(b) (6)

(b) (6)



(b) (6)

PET OWNER (b) (6)

DATE OF REPORT: 03/14/2018

ACCESSION # (b) (6)

(b) (6)

865 SENIOR SCREEN

URINALYSIS

TEST	RESULT	REF. RANGE
Crystals	NONE SEEN	

ENDOCRINOLOGY

TEST	RESULT	REF. RANGE
L Total T4 ^f	0.8	(1.0 - 4.0) ug/dL

NOTES

CHEMISTRY

a BOTH SDMA AND CREATININE ARE WITHIN THE REFERENCE INTERVAL which indicates kidney function is likely good. Evaluate a complete urinalysis and confirm there is no other evidence of kidney disease.

b RESULT VERIFIED BY REPEAT ANALYSIS

c Index of N, 1+, 2+ exhibits no significant effect on chemistry values.

d Index of N, 1+, 2+ exhibits no significant effect on chemistry values.

URINALYSIS

e Protein test is performed and confirmed by the sulfosalicylic acid test.

ENDOCRINOLOGY

f Interpretive ranges:

<1.0	Low
1.0-4.0	Normal
>4.0	High
2.1-5.4	Therapeutic

Dogs with no clinical signs of hypothyroidism and results within the normal reference range are likely euthyroid. Dogs with low T4 concentrations may be hypothyroid or "euthyroid sick". Occasionally, hypothyroid dogs can have T4 concentrations that are low normal. Dogs with clinical signs of hypothyroidism and low or low normal T4 concentrations may be evaluated further by submission of free T4 and canine TSH. A high T4 concentration in a clinically normal dog is likely variation of normal; however elevations may occur secondary to thyroid autoantibodies or rarely thyroid neoplasia. For dogs on thyroid supplement, acceptable 4-6 hour post pill total T4 concentrations generally fall within the higher end or slightly above the reference range.

(b) (6)

(b) (6)

Owner:
Patient:
Species:
Breed:
Age:
Gender:(b) (6)
CANINE
LABRADOR RETRIE
11Y
FS

(b) (6)

Account: 21467

Requisition #: (b) (6)
Accession #: (b) (6)
Order rec'd: 11/03/2017
Ordered by: (b) (7)(A)
Reported: 11/10/2017

TAURINE (WHOLE BLOOD)				
Test	Result			
TAURINE	168	(200 - 350)	L	<input type="checkbox"/>
Testing performed at University of California, Davis				

(b) (6)

11/10/2017

FINAL REPORT

PAGE 1 OF 1

From: [Jones, Jennifer L](#)
To: "CVCA - Cardiac Care for Pets" (b) (6)
Subject: RE: FDA Case investigation for (b) (6) (EON-350158)
Date: Friday, March 30, 2018 8:28:00 AM
Attachments: [image001.png](#)
[image004.png](#)
[image002.png](#)

Thank you for sending the records and reporting the case, (b) (6).
I hope you have a nice holiday and weekend,
Jennifer

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: CVCA - Cardiac Care for Pets (b) (6) [mailto:(b) (6)@cvcavets.com]
Sent: Wednesday, March 28, 2018 6:27 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: Re: FDA Case investigation for (b) (6) (EON-350158)

Attached is entire medical records for (b) (6). Please let us know if you need anything else-
Thank-

On Wed, Mar 28, 2018 at 6:08 PM, CVCA - Cardiac Care for Pets (b) (6) <(b) (6)@cvcavets.com> wrote:

Dear Dr. Jones,
Thank you for following up on our patient, (b) (6). We will be sending you our complete records for (b) (6) including the primary veterinarian history that we have and the history from her previous emergency room visit. Unfortunately, the diagnosis was made in October and the client has disposed of the diet. We will certainly keep this in mind for future patients with dilated cardiomyopathy which could potentially be diet-related and have those owners keep a sample and record the lot number for future testing/tracking. Thank you again for looking into this issue for our patients.

Sincerely,
(b) (6) - Cardiology

On Wed, Mar 28, 2018 at 2:40 PM, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov> wrote:

Good afternoon (b) (6),
Thank you for submitting your consumer complaint to FDA. I'm sorry to hear about (b) (6) illness.
As part of our investigation, we'd like to request:

- **Full Medical Records**

- Please email (preferred) or fax [\(301-210-4685\)](tel:301-210-4685) a copy of (b) (6) entire medical history (not just this event).
- Do you have records from her referring veterinarian?

- **Potentially Test Remaining OPEN product**

- Do you have any remaining product left?
- Is there a lot number or best by date for the leftover food?

- **Hold any remaining UNOPENED product** for potential collection.

I attached a copy of our Vet-LIRN network procedures. The procedures describe how Vet-LIRN operates and how veterinarians help with our case investigations.

Please respond to this email so that we can initiate our investigation.

Thank you kindly,

Dr. Jones

Jennifer L. A. Jones, DVM

Veterinary Medical Officer

U.S. Food & Drug Administration

Center for Veterinary Medicine

Office of Research

Veterinary Laboratory Investigation and Response Network (Vet-LIRN)

8401 Muirkirk Road, G704

Laurel, Maryland 20708

new tel: [240-402-5421](tel:240-402-5421)

fax: [301-210-4685](tel:301-210-4685)

e-mail: jennifer.jones@fda.hhs.gov

Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm>



CVCA - Cardiac Care for Pets

(b) (6)

Phone:

(b) (6)

Fax:

(b) (6)

Email: [\(b\)\(6\)@cvcavets.com](mailto:(b)(6)@cvcavets.com)

Visit our website at: www.cvcavets.com

"Like" us on Facebook at: www.facebook.com/CVCAVETS

"Follow" us on Instagram at: www.instagram.com/CVCAVETS

We want to hear from you! Access our online survey by clicking [here](#).

If there is anything that we can do to improve our service for you, please do not hesitate to contact us directly. We would greatly appreciate your feedback and invite you to fill out a survey based on your experience with CVCA.

Share your photos with us!

If you have a photo that you would like to share, we would love to post it on our Facebook page. Like us on [Facebook](#) and post to our wall or you can email the image with a fun fact to cvcainfo@cvcavets.com and we will forward it to our Facebook administrator.

Please note – Images are usually posted within 1 month of submission.

--

CVCA - Cardiac Care for Pets

(b) (6)

Phone: (b) (6)

Fax: (b) (6)

Email: [@cvcavets.com](mailto:cvcavets.com)

Visit our website at: www.cvcavets.com

"Like" us on Facebook at: www.facebook.com/CVCAVETS

"Follow" us on Instagram at: www.instagram.com/CVCAVETS

We want to hear from you! Access our online survey by clicking [here](#).

If there is anything that we can do to improve our service for you, please do not hesitate to contact us directly. We would greatly appreciate your feedback and invite you to fill out a survey based on your experience with CVCA.

Share your photos with us!

If you have a photo that you would like to share, we would love to post it on our Facebook page. Like us on [Facebook](#) and post to our wall or you can email the image with a fun fact to cvcainfo@cvcavets.com and we will forward it to our Facebook administrator.

Please note – Images are usually posted within 1 month of submission.

From: Freeman, Lisa
To: Jones, Jennifer L
Subject: RE: reported cases
Date: Thursday, November 08, 2018 6:25:48 AM
Attachments: [image001.png](#)
[image004.png](#)
[image005.jpg](#)

Hi Jen

You should have (b) (6) now – I submitted him on 10/25/18 (report 246795).

I have about 8 more to report that I've gotten behind on – I'll catch up on those this weekend.

(b) (4), (b) (5)
(b) (4), (b) (5) We've been hearing a lot of confusion and misinformation so hopefully this will remind people that it's not just taurine deficiency and it's not just grain-free diets. And that people should be reporting cases to you to help get this figured out quickly. So, you may start to get more cases reported.

Also, I was talking to Darcy yesterday and we were wondering if it would be worth another call to catch up.

Thanks!

Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Sent: Wednesday, November 07, 2018 10:11 AM
To: Freeman, Lisa <lisa.freeman@tufts.edu>
Subject: RE: reported cases

Hi Lisa,

We have all of the cases you listed below except (b) (6). It's fine to send me the additional records for the cases

Thank you for your tireless efforts at getting us the information.

It's greatly appreciated!!

Jen

Jennifer Jones, DVM
Veterinary Medical Officer

Tel: 240-402-5421



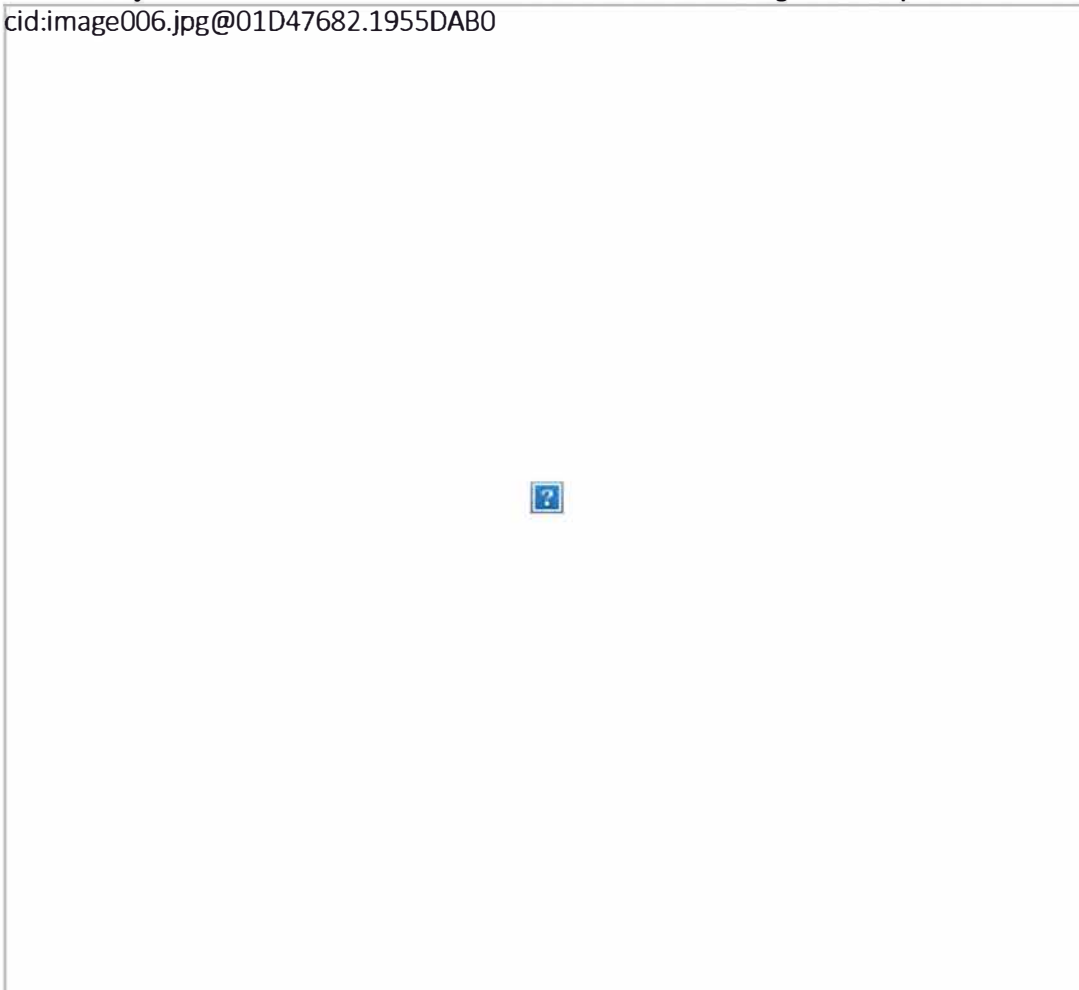
From: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Sent: Monday, October 01, 2018 3:51 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: reported cases

Hi Jen

I was looking through which cases I've submitted (have a bunch more to add) and saw that 3 were in a separate account and there a few that are not showing up as having been reported.

1. Could you check to see that these 3 are listed as having been reported?

cid:image006.jpg@01D47682.1955DAB0



2. Also, I have a 3 others that are not listed in my account but I'm pretty sure I reported. If not, I'll get them submitted:

- (b) (6)
- (b) (6)
- (b) (6)

3. I keep sending you the extra medical records that won't fit in the reporting portal. Is there someone else I should send these to so I don't keep clogging your inbox?

Many thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

From: Jones, Jennifer L
To: Palmer, Lee Anne; Rotstein, David; Palmer, Lee Anne; Queen, Jackie L
Cc: Ceric, Olga; Nemser, Sarah; "Reimschuessel, Renate (Renate.Reimschuessel@fda.hhs.gov)"
Subject: RE: Zignature Kangaroo Formula: 800.261- EON-351031 (b) (6)-owner (b) (6)-vet
Date: Wednesday, May 09, 2018 6:53:00 AM
Attachments: EON-351031- (b) (6) MRx.pdf
image001.png
image005.png
image003.png

This was the product with low Taurine we recently tested (per feline AAFCO minimum Tau).

Golden Retriever with low blood taurine and a persistent history of arytenoid dysfunction, possible doxy +/- prednisone responsive infectious (Bartonella?) arytenoid granulomas? Since 9 months old

MRx summary:

Presenting complaint 2/23/2018: CHF possible, consult; tachycardia, last 3 days dyspneic, no cough, poor appetite for 2 days, usually ravenous, decreased energy level, on pred (5 mg EOD) over a year, tried soloxine but discontinued because it wasn't helping; long history of a panting and swallowing disorder → diagnosed w/ DCM & L-CHF, tentative pulmonary edema → start furosemide, pimobendan, and Taurine → 2/27 breathing better, eating ok, increased prednisone for gagging → 3/1 Tau low, dog still on Zignature Kangaroo diet → vet said legumes in the diet likely prevent Met & Cys absorption → switched to Royal Canin Kangaroo & Oat; the dog was on Zignature Kangaroo last 2-3 years, eats milkbones and baked dog treats from a bakery; before the Zignature, he ate Acana Ranch Lamb, Natural Balance Bison & SP, Natural Balance Fish & SP, Zignature Trout & Salmon → no supplements were taken before the DCM diagnosis → by 3/13 dog was eating Royal Canin Kangaroo → 3/22 restless at night but RR = 22, try melatonin

PE 2/23: 40 kg, HR 120, gallop, panting; at rest/lying down still tachypneic

Labs: 2/23 **Whole Blood Tau:** 119 (200-350)

2/23 Echocardiogram: dilated LV w/ poor systolic function, LA enlarged, mod MR & TR, dec aortic and pulmonic flow

Prior MHx: 5/2014 aerophagia since 9 months old, episodes of gagging/choking with neck extension; 11/2014 myasthenia gravis negative; 5/2015 cerenia helps, gagging episodes increasing in frequency, no megaesophagus, nodule on left vocal fold w/ asymmetry of arytenoid function-granulomatous inflammation and treated with Doxycycline for possible Bartonella (never tested); 6/2015 stopped air issues; 9/2015 good for two months then flair up of signs, then gone again, retreat with doxy; 3/2017 T4 & TSH low with WBC/NP elevated, recheck difficulty swallowing and upper airway noise → trial soloxine

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Jones, Jennifer L
Sent: Friday, April 13, 2018 6:39 AM
To: Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>
Cc: Rotstein, David <David.Rotstein@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Subject: RE: Zignature Kangaroo Formula: (b) (6) - EON-351031

Thanks, Lee Anne. No, I wasn't expecting it, but I can start with MRx!

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Palmer, Lee Anne
Sent: Thursday, April 12, 2018 1:39 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Cc: Rotstein, David <David.Rotstein@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Subject: FW: Zignature Kangaroo Formula (b) (6) - EON-351031

Hi Jen – were you expecting this one? Thx - LA

From: PFR Event [mailto:pfrpreventcreation@fda.hhs.gov]
Sent: Thursday, April 12, 2018 1:36 PM
To: Cleary, Michael * <Michael.Cleary@fda.hhs.gov>; HQ Pet Food Report Notification <HQPetFoodReportNotification@fda.hhs.gov>; (b) (6)
Subject: Zignature Kangaroo Formula: (b) (6) - EON-351031

A PFR Report has been received and PFR Event [EON-351031] has been created in the EON System

A "PDF" report by name "2045676-report pdf" is attached to this email notification for your reference

Below is the summary of the report:

EON Key: EON-351031

ICSR #: 2045676

EON Title: PFR Event created for Zignature Kangaroo Formula; 2045676

AE Date	02/22/2018	Number Fed/Exposed	1
Best By Date		Number Reacted	1
Animal Species	Dog	Outcome to Date	Stable

Breed	Retriever - Golden		
Age	6 Years		
District Involved	PFR- (b) (6) DO		

Product information

Individual Case Safety Report Number: 2045676

Product Group: Pet Food

Product Name: Zignature Kangaroo Formula

Description: Feb 23, 2018 Patient presented to the cardiology service at (b) (6) for tachypnea. He was diagnosed with dilated cardiomyopathy and left side congestive heart failure. Whole blood taurine level was 119 (ref 200-350, critical level <150). At the time, patient consuming Zignature Kangaroo Formula and was advised to change.

Submission Type: Initial

Report Type: Adverse Event (a symptom, reaction or disease associated with the product)

Outcome of reaction/event at the time of last observation: Stable

Number of Animals Treated With Product: 1

Number of Animals Reacted With Product: 1

Product Name	Lot Number or ID	Best By Date
Zignature Kangaroo Formula		

Sender information

(b) (6)

Owner information

(b) (6)

To view this PFR Event, please click the link below:

<https://eon.fda.gov/eon/> (b) (6)

To view the PFR Event Report, please click the link below:

<https://eon.fda.gov/> (b) (6)

This email and attached document are being provided to you in your capacity as a Commissioned Official with the U.S. Department of Health and Human Services as authorized by law. You are being provided with this information pursuant to your signed Acceptance of Commission.

This email message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential. Any dissemination, distribution, or copying is strictly prohibited.

The information is provided as part of the Federal-State Integration initiative. As a Commissioned Official and state government official, you are reminded of your obligation to protect non-public information, including trade secret and confidential commercial information that you receive from the U.S. Food and Drug Administration from further disclosure. The information in the report is intended for situational awareness and should not be shared or acted upon independently. Any and all actions regarding this information should be coordinated through your local district FDA office.

Failure to adhere to the above provisions could result in removal from the approved distribution list. If you think you received this email in error, please send an email to FDAREportableFoods@fda.hhs.gov immediately.

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
4/12/2018	C	(b) (6)	MEDICAL COMMENTS ***ADDENDUM 4/20/2018 4/12/2018 13:26 FDA Safety Reporting Portal - Individual Case Safety Report Number (ICSR) 2045676 ADDENDUM on 4/20/2018 at 08:34:23 from (b) (6) permission signed and returned to (b) (6)
3/24/2018	P	(b) (6)	1.00 [None] of Postage (UPS) -1 Lb (POSTA) Rx #: 2863492 0 Of 0 Refills ***SHIP ONLINE ORDERS UPS ONLY!!!*** Lasix
3/24/2018	C	(b) (6)	PHARMACY NOTE TTO. Meds have been refilled
3/24/2018	P	(b) (6)	100.00 tablet of Lasix (Salix / Furosemide) 50mg Tablet (M569) Rx #: 2852561 1 Of 12 Refills Filled by: (b) (6) 1 1/2 TABLETS BY MOUTH TWO TIMES A DAY
3/22/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/22/2018 13:03 dog is restless at night, making breathing sound, but sRR is consistently at 22 bpm, so i do not think do has pulmonary edema, will try melatonin, recheck in end of april Hey His Melatonin dose is 4 or 5 mg once to three times a day. Depending on size tablet you get, a 4 mg tablet or a 5 mg tablet, then start by giving 1 tablet once day, 30 minutes before bed (b) (6)

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
--	--	--

Date	Type	Staff	History
3/13/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/13/2018 10:36 SWO - Owner consented to reporting (b) (6) case to the FDA. He has been on the Zignature Kangaroo for the past 2-3 years. Treats include Milkbones and baked dog treats from pet bakery. Prior to the Zignature Kangaroo, he consumed the Acana Ranch Lamb, Natural Balance Sweet Potato and Bison, Natural Balance Sweet Potato and Fish, Zignature Trout & Salmon. He was receiving no supplements prior to his DCM diagnosis. Owner will forward me a copy of her most recent Chewy.com receipt for the Zignature. She does not have the bag anymore. I will email her for additional information. She is now feeding the Royal Canin Kangaroo and Oats.
3/1/2018	D	(b) (6)	Taurine Deficiency Final
3/1/2018	C	(b) (6)	COMMUNICATIONS WITH DOCTOR 3/1/2018 13:22 i called vet, to let them know taurine is low, she is still on kangaroo diet from Zignature, rec to change diet. The legumes in diet are most likely preventing methionine and cystine absorption, should switch to Royal Canin kangaroo and oats, i originally lm and he called back. he said he would call owner
3/1/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/1/2018 13:20 i called client to let her know taurine is low, she is still on kangaroo diet from Zignature, rec she talk to her vet at last appt, and she did to day at a recheck, and told her to wait. The legumes in diet are most likely preventing methionine and cystine absorption, should switch to Royal Canin kangaroo and oats, I will call her vet.
2/27/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 2/27/2018 11:03 i called owner, dog is breathing better, eating fine, getting sRR 18-26, did have throat issues, does gagging, pred helped, increased pred again, continue as planned, waiting on taurine level. if normla will start enalapril
2/24/2018	L	(b) (6)	Miscellaneous results from (b) (6)

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
--	--	--

Date	Type	Staff	History
------	------	-------	---------

(East) Requisition ID: (b) (6) Posted Final
 Asc: (b) (6) Profile: Taurine RE: 16759 Taurine 119
 Normal Values (nmols/ml)

Level	Normal Range	Critical
Cat Plasma	60-120	Less than
40		
Whole Blood	300-600	Less than
200		
Dog Plasma	60-120	Less than
40		
Whole Blood	200-350	Less than
150		

TEST PERFORMED AT (b) (6)

2/23/2018	C	(b) (6)	PHARMACY NOTE Called (b) (6), spoke to (b) (6) Ordered Pimobendan 10 mg tiny tablets - 1 tablet two times a day, #100, 8 refills
-----------	---	---------	--

2/23/2018	D	(b) (6)	Pulmonary Edema Tentative
2/23/2018	D	(b) (6)	Taurine Deficiency Tentative Date Diagnosis made final: 03/01/18
2/23/2018	D	(b) (6)	Dilated Cardiomyopathy Tentative
2/23/2018	I	(b) (6)	Cardiology Discharge Instructions

(b) (6)
2/23/2018

A cardiologist has evaluated (b) (6) and has diagnosed her with Dilated Cardiomyopathy (DCM). DCM means your pet has poor muscle contraction of the heart. This means the heart muscle does not pump as well as a normal dog. The heart has enlarged due to the poor muscle contraction. The change in the heart has caused fluid to form in the lungs, causing increased respiratory rate.

Please take a sleeping respiratory rate rate (sRR) at home. WHILE YOUR PET IS SLEEPING, count the number of times they breathe in over 15 seconds. Your pet should have 8 breathes or less over 15 seconds while sleeping. Do this once a day over the next 3 days, then 2 times a week thereafter.

The free app software for iPhone and Google Play that can help with this is Cardalis

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
			<p>I have submitted blood for a taurine level. The result may not return for 2 weeks. In the mean time, please start Taurine at home, 2 gram two times a day with food. This can be purchased at any health food store. I will call in about 2 weeks with a taurine level.</p> <p>MEDICATIONS: Furosemide 50 mg tablets 1 1/2 tablet two times a day Furosemide: Also called Salix or Lasix. This is a diuretic and will help clear the fluid from your pet's lungs. Your pet may drink more on this medication. Side effects include electrolyte abnormalities (if they stop eating), dehydration and kidney enzyme elevations. The blood work can be done to monitor these. This medication will be probably given for the life of your pet. YOU CAN GET REFILLS OF THIS MEDICATION FROM YOUR VETERINARIAN OR HERE. THIS SIZE TABLET IS NOT AVAILABLE IN HUMAN PHARMACIES.</p> <p>Pimobendan (b) (6) 10 mg tiny tablets - 1 tablet two times a day Pimobendan is a phosphodiesterase inhibitor that gives increased contractility and arterial vasodilation. This will help the heart function better, allow you dog to feel better and live longer. Any medication can upset the stomach. This drug does not typically cause this, but if you see any changes, please stop the drug till you talk to a doctor here at (b) (6). PLEASE GIVE THIS MEDICATION WITH (b) (6) MEALS. Even though package insert recommends giving on empty stomach, we have adjusted the dose so that you can give with meals. Giving on empty stomach is more likely to make your pet nauseous. We will script this drug through (b) (6) Please call them in 4-5 days to order it, once we see that your dog will tolerate the drug.</p> <p>Watch for the following clinical signs and call a veterinarian if you see any of these: Excessive panting or wheezing Restlessness, unable to get comfortable Decreased appetite Lethargy/weakness, less interactive or hiding Collapse or fainting Sudden rear leg or front leg lameness Open-mouth breathing</p> <p>It has been a pleasure meeting you and caring for your (b) (6) Thank you for entrusting us with her care. If you have any further questions or problems, don't hesitate to call.</p> <p>(b) (6) (b) (6)</p>
2/23/2018	P	(b) (6)	30.00 tablet of Pimobendan 10mg tiny tab (cpd) (MMP0T8) Rx #: 2852563 0 Of 10 Refills

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
2/23/2018	P	(b) (6)	1 TABLET BY MOUTH TWO TIMES A DAY 100.00 tablet of Lasix (Salix / Furosemide) 50mg Tablet (M569) Rx #: 2852561 0 Of 12 Refills 1 1/2 TABLETS BY MOUTH TWO TIMES A DAY
2/23/2018	C	(b) (6)	CARDIAC EVALUTION - CLOSED 02/24/2018 - Cardiac Evaluation

Date of evaluation: Friday, February 23, 2018

CHIEF COMPLAINT: tachypnea

HISTORY: last 3 days has been working hard to breath. No coughing. Appetite has been poor last 2 days, usually ravenous. Energy level seems down. No cardiac medications On 1/2 10 mg pred EOD for over year, Tried thyroid medication but stopped it, did not help. Has long history of panting and swallowing disorder.

PHYSICAL EXAM: BAR. HR = 120, regular rhythm, no murmur, gallop noted, pulses normal and synchronous. Mild tachypnea but panting, when rests lying down, still tachypnea. Normal bronchovesicular sounds bilaterally, no crackles or wheezes ausculted. BCS 5/9 PCS 0/4

ECHOCARDIOGRAM 2/23/18: BW 40 kg BSA 1.14

IVSd: 10 mm LVIDd: 64 mm LVPWd: 9 mm EPSS 21 mm
IVSs: 14 mm LVIDs: 52 mm LVPWs: 11 mm %FS: 19 % Pa: 21 mm
Ao: 24 mm LAD: 43 mm LA:Ao ratio 1.79 LA max: 48 mm LLAD: 56 mm
RWT = IVSd+LVPWd/LVIDd = 0.30, LVID long 90 mm, Sphericity index 1.41 (Lax/Sax,<1.65=increased sphericity).
Norm LA:Ao < 1.7, Normal LLAD < 42.93 mm, LVIDdn = 2.16 (N<1.73), LIVDsn = 1.63 (N<1.4)
MV E vel: 132, MV Dec T:89, MV A vel: 67, IVRT:71 ms, E:A 1.97 (N 1-2)E:IVRT 1.86 (N<2.5) Ea 10 E:Ea 13.2 (N<14.5)
Pa distensibility (mm): 11.7 - 5 = 57 %, PEP/ET = 96/170 = 0.56, > 0.4 is abnormal, with myocardial failure
Tricuspid peak flow velocity 3.2 m/s, gradient 41 mmHg, acceleration time 88 ms, PAET 177 ms, ratio = 0.50
(ratio greater than 0.30 is considered normal)
100% spec for PH if AT< 45 ms +/-or AT:ET < 0.25, 100% spec for Normal if AT>64 ms +/-or AT:ET > 0.42
Grey zone for predicting: AT <58 ms (Se 88%, Sp 80%), AT:ET < 0.31 (Se 73% and Sp 87%)

COMMENTS: dilated LV with poor systolic function. Left atrial enlargement. Large EPSS. Moderate MR and TR. Reduce aortic and pulmonic flows. no pleural or pericardial effusion

DIAGNOSIS/PROBLEM LIST: dilated cardiomyopathy (DCM), left side congestive heart failure (LCHF)

SUMMARY: The dilated cardiomyopathy may be related to diet and taurine deficiency. There have been personal communications amongst cardiologist of a rash of cases of Golden Retrievers on grain free and/or kangaroo diets that have taurine deficiency cardiomyopathy. We pulled a whole blood level taurine today and started 2 grams of taurine BID. I also started furosemide and pimobendan as below. If taurine deficiency

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

(b) (6)

Page 5 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
--	--	--

Date	Type	Staff	History
------	------	-------	---------

cardiomyopathy, this could be reversible. It could take 2 months to see echo changes, but dog may feel better within a month. Recheck echocardiogram in 2 months. We should recheck a taurine level in 2 weeks. They will most likely do that with (b) (6).

MEDICATIONS:

Furosemide 50 mg tablets 1 1/2 tablet two times a day
 Pimobendan (b) (6) 10 mg tiny tablets - 1 tablet two times a day
 Taurine at home, 2 grams two times a day with food.

2/23/2018	V	(b) (6)	Feb 23, 2018 01:06 PM Staff: (b) (6) ----- Weight : 40.00 kilograms room 14
2/23/2018	CK	(b) (6)	CHF poss, setup by rdvm Reason for Visit: Consult Date Patient Checked Out: 02/23/18 Practice TF
2/23/2018	CB	(b) (6)	Callback - Call Client Back (CB) ---- Note from (b) (6) on 2/23/2018 at 15:51:32 ---- Called (b) (6), spoke to (b) (6). ---- Note from (b) (6) on 2/23/2018 at 15:06:34 ---- Pimobendan (b) (6) 10 mg tiny tablets - 1 tablet two times a day, #100, 8 refills

2/22/2018	TC	(b) (6)	RECORDS FROM RDVM/LDVM (see attachment) - TENTATIVE 2/22/2018 14:47 rDVM records attached. - Attachment(s)
-----------	----	---------	---

3/10/2017	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/10/2017 10:26 updated owner regarding (b) (6) recommending trial of soloxine. can be low from pred. but worth a try. can consider fluoro study in future. called into rdvm thyrotab 0.8 mg bid ; recheck t4 4 hours post pill in a month
-----------	---	---------	---

3/8/2017	L	(b) (6)	Endocrinology results from (b) (6) (East) Requisition ID: (b) (6) Posted Final
----------	---	---------	---

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
------	------	-------	---------

Test	Result	Reference Range
TSH	<0.03 ng/mL	0 - 0.60
Ascn: (b) (6)	Profile: (b) (6)	

3/7/2017 C RAD RADIOLOGY REVIEW - CLOSED 03/08/2017
The right lateral views of the neck and thorax obtained today have been reviewed.
There are no significant abnormalities in the extra-thoracic soft tissues, visible skeletal structures, pleural space, pulmonary parenchyma and vessels, cardiovascular structures, mediastinum, and cranial abdomen.
An endoscopic evaluation may be considered for further investigation of the previously diagnosed arytenoid nodule.

This review was written by: (b) (6)

3/7/2017 V (b) (6) Mar 7, 2017 04:21 PM Staff: (b) (6)

Weight : 41.40 kilograms

3/7/2017 CK (b) (6) recheck for (b) (6)
Reason for Visit: Recheck
Date Patient Checked Out: 03/07/17 Practice TF

3/7/2017 C (b) (6) IM PHYSICAL EXAM NEW
3/7/2017 10:10

Chief Complaint: reevaluation of hard swallowing; upper airway noise

History: (b) (6) was originally evaluated in 2015 for hard swallowing, gagging. A laryngeal exam at that time revealed a nodule on the larynx which was biopsied as granulomatous. He has been on low dose prednisone since. Owner still notices hard swallowing and sometimes regurgitation. He also has upper airway noise when sleeping- breathes through nose and no nasal discharge. Occasional hoarse bark. No diarrhea, no pu/pd. He has gained weight. In 2015 a myasthenia titer was negative. Diet includes zignature kangaroo. unsure of current dose of pred 1 tab in morning and sometimes 1/2 tab at night unsure what strength

Previous Medical Problems:

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
------	------	-------	---------

Medications/Supplements:

Current Diet:

- Frequency:

- Amount:

Subjective:

Mentation: Quiet, Alert, Responsive

Objective Findings

Temperature: 101.8 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec.

Hydration Status: normal

Pain Score: /4

Weight: 41.4 kilograms

Body Condition Score/Muscle Score: 8/9/

Oropharyngeal: Normal

Eyes/Ears: fundic normal

Integument: Normal

Peripheral Lymph Nodes: Normal size

Cardiovascular/Respiratory: heart ausculted normal; lungs clear; occasionally hard swallowing in the room

Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful.

Urogenital: Normal

Musculoskeletal/neurologic: normal ambulation; weak gag; hard swallowing during exam

Rectal: Normal

Diagnostics:

Lab Work: see below

Radiographic Findings: Thoracic radiograph unremarkable- no megaesophageous, lateral laryngeal radiograph normal

Other Diagnostics:

Problems/Differential Diagnoses/Assessment:

Hard swallowing- rule out esophageal motility disorder, laryngeal / pharyngeal dysfunction , other types of neuromuscular condition; Low T4 consider secondary to chronic pred, hypothyroidism. Can consider trial of soloxine and recheck after a month. Other diagnostics to consider would be a fluoroscopy study of Leo swallowing.

Treatment:

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

Plan/Recommendations:

3/7/2017 L Hematology results from (b) (6) Requisition

ID:	(b) (6)	Posted	Final	Reference Range
Test		Result		
HCT		45 %		36 - 60
HGB		14.9 g/dL		12.1 - 20.3
MCHC		33 g/dL		30 - 38
WBC		19.6 10 ³ /uL H		4.0 - 15.5
Bands		0 %		0 - 3
RBC		6.1 10 ⁶ /uL		4.8 - 9.3
MCV		73 fL		58 - 79
MCH		24.3 pg		19 - 28
ABS BASO		0 /uL		0 - 150
Platelet C		128 10 ³ /uL L		170 - 400
Platelet E		ADEQUATE		
Neutrophil		91 % H		60 - 77
Lymphocyte		6 % L		12 - 30
Monocytes		3 %		3 - 10
Eosinophil		0 % L		2 - 10
Basophils		0 %		0 - 1
Absolute N		17836 /uL H		2060 - 10600
Absolute L		1176 /uL		690 - 4500
Absolute M		588 /uL		0 - 840
Absolute E		0 /uL		0 - 1200

Ascن: (b) (6) Profile: Complete Blood Count

Platelet count reflects the minimum number due to platelet clumping.

3/7/2017 L Chemistry results from (b) (6) Requisition

ID:	(b) (6)	Posted	Final	Reference Range
Test		Result		
ALB		3.8 g/dL		2.7 - 4.4
ALKP		48 IU/L		5 - 131
ALT		33 IU/L		12 - 118
AMYL		461 IU/L		290 - 1125
AST		15 IU/L		15 - 66
BUN/UREA		19 mg/dL		6 - 31
Ca		10.0 mg/dL		8.9 - 11.4
Chloride		109 mEq/L		102 - 120
CHOL		209 mg/dL		92 - 324
CK		67 IU/L		59 - 895
CREA		0.2 mg/dL L		0.5 - 1.6
GGT		2 IU/L		1 - 12

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 9 of 30

Date: 4/20/2018 5:17 PM

FDA-CVM-FOIA-2019-1704-000882

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

GLU	72 mg/dL	70 - 138
Mg	1.9 mEq/L	1.5 - 2.5
PHOS	4.6 mg/dL	2.5 - 6.0
Potassium	4.5 mEq/L	3.6 - 5.5
Sodium	148 mEq/L	139 - 154
TBIL	0.2 mg/dL	0.1 - 0.3
TP	6.6 g/dL	5.0 - 7.4
TRIG	32 mg/dL	29 - 291
GLOB	2.8 g/dL	1.6 - 3.6
A/G Ratio	1.4	0.8 - 2.0
B/C Ratio	95 H	4 - 27
Na/K Ratio	33	27 - 38

3/7/2017 L

Endocrinology results from (b) (6)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Test Result Reference Range
 T4 0.6 ug/dL L 0.8 - 3.5
 Ascen: (b) (6) Profile: Total T4

The Total T4 result is less than 1.0 mcg/dl. A Free-T4 by equilibrium dialysis may be helpful in supporting the diagnosis of hypothyroidism in patients demonstrating clinical signs compatible with hypothyroidism. Please contact Customer Service for this additional testing.

3/7/2017 L

Miscellaneous results from (b) (6)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Ascen: (b) (6) Profile: Superchem
 RE: 1045 PrecisionP 50 U/L 24 - 140
 Pancreatitis is unlikely, but a normal PrecisionPSL result does not completely exclude pancreatitis as a cause for gastrointestinal signs.
 RE: 11067 Comment
 Hemolysis 1+ No significant interference.

3/6/2017 C

(b) (6)

COMMUNICATIONS WITH CLIENT
 3/6/2017 12:55
 sto confirmed appt w/ (b) (6) @ 330 on 3/7

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
--	--	--

Date	Type	Staff	History
2/26/2017	C	(b) (6)	COMMUNICATIONS WITH CLIENT 2/26/2017 10:15 LMOM to confirm 3:30 pm (b) (6) appt tomorrow
2/23/2017	TC	(b) (6)	RECORDS FROM RDVM/LDVM (see attachment) - TENTATIVE 2/23/2017 20:36 Records from (b) (6) - Attachment(s)
2/23/2017	C	(b) (6)	COMMUNICATIONS WITH DOCTOR 2/23/2017 17:18 SW (b) (6) of (b) (6) to request updated records from 5/3/15 forward be faxed
2/20/2016	C	(b) (6)	RECEPTION ACTIONS NOTE faxed ref letters and labs to (b) (6) per (b) (6) req
9/28/2015	C	(b) (6)	OUTSIDE PHARMACY RX ***ADDENDUM 10/2/2015 - Closed Sep 30/2015 Rx #: 0172 Prescribing doctor: (b) (6) Pharmacy prescription called in to: (b) (6) Pharmacy Phone #: (b) (6) Pharmacy Fax #: (b) (6) Medication: Doxycycline 100mg Quantity and Unit of Measure: #56 # of Refills: none Rx Instructions: 2t po q12h Is this medication a controlled substance?

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
			Additional Comments: faxed ADDENDUM on 10/1/2015 at 21:11:18 from (b) (6) Re-faxed as per request of (b) (6). ADDENDUM on 10/2/2015 at 11:27:39 from (b) (6) they only have 200mg tablets ADDENDUM on 10/2/2015 at 13:26:23 from (b) (6) Owner said (b) (6) charged more than Target, refaxing script to Target fax (b) (6).
9/28/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 9/28/2015 13:29 (b) (6) was good for 2 months, then small flair up, then went away again for a few months. last time, we discussed repeat abx treat may not be helpful. discussed that we can repeat abx treatment as it worked for such a long period of time. discussed dual treatment for bartonella vs considering doxycycline and niacinamide. will try doxy/niacinamide and recheck 2 wks. will rx doxy to local rdvm, niacinamide 500 mg PO q 8 hr to get at local health store (OTC)
6/1/2015	C	(b) (6)	OUTSIDE PHARMACY RX - Closed Jun 04/2015 Rx #: (b) (6) Prescribing doctor: (b) (6) Pharmacy prescription called in to: Target Pharmacy Pharmacy Phone #: (b) (6) Pharmacy Fax #: Medication: Doxycycline 100 mg Quantity and Unit of Measure: #60/ 100 mg # of Refills: 0 Rx Instructions: Give 2 tab PO q 12hr Is this medication a controlled substance? Yes No Additional Comments: Called into Target Pharmacy in (b) (6)

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
6/1/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 6/1/2015 16:05 within the last 3 days stopped doing the neck movement/episodes that he was having. still sounds congested. when he barks there sounds like there is something in there. would continue abx for bartonella unless we are planning to rescope him. owner needs refill of doxycycline. will touch base in 1-2 wks.
5/17/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/17/2015 10:26 swo and asked how (b) (6) is doing, owner said she started ab's yesterday and so far he is doing well, owner will recheck in one week
5/15/2015	C	(b) (6)	OUTSIDE PHARMACY RX - Closed May 17/2015 Rx #: 0042 Prescribing doctor: (b) (6) Pharmacy prescription called in to: (b) (6) Pharmacy Phone #: n/a Pharmacy Fax #: (b) (6) Medication: Enrofloxacin 136mg Quantity and Unit of Measure: 45 # of Refills: 0 Rx Instructions: Give 1.5 tab (204mg) po q 24hr Is this medication a controlled substance? Additional Comments: Faxed to (b) (6)
5/15/2015	C	(b) (6)	OUTSIDE PHARMACY RX Rx #: 90115000043

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
--	--	--

Date	Type	Staff	History
<p>Prescribing doctor: (b) (6)</p> <p>Pharmacy prescription called in to: Target- (b) (6)</p> <p>Pharmacy Phone #: (b) (6)</p> <p>Pharmacy Fax #:</p> <p>Medication: Doxycycline 100mg</p> <p>Quantity and Unit of Measure: #60</p> <p># of Refills: 0</p> <p>Rx Instructions: Give 2 tab PO q12hr</p> <p>Is this medication a controlled substance? No</p> <p>Additional Comments:</p>			
5/15/2015	C	(b) (6)	<p>COMMUNICATIONS WITH CLIENT ***ADDENDUM 5/15/2015</p> <p>5/15/2015 16:27</p> <p>SWO per (b) (6), cost of bartonella test is \$342 which is something she can do via tech appt. or if O would prefer (b) (6) is OK with treating with AB's w/o testing. O wanted to know how long the course of AB's would be- per (b) (6) it would be a 2-4 week course. O also wanted to know if there is a chance of needing another course of AB's after the initial 2-4wk course, per (b) (6) P would not go on another course of AB's at that point. O would like go to skip blood test due to cost and try treating with AB's first. Would like called into Target Pharmacy in (b) (6)</p> <p>ADDENDUM on 5/15/2015 at 18:45:06 from (b) (6)</p> <p>called O, there are two medications- one is only veterinary can call into (b) (6) and the other can be called into target in (b) (6). O OK with this plan. Called (b) (6) into target pharm and rx to be faxed to (b) (6).</p>
5/12/2015	C	(b) (6)	<p>COMMUNICATIONS WITH CLIENT</p> <p>5/12/2015 14:50</p> <p>called owner with results. granulomatous inflammation. can be infectious, inflammatory or immune mediated disease. discussed type of inflammation present, there is concern for possible infectious organism. discussed bartonella and that this can be difficult to diagnose. discussed triple blood draw and</p>

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
			performing PCR and serology. discussed infecitous disease CE and the recommendations for testing for bartonella. will look into cost for tests and then take it from there. this may not be the cause for his signs. discussed whether inflammation causes dysfunction or dysfunction started first. may need steroids or doxepin. will be in touch with owner as soon as i can get pricing information. last night he had the worst night. couldn't lay down. panting like crazy.
5/12/2015	C	(b) (6)	<p>IM TREATMENT NEW 5/12/2015</p> <p>Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion</p> <p>nodule on vocal fold with assymetry of arytenoid function: granulomatous inflammation</p> <p>consider infectious disease screening; however due to length of time this has been doing on this is considered less likely. Consider treatment with anti-inflammatory doses of prednisone for possible immune mediated vs sterile inflammation</p> <p>if no improvement with either abx therapy, anti-inflammatory to possibly immunosuppressive steroid therapy, consider doxepin</p> <p>Treatment: no treatment implemented today</p> <p>Recommended Follow-up Care: looking into pricing for bartonella testing. will recheck/touch base with owner when this is available; may go to local rDVM for testing due to proximity</p>
5/8/2015	L		<p>Miscellaneous results from (b) (6) (b) (6) Requisition ID: (b) (6) Posted Final Asc: (b) (6) Profile: Histopathology, Full Written Report RE: 7801 History: Nodule on glottal opening. Episodes since he was 9 months old. Episodes are described as extending his neck repeatedly and gagging/choking and swallowing. (b) (6) would swallow hard repeatedly and</p>

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

(b) (6)

Patient History Report

Client: (b) (5)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
			<p>have continual lip licking with a stridorous noise when breathing. He licks the air. He will intermittently vomit, but not with every episode. He has been treated with sucralfate, Cerenia and Pepcid. The Cerenia seems to help, but does not completely resolve the signs.</p> <p>-</p> <p>Received: Multiple fragments - all processed. RE: 601 Biopsy DESCRIPTION/MICROSCOPIC FINDINGS/COMMENTS:</p> <p>Sections of fragments of an ulcerated inflammatory mass lesion affecting the glottal region are examined. This lesion is composed of collagen bundles and fibroblasts arranged haphazardly among moderate numbers of capillaries. There are moderate numbers of neutrophils in the stroma. There also is mild edema. No neoplasia or infectious organisms are seen.</p> <p>MICROSCOPIC FINDINGS: Chronic-active, proliferative and granulomatous, inflammation</p> <p>PROGNOSIS: Good</p> <p>COMMENT: No neoplasia or infectious organisms are seen. These proliferative inflammatory lesions are common. Most of these lesions develop secondary to ruptured ducts of submucosal glands but some are a reaction to a small penetrating foreign body. Excision usually is curative.</p> <p>PATHOLOGIST:</p> <p>PATHOLOGIST: (b) (6) DVM, (b) (6) email: (b) (6), ph: (b) (6)</p>
5/7/2015	I	(b) (6)	For your pet's safety, he/she was intubated for the anesthetic. You may notice

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
5/7/2015	I	(b) (6)	some coughing for the next couple of days. This is normal due to a small amount of irritation to the throat from the endotracheal tube. If the coughing seems excessive please contact our office. (b) (6) received an anesthetic. Please keep him confined until full recovery. Restrict water intake to small amounts at a time for the next 12-24 hours. Restrict food intake to small amounts also; 1/3 of the normal ration this evening. Because the anesthetic can lower his body temperature, keep him where it is warm and dry. Today's oropharyngeal exam revealed a small white nodule, irregular on the left medial aspect, mid way up vocal fold. with suspected kissing lesion on the right aryepiglottic fold; Assymetry to the left and right arytenoid with seemingly inappropriate function of the left with collapse towards midline; both arytenoids were able to abduct when inspiring but were asymmetrical when this was occurring. edematous and swollen corniculate tubercle bilaterally; prominent tonsils which were erythematous and out of crytps - nodule on vocal fold with assymetry of arytenoid function: r/o: pharyngeal or laryngeal dysfunction secondary to inflammation, neurogenic or infiltrative
5/7/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/7/2015 14:10 called owner post procedure. discussed scope findings. and discussed possible causes for findings. no treatment recommended until results available. okay to d/c at 5 pm.
5/7/2015	C	(b) (6)	ENDOSCOPIC EVALUATION Upper Gastrointestinal: oropharyngeal exam: small white nodule, irregular on the left medial aspect, mid way up vocal fold. with suspected kissing lesion on the right aryepiglottic fold; Assymetry to the left and right arytenoid with seemingly inappropriate function of the left with collapse towards midline; both arytenoids were able to abduct when inspiring but were asymmetrical when this was occurring. edematous and swollen corniculate tubercle bilaterally; prominent tonsils which were erythematous and out of crytps Lower Gastrointestinal: Bronchoscopy: Rhinoscopy: Cystoscopy:

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
			<p>Other:</p> <p>Biopsies: 3 biopsies obtained with minimal bleeding</p> <p>Culture/Sensitivity: Visual Inspection: suspected dysfunction of the left arytenoid with nodule present on the left vocal fold.</p> <p>Initial Recommendations: consider doxepin 100 mg PO q 12 hr pending biopsy results.</p>
5/7/2015	C	(b) (6)	<p>IM TREATMENT NEW 5/7/2015</p> <p>Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion</p> <p>nodule on vocal fold with asymmetry of arytenoid function: r/o: pharyngeal or laryngeal dysfunction secondary to inflammation, neurogenic or infiltrative</p> <p>Treatment: no treatment today</p> <p>Recommended Follow-up Care: pending biopsies consider doxepin 100 mg PO q 12 hr</p>
5/7/2015	C	(b) (6)	<p>IM PHYSICAL EXAM Chief Complaint:</p> <p>History: (b) (6) presented for endoscopic evaluation - prior hx:</p> <p>(b) (6) is a 3 yo MN golden retriever presenting for further evaluation of episodes that he has been having since he was 9 months old. He was evaluated in May 2014 and lab work and u/s were performed but did not elucidate the cause of his episodes. He was additionally evaluated by (b) (6) and the owner was told the problem was likely neurological but may not be treatable. The owner says the episodes are becoming more frequent and lasting longer. The episodes are described as extending his neck repeatedly and gagging/choking and swallowing. The owner showed a video at the consult and this behavior was witnessed where (b) (6) would swallow hard</p>

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
------	------	-------	---------

repeatedly and have continual lip licking with a stridorous noise when breathing. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is initiated by drinking and occurred in the exam room after drinking water. Eating is not as much of a trigger. He is eating dry food which the owner waters down. The owner has not tried canned food. She doesn't think that the episodes are related to consistency. He does not have episodes when active and out/about. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. On the evening of an episode he will snore when sleeping. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He is eating well. He seems to be acting normally otherwise. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.

Significant Physical Exam Findings: Mentation: BAR
Temperature: 102.4 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec.
Hydration Status: adequate
Weight: 36.6 kilograms
Body Condition Score: 7/9
Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum; normal cervical palpation
Eyes/Ears: clear OU; fundic exam WNL OU; clean AU
Integument: full coat; no ectoparasites
Peripheral Lymph Nodes: Normal size
Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic
Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful.
Urogenital: neutered male; no prepuce d/c
Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed.

Lab Work: Chemistry: BUN: 11, Creat: 1.4 - NSF
CBC: HCT: 46.9%, WBC: 8.14, neut: 4.10, PLT: 57k

Radiographic Findings: CHIEF COMPLAINT/HISTORY: 5/3/2015. Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure.

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) **Patient:** (b) (6)
Phone: (b) (6) **Species:** Canine **Breed:** Retriever, Golden
Address: (b) (6) **Age:** 6 Yrs. 2 Mos. **Sex:** Neutered Male
Color: Blonde

Date	Type	Staff	History
------	------	-------	---------

FINDINGS: Three views of the thorax are available for review.

No significant abnormalities are present in the extra-thoracic soft tissues, skeletal structures, pleural and mediastinal spaces, pulmonary and cardiovascular structures, as well as in the visible cranial abdomen.

SUMMARY/CONCLUSIONS:

1. Normal thorax with no evidence of megaesophagus.

5/7/2015 L

Chemistry results from (b) (6) **In-clinic**
Laboratory Requisition ID: (b) (6) **Posted** **Final**

Test	Result	Reference Range
ALB =	3.2 g/dL	2.3 - 4.0
ALKP =	73 U/L	23 - 212
ALT =	31 U/L	10 - 125
AMYL =	744 U/L	500 - 1500
BUN/UREA =	11 mg/dL	7 - 27
Ca =	9.4 mg/dL	7.9 - 12.0
Chloride =	112 mmol/L	109 - 122
CHOL =	257 mg/dL	110 - 320
CREA =	1.4 mg/dL	0.5 - 1.8
GGT <	< 0 U/L	0 - 11
GLU =	97 mg/dL	74 - 143
LIPA =	1120 U/L	200 - 1800
PHOS =	4.0 mg/dL	2.5 - 6.8
Potassium =	4.7 mmol/L	3.5 - 5.8
Sodium =	153 mmol/L	144 - 160
TBIL =	0.3 mg/dL	0.0 - 0.9
TP =	6.0 g/dL	5.2 - 8.2
GLOB =	2.8 g/dL	2.5 - 4.5
ALB/GLOB =	1.1	
BUN/CREA =	8	
Na/K =	33	
OSM calc =	303 mmol/kg	

PCV=49% TS= 6.8g/dl (serum norm)

5/7/2015 V

(b) (6)

May 7, 2015 10:20 AM Staff: (b) (6)

Weight : 36.60 kilograms

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
------	------	-------	---------

Temperature : 102.4
Pulse : 100
Respiration : pant
mm pk, crt <2s

5/7/2015 L

Hematology results from (b) (6) **In-clinic**
Laboratory Requisition ID: (b) (6) **Posted** **Final**

Test	Result	Reference Range
HCT =	46.9 %	37.3 - 61.7
HGB =	16.3 g/dL	13.1 - 20.5
MCHC =	34.8 g/dL	32.0 - 37.9
WBC =	8.14 K/uL	5.05 - 16.76
NEUT =	4.10 K/uL	2.95 - 11.64
%NEUT =	50.4 %	
EOS =	0.71 K/uL	0.06 - 1.23
%EOS =	8.7 %	
PLT *	* 57 K/uL L	148 - 484
Retics =	21.5 K/uL	10.0 - 110.0
%Retics =	0.3 %	
RBC =	6.94 M/uL	5.65 - 8.87
MCV =	67.6 fL	61.6 - 73.5
MCH =	23.5 pg	21.2 - 25.9
RDW =	18.1 %	13.6 - 21.7
MPV =	--.-- fL	8.7 - 13.2
PDW =	--.-- fL	9.1 - 19.4
PCT =	--.-- %	0.14 - 0.46
LYMPHS =	2.88 K/uL	1.05 - 5.10
%LYMPHS =	35.4 %	
MONOS =	0.43 K/uL	0.16 - 1.12
%MONOS =	5.3 %	
BASO =	0.02 K/uL	0.00 - 0.10
%BASO =	0.2 %	

5/7/2015 C (b) (6)
RADIOGRAPHIC REPORT

RADIOLOGY REPORT - FINAL 05/07/2015

CHIEF COMPLAINT/HISTORY: 5/3/2015. Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure.

FINDINGS: Three views of the thorax are available for review.

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 21 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
------	------	-------	---------

No significant abnormalities are present in the extra-thoracic soft tissues, skeletal structures, pleural and mediastinal spaces, pulmonary and cardiovascular structures, as well as in the visible cranial abdomen.

SUMMARY/CONCLUSIONS:

1. Normal thorax with no evidence of megaesophagus.

5/7/2015	CK	(b) (6)	Drop off for procedure w/ (b) (6) - CXR, chem III, CBC Reason for Visit: Medicine Procedure Date Patient Checked Out: 05/07/15 Practice TF
----------	----	---------	--

5/6/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/6/2015 11:48 Spoke to O and confirmed (b) (6) procedure for tomorrow. Dropping off between 9:30 -10am. Told O no food after midnight and no water after 6am tomorrow. O knows she will not speak to (b) (6) at drop off. She thanked me for calling.
----------	---	---------	---

5/3/2015	C	(b) (6)	IM TREATMENT NEW 5/3/2015 Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure recommend further evaluation including thoracic radiographs, sedated oral exam and endoscopy +/- fluoroscopy and esophagram. Treatment: no treatment implemented Recommended Follow-up Care: to return Thursday for further evaluation - chemistry, CBC thoracic radiographs, oral exam and endoscopy
----------	---	---------	--

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.	Color:	Blonde

Date	Type	Staff	History
5/3/2015	C	(b) (6)	<p>IM PHYSICAL EXAM</p> <p>Chief Complaint:</p> <p>History: (b) (6) is a 3 yo MN golden retriever presenting for further evaluation of episodes that he has been having since he was 9 months old. He was evaluated in May 2014 and lab work and u/s were performed but did not elucidate the cause of his episodes. He was additionally evaluated by (b) (6) and the owner was told the problem was likely neurological but may not be treatable. The owner says the episodes are becoming more frequent and lasting longer. The episodes are described as extending his neck repeatedly and gagging/choking and swallowing. The owner showed a video at the consult and this behavior was witnessed where (b) (6) would swallow hard repeatedly and have continual lip licking with a stridorous noise when breathing. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is initiated by drinking and occurred in the exam room after drinking water. Eating is not as much of a trigger. He is eating dry food which the owner waters down. The owner has not tried canned food. She doesn't think that the episodes are related to consistency. He does not have episodes when active and out/about. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. On the evening of an episode he will snore when sleeping. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He is eating well. He seems to be acting normally otherwise. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.</p> <p>Significant Physical Exam Findings: Mentation: BAR Temperature: 101.7 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec. Hydration Status: adequate Weight: 36.7 kilograms Body Condition Score: 7.9 Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum; normal cervical palpation Eyes/Ears: clear OU; fundic exam WNL OU; clean AU Integument: full coat; no ectoparasites Peripheral Lymph Nodes: Normal size Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic</p>

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 23 of 30

Date: 4/20/2018 5:17
PM

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
			Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful. Urogenital: neutered male; no prepuce d/c Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed. Lab Work: none performed today Radiographic Findings: none performed today
5/3/2015	CK	(b) (6)	Reason for Visit: Recheck Date Patient Checked Out: 05/03/15 Practice (b) (6)
11/21/2014	C	(b) (6)	COMMUNICATIONS WITH CLIENT 11/21/2014 13:54 SWO - Myasthenia gravis test was negative, and so the next step for (b) (6) would be an esophageal scope to determine the cause for his clinical signs. Owner thankful, will call and schedule with IM after thanksgiving.
11/14/2014	CK	(b) (6)	swallowing issues Reason for Visit: Consult Date Patient Checked Out: 11/14/14 Practice (b) (6)
5/31/2014	C	(b) (6)	IM TREATMENT NEW 5/31/2014 Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with usual episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, primary GI disease, neuro disease -functional problem vs focal seizure Chemistry - NSF CBC - NSF T4: WNL No evidence of endocrine or metabolic disease based on screening labs.

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
------	------	-------	---------

Treatment: no treatment implemented at this time

Recommended Follow-up Care: recheck after owner discusses steps with insurance company - to consider chest radiographs, neuro consult, sedated oral exam and endoscopy

5/31/2014 C

(b) (6)

COMMUNICATIONS WITH CLIENT

5/31/2014 11:29

Spoke with owner and relayed that blood results are all normal. owner would like to speak with insurance prior to scheduling appt. next steps could be to get neuro consult, sedated oral exam and endoscopy

5/31/2014 L

Hematology results from

(b) (6)

Requisition

ID:	(b) (6)	Posted	Final	Reference Range
Test		Result		
HCT		46 %		36 - 60
HGB		15.9 g/dL		12.1 - 20.3
MCHC		34.6 g/dL		30 - 38
WBC		8.1 10 ³ /uL		4.0 - 15.5
Bands		0 %		0 - 3
RBC		6.3 10 ⁶ /uL		4.8 - 9.3
MCV		73 fL		58 - 79
MCH		25.2 pg		19 - 28
Platelet C		158 10 ³ /uL L		170 - 400
Platelet E		ADEQUATE		ADEQUATE -
Neutrophil		49 % L		60 - 77
Lymphocyte		46 % H		12 - 30
Monocytes		4 %		3 - 10
Eosinophil		1 % L		2 - 10
Basophils		0 %		0 - 1
Absolute N		3969 /uL		2060 - 10600
Absolute B		0 /uL		0 - 150
Absolute L		3726 /uL		690 - 4500
Absolute M		324 /uL		0 - 840
Absolute E		81 /uL		0 - 1200

Ascn: (b) (6) Profile: CBC

Platelet count reflects the minimum number due to platelet clumping.

5/31/2014 L

Chemistry results from

(b) (6)

Requisition

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

ID:	Posted	Final
Test	Result	Reference Range
ALB	3.5 g/dL	2.7 - 4.4
ALKP	42 U/L	5 - 131
ALT	28 U/L	12 - 118
AMYL	515 U/L	290 - 1125
AST	20 U/L	15 - 66
BUN/UREA	14 mg/dL	6 - 31
Ca	11.1 mg/dL	8.9 - 11.4
Chloride	109 mEq/L	102 - 120
CHOL	298 mg/dL	92 - 324
CK	40 U/L L	59 - 895
CREA	1.2 mg/dL	0.5 - 1.6
GGT	6 U/L	1 - 12
GLU	91 mg/dL	70 - 138
LIPA	428 U/L	77 - 695
Mg	1.7 mEq/L	1.5 - 2.5
PHOS	4.0 mg/dL	2.5 - 6.0
Potassium	4.8 mEq/L	3.6 - 5.5
Sodium	145 mEq/L	139 - 154
TBIL	0.1 mg/dL	0.1 - 0.3
TP	5.9 g/dL	5.0 - 7.4
TRIG	113 mg/dL	29 - 291
GLOB	2.4 g/dL	1.6 - 3.6
A/G Ratio	1.5 Ratio	0.8 - 2.0
B/C Ratio	12 Ratio	4 - 27

5/31/2014 L Endocrinology results from (b) (6)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Test Result Reference Range
 T4 1.6 ug/dL 0.8 - 3.5
 Ascen: (b) (6) Profile: Total T4

5/31/2014 L Miscellaneous results from (b) (6)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Ascen: (b) (6) Profile: Superchem
 RE: 1050 Na/K Ratio 30
 RE: 11067 Comment
 Hemolysis 1+. No significant analyte interference.

5/30/2014 C (b) (6) ULTRASOUND REPORT NEW

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client:	(b) (6)	Patient:	(b) (4)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.	Color:	Blonde

Date	Type	Staff	History
------	------	-------	---------

Referring Vet: Hospital:

ULTRASONOGRAPHIC FINDING: # of
Films:
Written: 5/30/2014

Liver The liver appeared diffusely normal; the liver margins were smooth.
Gallbladder The gall bladder appeared normal-the visible biliary tree is not dilated.
Spleen The spleen appeared normal.
Right Kidney The right kidney had good corticomedullary distinction; Smooth capsule; there were no nephroliths and the renal pelvis was not dilated. The right kidney measured: 6.73 cm
Left Kidney The left kidney had good corticomedullary distinction, Smooth capsule; there were no nephroliths and the renal pelvis was not dilated. The left kidney measured: 6.55 cm
Urinary Bladder The urinary bladder appeared normal; no urolith or masses seen.
Right Adrenal The right adrenal was normal size and shape measuring: 0.45 cm
Left Adrenal The left adrenal was normal size and shape measuring: 0.54 cm
Stomach The stomach appeared normal and empty of ingesta
Small Intestines The small intestine appeared normal in layering and thickness measuring 0.51 - duodenum
Colon The colon appeared normal.
Pancreas The pancreatic region appeared normal.
Lymph Nodes There was no obvious mesenteric or sublumbar lymphadenopathy.
Prostate Appeared small and symmetrical for a neutered male.
Uterus
Testicles Not visualized - neutered.
Ovaries

Additional Comments: There was no free fluid noted. There were no overt abnormalities noted to explain patient's clinical signs.

5/30/2014	C	(b) (6)	IM TREATMENT NEW 5/30/2014
Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with usual episodes of swallowing and what appears to be "air sucking" behavior. ddx include			

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
			<p>laryngeal, pharyngeal disease, esophageal disease, primary GI disease, neuro disease -functional problem vs focal seizure</p> <p>Treatment: no treatment implemented at this time</p> <p>Recommended Follow-up Care: pending lab results; consider fluroscopy, sedated oral exam and endoscopy with neuro exam prior.</p>

5/30/2014 C

(b) (6)

IM PHYSICAL EXAM NEW
5/30/2014 22:58

Presenting Complaint:

History: (b) (6) is a 2 yo MN golden retriever presenting for episodes that the owner describes and extending his neck repeatedly and gagging/choking. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is not associated with eating or drinking specifically but does occur after drinking. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He used to have diarrhea until his diet was switched to natural balance fish and sweet potato. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. These episodes seemed to start when (b) (6) was 9 mo old and has been progressively more frequent. The last 1-2 weeks he is having daily signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.

Mentation: BAR

Temperature: 102 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec.

Hydration Status: adequate

Weight: 37.3 kilograms

Body Condition Score: 7.9

Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum; normal thyroid palpation

Eyes/Ears: clear OU; fundic exam WNL OU; clean AU

Integument: full coat; no ectoparasites

Peripheral Lymph Nodes: Normal size

Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic

Abdominal Palpation: There was no obvious mass or organomegaly, and the

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History																				
			<p>abdomen was non-painful.</p> <p>Urogenital: neutered male; no prepuce d/c</p> <p>Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed.</p> <p>Rectal: Normal</p> <p>Lab Work: cbc, superchem, T4 pending to (b) (4)</p> <p>Radiographic Findings: none performed</p>																				
5/30/2014	I	(b) (6)	(b) (6) has unusual signs that appear to be a lot of swallowing air. At this time it is not clear why this is happening; however, our plans to further evaluate this include lab work to rule out metabolic abnormalities, GI malabsorption or thyroid problems. These tests are pending and I will call you when results are available. The next steps would include a neurology consultation, sedated oral exam followed by endoscopy to evaluate his clinical signs +/- chest radiographs.																				
5/30/2014	V	(b) (6)	May 30, 2014 12:26 PM Staff: (b) (6)																				

			Weight : 37.30 kilograms																				
5/30/2014	V		May 30, 2014 12:26 PM																				

5/30/2014	CK	(b) (6)	Consult for possible scope Reason for Visit: Consult Date Patient Checked Out: 05/30/14 Practice TF																				
5/30/2014	L	(b) (6)	Chemistry results from (b) (6) Services Requisition <table><tr><td>ID:</td><td>(b) (6)</td><td>Posted</td><td>Final</td><td></td></tr><tr><td>Test</td><td>Result</td><td></td><td></td><td>Reference Range</td></tr><tr><td>COBALAMIN</td><td>442 ng/L</td><td></td><td></td><td>284 - 836</td></tr><tr><td>FOLATE</td><td>6.9 ug/L</td><td></td><td></td><td>4.8 - 19.0</td></tr></table> <p>Asc: (b) (6)</p> <p>SS MN CANINE</p>	ID:	(b) (6)	Posted	Final		Test	Result			Reference Range	COBALAMIN	442 ng/L			284 - 836	FOLATE	6.9 ug/L			4.8 - 19.0
ID:	(b) (6)	Posted	Final																				
Test	Result			Reference Range																			
COBALAMIN	442 ng/L			284 - 836																			
FOLATE	6.9 ug/L			4.8 - 19.0																			
5/29/2014	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/29/2014 11:08 swo confirmed 5/30 apt at 1130																				

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
5/27/2014	C	(b) (6)	RECEPTION ACTIONS NOTE Receved fax from (b) (6). Placed in box under (b) (6)
5/27/2014	C	(b) (6)	RECEPTION ACTIONS NOTE ***ADDENDUM 5/27/2014 recv'd fax from (b) (6) and (b) (6) in black bx under (b) (6) ADDENDUM on 5/27/2014 at 12:49:24 from (b) (6) Recv'd fax from (b) (6). Placed in black box under (b) (6)

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

CARDIOLOGY DIET HISTORY FORM

Please answer the following questions about your pet

Pet's name: _____ Owner's name : _____ Today's date: _____

1. How would you assess your pet's appetite? (mark the point on the line below that best represents your pet's appetite)

Example: **Poor** _____ **Excellent**

Poor _____ **Excellent**

2. Have you noticed a change in your pet's appetite over the last 1-2 weeks? (check all that apply)

☐ Eats about the same amount as usual ☐ Eats less than usual ☐ Eats more than usual
☐ Seems to prefer different foods than usual ☐ Other _____

3. Over the last few weeks, has your pet (check one)

☐ Lost weight ☐ Gained weight ☐ Stayed about the same weight ☐ Don't know

4. Please list below ALL pet foods, people food, treats, snack, dental chews, rawhides, and any other food item that your pet currently eats. Please include the brand, specific product, and flavor so we know exactly what your pet is eating.

Food (include specific product and flavor) Form Amount How often? Fed since

Examples are shown in the table – **please provide enough detail that we could go to the store and buy the exact same food.**

Food (include specific product and flavor)	Form	Amount	How often?	Fed since
Nutro Grain Free Chicken, Lentil, & Sweet Potato Adult	dry	1 ½ cup	2x/day	Jan 2018
85% lean hamburger	microwaved	3 oz	1x/week	Jan 2015
Pupperoni original beef flavor	treat	½	1x/day	Aug 2015
Rawhide	treat	6 inch twist	1x/week	Dec 2015

*Any additional diet information can be listed on the back of this sheet

5. Do you give any dietary supplements to your pet (for example: vitamins, glucosamine, fatty acids, or any other supplements)? ☐ Yes ☐ No If yes, please list which ones and give brands and amounts:

Brand/Concentration

Amount per day

Taurine	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____
Carnitine	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____
Antioxidants	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____
Multivitamin	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____
Fish oil	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____
Coenzyme Q10	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____	_____

Other (please list):

Example: Vitamin C Nature's Bounty 500 mg tablets – 1 per day

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

6. How do you administer pills to your pet?

☐ I do not give any medications ☐ I put them directly in my pet's mouth without food
☐ I put them in my pet's dog/cat food ☐ I put them in a Pill Pocket or similar product
☐ I put them in foods (list foods): _____

Information below to be completed by the veterinarian:

Current body weight: _____ kg

Current body condition score (1-9): _____/9

Muscle Condition Score: ☐ normal muscle ☐ mild muscle loss ☐ moderate muscle loss ☐ severe muscle loss

From: [Hartogensis, Martine](#)
To: [Palmer, Lee Anne](#); [Jones, Jennifer L](#); [Rotstein, David](#); [Burkholder, William](#); [Norris, Anne](#); [DeLancey, Siobhan](#)
Cc: [McDermott, Patrick](#)
Subject: FW: DCM Comms Going Live Today
Date: Thursday, July 26, 2018 11:59:22 AM
Attachments: [image001.jpg](#)

Just a few points from PFI before our webinar today.

Martine

From: Tabor, Peter [mailto:peter@petfoodinstitute.org]
Sent: Thursday, July 26, 2018 11:38 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good morning, Martine. First, thanks for this opportunity to engage with FDA on this issue. As difficult as it can be at times, I think this is positive and consistent with PFI members' commitment to product safety and pet health. The more we can work together and the sooner in the process, the better.

We have a good game of phone tag going so just wanted to send a quick note in case we don't speak before the webinar at 2:00pm.

- Per our conversation, we'll pick up where we left off. I'll start posing the questions we sent o FDA in advance of the 19 July webinar.
- I know we're scheduled for one hour but I imagine there will be a lot of interest, so please advise if you/your colleagues are ok with going longer if necessary – hopefully no more than 10-15 minutes past our allotted time.
- One question I'll pose if others don't, perhaps near the end of the webinar, relates to FDA's messaging going forward on this issue. There's a lot of concern among pet food makers that an entire sector (grain-free) and a few ingredients (peas, lentils, legumes and potatoes) have been indicted when it appears that the issue is really about formulation by certain pet food makers since many grain-free diets and/or diets containing the aforementioned ingredients are not implicated. Also, any FDA messaging usually leads to a spike in calls to pet food makers' call centers, even if they don't make the products FDA may be investigating – the jerky treats investigation is a perfect example.

That's all for now. I am unavailable until around 1:00pm but feel free to call after that if we need to speak before the webinar at 2:00pm.

Regards,

Peter

O: + (b) (6)
M: + (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 7:15 PM
To: Tabor, Peter <peter@petfoodinstitute.org>
Cc: (b) (6); Milton, Nanette <Nanette.Milton@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Ok, thanks Peter!

Nanette, can you work with (b) (6) to schedule an hour continuation of the PFI webinar? We got cut off after the first hour...

Looks like Tuesday around 11 might work.

Thanks in advance!!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 19, 2018 at 4:40:25 PM EDT
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Cc: (b) (6)
Subject: RE: DCM Comms Going Live Today

Hi, Martine. Sorry this message is coming to you later than expected. If you could let us know whether Tuesday, 24 July in the morning (11:00am ET start time) works for you, I can notify our participants and get it on everyone's calendar.

Thanks again and we'll be in touch.

Regards,

Peter

O: + (b) (6)
M: + (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 11:30 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

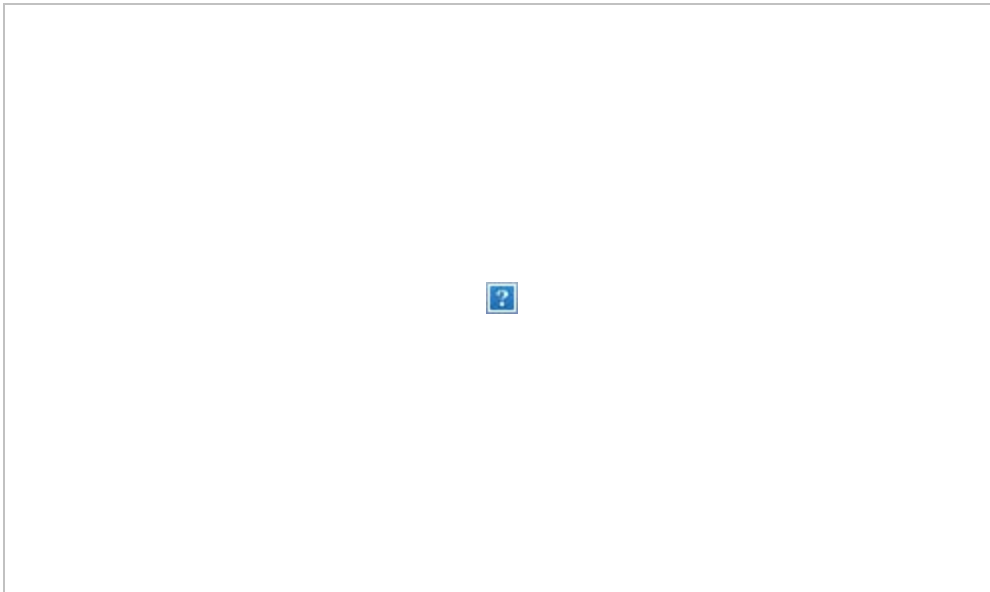
Hi Peter,

No worries and I am available now. (b) (6)

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 19, 2018 11:29 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Sorry about the technical difficulties. GoToMeeting is down around the country, apparently – see below.



Please let me know when you're free to chat. Hopefully we can find time in the next few days to reschedule.

Regards,

Peter

O: (b) (6)
M: + (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 9:50 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Welcome, and the epi slides...

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 19, 2018 9:42 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Great – thanks.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 9:40 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Here are the Vet-LIRN slides. I will be sending the epi slides in a bit.

Thanks!!

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 19, 2018 9:11 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good morning, Martine. Will you/your FDA colleagues want to present anything on the screen? I recall during our last webinar with you that we could not give you presenter privileges in GoToMeeting – something to do with your IT/firewall, I think. If you want me to put anything on the screen, please send it to me. I have the redacted version of your presentation from June and the public announcement. Thanks.

Regards,

Peter

O: + (b) (6)
M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Thursday, July 19, 2018 6:57 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: Re: DCM Comms Going Live Today

Ok, sounds good and thank you!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 18, 2018 at 10:40:10 PM EDT
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: Re: DCM Comms Going Live Today

Thanks, Martine. Most participants PFI producer members participants are SMEs, with a few corporate/legal reps in the mix. I really want this webinar to focus on the science behind FDA's notice and got broad agreement from members during our prep for this meeting today.

Sent using OWA for iPhone

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Wednesday, July 18, 2018 7:16:01 PM
To: Tabor, Peter
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Thank you so much for the list. Here are the folks invited from CVM:

Bill Burkholder
Siobhan DeLancey
Dave Rotstein
Pat McDermott
Jennifer Jones
Lauren Carey
Anne Norris
Lee Anne Palmer
David Edwards
Sarah Nemser
Janice Steinschneider
John Baker
Eric Nelson
Neal Bataller

Also, I recognize a few names on your list, but can you tell me (in general) if the PFI participants are mainly SMEs or leadership? We just want to get an idea of our audience.

Thanks very much in advance!

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Wednesday, July 18, 2018 4:58 PM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Attached is a list of PFI member participants in tomorrow's webinar. Also attached is the proposed agenda and the questions we sent you earlier, just for reference.

Did you already send us a list of FDA participants in the webinar? If not, can you send it this afternoon/evening?

Thanks and we look forward to the call.

Regards,

Peter

O: (b) (6)

M: (b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Monday, July 16, 2018 9:29 PM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter!

Looks great! Looking forward to our meeting Thursday!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 16, 2018 at 2:17:16 PM EDT
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Not sure if you're still in Denver or on your way home – I hope the AVMA meeting went well. I wanted to get your input on a draft agenda for the Thu webinar, to make the most of everyone's time.

Proposed Agenda

- Welcome, introductions and PFI anti-trust policy reminder – PFI, FDA (10 minutes)
- Overview of the issue, including the FDA notice and the data FDA presented to PFI in June – FDA (30 minutes, including Qs from PFI)
- Review of questions PFI sent to FDA for the webinar – PFI, FDA (50 minutes)
- Open Q&A – PFI, FDA (20 minutes)
- Conclusion and adjourn (10 minutes)

Please take a look and reply to me at your earliest convenience (today if possible) with thoughts or suggested tweaks. Thanks and safe travels home.

Regards,

Peter

O: + (b) (6)

M: + (b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Sent: Thursday, July 12, 2018 11:11 AM

To: Tabor, Peter <peter@petfoodinstitute.org>

Subject: RE: DCM Comms Going Live Today

Hi Peter,

Yes, let's touch base. I am in a meeting until 12 and can call you then. Does that work for you?

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]

Sent: Thursday, July 12, 2018 10:45 AM

To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Subject: Re: DCM Comms Going Live Today

Thanks for the heads-up, Martine. Very kind of you. My colleagues and I will review the info and I'll be in touch this afternoon.

I was under the impression that our webinar next week would inform FDA's and pet food makers' understanding of the issue, perhaps before any public messaging was issued. So this is

a little concerning. I imagine the public reaction might be quite severe and impact products that aren't implicated by FDA. Hopefully we can chat this afternoon.
Thanks again for reaching out.

Sent using OWA for iPhone

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Sent: Thursday, July 12, 2018 10:34:41 AM

To: Tabor, Peter

Subject: DCM Comms Going Live Today

Hi Peter,

I just left you a VM. I am attaching the DCM comms materials that will be going live today. Please feel free to share them with your members and let me know if you have any questions.

Martine

Martine Hartogenesis, DVM
FDA Center for Veterinary Medicine
Deputy Director, Office of Surveillance & Compliance
(240) 402-7178

From: Hartogensis, Martine
To: Palmer, Lee Anne; Jones, Jennifer L
Cc: Rotstein, David; Norris, Anne; Burkholder, William
Subject: FW: DCM Information - Champion Petfoods
Date: Tuesday, August 21, 2018 2:52:58 PM
Attachments: Jim Wagner vCard.vcf

Hi Lee Anne,

So sorry to bug you again! Anyway, just wondering if [REDACTED] (b) (5)

[REDACTED]

Many thanks in advance!

Martine

From: Jim Wagner [<mailto:JWagner@championpetfoods.com>]
Sent: Tuesday, August 21, 2018 1:02 PM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: DCM Information - Champion Petfoods

Dr. Hartogensis,

Good morning. I was speaking with Peter Tabor this morning regarding the DCM investigation.

I'm wondering if you could share with me any information regarding [REDACTED] (b) (4)

[REDACTED] (b) (4)

Thanks very much for your consideration.

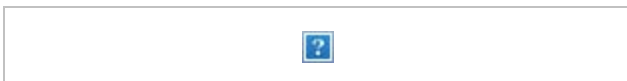
Kind regards,

Jim Wagner

VP | Quality Assurance & Regulatory
Champion Petfoods USA Inc

C: [REDACTED] (b) (6)

12871 Bowling Green Rd. | Auburn, Kentucky, United States | 42206



The information contained in this message is confidential and is intended for the addressee only. If you have received this message in error or there are any problems please notify the originator immediately. The unauthorized use, disclosure, copying or alteration of this message is strictly forbidden.

From: [Hartogenesis, Martine](#)
To: [Jones, Jennifer L](#); [Burkholder, William](#); [Palmer, Lee Anne](#); [Rotstein, David](#)
Cc: [Norris, Anne](#)
Subject: FW: Feedback on the September 4 webinar
Date: Monday, September 10, 2018 7:58:14 AM
Attachments: [Petfood Industry CDM Webinar Questions.xlsx](#)

Good Morning!

Just passing these questions along FYI that were sent in last week following the pet food industry.com webinar. Just some issues to consider in the DCM investigation. (b) (5)

[REDACTED]

Martine

From: Debbie Phillips <DPPhillips@wattglobal.com>
Sent: Friday, September 07, 2018 4:46 PM
To: pfit nutrition <pfitnutrition@gmail.com>; Freeman, Lisa <Lisa.Freeman@tufts.edu>; Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Cc: Norris, Anne <Anne.Norris@fda.hhs.gov>
Subject: Feedback on the September 4 webinar

Hello Greg, Lisa and Martine:

Thank you again for being part of our webinar on Tuesday. It garnered what I believe are record numbers in every category in terms of the webinars we organize:

Total Registrants = 683
Live Attendees = 360
Survey Responses = 165

Typically our webinars draw about 200-300 registrants, with live participation at 30-40%. So these results show what an important topic this is for the pet food industry.

I'm not sure how the survey response rate ranks; I can tell you that the responses showed overwhelmingly that the topic was relevant or very relevant to respondents, and they were satisfied to very satisfied with the webinar.

We also received what I believe is a record number of questions and comments during the webinar: 97! That's why I couldn't get to all of them ... but I am sharing them here in the attached spreadsheet. I color-coded them for the person I thought was most appropriate (if the questioner didn't specify the speaker) or as general comments or questions that were answered during the webinar. (Sorry, I tried sorting according to the color but my Excel skills only go so far!)

I don't necessarily expect you to answer the ones directed to you, but I hope you might find them

helpful as you continue to study this issue or if you write about it.

Please let me know if you have any questions. Thanks again!

Have a good weekend,
Debbie

DEBBIE PHILLIPS-DONALDSON
Editor-in-Chief, Petfood Industry/Petfood Forum
www.PetfoodIndustry.com
Watt Global Media
Office: +1.815.966.5424
Mobile: (b) (6)
dphillips@wattglobal.com
Skype: (b) (6)
www.gotomeet.me/DebbiePhillipsDonaldson

Register soon for upcoming Petfood Forum conferences!

Petfood R&D Showcase (Kansas State University, Manhattan, Kansas): October 9-11

Petfood Forum and Petfood Innovation Workshop 2019: April 29-May 1


Petfood Forum Europe 2019: June 13

Visit www.PetfoodForumEvents.com

Petfood Industry Webinar. 180904. FDA p

First Name	Last Name	Email Address
(b)	(4)	

(b) (4)



(b) (4)

(b) (4)

Possible dog food link to cardiomyopathy - Question & Answer

Blue (H) = Hartogenesis Green (F) = Freeman Purple (A) = Aldrich Orange (G) = General questions/comments Black (y) = Already

Question Asked

H: Potatoes have been sold at very high levels for many more years than Grain Free. How can potatoes be separated out and questioned differently since they have been sold for many more years and no evident concern? Maybe solve quicker and y: What percentage of the dogs with normal taurine levels had both whole blood and plasma taurine tested.

A: Can you elaborate on the soluble fiber-aurine interaction? Would insoluble fiber generate the same effect?

When Dr. Aldrich said potatoes are playing some part in this -It it white and or sweet potatoes?.

F: Can you ask Dr. Freeman about her research in this, her survey she is asking companies to fill out, and how this data will be reported?

A: For Greg - could he make an estimate on the highest level of legumes to be recommended in a product?

F: should we carefully advise use of grain free diets for apparently "at risk" breeds/types? Esp. for dogs where grain free is human choice rather than canine need.....
For Dr. Freeman: In the study that found Golden Retrievers and Cocker Spaniels had taurine deficiency, was this thought to be a genetic issue? Golden are not usually mentioned in the list of "typical breeds", but Cocker Spaniels are. Also, you y: Can Dr. Hartogenesis repeat the number of cases again and what the break out is? She went really fast. Thank you

Is there an increasing trend of case reporting after FDA announcement?

H: Will FDA take further steps regards this issue? If yes, what the timeline will be?

I represent a vet centric whole food nutrition company and we make both grain and grain free recipes made with real food. Our nutritionist learned about the issue through UC Davis 6 months ago. At that time we tested a cohort of dogs on our beef Sorry - I meant potatoes are the second ingredient.

We have also failed to see any cardiac issues in year long feeding trials an in our almost 8 years of food production in whole food recipes.

Isn't ingredient quality (ie: meal vs real USDA certified meat) a primary factor in amino acid nutrition?

Have any cases involved commercially prepared fresh, whole food diets?

What about working with companies that make grain free diets that do not have this issue? We'd be interested in working with the FDA.

y: as anyone looked at the source of Taurine used in these cases? You can get taurine from China for less than half the cost from japan or NZ.

How many companies involved? I have been told it only involves 3 companies?

Please define a "Boutique diet?"

Please define a "bag diet?"

With 6 of the top selling 7 formulas sold in US being grain free wouldn't you expect a higher number affected formulas being grain free?

A: Do you think this can have anything to do with the potential lectin content of these foods as this can affect the absorption of nutrients?

Dr. Aldrich - with the rise now of the veggie and vegan recipes aren't you afraid that these kind of health problems due probably to some misformulation will occur more frequently ? Because grain free just open the door to these new type of

y: Does this still appear to be fairly breed specific

Amy cases of mitral valve disease associated with these diets

A: Are there new varieties of legumes being grown & used

y: Was the taurine source looked at in the diet formulas? I am wondering if there may be an improvement with taurine supplementation in the diet vs taurine coming from the ingredients.

For the dogs taurine, was whole blood, serum or both tested?

Where are the recommendations Dr. Freeman discussed posted?

H: is the current sample size statistically significant?

G: How many dogs eat grain-free diets or diets with a lot of legume seeds in them?

A: I am not sure exactly how to phrase this but how often are the dietary needs of dogs and cats tested? Every couple years to address any changes of need? ie Taurine levels

dietary needs in commercial pet food that is

Also being commercial frozen raw pet food doesn't have things like Legumes and are very high in organ meat - how does this effect the Taurine issue?

G: get a lot of question from my customers that many vets aren't getting the nutrition training they need. Very Hills and RC centered. Any comments on that? Do they have the wrong idea?

y: Do you have a recommendation for dog owners feeding exotic/grain free/legumes at the moment?

Do you have any figures for this from other countries? For example the UK, where grain free is very popular at the moment

A: does chicken meal have lower levels of taurine and methionine than chicken by-product meal

Does this reflect in any way on products that have passed AAFCO feeding trials for maintenance that are now correlated with DCM? Are AAFCO feeding trials adequate to identify this type of issue?

y: Will Dr. Freeman please define "boutique"

A: Is Dr. Aldrich saying that formulating via the "nutrient levels" method not sound??

y: he seems to be saying that if they haven't done feeding trials, this is where we are going to end up?

H: Is there a direct correlation between pulses and potatoes with DCM? A recent Washington Post article seemed to point more towards pulses/legumes rather than potatoes.

y: Is this limited to the US? Any reports coming from Europe?

Pending more information, is there any reason not to supplement with L-Taurine and L-Carnitine? Any feedback on the dosing for dogs?

1) A: What is a high level of pulse / legume ingredient in a dog food?

2) H: Diets fed to case animals - any difference in case numbers between diets containing whole pulses vs pulse fractions (whole peas vs pea protein for example)

A: Dr. Aldrich mentioned increased fermentation in the colon and I wondered if anyone is studying that potential connection?

y: Has this webinar been submitted for veterinary CE units?

A: if rendered meal is a potential issue because of variability of amino acids, is fresh meats that are lightly cooked a better source? fresh cooked pet foods using muscle meats that are not rendered meals may be fine. please make a comment on

G: talking to vets will only get the vet to suggest a diet that they sell....this isn't necessarily the answer

Are veterinarians able to give the right nutritional advice, knowing that most veterinarians are not nutritionists, and had very limited nutrition training in vet school

H: Potatoes are not legumes or pulses. They are tubers, also considered nightshades. Are we confident they are also included in this or do the potato foods being investigated also include legume ingredients?

What do we know about the type of protein in the diets investigated? Could the problem be that legumes are very high in protein and so the protein levels of these foods are high but the MEAT protein is not? Wouldn't that cause a deficiency in an

y: please define "Boutique diet"

define "typical ingredients"

H: are pet food manufacturers required to test a breakdown of amino acids along with their protein content?

what percent of those ~150 were potato based and not legume/pulse based?

y: sounds like you're saying validation by feed trials is even more important. yes?

G: sounds like diet VARIATION might be an easy recommendation. should we make that one?

F: Jennifer, Does anyone of them know the taurine value in those kind of diets?

if a pet owner has a dog breed that is predisposed to DCM (great dane or boxer, for instance), and they are feeding a grain free diet, would it be recommended to have the dog tested even if the dog has not shown any signs of illness and "appears

H: Could there be a role played by solanine or saponin that come from tubers and legumes?

Do we foresee this causing AAFCO to change their nutrient level recommendations for any of the amino acids?

y: Can you give an example of a exotic, boutique, bag diet...ingredients etc that you reference that were involved in the cases reported as possible association to DCM

With the multitude of "grain free" diets available...what would your message be to the public about the grain free diets that are being fed to date and how to choose a grain free diet

H: Has a link to Selenium availability been studied deeply as research has found that selenium availability is often decreased by certain processing steps?

Is this study only related to kibble foods? Has there been a link to DCM to real, whole peas, or just pea derivatives used in kibble? If so, what's the maximum percentage of real peas you'd recommend having in a recipe?

G: Many veterinarians have no idea about foods and are not aware of the recent issues being discussed today? What then.

H: Does the FDA data support Dr. Freeman's assessment that smaller companies and exotic ingredients are implicated?

For the prospective study, is the food and biological (blood, feces, urine) just analyzing for taurine or also for all the sulfur amino acids, carnitine, betaine, choline, B6, B12, and folic acid? All of these participate in sulfur amino acid metabolism. Are other attributes of the animal being examined as well, specifically: estimate of body fat, age, level of exercise, and genetic (rather than phenotypic) evaluation.

When FSMA was implemented most companies moved to using greater temperatures to mitigate bacterial contamination, has anyone considered that we seriously ramped up heat damaged protein because of this? Does everyone understand that It appears that whole blood and plasma taurine are the primary measures being used to assess taurine status, but these values do not appear to correlate with DCM in many cases. Are there any other biomarkers of taurine status or taurine- Given the variability in taurine status in cases vs. controls (similar to Dr. Freeman's statement - many cases are not taurine responsive), what other nutrients may be involved?

Given this issue, what is the chance that AAFCO will work on providing a taurine recommendation for dogs in the future? It is unknown why the taurine-responsive DCM publications from the early 2000's were apparently ignored by AAFCO. Will it be

y: Have one specific diet or company been common in these cases?

F: Question for Dr Freeman please: May I ask the age of the dogs which have DCM but not Taurine deficient

y: Question for Dr Aldrich please: Would adding Taurine to the diet help when some dogs are showing a good or high level of Taurine in testing?

Since grain free canine diets are so popular, wouldn't it be reasonable to assume that it's not unusual for the majority of the diets to be grain free?

F: Hi Umesh from India, what was approximate duration of feeding grain free diets in affected dogs before developing DCM
Thank you

H: Has the FDA or cardiac vets rules out genetics in the cases being discussed? Thanks

y: AAFCO doesn't list taurine as an essential nutrient for dogs--you said that you looked at the foods and they weren't taurine deficient. What does that mean?

H: In regards to added legumes, is alfalfa considered one of the suspect ingredients?

F: It has been recommended that whole blood taurine levels are preferred over plasma taurine levels. UC Davis is one lab that does these however there is another lab that prefers 'plasma' as the sample of preference based on the equipment being

y: Do those patients w/ 'diet associated DCM' that have normal or high taurine levels respond to taurine supplementation in regards to the DCM changes?

what do you mean by Typical ingredient foods to go back to?

A lot of foods with grain have peas and pea protein also, so it depends on the %, and they would have lower % most likely?

A: are some meat proteins that are better than others for Taurine production.

G: i don't think you can label just the small manufacturers, because large ones also use exotic ingredients.

no way, Vet's will suggest Hill's and Royal Canin before better foods with better ingredients Vets have just started to get involved with foods in the past few years I think food is the last thing they are knowledgeable about in my opinion

H: Question for Dr Martine Hartogensis - Has the FDA looked at other issues that could lead to lower taurine status? For example trace mineral status? Legumes are higher in phytates which can bind minerals and cause similar issues? Also, has Question for Dr Martine Hartogensis: How many of the offending foods actually have supplied analyticals and digestibility information?

y: would anyone on the staff recommend their friends and family to feed grain free diets using these questionable ingredients? would you recommend them to stop feeding these diets?

/ answered during webinar

From: Carey, Lauren
To: Hartogensis, Martine; Jones, Jennifer L; Nemser, Sarah; Palmer, Lee Anne; Rotstein, David
Subject: RE: DCM Comms Going Live Today
Date: Thursday, July 19, 2018 9:27:38 AM
Attachments: PFI - 7-18-2018 DCM Presentation.ppt

Hi Martine,

Slides attached. I'm willing to make any changes. Just let me know.

Thanks,
Lauren

From: Hartogensis, Martine
Sent: Thursday, July 19, 2018 9:23 AM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: FW: DCM Comms Going Live Today

Hi!

If you are comfortable and want to send me slides for the webinar today, that would be great. PFI can put them on the shared screen.

Thanks!!
Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 19, 2018 9:11 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good morning, Martine. Will you/your FDA colleagues want to present anything on the screen? I recall during our last webinar with you that we could not give you presenter privileges in GoToMeeting – something to do with your IT/firewall, I think. If you want me to put anything on the screen, please send it to me. I have the redacted version of your presentation from June and the public announcement. Thanks.

Regards,

Peter

O: (b) (6)
(b) (6)

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>

Sent: Thursday, July 19, 2018 6:57 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: Re: DCM Comms Going Live Today

Ok, sounds good and thank you!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 18, 2018 at 10:40:10 PM EDT
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: Re: DCM Comms Going Live Today

Thanks, Martine. Most participants PFI producer members participants are SMEs, with a few corporate/legal reps in the mix. I really want this webinar to focus on the science behind FDA's notice and got broad agreement from members during our prep for this meeting today.

Sent using OWA for iPhone

From: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Sent: Wednesday, July 18, 2018 7:16:01 PM
To: Tabor, Peter
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Thank you so much for the list. Here are the folks invited from CVM:

Bill Burkholder
Siobhan DeLancey
Dave Rotstein
Pat McDermott
Jennifer Jones
Lauren Carey
Anne Norris
Lee Anne Palmer
David Edwards
Sarah Nemser
Janice Steinschneider
John Baker
Eric Nelson
Neal Bataller

Also, I recognize a few names on your list, but can you tell me (in general) if the PFI participants are mainly SMEs or leadership? We just want to get an idea of our audience.

Thanks very much in advance!

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Wednesday, July 18, 2018 4:58 PM
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Attached is a list of PFI member participants in tomorrow's webinar. Also attached is the proposed agenda and the questions we sent you earlier, just for reference.

Did you already send us a list of FDA participants in the webinar? If not, can you send it this afternoon/evening?

Thanks and we look forward to the call.

Regards,

Peter

O: + (b) (6)
(b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Sent: Monday, July 16, 2018 9:29 PM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter!

Looks great! Looking forward to our meeting Thursday!

Martine

From: Tabor, Peter <peter@petfoodinstitute.org>
Date: July 16, 2018 at 2:17:16 PM EDT
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Subject: RE: DCM Comms Going Live Today

Good afternoon, Martine. Not sure if you're still in Denver or on your way home – I hope the AVMA meeting went well. I wanted to get your input on a draft agenda for the Thu webinar, to make the most of everyone's time.

Proposed Agenda

Welcome, introductions and PFI anti-trust policy reminder – PFI, FDA (10 minutes)
Overview of the issue, including the FDA notice and the data FDA presented to PFI in June – FDA (30 minutes, including Qs from PFI)
Review of questions PFI sent to FDA for the webinar – PFI, FDA (50 minutes)
Open Q&A – PFI, FDA (20 minutes)
Conclusion and adjourn (10 minutes)

Please take a look and reply to me at your earliest convenience (today if possible) with thoughts or suggested tweaks. Thanks and safe travels home.

Regards,

Peter

O: + (b) (6)
(b) (6)

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Sent: Thursday, July 12, 2018 11:11 AM
To: Tabor, Peter <peter@petfoodinstitute.org>
Subject: RE: DCM Comms Going Live Today

Hi Peter,

Yes, let's touch base. I am in a meeting until 12 and can call you then. Does that work for you?

Martine

From: Tabor, Peter [<mailto:peter@petfoodinstitute.org>]
Sent: Thursday, July 12, 2018 10:45 AM
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>
Subject: Re: DCM Comms Going Live Today

Thanks for the heads-up, Martine. Very kind of you. My colleagues and I will review the info and I'll be in touch this afternoon.

I was under the impression that our webinar next week would inform FDA's and pet food makers' understanding of the issue, perhaps before any public messaging was issued. So this is a little concerning. I imagine the public reaction might be quite severe and impact products

that aren't implicated by FDA. Hopefully we can chat this afternoon.
Thanks again for reaching out.

Sent using OWA for iPhone

From: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov>

Sent: Thursday, July 12, 2018 10:34:41 AM

To: Tabor, Peter

Subject: DCM Comms Going Live Today

Hi Peter,

I just left you a VM. I am attaching the DCM comms materials that will be going live today. Please feel free to share them with your members and let me know if you have any questions.

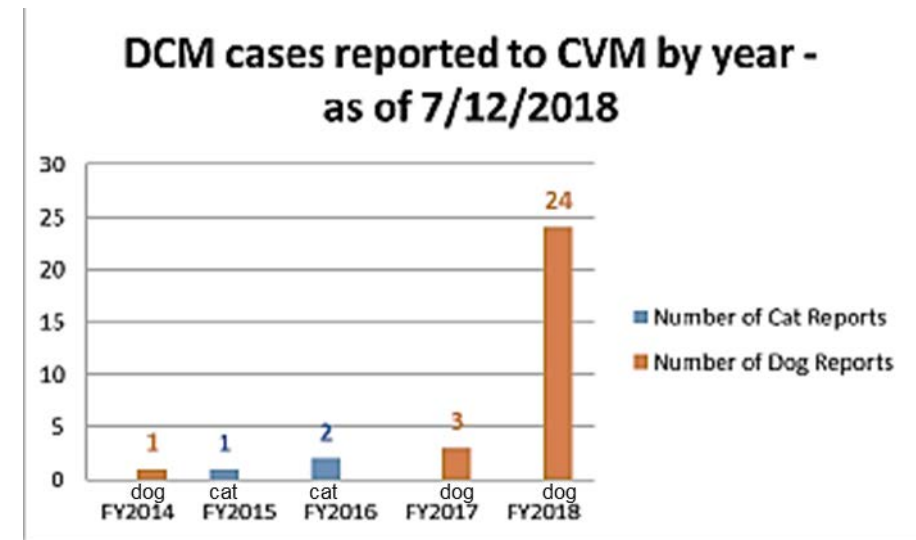
Martine

Martine Hartogenesis, DVM
FDA Center for Veterinary Medicine
Deputy Director, Office of Surveillance & Compliance
(240) 402-7178

DCM Reports as of 7/18/2018 Database Review

DCM Reports as of 7/12/2018 FDA CVM Update

- 31 reports
- 3 cat reports
 - 7 cats reacted, 1 cat died
- 28 dog reports
 - 30 dogs reacted, 3 died



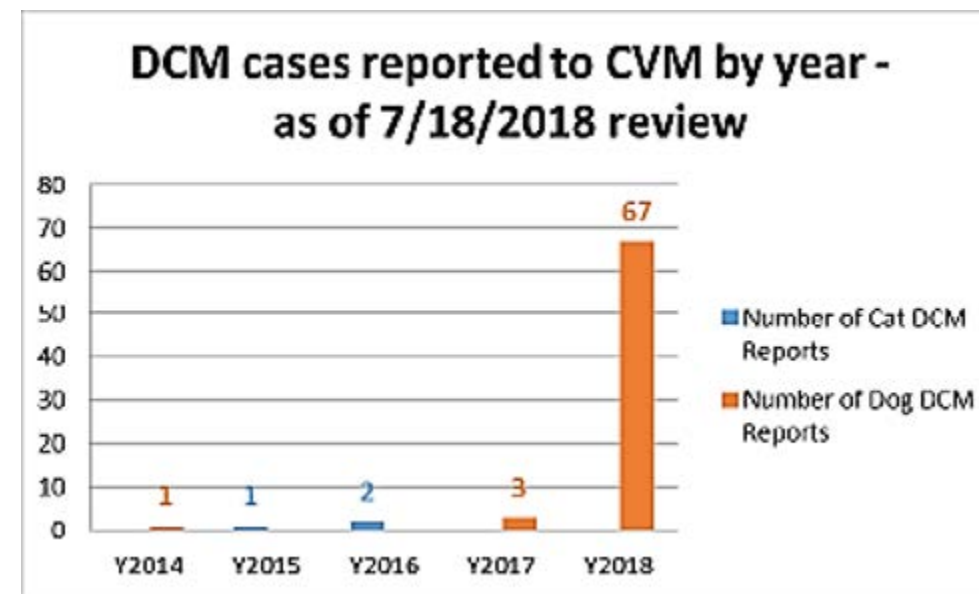
DCM Reports as of 7/12/2018 FDA CVM Update

- 31 reports discussed in CVM Update
- 28 dog reports

Dogs	Age (yrs)	Weight (lbs)	Gender	
Mean	7.7	62.6	F	12 (46%)
Range	2.5 - 13	11 - 141	M	14 (54%)
N	28	28	N	26

DCM Reports as of 7/18/2018 Review

- 7/12/2018: CVM Update discussing FDA investigation into potential connection between diet and cases of canine heart disease
- 80 new cardiac-type reports received as of 7/18/2018 review
 - 77 cardiac reports, 2 respiratory reports, 1 GF report did not fully complete report
 - 43 new reports specifically mention DCM in report narrative or within attachments
 - Several other GF food reports through Safety Reporting Portal. Likely reported due to GF diet article, but no cardiac signs.



DCM Reports as of 7/18/2018 Review

- 31 reports discussed in CVM Update
- Additional 43 DCM reports as of 7/18/18
 - Number likely to change as we review medical records
 - More reports coming in
- All new reports are dog reports

Dogs	Age (yrs)	Weight (lbs)	Gender	
Mean	7.4	62.4	F	27 (39%)
Range	1 - 13	11 - 145	M	42 (61%)
N	70	66	N	69

DCM Cases Reported to CVM as of 7/18/2018 Review

Breed	Number of Dogs
Golden Retriever	12
Mixed	12
Labrador Retriever	7
Great Dane	6
American Cocker Spaniel	3
Bulldog	2
Doberman Pinscher	2
French Bulldog	2
Saluki	2
Shih Tzu	2
Afghan Hound	1
Australian Shepherd	1
Basset Hound	1
Boxer	1
Bull Terrier	1
Chinese Crested - Hairless	1
Dalmation	1
German Shepherd Dog	1
Gordon Setter	1
Greyhound	1
Irish Terrier	1
Maltese	1
Miniature Pinscher	1
Miniature Schnauzer	1
Portuguese Water Dog	1
Schnauzer (unspecified)	1
Shetland Sheepdog	1
Standard Poodle	1
Vizsla	1
Whippet	1
Unknown	1

Foods Reported in Canine DCM Cases Received by CVM

Brands	Number of Reports	Flavor of Brand	Number of Reports
Zignature	9	Kangaroo Formula	7
		Lamb Formula	1
		Venison Formula	1
Nature's Domain	8	Salmon Meal & Sweet Potato	2
		Organic Chicken & Pea	2
		Turkey Meal & Sweet Potato	2
		Unknown	2
California Natural	7	Kangaroo & Red Lentils	5
		Kangaroo & Red Lentils; Venison & Green Lentils	1
		Venison & Sweet Potato(?)	1
Earthborn Holistic	7	Coastal Catch	2
		Meadow Feast	2
		Great Plains Feast	1
		Primitive Natural	1
		Unknown	1
4Health	6	Grain Free Large Breed	2
		Grain Free Beef & Potato	2
		Grain Free	1
		Large Breed Formula (unknown if Grain Free)	1
Blue Buffalo	4	Multiple Blue Buffalo Products	2
		Blue Basics Salmon & Potato Adult	3
Taste of the Wild	4	Pacific Stream Canine Formula with Smoked Salmon	1
		Sierra Mountain Canine Formula with Roasted Lamb	1
		Pacific Stream Canine Formula with Smoked Salmon; Prey Angus Beef	1
		Turkey Flavor; Bison Flavor	1
Fromm	3	Four-Star Lamb & Lentil Recipe	1
		Four-Star Surf & Turf	1
		Heartland Adult Gold	1

Foods Reported in Canine DCM Cases Received by CVM

Brands	Number of Reports	Flavor of Brand	Number of Reports
Nature's Recipe	3	Grain Free Salmon, Sweet Potato & Pumpkin Recipe	2
		Easy-To-Digest Fish Meal & Potato Recipe	1
Rachael Ray	3	Nutrish Cat Food	1
		Nutrish Dog Food	1
		Nutrish Zero Grain Free Salmon & Sweet Potato; Nutrish Zero Grain Beef, Potato & Bison	1
Acana	2	Lamb & Apple Singles Formula	1
Halo	2	Grain Free	1
		Salmon Dry Food	1
Merrick	2	Purrrfect Bistro Grain Free Real Chicken Recipe	1
		Grain Free Real Salmon + Sweet Potato Recipe	1
Natural Balance	2	L.I.D. Sweet Potato & Bison Formula	1
		L.I.D. Sweet Potato & Venison Formula	1
Fromm; Farmina	1	Four-Star Lamb & Lentil Recipe; Chicken & Pomegranate	1
Hill's	1	U/D Prescription Diet (not Grain Free)	1
Lotus; Nature's Variety	1	Oven-Baked Grain Free Fish; Instinct Raw Boost Chicken	1
Merrick; Wellness	1	Grain Free Rabbit & Chickpeas; Grain Free Wild Game	1
Evo	1	Grainfree Turkey & Chicken Formula Cat & Kitten	1
Nature's Variety	1	Instinct LID Lamb Meal & Peas Formula	1
NutriSource	1	Adult	1
Orijen	1	Unknown	1
Unknown	1	Limited Ingredient Kangaroo	1
Victor	1	Hi-Pro Plus (not Grain Free); Salmon & Sweet Potato	1

★ W- Gave an update →

② ★ choline →

(b) (5)
(b) (5)

→ Toxities →

(b) (6)

(b) (5)

(b) (5)

Legume seed oligosaccharides: How much is just right in dog and cat diets?



Working with legume seeds has its advantages for pet food, but the oligosaccharide concentrations that come with them must be taken into consideration. *S.Pijaset | iStockphoto.com*

With the popularity of grain-free diets, large concentrations of oligosaccharides are being introduced into dog and cat

foods. The legume seeds such as peas, lentils, chickpeas and various beans are the leading sources. These legume seeds bring great variety to the pet aisle, have more protein than the cereal grains, and possess other phytonutrients considered valuable to overall health. However, they carry with them significant quantities of fermentable oligosaccharides. In small amounts, these may be beneficial to the animal, but at large concentrations they can become an issue.

Finding when we cross the line from benefit to issue is important.

The impact of oligosaccharides on pet food formulations

Information regarding the impact of oligosaccharides on dogs and cats is not easily available. Perhaps this is due in part to the relative newness of these legume seeds in pet diets. So, one must extrapolate from the human and farm animal literature or look to work with soybeans to get an idea of what might be occurring. The legume seed oligosaccharides in the raffinose family are 3-5 carbon short chain sugars (raffinose, stachyose and verbascose). They are indigestible by mammalian enzymes and pass to the colon where they are fermented by the microflora.

Unfortunately, these oligosaccharides seem to be generally overlooked by pet food companies promoting their grain-free options; not so much for the benefit that they might provide, but for the sheer magnitude they contribute to soluble fiber in the colon. This can be especially exaggerated in the limited-ingredient diets in which legume seeds might comprise upwards of 40 percent of a formula.

The total concentration of oligosaccharides can be 6 percent to 9 percent of the legume seed mass. At that rate, they could

Dr. Aldrich is president of Pet Food & Ingredient Technology Inc. He is also the author of *Petfood Industry* magazine's monthly column, "Ingredient Insights."

contribute upwards of 2.5 percent to 3 percent oligosaccharides to the formula.

That is HUGE. Yes, there may be some benefit, but there can also be some challenges. Notably, this amount of excess fermentable substrate can tip the balance in the colon, shifting the populations within the colonic environment and altering the osmotic balance and gas production. That is to say, the contents of the bowel become more fluid and the result is soft stools, diarrhea and flatulence. There may also be alterations to nutritional balance by changing things like the enterohepatic recirculation of taurine and reductions in mineral utilization.

There is some work on the topic in the research literature. It generally shows equivocal results with little downside. This seems somewhat surprising on the surface because soft stools are a leading complaint among pet owners, more so for those owning larger dogs. So, what is to be done? Quantification of the oligosaccharides would be a natural first step, but that presumes a threshold level is known or established, which is not the case.

Validation testing with a population of animals representative of those being fed the diet might be in order. Most feeding studies are done with Beagle dogs and domestic shorthair "Tabby" cats. While Beagle dogs are great for most research, this may be one area

where they come up short. Specifically, they seem to produce more consistent stools than many other breeds. That's a good thing if you have to pick up after them. Not so good if you want to explore diet effects on a larger dog. As for cats, this is an area almost devoid of research information.

Managing legume seed oligosaccharides

So, in lieu of solid evidence, extrapolation can be valuable. If one assumes arbitrarily that 1 percent oligosaccharides is a threshold and the legume seeds contain no more than 4 percent oligosaccharides (which is a low estimate), then a formulation maximum could be 25 percent. That is a fairly

Looking back: Slow adoption of fructooligosaccharide in pet foods
www.PetfoodIndustry.com/articles/6006

generous portion, but would require the addition of a tuber starch from sweet potatoes, potatoes or tapioca to fill out the remainder of the formula in most extruded products. The complementary non-legume starch might be helpful for processing as well.

Another route to help manage oligosaccharide content

The Industry Leader in Pet food Testing for over 30 years



Today's petfood claims require solid data. At Summit Ridge Farms, we provide the pet food industry with accurate, reliable and precise research on all types of testing protocols for cats and dogs.

- Dental Protocols (as per VOHC)
- Palatability Testing
- Digestibility/ Metabolism Testing
- Stool Quality Analysis
- Blood Level Protocols
- AAFCO Nutritional Adequacy
- Urine pH
- Weight Loss Protocols
- Customized Tests Available
- Product Safety Testing



Setting the standard for pet food testing
 570.756.2656 • Fax 570.756.2826 • www.SRFarms.com



INGREDIENT ISSUES

is through processing. It can provide some benefit in the reduction or modification of the oligosaccharides in the legume seed. Soaking and/or washing (losses via leaching), autoclaving (pressure cooking), and extrusion have been shown to reduce their concentration by a percentage point or two. Work with navy beans would suggest that after being cooked/processed, they can be added into a formula at levels up to 25 percent without affecting stool consistency or diet digestibility. Additionally, sprouting the legume seeds will decrease the oligosaccharides substantially.

Finally, some effort has been made to include enzymes in the diet to decrease the level of oligosaccharides, much like a person would take "Beano" alongside a bowl of chili. The enzyme used most prominently for this is alpha-galactosidase. While it has been effective for humans and farm animals, in practice this enzyme has not been effective for dogs, quite possibly because of the very short transit time in the gut — enzymes take moisture, heat and time to do their thing.

Final considerations

In the end, working with legume seeds can provide many advantages to a pet food. However, the concentration of oligosaccharides that they carry with them must be considered. Dilution with another starch source from cereal grains or tubers can help offset this appreciable concentration of oligosaccharides. Judicious management of these legume seeds in the diet

can provide benefit to colonic fermentation and animal gut health. However, pushing the boundaries beyond 25 percent of the diet should be validated

in feeding assays to confirm that they are not having any negative effects on digestion and elimination that the pet and their owner would not appreciate. ■



Develop Products and Processes in a Food Development Laboratory

Imagine a full-scale extrusion pet food production facility fully staffed with experienced professionals ready to assist in all aspects of food product development or processing. The 1 Solution Group Product Development Facility allows you to work collaboratively with our experienced personnel to develop new products, perfect production processes and ultimately scale up for actual commercial manufacturing.

The 1 Solution Group Product Development Facility and staff provides clients a full scale, real world environment to develop and optimize products and the production process. We're one phone call away—it's time to put our knowledge to work for you.

1Solution
GROUP
Global Project Solutions Group
Feed/Food Processing

1 Solution Group
100 Airport Road
Sabetha, Kansas 66534

phone: 785 285 8411
fax: 785 284 3143
jnerbster@1solutiongroup.com
www.1solutiongroup.com

From: Freeman, Lisa
To: Jones, Jennifer L
Subject: as promised
Date: Wednesday, August 08, 2018 4:43:32 PM
Attachments: Canine DCM protocol external 7-8-18.docx

Hi Jennifer

Below are the WSAVA guidelines and also my blog that expands on the quality control measures.

<https://www.wsava.org/WSAVA/media/Arpita-and-Emma-editorial/Selecting-the-Best-Food-for-your-Pet.pdf>

<http://vetnutrition.tufts.edu/2016/12/questions-you-should-be-asking-about-your-pets-food/>

Also, I think I sent the attached to you before but resending in case.

Thanks

Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

Recommended DCM Protocol 6/27/18

1. Collect a complete diet history form on all patients at every visit (exact diet, treats, table food, rawhides/chews, supplements, and foods used for medication administration). See below and attached for diet history forms.
2. If patient is eating any diet besides those made by well-known, reputable companies or if eating a boutique, exotic ingredient, or grain-free (BEG) diet:
 - Have owner save all current foods they are feeding (including bags, cans, or other packaging)
 - Report case to the FDA (the FDA website includes other useful tips for suspected important information for pet food complaints):
<https://www.fda.gov/animalveterinary/safetyhealth/reportaproblem/ucm182403.htm>
3. Measure whole blood and plasma taurine. Recommend sending samples to the University of California Davis Amino Acid Laboratory: <http://www.vetmed.ucdavis.edu/vmb/labs/aal/>
 - If owner declines measuring both, we recommend at least measuring whole blood taurine
 - Reference ranges for risk of taurine-deficient dilated cardiomyopathy should be interpreted cautiously. In some cases (particularly golden retrievers), DCM has been diagnosed in dogs with whole blood taurine levels between 150-225 nmol/L. These patients have responded well to diet change and taurine supplementation such that the “no known risk for taurine deficiency” range may need to be breed specific. Due to ongoing research in golden retrievers with taurine responsive DCM, a whole blood taurine level of at least 250 nmol/L is recommended.
4. Consider screening other dogs in the household eating same diet
5. Start taurine supplementation. Although it is unclear whether dogs that are not taurine deficient gain any benefits from taurine supplementation, we currently recommend changing the diet and recommending taurine supplementation. Because there are such problems with the quality control of dietary supplements, be sure to recommend a taurine supplement with independent quality control testing. Taurine supplements that appeared to have good quality control in one study (although it is now an old study: Bragg RR. Composition, disintegrative properties, and labeling compliance of commercially available taurine and carnitine dietary products. JAVMA 2009) included: NOW, Solgar, Swanson, Twinlab, and Vitamin Shoppe.

Although the optimal dose is unknown, we recommend the following based on body weight:

- <10 kg: 250 mg q 12 hr
 - 10-25 kg: 500 mg q 12 hr
 - >25 kg: 1000 mg q 12 hr
6. Change the diet to one with more typical ingredients, including grains (e.g., chicken, beef, rice, corn, wheat) made by a well-known, reputable company with a long track record of producing good quality diets. Avoid grain-free diets. Changing to a raw, homecooked, or vegetarian diet is not protective (and may increase the risk for other nutritional deficiencies). If a patient requires a homecooked diet or has other medical conditions that require special considerations, consider referring the owner to a veterinary nutritionist (acvn.org) for optimal nutritional recommendations.
 7. Repeat echography in 3-4 months, although changes may take up to 6-9 months.

For a recent post on this topic on the Petfoodology website (including links to other posts about pet food, ingredients, food allergies, and other myths):

<http://vetnutrition.tufts.edu/2018/06/a-broken-heart-risk-of-heart-disease-in-boutique-or-grain-free-diets-and-exotic-ingredients/>

Meeting between FDA, Tufts, and Florida

Attendees: Anne Norris, Aurelie Pohl, Lauren Carey, Lisa Freeman, Sarah Peloquin, Siobhan DeLancey, William Burkholder, Darcy Adin, David Rotstein, Lee Anne Palmer

Discussed ACVIM findings-to be published soon.

(b) (4)

From: Darcy Adin
To: Jones, Jennifer L
Cc: Freeman, Lisa; adind@ufl.edu
Subject: checking in
Date: Wednesday, November 07, 2018 3:20:51 PM

Hi Jennifer,

I hope you are doing well! I wanted to check in with you to let you know that I have changed affiliations and am now working at the University of Florida (my new email is adind@ufl.edu, copied above).

Dr. Freeman and I wanted to check to see if your group be willing to have a follow up call regarding the dietary induced DCM issue?

Thanks!

Darcy

--

Darcy B. Adin, DVM, DACVIM (Cardiology)
Adjunct Clinical Assistant Professor of Cardiology
North Carolina State University
NC State Veterinary Hospital
1060 William Moore Drive
Raleigh, NC 27607
919-513-6032

From: Jones, Jennifer L
To: Rotstein, David; Queen, Jackie L; Palmer, Lee Anne; Carey, Lauren
Cc: "Reimschuessel, Renate (Renate.Reimschuessel@fda.hhs.gov)"; Ceric, Olgica; Nemser, Sarah
Subject: DCM cases-food-Iodine screening results
Date: Monday, April 23, 2018 10:31:00 AM
Attachments: 800.261-MSU-iodine results.pdf
image001.png
image004.png

FYI-Iodine < 10ppm for the foods tested. Exogenous thyrotoxicosis unlikely a cause of the DCM
Multiple EONs Involved:

- 800.218
 - EON-323515
 - EON-345822
- 800.261
 - EON-350158

Jennifer L. A. Jones, DVM

Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
new tel: 240-402-5421
fax: 301-210-4685
e-mail: jennifer.jones@fda.hhs.gov
Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm>



MICHIGAN STATE UNIVERSITY
**VETERINARY DIAGNOSTIC
LABORATORY**

Director: Dr. Rachel Y. Reams
4125 Beaumont Road
Lansing, MI 48910-8104
Phone: 517-353-1683
Fax: 517-353-5096
www.animalhealth.msu.edu

REPORT OF LABORATORY EXAMINATION

Client: RC107973/ U.S. Food & Drug Adm (71095)
Center for Veterinary Medicine
8401 Muirkirk Rd, G202 HFV 500
Laurel, MD 20708

Owner: FDA Vet-LIRN, -

Report #: C18103012
Received: 04/13/18 11:43
Printed: 04/20/18 14:32

Admit: Jones, Dr.
Herd:
Species: Non-Animal

Sex: Unknown
Age:

Page 1 of 1

Animal ID	Iodine Feed Wet or Dry?	Iodine, Feed (ug/g)
800261DOGKIBBLE	Dry	4.20
800218SUB2DOGKIBBLE	Dry	4.04
800218SUB6DOGKIBBLE	Dry	1.87
800218SUB5DOGKIBBLE	Dry	3.19
800218SUB4DOGKIBBLE	Dry	1.58

Case Comments

Method: ICP-MS

(b) (6)

4/20/2018 2:27:48 PM EDT

Questions for Cardiologists

(b) (6), (b) (5)

(b) (6), (b) (5)

(b) (6), (b) (5)

(b) (6), (b) (5)

(b) (6), (b) (5)

(b) (6), (b) (5)

CARDIOLOGY DIET HISTORY FORM

Please answer the following questions about your pet

Pet's name: _____ Owner's name : _____ Today's date: _____

1. How would you assess your pet's appetite? (mark the point on the line that best represents your pet's appetite)

Poor _____ **Excellent**

2. Describe your pet's appetite over the last few weeks? (check all that apply)

☐ Eats about the same amount as usual ☐ Eats less than usual ☐ Eats more than usual
☐ Seems to prefer different foods than usual ☐ Other _____

3. Over the last few weeks, has your pet (check one)

☐ Lost weight ☐ Gained weight ☐ Stayed about the same weight ☐ Don't know

4. Please list below ALL pet foods, people food, treats, snack, dental chews, rawhides, and any other food item that your pet currently eats. Please include the brand, specific product, and flavor so we know exactly what you pet is eating.

Food	Form	Amount	How often?	Fed since
<i>Examples:</i>				
Nutro Grain Free Chicken, Lentil, and Sweet Potato Adult	- dry	1 ½ cups	2x/day	Jan, 2017
Merrick Grain Free Cowboy Cookout	can	½ large can	1x/day	Jan, 2018
85% lean hamburger	microwaved	3 oz	1x/week	Jan, 2015
Pupperoni original beef flavor	treat	1/2	1x/day	Aug, 2015
Rawhide	treat	6 inch strip	1x/week	Dec, 2015

**Any additional diet information can be listed on the back of this sheet*

5. Do you give any dietary supplements to your pet (for example: vitamins, glucosamine, fatty acids, or any other supplements)? ☐ Yes ☐ No If yes, please list which ones and give brands and amounts:

	Brand	Tablet/capsule number, size, and frequency
Taurine	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____
Carnitine	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____
Antioxidants	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____
Multivitamin	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____
Fish oil/cod liver oil	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____
Coenzyme Q10	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____
Other (please list)	<input type="checkbox"/> Yes <input type="checkbox"/> No	_____

6. How do you administer pills to your pet?

☐ I do not give any medications
☐ I give them without any food
☐ I put them in my pet's dog/cat food
☐ I put them in a Pill Pocket or similar product
☐ I put them in foods (list foods): _____

Information below to be completed by the veterinarian:

Current body weight: _____ kg Current body condition score (1-9): ____/9

Muscle Condition Score: ☐ normal muscle ☐ mild muscle loss ☐ moderate muscle loss ☐ severe muscle loss

From: Hartogensis, Martine
To: Milton, Nanette; Palmer, Lee Anne; Rotstein, David; McDermott, Patrick; DeLancey, Siobhan; Burkholder, William; Norris, Anne; Jones, Jennifer L; Carey, Lauren
Cc: Edwards, David
Subject: RE: Information: PFI & CVM Webinar on July 19 (pre-meeting)
Date: Tuesday, July 17, 2018 2:32:24 PM
Attachments: Hartogensis AVMA Animal Food 2018.pptx

-----Original Appointment-----

From: Milton, Nanette
Sent: Thursday, July 12, 2018 11:26 AM
To: Milton, Nanette; Palmer, Lee Anne; Rotstein, David; McDermott, Patrick; DeLancey, Siobhan; Burkholder, William; Hartogensis, Martine; Norris, Anne; Jones, Jennifer L; Carey, Lauren
Cc: Edwards, David
Subject: Information: PFI & CVM Webinar on July 19 (pre-meeting)
When: Tuesday, July 17, 2018 1:30 PM-2:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: C/R 181 and WebEx

Hi Nanette,

Please send the attached questions to the CVM folks attending the webinar on the 19th.

Can you set up a pre-meeting from CVM so we can discuss?

Also, let PFI know who will be attending from CVM.

Thanks!
Martine

From: Dana Brooks [<mailto:Dana@petfoodinstitute.org>]
Sent: Thursday, July 12, 2018 9:23 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Cc: Tabor, Peter <peter@petfoodinstitute.org>
Subject: Information: PFI & CVM Webinar on July 19
Importance: High

Martine,

I wanted to reconfirm the webinar is scheduled for July 19. I'm sharing some questions with you in advance that may be asked by our members. These are the questions that our producer members presented to PFI as we informed them of the DCM incidents. I hope this is helpful to your team.

Please let us know who will be joining the call. We will do the same from our end.

Thank you so much,
Dana Brooks

-- Do not delete or change any of the following text. --

Join WebEx meeting

Meeting number (access code): (b) (6)
Meeting password: (b) (6)

Join by phone

+1-877-465-7975 US Toll Free

[Global call-in numbers](#) | [Toll-free calling restrictions](#)

[Can't join the meeting?](#)

If you are a host, [go here](#) to view host information.

IMPORTANT NOTICE: Please note that this WebEx service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.



U.S. FOOD & DRUG
ADMINISTRATION

Animal Food Safety

Martine Hartogensis, DVM
Deputy Director
Office of Surveillance & Compliance
Center for Veterinary Medicine
U.S. FOOD AND DRUG ADMINISTRATION

American Veterinary Medical Association
July 15, 2018



FDA-CVM-FOIA-2019-1704-000958

OVERVIEW

FDA





WHAT IS FDA'S ROLE IN ANIMAL FOOD?

FDA'S ROLE IN ANIMAL FOOD



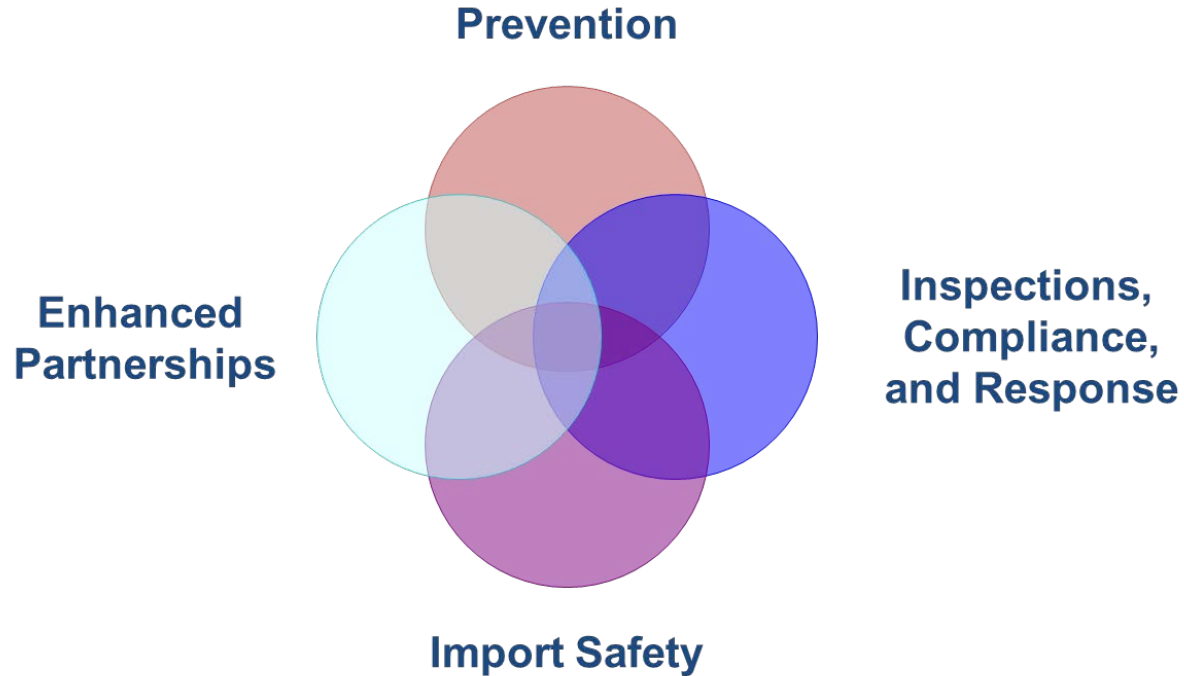
- Livestock, poultry and aquaculture feed
- Pet foods and pet treats
- Exotic animal diets, such as those used in zoos
- Nutritional supplements for animals
- Raw materials and ingredients

FDA'S ROLE IN ANIMAL FOOD



- Drug - based on intended use
- Food Additive - a component of food that is not GRAS
- Color Additive - capable of imparting color

FDA'S ROLE IN ANIMAL FOOD



FSMA



- ****Shifting the focus from responding to foodborne illness to preventing it****
- Accredited Third-Party Certification
- Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Food for Animals
- Foreign Supplier Verification Programs (FSVP)
- Mitigation Strategies to Protect Food Against Intentional Adulteration
- Sanitary Transportation of Human and Animal Food
- Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption
- Voluntary Qualified Importer Program (VQIP)

FDA'S ROLE IN ANIMAL FOOD

FDA

- An appropriate product name
- All ingredients in descending order of predominance by weight
- Statement of net quantity of contents, and
- Address of manufacturer or distributor



SUMMARY



WHAT IS AAFCO?





AAFCO IS A REGULATORY BODY?

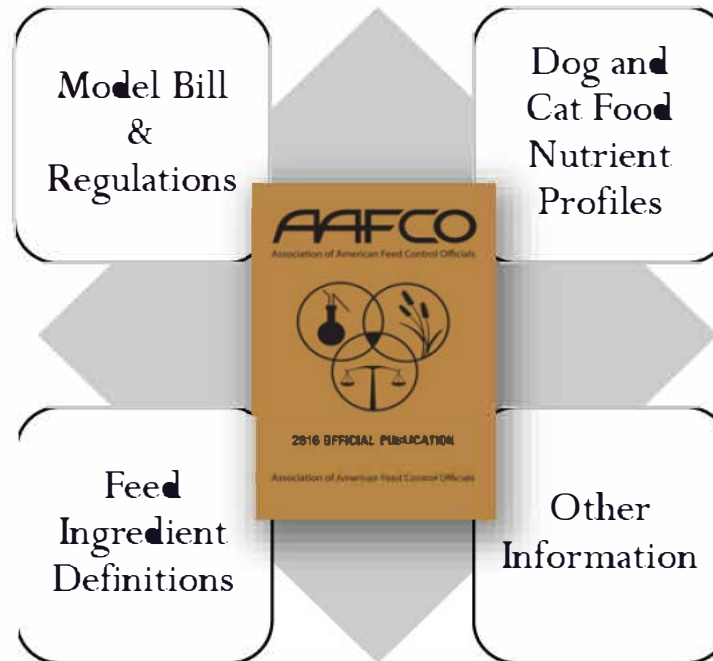
AAFCO



- An **association** with no regulatory authority
- **Members** are **government officials** responsible for enforcing laws regulating the safe production and labeling of animal food:
 - Federal government
 - State governments
 - International governments
- Develops **model** bills and **model** regulations that are adopted and implemented by many states

AAFCO OFFICIAL PUBLICATION

FDA



SUMMARY





WHAT CAN I PUT IN ANIMAL FOOD IN THE US?

- a. Anything that seems to be the latest craze and is marketable
- b. Articles that are GRAS, Approved Food or Color Additives, or defined AAFCO Feed Ingredients
- c. Common dietary supplements for people
- d. Internationally approved ingredients

REGULATORY CLASSES FOR ARTICLES ADDED TO ANIMAL FOOD



- **Food**
 - Unprocessed grains, meats, and fruits or vegetables with a history of use
- **Other ingredients or “articles”**
 - Any component or mixture added to and/or comprising a commercial animal food
 - Includes many different substances for various uses
 - Multiple regulatory pathways available

REGULATORY CLASSES FOR ARTICLES ADDED TO ANIMAL FOOD



- **Food additive**
 - Approved food additives are in 21 CFR 573
- **Generally recognized as safe for an intended use (GRAS)**
 - Partial list in 21 CFR 582
 - Previously affirmed GRAS by FDA in 21 CFR 584
 - Self-conclusion by qualified experts
 - FDA concurrence is not required
 - Voluntary GRAS Notifications
- **Defined feed ingredient**
 - Published in the *Official Publication of AAFCO*

REGULATORY CLASSES FOR ARTICLES ADDED TO ANIMAL FOOD



- **Color additive**
 - Colors the food itself or the tissues, milk or eggs from animals consuming the food
 - 21 CFR 73 and 74
- **New animal drug**
 - Intended for diagnosis, cure, mitigation, treatment or prevention of disease
 - Affects the structure or function of the animal other than by providing nutrition, taste, or aroma
 - 21 CFR 558



Animal Food AE

Voluntary Reporting
(veterinarian/pet owner)



Safety Reporting Portal:

- Pet Food Reports (PFRs)
- Livestock Food Reports (LFRs)

Small % received other
ways, including
MedWatch forms.

Consumer Complaint
Coordinators (District Offices):
Consumer Complaints in FACTS

<https://www.fda.gov/animalveterinary/safetyhealth/reportaproblem/com182403.htm>



Safety Reporting Portal

- Opened May 2010
- Accepts Pet Food Reports (PFRs), Livestock Food Reports (LFRs) and Reportable Food Registry reports (RFRs). Also used for drug reports from manufacturers, certain NIH clinical trial reports. LFRs (Livestock Food Reports) section opened in 2014
- Allows owners, veterinarians or concerned citizens to enter pet food reports online through a structured questionnaire
- Accepts PFR reports concerning adverse events, product problems or both
- Can upload medical records, photographs, other documents
- Not available for adverse drug event reports from consumers or veterinarians as this time



Safety Reporting Portal

[ABOUT THE PORTAL](#) [SAFETY REPORT DIRECTORY](#) [FAQS](#) [RELATED LINKS](#) [CONTACT US](#)

The Safety Reporting Portal

The Safety Reporting Portal (SRP) streamlines the process of reporting product safety issues to the Food & Drug Administration (FDA) and the National Institutes of Health (NIH).

Whatever your role, (manufacturer, health care professional, researcher, public health official, or concerned citizen), when you submit a safety report through this Portal, you make a vital contribution to the safety of America's food supply, medicines, and other products that touch us all.

Begin Reporting Here

1. Login

EMAIL

PASSWORD

[Forgot your password?](#)

☐

Remember me

[Log In](#)

2. Report As Guest

Not ready to create an account but would like to submit a report?

You can do that here.

[Report as Guest](#)

Account Benefits

- Save a draft
- Easier follow up
- View submissions
- Faster data entry

[Create Account](#)

Who Should Submit a Safety Report?

Organizations and people in certain professional roles, such as the following, may be required by law to submit safety reports under some circumstances.

- Food Manufacturers, Processors, Packers, and Holders
- Researchers
- An applicant of an approved drug product or a manufacturer, distributor or packer listed on the label of any drug product
- Drug Manufacturers
- Dietary supplement manufacturers, packers, and distributors

Others, including health care providers, public health officials, and other professionals, as well as consumers and concerned citizens, voluntarily submit reports if they encounter safety issues with a product and/or unanticipated harmful effects that they believe are related to a product.

[Learn more about mandatory and voluntary reporting.](#)

Reports You Can Submit Through this Portal

FDA safety issues involving:

- Marketed human drug and therapeutic biologics
- Human or animal reportable foods
- Animal drugs
- Animal foods
- Tobacco products
- Dietary supplements

NIH safety issues involving:

- NIH gene-transfer research

For other issues, [find out where to submit your report.](#)



Reporter is guided through required and optional questions

https://www.safetyreporting.fda.gov/fpr/WorkflowEditor.aspx?FormInstance=2F656C04EE380C14AE72DF3E03FB33C206C395E5

File Edit View Favorites Tools Help

Convert Select

Safety Reporting Portal

Back Tools

15

Welcome Guest

Name: Pet Food Safety
ID: 0650 (E)
Created: 05/07/2012

Introduction
Contact Information
Problem Summary
Precautions
Veterinarian Visits
Attachments

ONS Approval Number: 0910-0645
ONS Expiration Date: 09/30/2012
ONS Burden Statement

HOME PAGES RELATED LINKS CONTACT US FEEDBACK HELP

Problem Summary

*** Required**

Affected Animal Information

Number of animals given the product

For the following question, if more than one animal had a reaction, please submit additional reports for each animal.

*** Number of animals reacted**

Animal Name/Identifier

*** Species**

Age

Weight

Gender

*** Reproductive status**

*** Was the animal pregnant at time of event?**

Please select

Select Unit of Measure

Select Unit of Measure

☐ Female
☐ Male
☐ Mixed Population of Female and Male
☐ Unknown

☐ Intact
☐ Neutered
☐ Mixed
☐ Unknown

☐ Pregnant
☐ Not Pregnant
☐ Mixed Population Pregnancy Status
☐ Spawning

Done

Local Internet

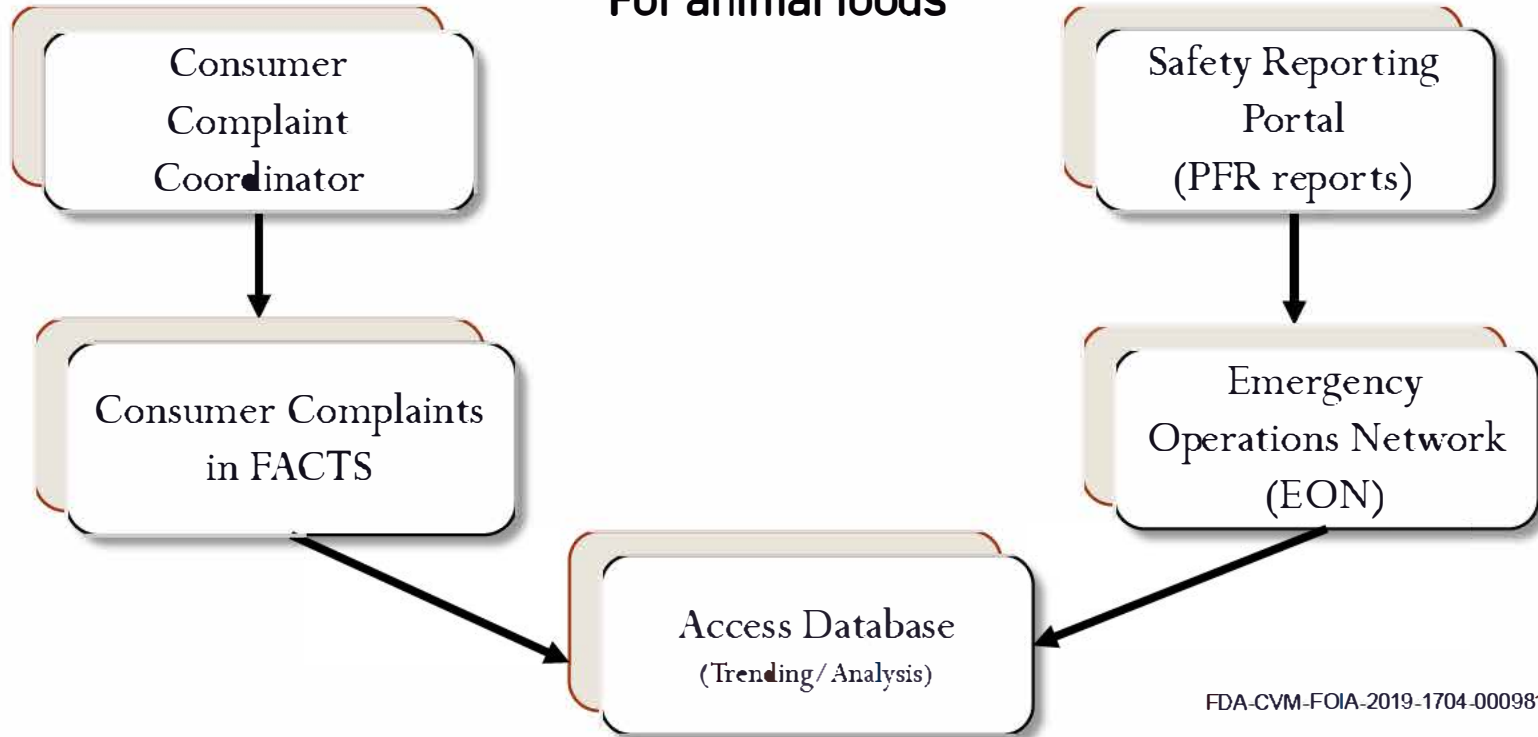
100%

Why an SRP for pet food reports? History: Mar. 15, 2007



- Pets - diet more limited, ingredients in common, can serve as sentinels for problem ingredients.
- Menu Foods announced recall of 60 million containers "cuts and gravy" style food - 100 brands
- Company had received complaints of animals in kidney failure ~ wheat gluten new supplier.

For animal foods



CVM Animal Food Response



- Regular meetings to discuss animal food related adverse events and product problems
- Includes CVM Experts in Veterinary Nutrition, Pathology, Compliance, Toxicology, Chemistry and Epidemiology
- Veterinary Laboratory Response Network (Vet-LRN)
- Share UTD information regarding ongoing investigations, signals, outbreaks, etc

FDA-CVM-FOIA-2019-1704-000982

Some Recent Pet Food Issues...

- *Listeria monocytogenes*, *Clostridium botulinum*, *Salmonella* sp. - recalls involving raw pet food
- Dilated Cardiomyopathy
- Elevated thyroid hormone - beef cans and treats
- Pentobarbital

RAW FOODS: Increased Consumer Reports of Sick Pets and Sick People



- Vet-LIRN Labs Test:
 - fecal samples
 - open products
(investigational testing)
- Isolate pathogens ↓
- Sequence DNA – Do they match?
- Regulatory Response
- States also do their own surveillance testing



Salmonella Reading in Raw Turkey-Based Pet Food: Human Illness and Multistate Outbreak



- Investigation-Index Case
 - Epidemiology: 2 children from a household with GI symptoms; culture positive for *Salmonella* Reading
 - Traceback: Raw turkey-based pet food
 - Microbiology:
 - Raw turkey and children had the same *S. Reading* based on Whole Genome Sequencing
 - Multi-drug resistant
 - FDA CVM Response: Class 1 Recall and Public Notification (Firm and FDA)
- Outbreak Investigation
 - Rare pattern of *S. Reading* led to identification of cases in multiple states
 - 81 cases in 25 states; 36 hospitalizations and no deaths
 - Non-human isolates found including 120 food isolates, raw turkey pet food, and 1 dog
 - 42/55 people interviewed had turkey exposure (raw and processed), raw turkey pet food
 - Possibly a persistent stain in the population, environment, or animal feed

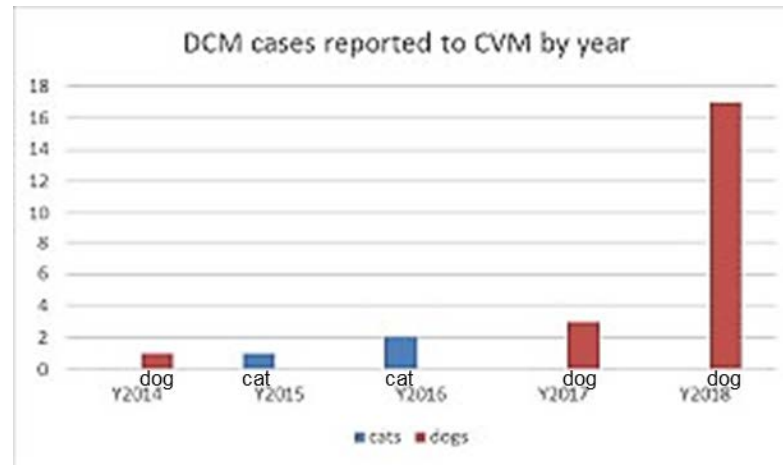
Dilated Cardiomyopathy (DCM) cases



- Approximately 24 cases of veterinary cardiologist-diagnosed DCM were reported to FDA CVM between 4/3/2014 and 6/12/2018
 - 3 of those 24 are cat cases — 7 cats involved
 - 21 dogs

DCM cases reported to CVM

Age (yrs)	Dogs	Wt (lbs)	Dogs	Gender	Dogs
Mean	7.5	Mean	58.6	F	8 (42%)
Range	2 - 13	Range	14 - 96	M	11 (58%)
N	20	N	17	N	19



DCM cases reported to CVM – dog breeds

Breed	Number of dogs
Golden Retriever	5
Labrador Retriever	3
American Cocker Spaniel	2
Afghan Hound	1
Bull Terrier	1
Bulldog	1
Dalmation	1
Doberman Pinscher	1
Great Dane	1
Miniature Schnauzer	1
Mixed	1
Shih Tzu	1
Unknown	1
Whippet	1

Foods reported in Canine DCM cases CVM has received

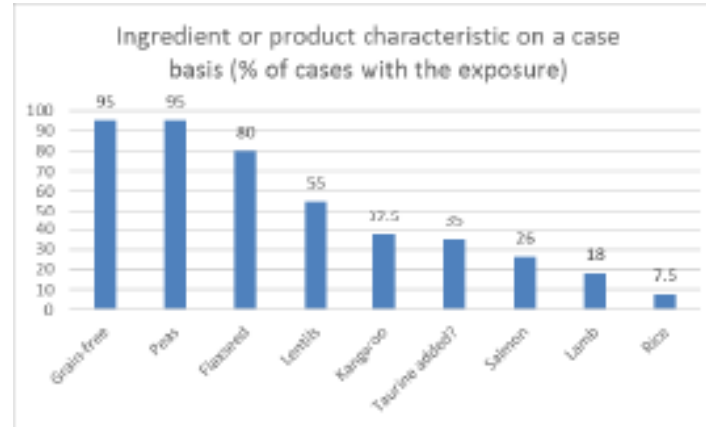
Brand	Flavor	Number of reports
California Naturals	GF L.I.D. Kangaroo & Red Lentils Recipe (1 also ate Venison/green lentils)	4
Zignature	Limited Ingredient Formula Kangaroo (3), 1 is lamb	4
4Health	Grain Free Formulas (one is unclear)	3
Nature's Recipe	Grain Free Salmon, Sweet Potato & Pumpkin Recipe (same household – 2 dogs)	2
Acana	Lamb & Apple Singles Formula	1
Blue Buffalo	Blue Basics GF Salmon & Potato; Blue Basics Salmon	1
Earthborn Holistic	Primitive Natural	1
Hill's	U/D Prescription Diet	1
Nature's Domain	Turkey Meal & Sweet Potato	1
Nature's Variety	Instinct LID Lamb Meal & Peas Formula	1
Taste of the Wild	Pacific Stream Canine Formula with Smoked Salmon	1

FDA-CVM-FOIA-2019-1704-000989

Dietary ingredient exposure on a case basis (n = 41)



	Ingredients on a case basis:		
	Yes	No	percent
Grain-free	39	2	95
Peas	38	2	95
Lentils	22	18	55
Flaxseed	32	8	80
Kangaroo	15	25	37.5
Lamb	7	31	18
Salmon	10	28	26
Rice	3	37	7.5
Taurine added?	14	26	35



Product Testing



U.S. FOOD & DRUG
ADMINISTRATION



Multiple products have been tested for:

- Minerals and Metals
 - Ca, Mg, P, Fe, Co, Cu, Zn, Se, I
- Amino Acids
 - Taurine, Cysteine, Methionine

Bottom Line:

No abnormalities identified



Product Testing Results



U.S. FOOD & DRUG
ADMINISTRATION

Product Name	Tau (%)	Cys (%)	Met (%)	Met-Cys (%)
Avg All GF foods	0.16	0.32	0.63	0.95
Avg All Non-GF Dog foods	0.14	0.34	0.61	0.95
Avg All Non-GF Cat Foods	0.22	0.46	0.77	1.23

- No AAFCO Tau requirement in dogs.
- Average Tau, Cys, Met, and Met-Cys content in Grain Free dog foods is similar to the non-GF dog foods.
- The **non-GF cat foods** tend to have higher average levels, because they have greater minimum AAFCO requirements.



Product Testing Results



**U.S. FOOD & DRUG
ADMINISTRATION**



Product	Grain Free?	Species	Tau (%)	Cys (%)	Met (%)	Met-Cys (%)
Product A	Yes	Canine	0.26	0.26	0.64	0.9
Product A	Yes	Canine	0.11	0.26	0.61	0.87
Product A	Yes	Canine	0.14	0.28	0.86	1.14
Product B	Yes	Canine	0.12	0.36	0.69	1.05
Product C	Yes	Canine	0.2	0.34	0.51	0.85
Product D	Yes	Canine	0.051	0.33	0.4	0.73
Product E	Yes	Canine	0.25	0.38	0.7	1.08
Product F	No	Canine	0.22	0.32	0.66	0.98
Product G	No	Canine	0.11	0.3	0.57	0.87
Product G	No	Canine	0.11	0.3	0.6	0.9
Product H	No	Canine	0.11	0.31	0.58	0.89
Product I	No	Canine	0.12	0.32	0.65	0.97
Product J	No	Both	0.19	0.46	0.6	1.06
Product K	No	Feline	0.24	0.42	0.78	1.2
Product L	No	Feline	0.24	0.5	0.94	1.44

- Because the Grain free and Non-GF foods have a similar Tau, Cys, Met, and Met-Cys content, we can look closely at one product.

- It has adequate Met and Met-Cys levels, which should enable a dog to make adequate Tau, without needing Tau in the food.

- However, the dog eating this diet had Whole blood Taurine.



Product Testing Results



**U.S. FOOD & DRUG
ADMINISTRATION**

Of the grain free products tested:

- Most GF products have more legume sources than Non-GF
- Most GF products have legume sources higher in the ingredient list than Non-GF

Product	Grain free	Dog Tau level	Tau added to product?	Met added to product?	# Legume Sources	Names (place in ingredient list)
A	Yes	wnl (2)	No	Met	4	red lentils (2), green lentils (3), peas (4), pea fiber (7)
A	Yes	store-bought	No	Met	4	red lentils (2), green lentils (3), peas (4), pea fiber (7)
A	Yes	292 (wnl)	No	Met	4	red lentils (2), green lentils (3), peas (4), pea fiber (7)
B	Yes	unknown	No	No	3	peas (2), green lentils (3), pea fiber (5)
C	Yes	unknown	Yes	Met	4	peas (3), lentils (4), chickpeas (5), pea flour (14)
D	Yes	Low	No	No	6	peas (3), chickpeas (4), pea flour (5), red lentils (8), green lentils (9), pea protein (11)
E	Yes	unknown	Yes	No	1	peas (4)
F	No		Yes	No	1	pea fiber (10)
G	No		No	Met	0	
H	No		No	Met	1	green peas (22)
I	No		No	Met	1	green peas (20)
J	No		Yes	No	3	soybean (3), pea protein (5), peas (9)
K	No		Yes (11+)	No	1	dried ground peas (12)
L	No		Yes	No	0	

FDA-CVM-FOIA-2019-1704-000994

Prospective Case Investigations



U.S. FOOD & DRUG
ADMINISTRATION

- Collecting well-documented cases with thorough feeding histories
 - Full medical records
 - Dietary and environmental exposure interviews
- Informed Diagnostic Testing
 - Clinical samples
 - Leftover product

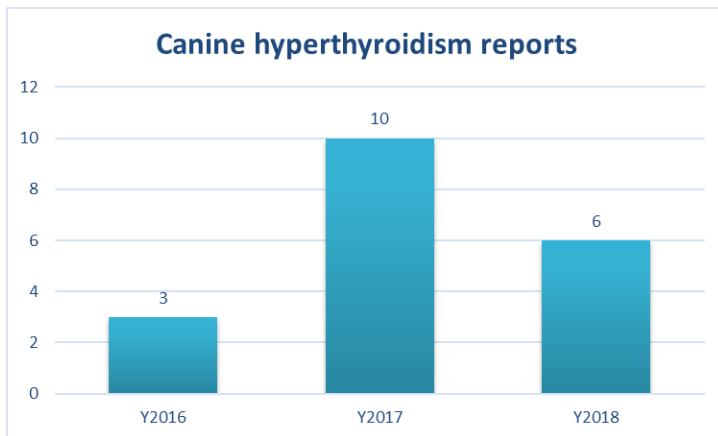


Canine Exogenous Thyrotoxicosis

- Although hypothyroidism is a common endocrine disorder in dogs, naturally occurring hyperthyroidism is considered rare or uncommon (Kohler, 2012 and Broome, 2015)
- Causes in **dogs**:
 - Neoplasia: usually a thyroid gland carcinoma (vs. adenoma in cats)
 - Excessive thyroid hormone replacement therapy in hypothyroid dogs
 - Dietary exposure (has been reported in both humans and dogs)
- Clinical signs can include weight loss, PU/PD, vomiting, diarrhea, agitation, restlessness, tachycardia and panting, however, clinical signs may unapparent
- Thyroid gland can enter food when it's not adequately trimmed away from "gullet" (laryngeal/tracheal area tissue). Thyroid hormones are not destroyed by gastric acid when eaten and are absorbed.



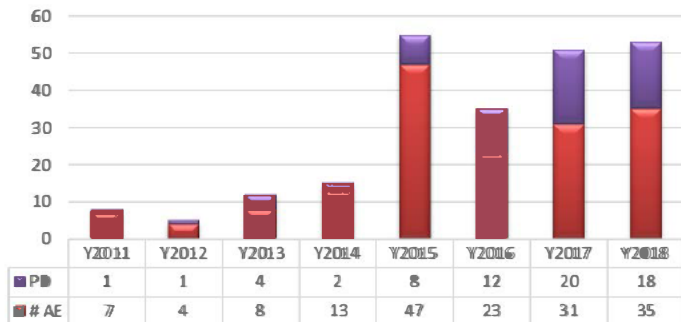
Dietary hyperthyroidism reports



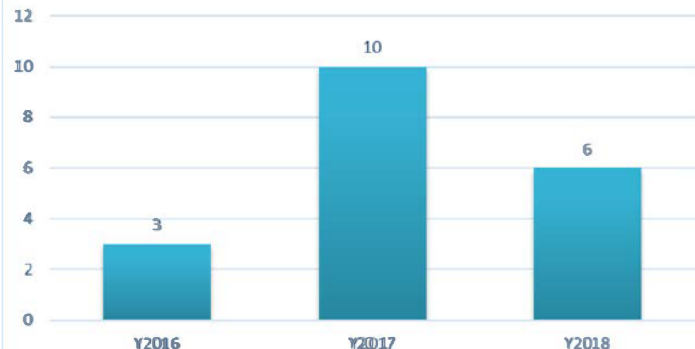
Primary Suspect Product	# reports
Wellness 95% Beef Canned food	4
Milo's Kitchen Grilled Burger Bites, Steak Grillers	4
Blue Buffalo Lamb and Rice Adult Recipe	2
American Jerky Bison Bars	2
Dave's 95% Premium Beef	1
Green Tripe w/ Trachea & Gullet	1
Real Meat Beef/Lamb Jerky	1
Merrick - multiple products	1
Stella & Chewy's Meal Mixers (beef)	1
Nature's Variety Beef/Barley Raw	1
K-9 Kravings All Life Stages Dog food	1

Reports for other types of issues

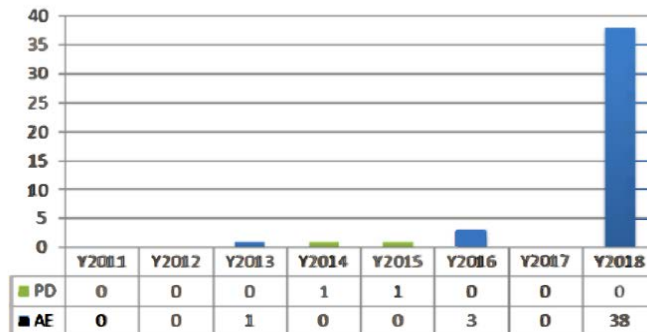
**Raw pet food reports by year reported
(1/2011 to 6/20/2018) - any species**



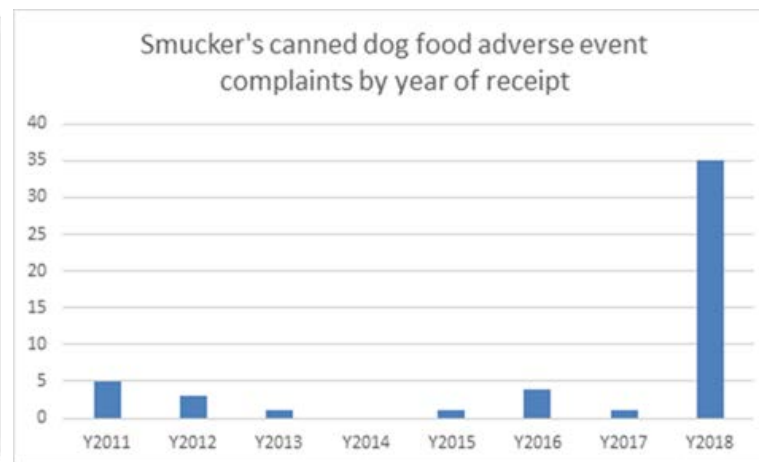
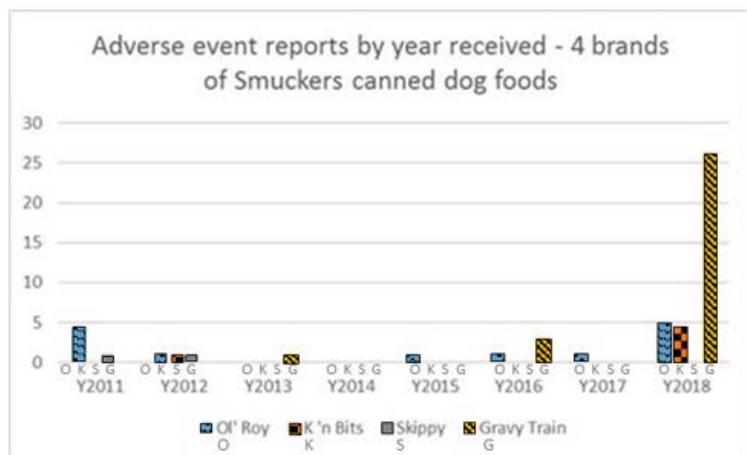
Canine hyperthyroidism reports



Gravy Train canned food reports



Adverse event reports for Smucker's canned food products by year of receipt





Take Home Points

- FDA regulates animal food @ federal level & AAFCO creates "model bills" for potential federal, state and international use.
- Animals can be sentinels for broader food issues
 - More limited diet generally (less variety)
- Report suspected cases to FDA!
 - We may follow up to obtain patient records, patient samples, and/or food samples.

(b) (6)

THANK YOU!

www.fda.gov/safefeed

From: [Hartogensis, Martine](#)
To: [Milton, Nanette](#); [Burkholder, William](#); [DeLancey, Siobhan](#); [Rotstein, David](#); [McDermott, Patrick](#); [Jones, Jennifer L](#); [Carey, Lauren](#); [Norris, Anne](#); [Palmer, Lee Anne](#)
Cc: [Edwards, David](#); [Reimschuessel, Renate](#); [Nemser, Sarah](#); [Steinschneider, Janice](#); [Baker, John D](#); [Nelson, Eric](#); [Bataller, Neal](#)
Subject: RE: Dilated Cardiomyopathy
Date: Wednesday, July 18, 2018 7:10:31 PM
Attachments: [20180718 Participants list for Grain Free Diet and DCM call with FDA.DOCX](#)

Good Evening!

I am attaching a list of PFI participants FYI. Please pass this along to anyone I may have missed.

Thank you!!

Martine

-----Original Appointment-----

From: Milton, Nanette
Sent: Friday, July 06, 2018 10:22 AM
To: Milton, Nanette; Burkholder, William; Hartogensis, Martine; DeLancey, Siobhan; Rotstein, David; McDermott, Patrick; Jones, Jennifer L; Carey, Lauren; Norris, Anne; Palmer, Lee Anne
Cc: Edwards, David; Reimschuessel, Renate; Nemser, Sarah; Steinschneider, Janice; Baker, John D; Nelson, Eric; Bataller, Neal
Subject: Dilated Cardiomyopathy
When: Thursday, July 19, 2018 10:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Webinar

Please join my meeting from your computer, tablet or smartphone.

<https://global.gotomeeting.com/join/> (b) (6)

You can also dial in using your phone.

United States: (b) (6)

Access Code: (b) (6)

Joining from a video-conferencing room or system?

Dial: (b) (6)

Cisco devices: (b) (6)

First GoToMeeting? Let's do a quick system check: <https://link.gotomeeting.com/system-check>

Hi Nanette,

Can you work with Dana Brooks from PFI to schedule a 1-2 hour webinar? The topic is Dilated Cardiomyopathy.

These folks should be included:

David Rotstein
Jennifer Jones (OR)
Lee Anne Palmer
Lauren Carey
Siobhan DeLancey
Anne Norris (in OD)
Bill Burkholder
Martine Hartogensis
Pat McDermott

Thanks very much in advance!
Martine

Member Name	Company
Royal Witcher	Sunshine Mills, Inc.
Gayan Hettiarachchi	Champion Pet Foods LP
Carlos Gonzalez	Hill's Pet Nutrition, Inc.
Bill Behnken	American Nutrition, Inc.
Sarah Barrett	Barrett Petfood Innovations
Valerie Zimmer	Perfection Pet Food
Alan Bostick	Sunshine Mills, Inc.
Jim Bolton	American Nutrition, Inc.
Chinedu Ogbonna	Champion Pet Foods LP
Jay Trivedi	Central Garden & Pet
Darren Stephens	American Nutrition, Inc.
Leslie Hancock-Monroe	The J.M. Smucker Company
Kim Spinelli	The J.M. Smucker Company
Marcie Campion	Cargill
John Dickerson	Cargill
Greg Thompson	Blue Buffalo Company
Nancy K Cook	Cook & Associates Consulting, LLC (Sunshine Mills, Inc.)
Steve Mills	American Nutrition, Inc.
Kelly Stevens	Blue Buffalo Company
Sandra Furbee	Nestle Purina PetCare Company
Jim Wagner	Champion Pet Foods LP
Todd Harper	Blue Buffalo Company
Raquel Maymir	Blue Buffalo Company
Jason Vickers	Mars Petcare US
James Chen	Central Garden & Pet
Royal Witcher	Sunshine Mills, Inc.
Kelly Stevens	Blue Buffalo Company
Stephanie Salinas	Central Garden & Pet
Gail Kuhlman	Mars Petcare US
Greg Reinhart	Blue Buffalo Company
Mark Brinkmann	Diamond Petfood
Nolan Frantz	Blue Buffalo Company
Chase Rasmussen	Tuffy's Pet Foods
Sean McNear	Blue Buffalo Company
Melissa Brookshire	Diamond Petfood
Roxanne Cool	The J.M. Smucker Company
Kelvin Hawkins	Nestle Purina PetCare Company
Heather Clarkson	Spectrum Brands, Inc.
Matt Golladay	BrightPet Nutrition Group
Christine Pendlebury	Champion Pet Foods LP
Gail Kuhlman	Mars Petcare US
David McLain	Perfection Pet Foods
Richard MacLean	Blue Buffalo Company
James Barritt	Mars Petcare US
Santo Perez	Spectrum Brands, Inc.
Allen Bingham	Bil-Jac Foods, Inc.

Natasha Bangel	Hill's Pet Nutrition, Inc.
Tom Forster	Hill's Pet Nutrition, Inc.
Tiffany Bierer	Mars Petcare US
Candance Sady	Hill's Pet Nutrition, Inc.
Leah Lambrakis	Simmons Pet Foods, Inc.
Dave Lemmon	The J.M. Smucker Company
Michael Wood	Merrick Pet Care, Inc.
Steven Zicker	Hill's Pet Nutrition, Inc.
Victoria Carmella	Blue Buffalo Company
Christina Germain	Nestle Purina PetCare Company
Brittany Vester Boler	Nestle Purina PetCare Company
Adam Ekonomon	The J.M. Smucker Company
Jay Hernandez	American Nutrition, Inc.
Kathy Gross	Hill's Pet Nutrition, Inc.
Larry Thompson	Nestle Purina PetCare Company
Tim Simonds	Merrick Pet Care, Inc.
Alex Cedeno	The J.M. Smucker Company
Jeff Johnston	Champion Pet Foods LP
Brad Schulz	C.J. Foods Inc.
Bruce Blackford	Midwestern Petfoods
George Collings	Midwestern Petfoods
Jeff Nunn	Midwestern Petfoods
Dan Rice	Champion Pet Foods LP

Patient History Report

Client: (b)(6) Phone: (b)(6) Address: (b)(6) (b)(6)	Patient: (b)(6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex : Neutered Male
---	---	---

Date	Type	Staff	History
4/12/2018	C	(b)(6)	MEDICAL COMMENTS ***ADDENDUM 4/20/2018 4/12/2018 13:26 FDA Safety Reporting Portal - Individual Case Safety Report Number (ICSR) 2045676 ADDENDUM on 4/20/2018 at 08:34:23 from (b)(6), BVSc, MRCVS, ACVIM permission signed and returned to (b)(6)
3/24/2018	P	(b)(6)	1.00 [None] of Postage (UPS) -1 Lb (POSTA) Rx #: 2863492 0 Of 0 Refills ***SHIP ONLINE ORDERS UPS ONLY!!!*** Lasix
3/24/2018	C	(b)(6)	PHARMACY NOTE TTO. Meds have been refilled
3/24/2018	P	(b)(6)	100.00 tablet of Lasix (Salix / Furosemide) 50mg Tablet (M569) Rx #: 2852561 1 Of 12 Refills Filled by: (b)(6) 1 1/2 TABLETS BY MOUTH TWO TIMES A DAY
3/22/2018	C	(b)(6)	COMMUNICATIONS WITH CLIENT 3/22/2018 13:03 dog is restless at night, making breathing sound, but sRR is consistently at 22 bpm, so i do not think do has pulmonary edema, will try melatonin, recheck in end of april Hey His Melatonin dose is 4 or 5 mg once to three times a day. Depending on size tablet you get, a 4 mg tablet or a 5 mg tablet, then start by giving 1 tablet once day, 30 minutes before bed (b)(6)

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
3/13/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/13/2018 10:36 (b) (6) - Owner consented to reporting (b) (6) case to the FDA. He has been on the Zignature Kangaroo for the past 2-3 years. Treats include Milkbones and baked dog treats from pet bakery. Prior to the Zignature Kangaroo, he consumed the Acana Ranch Lamb, Natural Balance Sweet Potato and Bison, Natural Balance Sweet Potato and Fish, Zignature Trout & Salmon. He was receiving no supplements prior to his DCM diagnosis. Owner will forward me a copy of her most recent Chewy.com receipt for the Zignature. She does not have the bag anymore. I will email her for additional information. She is now feeding the Royal Canin Kangaroo and Oats.
3/1/2018	D	(b) (6)	Taurine Deficiency Final
3/1/2018	C	(b) (6)	COMMUNICATIONS WITH DOCTOR 3/1/2018 13:22 i called vet, to let them know taurine is low, she is still on kangaroo diet from Zignature, rec to change diet. The legumes in diet are most likely preventing methionine and cystine absorption, should switch to Royal Canin kangaroo and oats, i originally lm and he called back. he said he would call owner
3/1/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/1/2018 13:20 i called client to let her know taurine is low, she is still on kangaroo diet from Zignature, rec she talk to her vet at last appt, and she did to day at a recheck, and told her to wait. The legumes in diet are most likely preventing methionine and cystine absorption, should switch to Royal Canin kangaroo and oats, I will call her vet.
2/27/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 2/27/2018 11:03 i called owner, dog is breathing better, eating fine, getting sRR 18-26, did have throat issues, does gagging, pred helped, increased pred again, continue as planned, waiting on taurine level. if normla will start enalapril
2/24/2018	L	(b) (6)	Miscellaneous results from (b) (6)

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6) **Patient:** (b) (6)
Phone: (b) (6) **Species:** Canine **Breed:** Retriever, Golden
Address: (b) (6) **Age:** 6 Yrs. 2 Mos. **Sex:** Neutered Male
Color: Blonde

Date	Type	Staff	History
(b) (6) Requisition ID: (b) (6) Posted Final Asc: (b) (6) Profile: Taurine RE: 16759 Taurine 119 Normal Values (amols/ml)			
			Normal Range
			Critical
Level			
Cat Plasma			60-120
40			Less than
Whole Blood			300-600
200			Less than
Dog Plasma			60-120
40			Less than
Whole Blood			200-350
150			Less than
TEST PERFORMED AT			(b) (4)

2/23/2018 C (b) (6) **PHARMACY NOTE**
 Called (b) (6) Pharmacy, spoke to (b) (6). Ordered Pimobendan 10 mg
 tiny tablets - 1 tablet two times a day, #100, 8 refills

2/23/2018 D (b) (6) **Pulmonary Edema Tentative**
 2/23/2018 D (b) (6) **Taurine Deficiency Tentative Date Diagnosis made final: 03/01/18**
 2/23/2018 D (b) (6) **Dilated Cardiomyopathy Tentative**
 2/23/2018 I (b) (6) **Cardiology Discharge Instructions**

(b) (6)
 2/23/2018

A cardiologist has evaluated (b) (6) and has diagnosed her with Dilated
 Cardiomyopathy (DCM) DCM means your pet has poor muscle contraction of the
 heart. This means the heart muscle does not pump as well as a normal dog. The
 heart has enlarged due to the poor muscle contraction. The change in the heart
 has caused fluid to form in the lungs, causing increased respiratory rate.

Please take a sleeping respiratory rate rate (sRR) at home. WHILE YOUR PET IS
 SLEEPING, count the number of times they breathe in over 15 seconds. Your pet
 should have 8 breathes or less over 15 seconds while sleeping. Do this once a day
 over the next 3 days, then 2 times a week thereafter.
 The free app software for iPhone and Google Play that can help with this is
 Cardalis

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

I have submitted blood for a taurine level. The result may not return for 2 weeks. In the mean time, please start Taurine at home, 2 gram two times a day with food. This can be purchased at any health food store. I will call in about 2 weeks with a taurine level.

MEDICATIONS:

Furosemide 50 mg tablets 1 1/2 tablet two times a day
Furosemide: Also called Salix or Lasix. This is a diuretic and will help clear the fluid from your pet's lungs. Your pet may drink more on this medication. Side effects include electrolyte abnormalities (if they stop eating), dehydration and kidney enzyme elevations. The blood work can be done to monitor these. This medication will be probably given for the life of your pet.
YOU CAN GET REFILLS OF THIS MEDICATION FROM YOUR VETERINARIAN OR HERE. THIS SIZE TABLET IS NOT AVAILABLE IN HUMAN PHARMACIES.

Pimobendan (b) (6) 10 mg tiny tablets - 1 tablet two times a day
Pimobendan is a phosphodiesterase inhibitor that gives increased contractility and arterial vasodilation. This will help the heart function better, allow you dog to feel better and live longer. Any medication can upset the stomach. This drug does not typically cause this, but if you see any changes, please stop the drug till you talk to a doctor here at (b) (6). PLEASE GIVE THIS MEDICATION WITH (b) (6) MEALS. Even though package insert recommends giving on empty stomach, we have adjusted the dose so that you can give with meals. Giving on empty stomach is more likely to make your pet nauseous.
We will script this drug through (b) (6) Please call them in 4-5 days to order it, once we see that your dog will tolerate the drug.

Watch for the following clinical signs and call a veterinarian if you see any of these:
Excessive panting or wheezing
Restlessness, unable to get comfortable
Decreased appetite
Lethargy/weakness, less interactive or hiding
Collapse or fainting
Sudden rear leg or front leg lameness
Open-mouth breathing

It has been a pleasure meeting you and caring for your (b) (6). Thank you for entrusting us with her care. If you have any further questions or problems, don't hesitate to call.

(b) (6)

2/23/2018 P (b) (6) 30.00 tablet of Pimobendan 10mg tiny tab (cpd) (MMPOT8)
 Rx #: 2852563 0 Of 10 Refills

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
2/23/2018	P	(b) (6)	1 TABLET BY MOUTH TWO TIMES A DAY 100.00 tablet of Lasix (Salix/ Furosemide) 50mg Tablet (M569) Rx #: 2852561 0 Of 12 Refills 1 1/2 TABLETS BY MOUTH TWO TIMES A DAY
2/23/2018	C	(b) (6)	CARDIAC EVALUTION - CLOSED 02/24/2018 - Cardiac Evaluation

Date of evaluation: Friday, February 23, 2018

CHIEF COMPLAINT: tachypnea

HISTORY: last 3 days has been working hard to breath. No coughing. Appetite has been poor last 2 days, usually ravenous. Energy level seems down. No cardiac medications On 1/2 10 mg pred EOD for over year, Tried thyroid medication but stopped it, did not help. Has long history of panting and swallowing disorder.

PHYSICAL EXAM: BAR. HR = 120, regular rhythm, no murmur, gallop noted, pulses normal and synchronous. Mild tachypnea but panting, when rests lying down, still tachypnea. Normal bronchovesicular sounds bilaterally, no crackles or wheezes ausculted. BCS 5/9 PCS 0/4

ECHOCARDIOGRAM 2/23/18: BW 40 kg BSA 1.14

IVSd: 10 mm LVIDd: 64 mm LVPWd: 9 mm EPSS 21 mm
 IVSs: 14 mm LVIDs: 52 mm LVPWs: 11 mm %FS: 19 % Pa: 21 mm
 Ao: 24 mm LAD: 43 mm LA:Ao ratio 1.79 LA max: 48 mm LLAD: 56 mm
 RWT = IVSd+LVPWd/LVIDd = 0.30, LVID long 90 mm, Sphericity index 1.41 (Lax/Sax, <1.65=increased sphericity).
 Norm LA:Ao < 1.7, Normal LLAD < 42.93 mm, LVIDdn = 2.16 (N<1.73), LVIDsn = 1.63 (N<1.4)
 MV E vel: 132, MV Dec T:89, MV A vel: 67, IVRT:71 ms, E:A 1.97 (N 1-2)E:IVRT 1.86 (N<2.5) Ea 10 E:Ea 13.2 (N<14.5)
 Pa distensibility (mm): 14.7 - 5 = 57 %, PEP/ET = 96/170 = 0.56, > 0.4 is abnormal, with myocardial failure
 Tricuspid peak flow velocity 3.2 m/s, gradient 41 mmHg, acceleration time 88 ms, PAET 177 ms, ratio = 0.50
 (ratio greater than 0.30 is considered normal)
 100% spec for PH if AT < 45 ms +/- or AT:ET < 0.25, 100% spec for Normal if AT>64 ms +/- or AT:ET > 0.42
 Grey zone for predicting: AT < 58 ms (Se 88%, Sp 80%), AT:ET < 0.31 (Se 73% and Sp 87%)

COMMENTS: dilated LV with poor systolic function. Left atrial enlargement. Large EPSS. Moderate MR and TR. Reduce aortic and pulmonic flows. no pleural or pericardial effusion

DIAGNOSIS/PROBLEM LIST: dilated cardiomyopathy (DCM), left side congestive heart failure (LCHF)

SUMMARY: The dilated cardiomyopathy may be related to diet and taurine deficiency. There have been personal communications amongst cardiologist of a rash of cases of Golden Retrievers on grain free and/or kangaroo diets that have taurine deficiency cardiomyopathy. We pulled a whole blood level taurine today and started 2 grams of taurine BID. I also started furosemide and pimobendan as below. If taurine deficiency

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
------	------	-------	---------

cardiomyopathy, this could be reversible. It could take 2 months to see echo changes, but dog may feel better within a month. Recheck echocardiogram in 2 months. We should recheck a taurine level in 2 weeks. They will most likely do that with (b) (6).

MEDICATIONS:

Furosemide 50 mg tablets 1 1/2 tablet two times a day
 Pimobendan (b) (6) 10 mg tiny tablets - 1 tablet two times a day
 Taurine at home, 2 grams two times a day with food.

2/23/2018	V	(b)	Feb 23, 2018 01:06 PM Staff: (b) ----- Weight : 40.00 kilograms room 14
2/23/2018	CK	(b) (6)	CHF poss, setup by rdvm Reason for Visit: Consult Date Patient Checked Out: 02/23/18 Practice TF Callback - Call Client Back (CB)
2/23/2018	CB	(b) (6)	---- Note from (b) (6) on 2/23/2018 at 15:51:32 ---- Called (b) (6), spoke to (b) (6). ---- Note from (b) (6), BVSc, MRCVS, ACVIM on 2/23/2018 at 15:06:34 ---- Pimobendan (b) (6) 10 mg tiny tablets - 1 tablet two times a day, #100, 8 refills

2/22/2018	TC	(b)	RECORDS FROM RDVM/LDVM (see attachment) - TENTATIVE 2/22/2018 14:47 rDVM records attached. - Attachment(s)
-----------	----	-----	---

3/10/2017	C	(b)	COMMUNICATIONS WITH CLIENT 3/10/2017 10:26 updated owner regarding (b) (6) - recommending trial of soloxine. can be low from pred. but worth a try. can consider fluoro study in future. called into rdvm thyrotab 0.8 mg bid ; recheck t4 4 hours post pill in a month
-----------	---	-----	---

3/8/2017	L	(b) (6)	Endocrinology results from (b) (6) (b) (6) Requisition ID: (b) (6) PBsted Final
----------	---	---------	--

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
------	------	-------	---------

Test	Result	Reference Range
TSH	<0.03 ng/mL	0 – 0.60
Asc#: (b) (6)	Profile: TSH	

3/7/2017 C (b) (6) **RADIOLOGY REVIEW - CLOSED 03/08/2017**
 The right lateral views of the neck and thorax obtained today have been reviewed. There are no significant abnormalities in the extra-thoracic soft tissues, visible skeletal structures, pleural space, pulmonary parenchyma and vessels, cardiovascular structures, mediastinum, and cranial abdomen. An endoscopic evaluation may be considered for further investigation of the previously diagnosed arytenoid nodule.

This review was written by: (b) (6), DVM, DACVR, DACVS

3/7/2017 V	(b) (6)	Mar 7, 2017 04:21 PM Staff: (b) (6)
		Weight : 41.40 kilograms

3/7/2017 CK	(b) (6)	recheck for (b) (6) Reason for Visit: Recheck Date Patient Checked Out: 03/07/17 Practice TF
-------------	---------	--

3/7/2017 C	(b) (6)	IM PHYSICAL EXAM NEW 3/7/2017 10:10
------------	---------	--

Chief Complaint: reevaluation of hard swallowing; upper airway noise

History: (b) (6) was originally evaluated in 2015 for hard swallowing, gagging. A laryngeal exam at that time revealed a nodule on the larynx which was biopsied as granulomatous. He has been on low dose prednisone since. Owner still notices hard swallowing and sometimes regurgitation. He also has upper airway noise when sleeping- breathes through nose and no nasal discharge. Occasional hoarse bark. No diarrhea, no pu/pd. He has gained weight. In 2015 a myasthenia titer was negative. Diet includes zignature kangaroo. unsure of current dose of pred 1 tab in morning and sometimes 1/2 tab at night unsure what strength

Previous Medical Problems:

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

Medications/Supplements:

Current Diet:

- Frequency:

- Amount:

Subjective:

Mentation: Quiet, Alert, Responsive

Objective Findings

Temperature: 101.8 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec.

Hydration Status: normal

Pain Score: /4

Weight: 41.4 kilograms

Body Condition Score/Muscle Score: 8/9/

Oropharyngeal: Normal

Eyes/Ears: fundic normal

Integument: Normal

Peripheral Lymph Nodes: Normal size

Cardiovascular/Respiratory: heart ausculted normal; lungs clear; occasionally hard swallowing in the room

Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful.

Urogenital: Normal

Musculoskeletal/neurologic: normal ambulation; weak gag; hard swallowing during exam

Rectal: Normal

Diagnostics:

Lab Work: see below

Radiographic Findings: Thoracic radiograph unremarkable- no megaesophageous, lateral laryngeal radiograph normal

Other Diagnostics:

Problems/Differential Diagnoses/Assessment:

Hard swallowing- rule out esophageal motility disorder, laryngeal/pharyngeal dysfunction, other types of neuromuscular condition; Low T4 consider secondary to chronic pred, hypothyroidism. Can consider trial of soloxine and recheck after a month. Other diagnostics to consider would be a fluoroscopy study of (b) (6) swallowing.

Treatment:

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) **Patient:** (b) (6)
Phone: (b) (6) **Species:** Canine **Breed:** Retriever, Golden
Address: (b) (6) **Age:** 6 Yrs. 2 Mos. **Sex:** Neutered Male
Color: Blonde

Date Type Staff History

Plan/Recommendations:

3/7/2017 L

Hematology results from (b) (4) (East) Requisition

ID: (b) (6)	Posted	Final	Reference Range
Test	Result		
HCT	45 %		36 - 60
HGB	14.9 g/dL		12.1 - 20.3
MCHC	33 g/dL		30 - 38
WBC	19.6 10 ³ /uL H		4.0 - 15.5
Bands	0 %		0 - 3
RBC	6.1 10 ⁶ /uL		4.8 - 9.3
MCV	73 fL		58 - 79
MCH	24.3 pg		19 - 28
ABS BASO	0 /uL		0 - 150
Platelet C	128 10 ³ /uL L		170 - 400
Platelet E	ADEQUATE		
Neutrophil	91 % H		60 - 77
Lymphocyte	6 % L		12 - 30
Monocytes	3 %		3 - 10
Eosinophil	0 % L		2 - 10
Basophils	0 %		0 - 1
Absolute N	17836 /uL H		2060 - 10600
Absolute L	1176 /uL		690 - 4500
Absolute M	588 /uL		0 - 840
Absolute E	0 /uL		0 - 1200

Asc n: (b) (6) **Profile:** Complete Blood Count

Platelet count reflects the minimum number due to platelet clumping.

3/7/2017 L

Chemistry results from (b) (4) (b) (6) Requisition

ID: (b) (6)	Posted	Final	Reference Range
Test	Result		
ALB	3.8 g/dL		2.7 - 4.4
ALKP	48 IU/L		5 - 131
ALT	33 IU/L		12 - 118
AMYL	461 IU/L		290 - 1125
AST	15 IU/L		15 - 66
BUN/UREA	19 mg/dL		6 - 31
Ca	10.0 mg/dL		8.9 - 11.4
Chloride	109 mEq/L		102 - 120
CHOL	209 mg/dL		92 - 324
CK	67 IU/L		59 - 895
CREA	0.2 mg/dL L		0.5 - 1.6
GGT	2 IU/L		1 - 12

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

GLU	72 mg/dL	70 - 138
Mg	1.9 mEq/L	1.5 - 2.5
PHOS	4.6 mg/dL	2.5 - 6.0
Potassium	4.5 mEq/L	3.6 - 5.5
Sodium	148 mEq/L	139 - 154
TBIL	0.2 mg/dL	0.1 - 0.3
TP	6.6 g/dL	5.0 - 7.4
TRIG	32 mg/dL	29 - 291
GLOB	2.8 g/dL	1.6 - 3.6
A/G Ratio	1.4	0.8 - 2.0
B/C Ratio	95 H	4 - 27
Na/K Ratio	33	27 - 38

3/7/2017 L

Endocrinology results from (b) (4)
(b) (6) Requisition ID: (b) (6) **Posted** **Final**
Test **Result** **Reference Range**
T4 0.6 ug/dL L 0.8 - 3.5
Asc: (b) (6) **Profile:** Total T4

The Total T4 result is less than 1.0 mcg/dl. A Free-T4 by equilibrium dialysis may be helpful in supporting the diagnosis of hypothyroidism in patients demonstrating clinical signs compatible with hypothyroidism. Please contact Customer Service for this additional testing.

3/7/2017 L

Miscellaneous results from (b) (4)
(b) (6) Requisition ID: (b) (6) **Posted** **Final**
Asc: (b) (6) **Profile:** Superchem
RE: 1045 PrecisionP 50 U/L 24 - 140
Pancreatitis is unlikely, but a normal PrecisionPSL result does not completely exclude pancreatitis as a cause for gastrointestinal signs.
RE: 11067 Comment
Hemolysis 1+ No significant interference.

3/6/2017 C

(b) (6) **COMMUNICATIONS WITH CLIENT**
3/6/2017 12:55
(b) (6) confirmed appt w/ (b) (6) @ 330 on 3/7

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
2/26/2017	C	(b) (6)	COMMUNICATIONS WITH CLIENT 2/26/2017 10:15 (b) (6) to confirm 3:30 pm (b) (6) appt tomorrow
2/23/2017	TC	(b) (6)	RECORDS FROM RDVM/LDVM (see attachment) - TENTATIVE 2/23/2017 20:36 Records from (b) (6) - Attachment(s)
2/23/2017	C	(b) (6)	COMMUNICATIONS WITH DOCTOR 2/23/2017 17:18 (b) (6) of (b) (6) to request updated records from 5/3/15 forward be faxed
2/20/2016	C	(b) (6)	RECEPTION ACTIONS NOTE faxed ref letters and labs to (b) (6) per o's req
9/28/2015	C	(b) (6)	OUTSIDE PHARMACY RX ***ADDENDUM 10/2/2015 - Closed Sep 30/2015 Rx #: 0172 Prescribing doctor: (b) (6) Pharmacy prescription called in to: (b) (6) Pharmacy Phone #: (b) (6) Pharmacy Fax #: (b) (6) Medication: Doxycycline 100mg Quantity and Unit of Measure: #56 # of Refills: none Rx Instructions: 2t po q12h Is this medication a controlled substance?

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
------	------	-------	---------

Additional Comments: faxed
 ADDENDUM on 10/1/2015 at 21:11:18 from (b) (6)
 Re-faxed as per request of (b) (6).
 ADDENDUM on 10/2/2015 at 11:27:39 from (b) (6)
 they only have 200mg tablets
 ADDENDUM on 10/2/2015 at 13:26:23 from (b) (6)
 Owner said (b) (6) charged more than Target, refaxing script to Target fax
 # (b) (6).

9/28/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 9/28/2015 13:29 (b) was good for 2 months, then small flair up, then went away again for a few months. last time, we discussed repeat abx treat may not be helpful. discussed that we can repeat abx treatment as it worked for such a long period of time. discussed dual treatment for bartonella vs considering doxycycline and niacinamide. will try doxy/niacinamide and recheck 2 wks. will rx doxy to local rdvm, niacinamide 500 mg PO q 8 hr to get at local health store (OTC)
-----------	---	---------	--

6/1/2015	C	(b) (6)	OUTSIDE PHARMACY RX - Closed Jun 04/2015 Rx #: PIYM90115000055 Prescribing doctor: (b) (6) Pharmacy prescription called in to: Target Pharmacy Pharmacy Phone #: (b) (6) Pharmacy Fax #: Medication: Doxycycline 100 mg Quantity and Unit of Measure: #60/ 100 mg # of Refills: 0 Rx Instructions: Give 2 tab PO q 12hr Is this medication a controlled substance? Yes No Additional Comments: Called into Target Pharmacy in (b) (6)
----------	---	---------	--

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
6/1/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 6/1/2015 16:05 within the last 3 days stopped doing the neck movement/episodes that he was having. still sounds congested. when he barks there sounds like there is something in there. would continue abx for bartonella unless we are planning to rescope him. owner needs refill of doxycycline. will touch base in 1-2 wks.
5/17/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/17/2015 10:26 (b) (6) and asked how (b) (6) is doing, owner said she started ab's yesterday and so far he is doing well, owner will recheck in one week
5/15/2015	C	(b) (6)	OUTSIDE PHARMACY RX - Closed May 17/2015 Rx #: 0042 Prescribing doctor: (b) (6) Pharmacy prescription called in to: (b) (6) Pharmacy Phone #: n/a Pharmacy Fax #: (b) (6) Medication: Enrofloxacin 136mg Quantity and Unit of Measure: 45 # of Refills: 0 Rx Instructions: Give 1.5 tab (204mg) po q 24hr Is this medication a controlled substance? Additional Comments: Faxed to (b) (6)
5/15/2015	C	(b) (6)	OUTSIDE PHARMACY RX Rx #: 90115000043

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

Prescribing doctor: (b) (6)

Pharmacy prescription called in to: Target- (b) (6)

Pharmacy Phone #: (b) (6)

Pharmacy Fax #:

Medication: Doxycycline 100mg

Quantity and Unit of Measure: #60

of Refills: 0

Rx Instructions: Give 2 tab PO q12hr

Is this medication a controlled substance? No

Additional Comments:

5/15/2015 C (b) (6) COMMUNICATIONS WITH CLIENT ***ADDENDUM 5/15/2015
 5/15/2015 16:27
 (b) (6) per (b) (6), cost of bartonella test is \$342 which is something she can do via tech appt. or if O would prefer (b) (6) is OK with treating with AB's w/o testing. O wanted to know how long the course of AB's would be- per (b) (6) it would be a 2-4 week course. O also wanted to know if there is a chance of needing another course of AB's after the initial 2-4wk course, per (b) (6) P would not go on another course of AB's at that point. O would like to skip blood test due to cost and try treating with AB's first. Would like called into Target Pharmacy in (b) (6)
 ADDENDUM on 5/15/2015 at 18:45:06 from (b) (6)
 called O, there are two medications- one is only veterinary can call into (b) (6) (b) (6) and the other can be called into target in (b) (6). O OK with this plan. Called doxy into target pharm and rx to be faxed to (b) (6).

5/12/2015 C (b) (6) COMMUNICATIONS WITH CLIENT
 5/12/2015 14:50
 called owner with results. granulomatous inflammation. can be infectious, inflammatory or immune mediated disease. discussed type of inflammation present, there is concern for possible infectious organism. discussed bartonella and that this can be difficult to diagnose. discussed triple blood draw and

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) **Patient:** (b) (6)
Phone: (b) (6) **Species:** Canine **Breed:** Retriever, Golden
Address: (b) (6) **Age:** 6 Yrs. 2 Mos. **Sex:** Neutered Male
(b) (6) **Color:** Blonde

Date	Type	Staff	History
------	------	-------	---------

performing PCR and serology. discussed infectious disease CE and the recommendations for testing for bartonella. will look into cost for tests and then take it from there. this may not be the cause for his signs. discussed whether inflammation causes dysfunction or dysfunction started first. may need steroids or doxepin. will be in touch with owner as soon as i can get pricing information. last night he had the worst night. couldn't lay down. panting like crazy.

5/12/2015	C	(b) (6)	IM TREATMENT NEW 5/12/2015
-----------	---	---------	-------------------------------

Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion

nodule on vocal fold with asymmetry of arytenoid function: granulomatous inflammation

consider infectious disease screening; however due to length of time this has been doing on this is considered less likely. Consider treatment with anti-inflammatory doses of prednisone for possible immune mediated vs sterile inflammation

if no improvement with either abx therapy, anti-inflammatory to possibly immunosuppressive steroid therapy, consider doxepin

Treatment: no treatment implemented today

Recommended Follow-up Care: looking into pricing for bartonella testing. will recheck/touch base with owner when this is available; may go to local rDVM for testing due to proximity

(b) (6) L

Miscellaneous results from (b) (4)

(b) (6) **Requisition ID:** (b) (6) **Posted** **Final**
Asc: (b) (6) **Profile:** Histopathology, Full Written Report

RE: 7801 History:

Nodule on glottal opening. Episodes since he was 9 months old.

Episodes are described as extending his neck repeatedly and gagging/choking and swallowing. (b) (6) would swallow hard repeatedly and

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative med note, V: Vital signs

(b) (6)

Page 15 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
			<p>have continual lip licking with a stridorous noise when breathing. He licks the air. He will intermittently vomit, but not with every episode. He has been treated with sucralfate, Cerenia and Pepcid. The Cerenia seems to help, but does not completely resolve the signs.</p> <p>Received: Multiple fragments - all processed. RE: 601 Biopsy DESCRIPTION/MICROSCOPIC FINDINGS/COMMENTS:</p> <p>Sections of fragments of an ulcerated inflammatory mass lesion affecting the glottal region are examined. This lesion is composed of collagen bundles and fibroblasts arranged haphazardly among moderate numbers of capillaries. There are moderate numbers of neutrophils in the stroma. There also is mild edema. No neoplasia or infectious organisms are seen.</p> <p>MICROSCOPIC FINDINGS: Chronic-active, proliferative and granulomatous, inflammation</p> <p>PROGNOSIS: Good</p> <p>COMMENT: No neoplasia or infectious organisms are seen. These proliferative inflammatory lesions are common. Most of these lesions develop secondary to ruptured ducts of submucosal glands but some are a reaction to a small penetrating foreign body. Excision usually is curative</p> <p>PATHOLOGIST:</p> <p>PATHOLOGIST: (b) (6) DVM, PhD, DIPLOMATE ACVP email: (b) (6).com, ph: (b) (6)</p>
(b) (6)	I	(b) (6)	For your pet's safety, he/she was intubated for the anesthetic. You may notice

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

(b) (6)	I	(b) (6)	<p>some coughing for the next couple of days. This is normal due to a small amount of irritation to the throat from the endotracheal tube. If the coughing seems excessive please contact our office.</p> <p>(b) received an anesthetic. Please keep him confined until full recovery. Restrict water intake to small amounts at a time for the next 12-24 hours. Restrict food intake to small amounts also; 1/3 of the normal ration this evening. Because the anesthetic can lower his body temperature, keep him where it is warm and dry. Today's oropharyngeal exam revealed a small white nodule, irregular on the left medial aspect, mid way up vocal fold. with suspected kissing lesion on the right aryepiglottic fold; Assymetry to the left and right arytenoid with seemingly inappropriate function of the left with collapse towards midline; both arytenoids were able to abduct when inspiring but were asymmetrical when this was occurring. edematous and swollen corniculate tubercle bilaterally; prominent tonsils which were erythematous and out of crypts</p> <p>- nodule on vocal fold with assymetry of arytenoid function: r/o: pharyngeal or laryngeal dysfunction secondary to inflammation, neurogenic or infiltrative</p>
(b) (6)	I	(b) (6)	

(b) (6)	C	(b) (6)	<p>COMMUNICATIONS WITH CLIENT</p> <p>(b) (6) 14:10</p> <p>(b) (6) discussed scope findings. and discussed possible causes for findings. no treatment recommended until results available. okay to d/c at 5 pm.</p>
---------	---	---------	---

(b) (6)	C	(b) (6)	<p>ENDOSCOPIC EVALUATION</p> <p>Upper Gastrointestinal: oropharyngeal exam: small white nodule, irregular on the left medial aspect, mid way up vocal fold. with suspected kissing lesion on the right aryepiglottic fold; Assymetry to the left and right arytenoid with seemingly inappropriate function of the left with collapse towards midline; both arytenoids were able to abduct when inspiring but were asymmetrical when this was occurring. edematous and swollen corniculate tubercle bilaterally; prominent tonsils which were erythematous and out of crypts</p> <p>Lower Gastrointestinal:</p> <p>Bronchoscopy:</p> <p>Rhinoscscopy:</p> <p>Cystoscopy:</p>
---------	---	---------	--

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

Other:

Biopsies: 3 biopsies obtained with minimal bleeding

Culture/Sensitivity:

Visual Inspection: suspected dysfunction of the left arytenoid with nodule present on the left vocal fold.

Initial Recommendations: consider doxepin 100 mg PO q 12 hr pending biopsy results.

(b) (6)	C	(b) (6)	IM TREATMENT NEW (b) (6) <p>Internal Medicine Assessment: (b) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion</p> <p>nodule on vocal fold with asymmetry of arytenoid function: r/o: pharyngeal or laryngeal dysfunction secondary to inflammation, neurogenic or infiltrative</p> <p>Treatment: no treatment today</p> <p>Recommended Follow-up Care: pending biopsies consider doxepin 100 mg PO q 12 hr</p>
---------	---	---------	---

(b) (6)	C	(b) (6)	IM PHYSICAL EXAM Chief Complaint: <p>History: (b) presented for endoscopic evaluation - prior hx:</p> <p>(b) is a 3 yo MN golden retriever presenting for further evaluation of episodes that he has been having since he was 9 months old. He was evaluated in May 2014 and lab work and u/s were performed but did not elucidate the cause of his episodes. He was additionally evaluated by (b) and the owner was told the problem was likely neurological but may not be treatable. The owner says the episodes are becoming more frequent and lasting longer. The episodes are described as extending his neck repeatedly and gagging/choking and swallowing. The owner showed a video at the consult and this behavior was witnessed where (b) would swallow hard</p>
---------	---	---------	--

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative med note, V: Vital signs

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)
(b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
			<p>repeatedly and have continual lip licking with a stridorous noise when breathing. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is initiated by drinking and occurred in the exam room after drinking water. Eating is not as much of a trigger. He is eating dry food which the owner waters down. The owner has not tried canned food. She doesn't think that the episodes are related to consistency. He does not have episodes when active and out/about. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. On the evening of an episode he will snore when sleeping. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He is eating well. He seems to be acting normally otherwise. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.</p> <p>Significant Physical Exam Findings: Mentation: BAR Temperature: 102.4 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec. Hydration Status: adequate Weight: 36.6 kilograms Body Condition Score: 7/9 Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum; normal cervical palpation Eyes/Ears: clear OU; fundic exam WNL OU; clean AU Integument: full coat; no ectoparasites Peripheral Lymph Nodes: Normal size Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful. Urogenital: neutered male; no prepuce d/c Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed.</p> <p>Lab Work: Chemistry: BUN: 11, Creat: 1.4 - NSF CBC: HCT: 46.9%, WBC: 8.14, neut: 4.10, PLT: 57k</p> <p>Radiographic Findings: CHIEF COMPLAINT/HISTORY: 5/3/2015. Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure.</p>

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative med note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

FINDINGS: Three views of the thorax are available for review.

No significant abnormalities are present in the extra-thoracic soft tissues, skeletal structures, pleural and mediastinal spaces, pulmonary and cardiovascular structures, as well as in the visible cranial abdomen.

SUMMARY/CONCLUSIONS:

1. Normal thorax with no evidence of megaesophagus.

(b) (6) L

Chemistry results from (b) (6)		In-clinic
Laboratory Test	Requisition ID (b) (6)	Posted Final
Test Result		Reference Range
ALBe=	3.2 g/dL	2.3 - 4.0
ALKP =	73 U/L	23 - 212
ALTe=	31 U/L	10 - 125
AMYLE=	744 U/L	500 - 1500
BUN/UREAe=	11 mg/dL	7 - 27
Cae=	9.4 mg/dL	7.9 - 12.0
Chloridee=	112 mmol/L	109 - 122
CHOLe=	257 mg/dL	110 - 320
CREAe=	1.4 mg/dL	0.5 - 1.8
GGT <	< 0 U/L	0 - 11
GLU =	97 mg/dL	74 - 143
LIPAe=	1120 U/L	200 - 1800
PHOS =	4.0 mg/dL	2.5 - 6.8
Potassium=	4.7 mmol/L	3.5 - 5.8
Sodium=	153 mmol/L	144 - 160
TBIL =	0.3 mg/dL	0.0 - 0.9
TP =	6.0 g/dL	5.2 - 8.2
GLOBe=	2.8 g/dL	2.5 - 4.5
ALB/GLOBe=	1e1	
BUN/CREAe=	8	
Na/K =	33	
OSM calc =	303 mmol/kg	

PCV=49% TS= 6.8g/dl (serum norm)

(b) (6) V

(b)

(b) (6) 10:20 AM Staff: (b)

Weight : 36.60 kilograms

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6) **Patient:** (b) (6)
Phone: (b) (6) **Species:** Canine **Breed:** Retriever, Golden
Address: (b) (6) **Age:** 6 Yrs. 2 Mos. **Sex:** Neutered Male
Color: Blonde

Date	Type	Staff	History
------	------	-------	---------

Temperature : 102.4
 Pulse : 100
 Respiration : pant
 mm pk, crt <2s

(b) (6) L

Hematology results from (b) (6) **In-clinic**
Laboratory Requisition ID: (b) (6) **Posted** **Final**

Test	Result	Reference Range
HCT =	46.9 %	37.3 - 61.7
HGB =	16.3 g/dL	13.1 - 20.5
MCHC =	34.8 g/dL	32.0 - 37.9
WBC =	8.14 K/uL	5.05 - 16.76
NEUTe=	4.10 K/uL	2.95 - 11.64
%NEUTe=	50.4 %	
EOS =	0.71 K/uL	0.06 - 1.23
%EOS =	8.7 %	
PLT *	* 57 K/uL L	148 - 484
Retics =	21.5 K/uL	10.0 - 110.0
%Retics =	0.3 %	
RBC =	6.94 M/uL	5.65 - 8.87
MCV =	67.6 fL	61.6 - 73.5
MCH =	23.5 pg	21.2 - 25.9
RDW =	18.1 %	13.6 - 21.7
MPV -	--- fL	8.7 - 13.2
PDW -	--- fL	9.1 - 19.4
PCT -	--- %	0.14 - 0.46
LYMPHSe=	2.88 K/uL	1.05 - 5.10
%LYMPHSe=	35.4 %	
MONOSe=	0.43 K/uL	0.16 - 1.12
%MONOSe=	5.3 %	
BASO =	0.02 K/uL	0.00 - 0.10
%BASO =	0.2 %	

(b) (6) C

RADIOLOGY REPORT - FINAL (b) (6)

RADIOGRAPHIC REPORT

CHIEF COMPLAINT/HISTORY: 5/3/2015. Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure.

FINDINGS: Three views of the thorax are available for review.

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative med note, V: Vital signs

(b) (6)

Page 21 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

No significant abnormalities are present in the extra-thoracic soft tissues, skeletal structures, pleural and mediastinal spaces, pulmonary and cardiovascular structures, as well as in the visible cranial abdomen.

SUMMARY/CONCLUSIONS:

1. Normal thorax with no evidence of megaesophagus.

(b) (6)	CK	(b) (6)	Drop off for procedure w/ (b) (6) - CXR, chem III, CBC Reason for Visit: Medicine Procedure Date Patient Checked Out: (b) (6) Practice TF
---------	----	---------	---

(b) (6)	C	(b) (6)	COMMUNICATIONS WITH CLIENT (b) (6) 11:48 Spoke to O and confirmed (b) (6) procedure for tomorrow. Dropping off between 9:30 -10am. Told O no food after midnight and no water after 6am tomorrow. O knows she will not speak to (b) (6) at drop off. She thanked me for calling.
---------	---	---------	--

5/3/2015	C	(b) (6)	IM TREATMENT NEW 5/3/2015 Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure recommend further evaluation including thoracic radiographs, sedated oral exam and endoscopy +/- fluoroscopy and esophagram. Treatment: no treatment implemented Recommended Follow-up Care: to return (b) (6) for further evaluation - chemistry, CBC thoracic radiographs, (b) (6)
----------	---	---------	---

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative med note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
5/3/2015	C	(b) (6)	<p>IM PHYSICAL EXAM</p> <p>Chief Complaint:</p> <p>History: (b) (6) is a 3 yo MN golden retriever presenting for further evaluation of episodes that he has been having since he was 9 months old. He was evaluated in May 2014 and lab work and u/s were performed but did not elucidate the cause of his episodes. He was additionally evaluated by (b) (6) and the owner was told the problem was likely neurological but may not be treatable. The owner says the episodes are becoming more frequent and lasting longer. The episodes are described as extending his neck repeatedly and gagging/choking and swallowing. The owner showed a video at the consult and this behavior was witnessed where (b) (6) would swallow hard repeatedly and have continual lip licking with a stridorous noise when breathing. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is initiated by drinking and occurred in the exam room after drinking water. Eating is not as much of a trigger. He is eating dry food which the owner waters down. The owner has not tried canned food. She doesn't think that the episodes are related to consistency. He does not have episodes when active and out/about. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. On the evening of an episode he will snore when sleeping. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He is eating well. He seems to be acting normally otherwise. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.</p> <p>Significant Physical Exam Findings: Mentation: BAR Temperature: 101.7 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec. Hydration Status: adequate Weight: 36.7 kilograms Body Condition Score: 7.9 Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum; normal cervical palpation Eyes/Ears: clear OU; fundic exam WNL OU; clean AU Integument: full coat; no ectoparasites Peripheral Lymph Nodes: Normal size Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic</p>

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
------	------	-------	---------

Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful.
 Urogenital: neutered male; no prepuce d/c
 Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed.

Lab Work: none performed today

Radiographic Findings: none performed today

5/3/2015	CK	(b) (6)	Reason for Visit: Recheck Date Patient Checked Out: 05/03/15 Practice TF
----------	----	---------	---

11/21/2014	C	(b)	COMMUNICATIONS WITH CLIENT 11/21/2014 13:54 (b) (6) - Myasthenia gravis test was negative, and so the next step for (b) (6) would be an esophageal scope to determine the cause for his clinical signs. Owner thankful, will call and schedule with IM after thanksgiving.
------------	---	-----	--

11/14/2014	CK	(b)	swallowing issues Reason for Visit: Consult Date Patient Checked Out: 11/14/14 Practice TF
------------	----	-----	--

5/31/2014	C	(b) (6)	IM TREATMENT NEW 5/31/2014 Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with usual episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, primary GI disease, neuro disease -functional problem vs focal seizure Chemistry - NSF CBCe NSF T4: WNL No evidence of endocrine or metabolic disease based on screening labs.
-----------	---	---------	---

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative med note, V: Vital signs

Patient History Report

Client: (b) (6) **Patient:** (b) (6)
Phone: (b) (6) **Species:** Canine **Breed:** Retriever, Golden
Address: (b) (6) **Age:** 6 Yrs. 2 Mos. **Sex:** Neutered Male
Color: Blonde

Date	Type	Staff	History
------	------	-------	---------

Treatment: no treatment implemented at this time

Recommended Follow-up Care: recheck after owner discusses steps with insurance company - to consider chest radiographs, neuro consult, sedated oral exam and endoscopy

5/31/2014	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/31/2014 11:29 Spoke with owner and relayed that blood results are all normal. owner would like to speak with insurance prior to scheduling appt. next steps could be to get neuro consult, sedated oral exam and endoscopy
-----------	---	---------	--

5/31/2014	L		Hematology results from (b) (6) Requisition <table border="1"> <thead> <tr> <th>ID:</th> <th>(b) (6)</th> <th>Posted</th> <th>Final</th> <th>Reference Range</th> </tr> </thead> <tbody> <tr> <td>Test</td> <td></td> <td>Result</td> <td></td> <td></td> </tr> <tr> <td>HCT</td> <td></td> <td>46 %</td> <td></td> <td>36 - 60</td> </tr> <tr> <td>HGB</td> <td></td> <td>15.9 g/dL</td> <td></td> <td>12.1 - 20.3</td> </tr> <tr> <td>MCHC</td> <td></td> <td>34.6 g/dL</td> <td></td> <td>30 - 38</td> </tr> <tr> <td>WBC</td> <td></td> <td>8.1 10³/uL</td> <td></td> <td>4.0 - 15.5</td> </tr> <tr> <td>Bands</td> <td></td> <td>0 %</td> <td></td> <td>0 - 3</td> </tr> <tr> <td>RBC</td> <td></td> <td>6.3 10⁶/uL</td> <td></td> <td>4.8 - 9.3</td> </tr> <tr> <td>MCV</td> <td></td> <td>73 fL</td> <td></td> <td>58 - 79</td> </tr> <tr> <td>MCH</td> <td></td> <td>25.2 pg</td> <td></td> <td>19 - 28</td> </tr> <tr> <td>Platelet C</td> <td></td> <td>158 10³/uL L</td> <td></td> <td>170 - 400</td> </tr> <tr> <td>Platelet E</td> <td></td> <td>ADEQUATE</td> <td></td> <td>ADEQUATE -</td> </tr> <tr> <td>Neutrophil</td> <td></td> <td>49 % L</td> <td></td> <td>60 - 77</td> </tr> <tr> <td>Lymphocyte</td> <td></td> <td>46 % H</td> <td></td> <td>12 - 30</td> </tr> <tr> <td>Monocytes</td> <td></td> <td>4 %</td> <td></td> <td>3 - 10</td> </tr> <tr> <td>Eosinophil</td> <td></td> <td>1 % L</td> <td></td> <td>2 - 10</td> </tr> <tr> <td>Basophils</td> <td></td> <td>0 %</td> <td></td> <td>0 - 1</td> </tr> <tr> <td>Absolute N</td> <td></td> <td>3969 /uL</td> <td></td> <td>2060 - 10600</td> </tr> <tr> <td>Absolute B</td> <td></td> <td>0 /uL</td> <td></td> <td>0 - 150</td> </tr> <tr> <td>Absolute L</td> <td></td> <td>3726 /uL</td> <td></td> <td>690 - 4500</td> </tr> <tr> <td>Absolute M</td> <td></td> <td>324 /uL</td> <td></td> <td>0 - 840</td> </tr> <tr> <td>Absolute E</td> <td></td> <td>81 /uL</td> <td></td> <td>0 - 1200</td> </tr> </tbody> </table> <p>Asc: (b) (6) Profile: CBC</p> <p>Platelet count reflects the minimum number due to platelet clumping.</p>	ID:	(b) (6)	Posted	Final	Reference Range	Test		Result			HCT		46 %		36 - 60	HGB		15.9 g/dL		12.1 - 20.3	MCHC		34.6 g/dL		30 - 38	WBC		8.1 10 ³ /uL		4.0 - 15.5	Bands		0 %		0 - 3	RBC		6.3 10 ⁶ /uL		4.8 - 9.3	MCV		73 fL		58 - 79	MCH		25.2 pg		19 - 28	Platelet C		158 10 ³ /uL L		170 - 400	Platelet E		ADEQUATE		ADEQUATE -	Neutrophil		49 % L		60 - 77	Lymphocyte		46 % H		12 - 30	Monocytes		4 %		3 - 10	Eosinophil		1 % L		2 - 10	Basophils		0 %		0 - 1	Absolute N		3969 /uL		2060 - 10600	Absolute B		0 /uL		0 - 150	Absolute L		3726 /uL		690 - 4500	Absolute M		324 /uL		0 - 840	Absolute E		81 /uL		0 - 1200
ID:	(b) (6)	Posted	Final	Reference Range																																																																																																													
Test		Result																																																																																																															
HCT		46 %		36 - 60																																																																																																													
HGB		15.9 g/dL		12.1 - 20.3																																																																																																													
MCHC		34.6 g/dL		30 - 38																																																																																																													
WBC		8.1 10 ³ /uL		4.0 - 15.5																																																																																																													
Bands		0 %		0 - 3																																																																																																													
RBC		6.3 10 ⁶ /uL		4.8 - 9.3																																																																																																													
MCV		73 fL		58 - 79																																																																																																													
MCH		25.2 pg		19 - 28																																																																																																													
Platelet C		158 10 ³ /uL L		170 - 400																																																																																																													
Platelet E		ADEQUATE		ADEQUATE -																																																																																																													
Neutrophil		49 % L		60 - 77																																																																																																													
Lymphocyte		46 % H		12 - 30																																																																																																													
Monocytes		4 %		3 - 10																																																																																																													
Eosinophil		1 % L		2 - 10																																																																																																													
Basophils		0 %		0 - 1																																																																																																													
Absolute N		3969 /uL		2060 - 10600																																																																																																													
Absolute B		0 /uL		0 - 150																																																																																																													
Absolute L		3726 /uL		690 - 4500																																																																																																													
Absolute M		324 /uL		0 - 840																																																																																																													
Absolute E		81 /uL		0 - 1200																																																																																																													

5/31/2014	L		Chemistry results from (b) (6) Requisition
-----------	---	--	---

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative med note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

ID: (b) (6)	Posted	Final	
Test	Result	Reference	Range
ALB	3.5 g/dL	2.7 - 4.4	
ALKP	42 U/L	5 - 131	
ALT	28 U/L	12 - 118	
AMYL	515 U/L	290 - 1125	
AST	20 U/L	15 - 66	
BUN/UREA	14 mg/dL	6 - 31	
Ca	11.1 mg/dL	8.9 - 11.4	
Chloride	109 mEq/L	102 - 120	
CHOL	298 mg/dL	92 - 324	
CK	40 U/L L	59 - 895	
CREA	1.2 mg/dL	0.5 - 1.6	
GGT	6 U/L	1 - 12	
GLU	91 mg/dL	70 - 138	
LIPA	428 U/L	77 - 695	
Mg	1.7 mEq/L	1.5 - 2.5	
PHOS	4.0 mg/dL	2.5 - 6.0	
Potassium	4.8 mEq/L	3.6 - 5.5	
Sodium	145 mEq/L	139 - 154	
TBIL	0.1 mg/dL	0.1 - 0.3	
TP	5.9 g/dL	5.0 - 7.4	
TRIG	113 mg/dL	29 - 291	
GLOB	2.4 g/dL	1.6 - 3.6	
A/G Ratio	1.5 Ratio	0.8 - 2.0	
B/C Ratio	12 Ratio	4 - 27	

5/31/2014 L Endocrinology results from (b) (4)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Test Result Reference Range
 T4 1.6 ug/dL 0.8 - 3.5
 Asc: (b) (6) Profile: Total T4

5/31/2014 L Miscellaneous results from (b) (4)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Asc: (b) (6) Profile: Superchem
 RE: 1050 Na/K Ratio 30
 RE: 11067 Comment
 Hemolysis 1+. No significant analyte interference.

5/30/2014 C (b) (6) ULTRASOUND REPORT NEW

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
	Color: Blonde	

Date	Type	Staff	History
			<p>laryngeal, pharyngeal disease, esophageal disease, primary GI disease, neuro disease -functional problem vs focal seizure</p> <p>Treatment: no treatment implemented at this time</p> <p>Recommended Follow-up Care: pending lab results; consider fluroscopy, sedated oral exam and endoscopy with neuro exam prior.</p>

5/30/2014 C (b) (6)

IM PHYSICAL EXAM NEW
5/30/2014 22:58

Presenting Complaint:

History: (b) (6) is a 2 yo MN golden retriever presenting for episodes that the owner describes and extending his neck repeatedly and gagging/choking. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is not associated with eating or drinking specifically but does occur after drinking. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He used to have diarrhea until his diet was switched to natural balance fish and sweet potato. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. These episodes seemed to start when (b) (6) was 9 mo old and has been progressively more frequent. The last 1-2 weeks he is having daily signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.

Mentation: BAR

Temperature: 102 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec.

Hydration Status: adequate

Weight: 37.3 kilograms

Body Condition Score: 7.9

Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum; normal thyroid palpation

Eyes/Ears: clear OU; fundic exam WNL OU; clean AU

Integument: full coat; no ectoparasites

Peripheral Lymph Nodes: Normal size

Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic

Abdominal Palpation: There was no obvious mass or organomegaly, and the

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 28 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History									
			<p>abdomen was non-painful.</p> <p>Urogenital: neutered male; no prepuce d/c</p> <p>Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed.</p> <p>Rectal: Normal</p> <p>Lab Work: cbc, superchem, T4 pending to (b)(4)</p> <p>Radiographic Findings: none performed</p>									
5/30/2014	I	(b)(6)	<p>(b) has unusual signs that appear to be a lot of swallowing air. At this time it is not clear why this is happening; however, our plans to further evaluate this include lab work to rule out metabolic abnormalities, GI malabsorption or thyroid problems. These tests are pending and I will call you when results are available. The next steps would include a neurology consultation, sedated oral exam followed by endoscopy to evaluate his clinical signs +/- chest radiographs.</p>									
5/30/2014	V	(b)	<p>May 30, 2014 12:26 PM Staff: (b)</p> <p>-----</p> <p>Weight : 37.30 kilograms</p>									
5/30/2014	V		<p>May 30, 2014 12:26 PM</p> <p>-----</p>									
5/30/2014	CK	(b)(6)	<p>Consult for possible scope</p> <p>Reason for Visit: Consult</p> <p>Date Patient Checked Out: 05/30/14 Practice TF</p>									
5/30/2014	L	(b)(6)	<p>Chemistry results from (b)(4) Requisition ID: (b)(6) Posted Final</p> <table><thead><tr><th>Test</th><th>Result</th><th>Reference Range</th></tr></thead><tbody><tr><td>COBALAMIN</td><td>442 ng/L</td><td>288 - 8960</td></tr><tr><td>FOLATE</td><td>6.9 ug/L</td><td>4.8 - 19.0</td></tr></tbody></table> <p>Asc: (b)(6)</p> <p>SS MN CANINE</p>	Test	Result	Reference Range	COBALAMIN	442 ng/L	288 - 8960	FOLATE	6.9 ug/L	4.8 - 19.0
Test	Result	Reference Range										
COBALAMIN	442 ng/L	288 - 8960										
FOLATE	6.9 ug/L	4.8 - 19.0										
5/29/2014	C	(b)(6)	<p>COMMUNICATIONS WITH CLIENT</p> <p>5/29/2014 11:08</p> <p>(b)(6) confirmed 5/30 apt at 1130</p>									

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)
Phone: (b) (6)
Address: (b) (6)
(b) (6)

Patient: (b) (6)
Species: Canine
Age: 6 Yrs. 2 Mos.
Color: Blonde

Breed: Retriever, Golden
Sex: Neutered Male

Date	Type	Staff	History
5/27/2014	C	(b) (6)	RECEPTION ACTIONS NOTE Received fax from (b) (6). Placed in box under (b) (6)
5/27/2014	C	(b) (6)	RECEPTION ACTIONS NOTE ***ADDENDUM 5/27/2014 recv'd fax from (b) (6) and (b) (6) in black bx under (b) (6). ADDENDUM on 5/27/2014 at 12:49:24 from (b) (6) Recv'd fax from (b) (6). Placed in black box under (b) (6)

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

From: [Milton, Nanette](#)
To: [Palmer, Lee Anne](#); [Rotstein, David](#); [McDermott, Patrick](#); [DeLancey, Siobhan](#); [Burkholder, William](#); [Hartogenesis, Martine](#); [Norris, Anne](#); [Jones, Jennifer L](#); [Carey, Lauren](#)
Subject: Information: PFI & CVM Webinar on July 19 (pre-meeting)
Attachments: [PFI Questions for CVM Regarding DCM.docx](#)

Hi Nanette,

Please send the attached questions to the CVM folks attending the webinar on the 19th.

Can you set up a pre-meeting from CVM so we can discuss?

Also, let PFI know who will be attending from CVM.

Thanks!
Martine

From: Dana Brooks [mailto:Dana@petfoodinstitute.org <<mailto:Dana@petfoodinstitute.org>>]
Sent: Thursday, July 12, 2018 9:23 AM
To: Hartogenesis, Martine <Martine.Hartogenesis@fda.hhs.gov <<mailto:Martine.Hartogenesis@fda.hhs.gov>> >
Cc: Tabor, Peter <peter@petfoodinstitute.org <<mailto:peter@petfoodinstitute.org>> >
Subject: Information: PFI & CVM Webinar on July 19
Importance: High

Martine,

I wanted to reconfirm the webinar is scheduled for July 19. I'm sharing some questions with you in advance that may be asked by our members. These are the questions that our producer members presented to PFI as we informed them of the DCM incidents. I hope this is helpful to your team.

Please let us know who will be joining the call. We will do the same from our end.

Thank you so much,
Dana Brooks

-- Do not delete or change any of the following text. --

Join WebEx meeting <<https://fda1.webex.com/fda1/j.php?MTID=md1669c061ce203d0436a270da081f36e>>
Meeting number (access code): (b) (6)
Meeting password: (b) (6)

Join by phone
+1-877-465-7975 US Toll Free
Global call-in numbers <<https://fda1.webex.com/fda1/globalcallin.php?serviceType=MC&ED=7002862&tollFree=1>> | Toll-free calling restrictions
<https://e-meetings.verizonbusiness.com/global/pdf/Verizon_Audio_Conferencing_Global_Access_Information_August2017.pdf>

Can't join the meeting? <<https://collaborationhelp.cisco.com/article/WBX000029055>>

If you are a host, go here <<https://fda1.webex.com/fda1/j.php?MTID=m0dab1d42838e7d6c5224d9d372e353d1>> to view host information.

IMPORTANT NOTICE: Please note that this WebEx service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

PFI Questions for FDA CVM Regarding DCM

Questions Regarding the Language and Overall Scope of the Investigation

Is “grain-free” an adequate descriptor of the category of diets being examined?

Dr. Lisa Freeman at Tufts University indicates the incidence of DCM is associated with more than just grain-free diets: <http://vetnutrition.tufts.edu/2018/06/a-broken-heart-risk-of-heart-disease-in-boutique-or-grain-free-diets-and-exotic-ingredients/>.

Will FDA CVM consider the need for further evaluation of any link between pet food diets and incidence of DCM before deciding whether to issue a public notice?

Questions Regarding Investigation History

Can FDA CVM share more information regarding the breeds of dogs and ages involved in its observations, including information on which breeds it believes are predisposed to DCM? Also, has FDA CVM looked into the relationships between dogs exhibiting DCM to determine whether/how genetics could be playing a role in the observed cases of DCM?

Can the FDA share the details around the formal diagnoses of DCM in these dogs? Were the diagnoses based on clinical pathology blood or serum samples alone? Was there any supporting electrocardiographic data for these animals? Similarly, were the diagnoses confirmed with medical imaging data or post-mortem gross pathology/histopathology evaluations?

Can FDA CVM share the comprehensive diet histories of the impacted animals and the total dietary fiber, soluble fiber and viscous fiber content of the diets tested?

Is a nutritionist gathering diet history information as part of FDA’s investigation?

What were the protein sources and digestibility in each of these diets?

Were any (paired or whole) blood or plasma tests for taurine performed? Was any urine taurine measured before or after treatment?

In the case of the dog that improved with a diet change from one grain-free diet to another, what were the dietary taurine levels, total dietary fiber levels and digestibility percentages of the implicated and treatment diets?

In dogs whose condition improved, in addition to diet change, what level of taurine supplementation was given?

How much of the research presented at the ACVIM forum (on June 14) represents the full series of complaints that FDA CVM is investigating?

Does FDA CVM believe that other brands are implicated as well, and, if so, what are the data used by the agency to reach this conclusion?

Is there a common supplier or co-manufacturer of ingredients and/or products?

Given that not all grain-free diets are linked to an increase in DCM, has the agency evaluated other grain-free diets that share the same legume sources as the diets consumed by dogs that developed DCM?

Are there other pathologies being considered?

Research presented at ACVIM did not definitively conclude that the recently observed increase in DCM is a taurine issue (although low taurine has previously been linked to increased incidence of DCM).

What is known about the formulations, ingredient handling and processing conditions for the diets that FDA CVM considers possibly associated with DCM?

What is known about the amino acid balance in the diets containing pulses?

Questions Regarding Certain Product Attributes and the Incidence of DCM

Has FDA CVM considered whether there might be a connection between products that are not adding sufficient sources of vitamins and minerals and the incidence of DCM?

What evaluations have been done to determine the presence/absence of sufficient vitamins and minerals in any of the diets identified as linked to incidents of DCM?

Has FDA CVM considered what impact other dietary factors have on the intestinal tract in light of the tendency of many grain-free diets to contain higher levels of soluble fiber as compared to conventional diets?

If taurine is not recognized as an essential nutrient for dogs and there is no standard developed, is FDA CVM considering recommending a minimum taurine level for all dog food diets?

If a taurine requirement were to be proposed for dogs, would the requirement be based on repletion data or data shown to maintain normal blood taurine levels?

Since the whole blood taurine was normal in tested dogs that were fed a grain-free diet, is taurine supplementation through food effective?

Are the taurine dosage levels used in the treatment of DCM cases safe for long-term use?

Is FDA CVM examining the presence of certain legumes and their levels as potentially impacting the synthesis of taurine? If so, what conclusions have been drawn?

What other anti-nutrient factors may be present in legumes, tubers and other non-grain-type ingredients? Can these factors be measured in the finished product and can safe-levels be set against these?

Green peas have been a common ingredient in single animal protein source diets since the 1990s. Have there been any proposed mechanisms to explain why there is an emergence of pea- association in DCM?

Given the growing trend today toward pet food recipes that utilize novel ingredients over conventional ingredient diets (such as corn, wheat, soy, chicken, pork), is there consideration that the current generation of pet foods will require a unique set of nutrient requirements based on new knowledge of ingredient-nutrient interactions and manufacturing capabilities? What efforts would be needed to redefine nutrient requirements?

Diets reported in cases received by FDA-CVM between 7/12/2018 and 8/14/2018 per online searches

4Health GF Beef & Potato:

Ingredients:

Beef, Beef Meal, Pea Protein, Dried Peas, Whole Potato, Pea Flour, Poultry Fat (preserved with Mixed Tocopherols), Dried Plain Beet Pulp, Natural Flavor, Whole Flaxseed, Salt, Potassium Chloride, Brewers Dried Yeast, Zinc Protein, Vitamin E Supplement, Iron Protein, L-Ascorbyl-2-Polyphosphate (source of Vitamin C), Choline Chloride, Manganese Protein, Dried Bacillus Coagulans Fermentation Product, Copper Protein, Niacin, d-Calcium Pantothenate, Biotin, Sodium Selenite, Vitamin A Supplement, Riboflavin Supplement, Thiamine Mononitrate, Vitamin B12 Supplement, Calcium Iodate, Pyridoxine Hydrochloride (source of Vitamin B6), Vitamin D3 Supplement, Folic Acid.

4Health GF Large breed formula:

Ingredients:

Turkey, Turkey Meal, Garbanzo Beans, Lentils, Peas, Potatoes, Tapioca, Chicken Fat (Preserved with Mixed Tocopherols), Egg Product, Tomato Pomace, Natural Flavor, Flaxseed, Ocean Fish Meal, Salt, Choline Chloride, Glucosamine Hydrochloride, Dried Chicory Root, Tomatoes, Blueberries, Raspberries, Chondroitin Sulfate, Yucca Schidigera Extract, Dried Lactobacillus Acidophilus Fermentation Product, Dried Bifidobacterium Animalis Fermentation Product, Dried Lactobacillus Reuteri Fermentation Product, Vitamin E Supplement, Beta Carotene, Iron Protein, Zinc Protein, Copper Protein, Ferrous Sulfate, Zinc Sulfate, Copper Sulfate, Potassium Iodide, Thiamine Mononitrate (Vitamin B1), Manganese Protein, Manganese Oxide, Ascorbic Acid, Vitamin A Supplement, Biotin, Niacin, Calcium Pantothenate, Manganese Sulfate, Sodium Selenite, Pyridoxine Hydrochloride (Vitamin B6), Vitamin B12 Supplement, Riboflavin (Vitamin B2), Vitamin D Supplement, Folic Acid.

ALL Acana products are grain-free per their website

Acana Singles Lamb & Apple (single protein source):

ACANA Lamb & Apple features one single, easily digestible animal protein. Fresh and raw lamb meat, organs and cartilage are delivered in WholePrey ratios and supply virtually all the necessary nutrients, vitamins and amino acids naturally and completely.

Deboned lamb, lamb meal, whole lentils, whole peas, lamb liver, pollock oil, lentil fiber, pea starch, lamb fat, apples, natural lamb flavor, lamb cartilage, lamb tripe, pumpkin, salt, mixed tocopherols (preservative), zinc protein, dried kelp, calcium pantothenate, taurine, freeze dried lamb liver, copper protein, chicory root, turmeric, dried lactobacillus acidophilus fermentation product, dried bifidobacterium animalis fermentation product, dried lactobacillus casei fermentation product.

Acana Pork & Squash Singles:

Deboned pork, pork meal, whole lentils, pork liver, pork fat, whole peas, lentil fiber, pea starch, butternut squash, pollock oil, natural pork flavor, pork cartilage, pumpkin, salt, mixed tocopherols (preservative), zinc protein, dried kelp, calcium pantothenate, taurine, freeze dried pork liver, copper protein, chicory root, turmeric, dried lactobacillus acidophilus

fermentation product, dried bifidobacterium animalis fermentation product, dried lactobacillus casei fermentation product

Acana Duck & Pear Singles:

Deboned duck, duck meal, whole lentils, whole peas, duck liver, duck fat, lentil fiber, pears, pollock oil, pea starch, natural duck flavor, duck cartilage, pumpkin, salt, mixed tocopherols (preservative), zinc proteinate, dried kelp, calcium pantothenate, vitamin A acetate, freeze dried duck liver, copper proteinate, chicory root, turmeric, dried lactobacillus acidophilus fermentation product, dried bifidobacterium animalis fermentation product, dried lactobacillus casei fermentation product.

Blue Buffalo Life Protection Formula Chicken & Brown Rice NOT GF:

(b) (4)

Blue Buffalo Freedom Chicken (GF)

(b) (4)

(b) (4)

Blue Buffalo Blue Basics Salmon & Potato Recipe Adult (Limited-Ingredient, Grain Free)

(b) (4)

Blue Buffalo Life Protection Lamb (NOT GF):

(b) (4)

Blue Buffalo Wilderness Chicken

(b) (4)

Blue Buffalo Wilderness Salmon:

(b) (4)

California Natural – LID – GF – Kangaroo Red Lentils

Ingredients

Kangaroo; Red Lentils; Green Lentils; Peas; Sunflower Oil (Preserved with Mixed Tocopherols); Flaxseed; Pea Fiber; Dicalcium Phosphate; Natural Flavors; Calcium Carbonate; Salt; DL-Methionine; Minerals (Zinc Proteinate, Iron Proteinate, Copper Proteinate, Manganese Proteinate, Calcium Iodate); Vitamins (Betaine Hydrochloride, Vitamin A Supplement, Niacin Supplement, Calcium Pantothenate, Beta

Carotene, Vitamin B12 Supplement, Vitamin D3 Supplement, Riboflavin Supplement, Pyridoxine Hydrochloride, Thiamine Mononitrate, Biotin, Folic Acid); Vitamin E Supplement; Rosemary Extract

Cal Naturals Venison and Green Lentils:

Ingredients

Venison, Green Lentils, Red Lentils, Peas, Sunflower Oil (Preserved with Mixed Tocopherols), Flaxseed, Pea Fiber, Calcium Carbonate, Dicalcium Phosphate, Natural Flavors, Salt, Potassium Chloride, DL-Methionine, Taurine, Minerals (Zinc Proteinates, Iron Proteinates, Copper Proteinates, Manganese Proteinates, Calcium Iodate) Vitamin E Supplement, Vitamins (Betaine Hydrochloride, Vitamin A Supplement, Niacin Supplement, Calcium Pantothenate, Beta Carotene, Vitamin B12 Supplement, Vitamin D3 Supplement, Riboflavin Supplement, Pyridoxine Hydrochloride, Thiamine Mononitrate, Biotin, Folic Acid) Rosemary Extract

Canidae GF Pure Land Bison LID

Bison, lamb meal, sweet potatoes, peas, lentils, carrots, pork meal, tapioca, canola oil, sun-dried alfalfa, natural flavor, minerals (iron proteinates, zinc proteinates, copper proteinates, ferrous sulfate, zinc sulfate, copper sulfate, potassium iodide, manganese proteinates, manganous oxide, manganese sulfate, sodium selenite), vitamins (vitamin E supplement, thiamine mononitrate, ascorbic acid, vitamin A supplement, biotin, niacin, calcium pantothenate, pyridoxine hydrochloride, vitamin B12 supplement, riboflavin, vitamin D3 supplement, folic acid), choline chloride, mixed tocopherols (a preservative), dried enterococcus faecium fermentation product, dried lactobacillus acidophilus fermentation product, dried lactobacillus casei fermentation product, dried lactobacillus plantarum fermentation product, dried trichoderma longibrachiatum fermentation extract.

Canidae GF Pure Fields Small Breed:

(b) (4)

Diamond Naturals Grain-free: example – chose beef, but chicken & white fish flavors also had same top pulses

Beef, lamb meal, sweet potatoes, peas, lentils, pea flour, canola oil (preserved with mixed tocopherols), tomato pomace, flaxseed, fish meal, natural flavor, salmon oil (source of DHA), salt, DL-methionine, choline chloride, taurine, dried chicory root, yucca schidigera extract, tomatoes, blueberries, raspberries, dried Lactobacillus plantarum fermentation product, dried Bacillus subtilis fermentation product, dried Lactobacillus acidophilus fermentation product, dried Enterococcus faecium fermentation product, dried Bifidobacterium animalis fermentation product, vitamin E supplement, iron proteinate, zinc proteinate, copper proteinate, ferrous sulfate, zinc sulfate, copper sulfate, potassium iodide, thiamine mononitrate (vitamin B1), manganese proteinate, manganous oxide, ascorbic acid, vitamin A supplement, biotin, niacin, calcium pantothenate, manganese sulfate, sodium selenite, pyridoxine hydrochloride (vitamin B6), vitamin B12 supplement, riboflavin (vitamin B2), vitamin D supplement, folic acid.

Earthborn Holistic Coastal Catch: (Grain-free Formulas – ALL their dry foods)

(b) (4)

Earthborn Holistic Meadow Feast (GF):

(b) (4)

Earthborn Holistic Great Plains (GF):

(b) (4)

(b) (4)

First-Mate Weight Control Senior Pacific Ocean Fish Meal Formula LID GF dry

Ingredients

(b) (4)

(b) (4)

Fromm:

Fromm Heartland Gold Large Breed (GF)

(b) (4)

Fromm Four Star Lamb & Lentil (GF)

(b) (4)

Fromm Four Star Surf & Turf (GF)

(b) (4)

Farmina – Chicken and Pomegranate – has both no grain and low grain dry foods (not sure which fed)

Halo Salmon (no other info)

Ingredients

(b) (4)

(b) (4)

Halo Salmon GF – ingredients not given

Kirkland Signature Healthy Weight Formula:

Chicken meal, brown rice, peas, cracked pearly barley, millet, powdered cellulose, oatmeal, chicken, rice bran, potatoes, dried beet pulp, chicken fat (preserved with natural tocopherols), natural flavor, flaxseed, fish meal, egg product, choline chloride, glucosamine hydrochloride, dried chicory root, chondroitin sulfate, L-Carnitine, dried Lactobacillus acidophilus fermentation product, dried Bifidobacterium animalis fermentation product, dried Lactobacillus reuteri fermentation product, carrots, dried kelp, apples, cranberries, rosemary extract, parsley flake, vitamin E supplement, iron proteinate, zinc sulfate, copper sulfate, potassium iodide, thiamine mononitrate, manganese proteinate, manganous oxide, ascorbic acid, vitamin A supplement, biotin, niacin, calcium pantothenate, manganese sulfate, sodium selenite, pyridoxine hydrochloride (vitamin B6), vitamin B12 supplement, riboflavin, vitamin D supplement, folic acid.

Lotus Oven-Baked Fish Recipe Grain-free Dry dog food:

Sardine, Pollock, Dried Potato, Dried Peas, Dried Egg Product, Pea Fiber, Tapioca Flour, Organic Soybean Oil(Preserved with Mixed Tocopherols and Citric Acid) Brewers Dried Yeast, Dicalcium Phosphate, Sweet Potatoes, Monosodium Phosphate, Whole Ground Flaxseed, Calcium Carbonate, Sea Salt, Salmon Oil, Olive Oil, Carrots, Apples, Garlic, Spinach, Pumpkin, Blueberries, Dried Kelp, Zinc Proteinate, Iron Proteinate, Vitamin E Supplement, Copper Proteinate, Manganese Proteinate, Niacin, Sodium Selenite, Calcium Pantothenate, Inulin, Yucca Schidigera, Dried Lactobacillus Acidophilus Fermentation Solubles, Lactobacillus Lactis Fermentation Solubles and Lactobacillus Casei Fermentation Solubles, Folic Acid, Vitamin A Supplement, Riboflavin Supplement, Calcium Iodate, Vitamin B12 Supplement, Thiamine Mononitrate, Pyridoxine Hydrochloride, Vitamin D3 Supplement, Rosemary Extract.

Merrick Lil' Plates - TUBBED: (GF) (lots of other flavors – all gf)

Petite Pot Pie: Deboned Chicken, Chicken Broth, Turkey Broth, Chicken Liver, Dried Egg Whites, Potato Starch, Potatoes, Carrots, Peas, Apples, Guar Gum, Sunflower Oil, Tricalcium Phosphate, Salt, Sodium Phosphate, Natural Flavor, Potassium Chloride, Calcium Carbonate, Minerals (Zinc Amino Acid Chelate, Iron Amino Acid Chelate, Copper Amino Acid Chelate, Manganese Amino Acid Chelate, Sodium Selenite, Cobalt Amino Acid Chelate, Potassium Iodide), Choline Chloride, Vitamins (Vitamin E Supplement, Thiamine Mononitrate, Niacin Supplement, D-Calcium Pantothenate, Vitamin A Supplement, Riboflavin

Supplement, Biotin, Vitamin B12 Supplement, Pyridoxine Hydrochloride, Vitamin D3 Supplement, Folic Acid), Rosemary, Sage, Thyme, Xanthan Gum.

(b) (4)

(b) (4)

Merrick Grain-free Rabbit and Chickpea:

(b) (4)

Wellness CORE Grain-free Wild Game (proteins vary)

New Formulation: Duck, Lamb Meal, Chickpeas, Peas, Turkey Meal, Lentils, Pea Protein, Chicken Fat (Preserved with Mixed Tocopherols), Tomato Pomace, Wild Boar, Rabbit, Ground Flaxseed, Dried Egg Product, Natural Duck Flavor, Choline Chloride, Spinach, Broccoli, Potassium Chloride, Kale, Vitamin E Supplement, Carrots, Parsley, Apples, Blueberries, Taurine, Mixed Tocopherols Added to Preserve Freshness, Zinc Proteinate, Glucosamine Hydrochloride, Chondroitin Sulfate, Zinc Sulfate, Calcium

Carbonate, Niacin, Ferrous Sulfate, Iron Proteinate, Beta-Carotene, Vitamin A Supplement, Copper Sulfate, Thiamine Mononitrate, Copper Proteinate, Manganese Proteinate, Manganese Sulfate, D-Calcium Pantothenate, Sodium Selenite, Pyridoxine Hydrochloride, Chicory Root Extract, Yucca Schidigera Extract, Riboflavin, Vitamin D3 Supplement, Biotin, Calcium Iodate, Vitamin B12 Supplement, Folic Acid, Ascorbic Acid (Vitamin C), Dried Lactobacillus Plantarum Fermentation Product, Dried Enterococcus Faecium Fermentation Product, Dried Lactobacillus Casei Fermentation Product, Dried Lactobacillus Acidophilus Fermentation Product, Rosemary Extract, Green Tea Extract, Spearmint Extract.

Old Formulation:

(b) (4)



Natural Balance (Dick Van Patten's) LID Sw P & Venison

(b) (4)



Sweet Potatoes, Venison, Pea Protein, Potato Protein, Canola Oil (Preserved with Mixed Tocopherols), Brewers Dried Yeast, Natural Flavor, Dicalcium Phosphate, Salmon Oil (Preserved with Mixed Tocopherols), Flaxseed, Dried Potato Products, Calcium Carbonate, Salt, DL-Methionine, Minerals (Zinc Proteinate, Zinc Sulfate, Ferrous Sulfate, Iron Proteinate, Copper Sulfate, Copper Proteinate, Manganese Sulfate, Manganese Proteinate, Calcium Iodate, Sodium Selenite), Choline Chloride, Vitamins (Vitamin E Supplement, Niacin, D-Calcium Pantothenate, Vitamin A Supplement, Riboflavin Supplement, Thiamine Mononitrate, Vitamin D3 Supplement, Pyridoxine Hydrochloride, Folic Acid, Biotin, Vitamin B12

Supplement), Taurine, Mixed Tocopherols (Preservative), Rosemary Extract, Green Tea Extract, Spearmint Extract.

Natural Balance Sw P and Bison:

(b) (4)

Old Formula:

(b) (4)

Natural Balance LID chicken & sw pot gf:

(b) (4)

Natural Balance Sw Pot and Fish LID GF

Sweet Potatoes, Salmon, Menhaden Fish Meal, **Potato Protein**, Canola Oil (Preserved with Mixed Tocopherols), Natural Flavor, **Dried Potato Products**, Salt, Salmon Oil (Preserved with Mixed Tocopherols), DL-Methionine, Minerals (Zinc Proteinates, Zinc Sulfate, Ferrous Sulfate, Iron Proteinates, Copper Sulfate, Copper Proteinates, Manganese Sulfate, Manganese Proteinates, Calcium Iodate, Sodium Selenite), Vitamins (Vitamin E Supplement, Niacin, D-Calcium Pantothenate, Vitamin A Supplement, Riboflavin Supplement, Thiamine Mononitrate, Vitamin D3 Supplement, Pyridoxine Hydrochloride, Folic

Acid, Biotin, Vitamin B12 Supplement), Choline Chloride, Flaxseed, Potassium Chloride, Taurine, Citric Acid (Preservative), Mixed Tocopherols (Preservative), Rosemary Extract.

Nature's Domain (Kirkland – GF) Salmon & Sw P

Salmon meal, sweet potatoes, peas, potatoes, canola oil, ocean fish meal, pea protein, potato fibre, natural flavour, flaxseed, salt, choline chloride, dried chicory root, tomatoes, blueberries, raspberries, yucca schidigera extract, dried Lactobacillus acidophilus fermentation product, dried Bifidobacterium animalis fermentation product, dried Lactobacillus reuteri fermentation product, vitamin E supplement, iron proteinate, zinc proteinate, copper proteinate, ferrous sulfate, zinc sulfate, copper sulfate, potassium iodide, thiamine mononitrate (vitamin B1), manganese proteinate, manganous oxide, ascorbic acid, vitamin A supplement, biotin, niacin, calcium pantothenate, manganese sulfate, sodium selenite, pyridoxine hydrochloride (vitamin B6), vitamin B12 supplement, riboflavin (vitamin B2), vitamin D supplement, folic acid.

Nature's Domain GF turkey meal & sw p:

Turkey meal, sweet potatoes, peas, potatoes, canola oil, tomato pomace, flaxseed, natural flavor, salmon oil (a source of DHA), salt, choline chloride, dried chicory root, tomatoes, blueberries, raspberries, yucca schidigera extract, dried Lactobacillus acidophilus fermentation product, dried Bifidobacterium animalis fermentation product, dried Lactobacillus reuteri fermentation product, vitamin E supplement, iron proteinate, zinc proteinate, copper proteinate, ferrous sulfate, zinc sulfate, copper sulfate, potassium iodide, thiamine mononitrate (vitamin B1), manganese proteinate, manganous oxide, ascorbic acid, vitamin A supplement, biotin, niacin, calcium pantothenate, manganese sulfate, sodium selenite, pyridoxine hydrochloride (vitamin B6), vitamin B12 supplement, riboflavin (vitamin B2), vitamin D supplement, folic acid.

Nature's Domain Organic Chicken and Pea (GF):

Organic chicken, organic peas, organic lentils, organic garbanzo beans, organic sweet potatoes, organic potatoes, organic canola oil (preserved with mixed tocopherols), organic sunflower meal, organic canola meal, organic flaxseed, natural flavor, organic pea protein, calcium carbonate, choline chloride, taurine, organic kelp, vitamin E supplement, iron proteinate, zinc proteinate, copper proteinate, ferrous sulfate, zinc sulfate, copper sulfate, potassium iodide, thiamine mononitrate (vitamin B1), manganese proteinate, manganous oxide, ascorbic acid, vitamin A supplement, biotin, niacin, calcium pantothenate, manganese sulfate, sodium selenite, pyridoxine hydrochloride (vitamin B6), vitamin B12 supplement, riboflavin (vitamin B2), vitamin D supplement, folic acid.

Nature's Domain Beef meal and sw pot (GF):

Beef meal, sweet potatoes, garbanzo beans, peas, canola oil, egg product, pea flour, tomato pomace, flaxseed, brewers yeast, natural flavor, potato protein, pea protein, salmon oil (a source of DHA), salt, choline chloride, dried chicory root, yucca schidigera extract, tomatoes, blueberries, raspberries, dried Lactobacillus acidophilus fermentation product, dried Bifidobacterium animalis fermentation product, dried Lactobacillus reuteri fermentation product, vitamin E supplement, iron proteinate, zinc proteinate, copper proteinate, ferrous sulfate, zinc sulfate, copper sulfate, potassium iodide, thiamine mononitrate

(vitamin B1), manganese proteinate, manganous oxide, ascorbic acid, vitamin A supplement, biotin, niacin, calcium pantothenate, manganese sulfate, sodium selenite, pyridoxine hydrochloride (vitamin B6), vitamin B12 supplement, riboflavin (vitamin B2), vitamin D supplement, folic acid.

Nature's Recipe Easy to Digest Fish Meal & Potato Recipe (Rice, but not GF) (Says NO corn, beef, wheat)

(b) (4)

NutriSource chicken pea GF

Chicken, chicken meal, peas, pea starch, pea flour, chicken fat (preserved with mixed tocopherols and citric acid), flax seeds, alfalfa meal, natural turkey and chicken flavors, salmon meal (a source of fish oil), dried tomato pomace, sunflower oil, dried brewers yeast, dried egg product, salt, potassium chloride, minerals (zinc proteinate, iron proteinate, copper proteinate, manganese proteinate, cobalt proteinate, selenium yeast), vitamins (vitamin A acetate, vitamin D3 supplement, vitamin E supplement, niacin, d-calcium pantothenate, thiamine mononitrate, pyridoxine hydrochloride, riboflavin supplement, folic acid, biotin, vitamin B12 supplement), lactic acid, glucosamine hydrochloride, choline chloride, L-ascorbyl-2-polyphosphate (source of vitamin C), chondroitin sulfate, yucca schidigera extract, calcium iodate, rosemary extract, yeast culture (*Saccharomyces cerevisiae*), dried *Lactobacillus acidophilus* fermentation product, dried *Enterococcus faecium* fermentation product, dried *Aspergillus niger* fermentation extract, dried *Trichoderma longibrachiatum* fermentation extract, dried *Bacillus subtilis* fermentation extract.

Petcurean GO! LID Venison Sensitivity & Shine (GF, termed "zero-grain"):

(b) (4)

Pure Balance Wild & Free (GF) – Walmart

(b) (4)

Purina ONE Lamb & Rice:

Lamb (Source of Glucosamine), **Rice Flour**, Whole Grain Corn, Whole Grain Wheat, Chicken By-Product Meal (Source of Glucosamine), Corn Gluten Meal, Soybean Meal, Beef Fat Naturally Preserved with Mixed-Tocopherols, Mono and Dicalcium Phosphate, Glycerin, Calcium Carbonate, Liver Flavor, Salt, Caramel Color, Soybean Oil, Potassium Chloride, Dried Carrots, Dried Peas, Vitamins [Vitamin E Supplement, Niacin (Vitamin B-3), Vitamin A Supplement, Calcium Pantothenate (Vitamin B-5), Thiamine Mononitrate (Vitamin B-1), Vitamin B-12 Supplement, Riboflavin Supplement (Vitamin B-2), Pyridoxine Hydrochloride (Vitamin B-6), Folic Acid (Vitamin B-9), Menadione Sodium Bisulfite Complex (Vitamin K), Vitamin D-3 Supplement, Biotin (Vitamin B-7)], Minerals [Zinc Sulfate, Ferrous Sulfate, Manganese Sulfate, Copper Sulfate, Calcium Iodate, Sodium Selenite], Choline Chloride, L-Lysine Monohydrochloride, Sulfur. V-4162.

Rachael Ray Nutrish Zero-Grain Salmon and Sw Pot:

(b) (4)

Taste of the Wild Sierra Mountain Lamb (All flavors of dry dog food are GF)

Lamb, lamb meal, **sweet potatoes**, egg product, **lentils, peas, pea flour**, canola oil, potatoes, dried yeast, roasted lamb, tomato pomace, natural flavor, salmon oil (a source of DHA), salt, DL-methionine, choline chloride, taurine, dried chicory root, tomatoes, blueberries, raspberries, yucca schidigera extract, dried Lactobacillus plantarum fermentation product, dried Bacillus subtilis fermentation product, dried Lactobacillus acidophilus fermentation product, dried Enterococcus faecium fermentation product, dried Bifidobacterium animalis fermentation product, vitamin E supplement, iron proteinate, zinc proteinate, copper proteinate, ferrous sulfate, zinc sulfate, copper sulfate, potassium iodide, thiamine mononitrate (vitamin B1), manganese proteinate, manganous oxide, ascorbic acid, vitamin A supplement., Biotin,

niacin, calcium pantothenate, manganese sulfate, sodium selenite, pyridoxine hydrochloride (vitamin B6), vitamin B12 supplement, riboflavin (vitamin B2), vitamin D supplement, folic acid.

V-Dog Kinder Kibble Vegan Adult Dry (RICE, not really GF):

Dried Peas, Pea Protein, Brown Rice, Oatmeal, Potato Protein, Sorghum, Canola Oil (Preserved with Mixed Tocopherols) , Natural Flavor, Suncured Alfalfa Meal, Brewers Dried Yeast, Dicalcium Phosphate, Flaxseeds, Millet, Calcium Carbonate, Lentils, Peanut Hearts, Quinoa, Sunflower Chips, Salt, Potassium Chloride, Choline Chloride, Taurine, Dried Carrots, Minerals (Ferrous Sulfate, Zinc Sulfate, Copper Sulfate, Sodium Selenite, Manganese Sulfate, Calcium Iodate), DL-methionine, Dried Parsley, Vitamins (Vitamin E Supplement, Vitamin A Supplement, Niacin Supplement, D-calcium Pantothenate, Riboflavin Supplement, Vitamin D2 Supplement, Thiamine Mononitrate, Vitamin B12 Supplement, Pyridoxine Hydrochloride, Biotin, Folic Acid), L-Ascorbyl-2-Polyphosphate (A Source Of Vitamin C), Preserved with Citric Acid, Preserved with Mixed Tocopherols, Dried Blueberries, Dried Cranberries, Dried Celery, Yucca Schidigera Extract, Dried Lettuce, L-Carnitine, Dried Watercress, Dried Spinach, Rosemary Extract.

Victor Hi-Pro Plus Formula Dry Dog food (no corn, wheat, soy or glutens) NOT GF

(b) (4)

Whole Hearted GF Lamb and Lentil

Lamb, lamb meal, **lentils, chickpeas, peas, pea flour**, canola oil (preserved with mixed tocopherols), fava beans, flaxseed, tomato pomace, natural flavor, salmon oil, salt, choline chloride, dried chicory root, yucca schidigera extract, dried Lactobacillus acidophilus fermentation product, dried Bifidobacterium animalis fermentation product, dried Lactobacillus reuteri fermentation product, vitamin E supplement, iron proteinate, zinc proteinate, copper proteinate, ferrous sulfate, zinc sulfate, copper sulfate, potassium iodide, thiamine mononitrate (source of vitamin B1), manganese proteinate, manganous oxide, ascorbic acid (preservative), vitamin A supplement, biotin, niacin, calcium pantothenate, manganese sulfate, sodium selenite, pyridoxine hydrochloride (source of vitamin B6), vitamin B12 supplement, riboflavin (vitamin B2), vitamin D3 supplement, folic acid.

Signature Kangaroo LID GF dry:

Kangaroo, Kangaroo Meal, Peas, Chickpeas, Pea Flour, Sunflower Oil (preserved with Citric Acid), Flaxseed, Red Lentils, Green Lentils, Dehydrated Alfalfa Meal, Pea Protein, Natural Flavors, Salt, Minerals (Zinc Proteinate, Iron Proteinate, Copper Proteinate, Manganese Proteinate, Cobalt Proteinate, Selenium Yeast), Choline Chloride, Potassium Chloride, Calcium Carbonate, Vitamins (Vitamin A, Acetate, Vitamin D3 Supplement, Vitamin E Supplement, Niacin, d-Calcium Pantothenate, Thiamine Mononitrate, Pyridoxine Hydrochloride, Riboflavin Supplement, Folic Acid, Biotin, Vitamin B12 Supplement), Lactic Acid, Calcium Iodate, Preserved With Mixed Tocopherols.

Signature Whitefish LID GF dry:

(b) (4)

Signature Venison LID GF Dry:

(b) (4)

Signature Lamb LID GF dry:

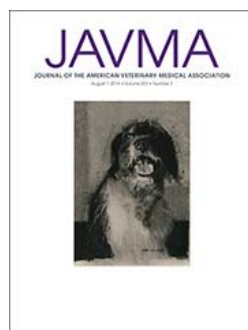
(b) (4)

Signature Zssential LID GF dry:

(b) (4)

(b) (4)

AUGUST 01, 2018



JAVMAnews

ISSUES

August 01, 2018

Unusual pet diets may be linked to heart disease

By Greg Cima

Posted July 11, 2018

Some specialty diets may be causing heart disease in dogs, and researchers are trying to identify the connection.

Dr. Lisa M. Freeman, a nutritionist and professor at the Cummings School of Veterinary Medicine at Tufts University, wrote June 4 on the university's Petfoodology blog about a 4-year-old Beagle-Labrador mixed-breed dog saved from life-threatening dilated cardiomyopathy with treatment and a change of diet. Before treatment, the dog had been eating grain-free pet food containing kangaroo meat and chickpeas.

"It appears that diet may be increasing dogs' risk for heart disease because owners have fallen victim to the many myths and misperceptions about pet food," she wrote. "If diet proves to be the cause, this truly is heart-breaking to me."

Anne Norris, a spokeswoman for the Food and Drug Administration's Office of Foods and Veterinary Medicine, said the agency is studying a possible connection and will share more information when possible. Dr. Freeman had noted that the FDA and cardiologists are investigating a possible link between diet and dilated cardiomyopathy.

A dog or cat with dilated cardiomyopathy has an enlarged, weak heart, which can cause abnormal rhythms, congestive heart failure, and death.

Cats and at least some dogs can develop dilated cardiomyopathy if their diets contain too little taurine, an amino acid found in meat and milk. It is a neurotransmitter and cell membrane stabilizer, among other functions, according to the National Institutes of Health.

Despite the known link between dilated cardiomyopathy and taurine deficiency, most dogs that develop the disease have taurine concentrations within reference limits. The cause of cardiomyopathy in those dogs is typically unknown, but Dr. Freeman wrote that she has seen a consistent connection with boutique diets.

The Cummings Veterinary Medical Center also is warning people that they should tell a veterinary cardiologist if their pets have heart disease and eat foods that are homemade, raw, or vegetarian or that are made by small companies.

Information from the Morris Animal Foundation, which is funding research on dilated cardiomyopathy at the University of California-Davis, indicates the number of dogs with the disease may have increased recently among Golden Retrievers. Dr. Josh Stern, a cardiologist, is studying potential genetic links between Golden Retrievers and the disease.

"I suspect that Golden Retrievers might have something in their genetic make-up that makes them less efficient at making taurine," Dr. Stern said in an article from the foundation. "Couple that with certain diets, and you've given them a double hit. If you feed them a diet that has fewer building blocks for taurine or a food component that inhibits this synthesis, they pop up with DCM."



AVMA Journals

JAVMA

[Scientific Articles](#)
[News Archives](#)
[News Photo Galleries](#)
[Business Classifieds](#)
[About JAVMA](#)

AJVR

[Read AJVR](#)
[About AJVR](#)



Convention Newspaper

AVMA Collections

AVMA@Work Blog

Newsletters

Hot Issues

RSS Feeds

Press Room



Dr. Freeman recommends that owners submit a report to the FDA when their dogs are determined to have dilated cardiomyopathy. The [Department of Health and Human Services accepts reports to the FDA](#).



OTHER AVMA SITES

[Externs on the Hill](#)
[National Pet Week](#)

[Animal Health SmartBrief](#)
[WebMD® Pet Health Community](#)



[Contact](#) | [AVMA Careers](#) | [Help](#) | [Site Map](#) | [Privacy](#) | [Terms of Use](#)

Copyright © 2018 American Veterinary Medical Association

From: [Jones, Jennifer L](#)
To: ["Darcy Adin"; Freeman, Lisa](#)
Cc: adind@ufl.edu
Subject: RE: checking in
Date: Thursday, November 15, 2018 10:57:00 AM
Attachments: [image003.png](#)
[image004.png](#)
[image005.png](#)

Great! I sent a calendar appointment. Please forward as necessary.
Would you be willing to forward me a copy of the DCM article for JAVMA? I'd like to share it with our communication team. They may get some inquiries after it's release, and it would help them prepare.

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Darcy Adin <dbadin@ncsu.edu>
Sent: Thursday, November 15, 2018 8:01 AM
To: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Cc: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; adind@ufl.edu
Subject: Re: checking in

Hi Jennifer,
Based on Lisa's times, I could do the 3rd from 9-1 and the 4th from 9-1.
Thanks!
Darcy

On Nov 15, 2018, at 7:55 AM, Freeman, Lisa <Lisa.Freeman@tufts.edu> wrote:

Hi Jen
Dec 3 (9-1 or after 3), 4 (anytime), or 5 (10-3) would work for me.
Thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Sent: Thursday, November 15, 2018 7:44 AM
To: Darcy Adin <dbadin@ncsu.edu>
Cc: Freeman, Lisa <lisa.freeman@tufts.edu>; adind@ufl.edu
Subject: RE: checking in

Good morning Darcy and Lisa,
Yes, let's plan for a meeting after Thanksgiving. When in early December would work well for you?
Thanks,
Jen

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421

[<image001.png>](#)



From: Darcy Adin <dbadin@ncsu.edu>
Sent: Wednesday, November 07, 2018 3:20 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Cc: Freeman, Lisa <lisa.freeman@tufts.edu>; adind@ufl.edu
Subject: checking in

Hi Jennifer,

I hope you are doing well! I wanted to check in with you to let you know that I have changed affiliations and am now working at the University of Florida (my new email is adind@ufl.edu, copied above).

Dr. Freeman and I wanted to check to see if your group be willing to have a follow up call regarding the dietary induced DCM issue?

Thanks!
Darcy

--

Darcy B. Adin, DVM, DACVIM (Cardiology)
Adjunct Clinical Assistant Professor of Cardiology
North Carolina State University
NC State Veterinary Hospital
1060 William Moore Drive
Raleigh, NC 27607
919-513-6032

From: [Palmer, Lee Anne](#)
To: [Jones, Jennifer L](#); [Rotstein, David](#); [Queen, Jackie L](#); [Carey, Lauren](#)
Cc: [Reimschuessel, Renate](#); [Ceric, Olgica](#); [Nemser, Sarah](#)
Subject: RE: DCM cases-food-Iodine screening results
Date: Friday, May 04, 2018 10:20:58 AM
Attachments: [image002.png](#)
[image004.png](#)
[image007.png](#)
[image010.png](#)
[image012.png](#)

I know dogs can synthesize taurine, so if met and cyst are adequate

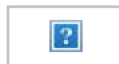
(b) (5)

(b) (5)

From: Jones, Jennifer L
Sent: Friday, May 4, 2018 10:04 AM
To: Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Cc: Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>; Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>
Subject: RE: DCM cases-food-Iodine screening results

There is no minimum for dogs...it is apparently a conditionally essential amino acid because dogs can make it from methionine and cystine.

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Palmer, Lee Anne
Sent: Friday, May 04, 2018 10:01 AM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Cc: Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>; Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>
Subject: RE: DCM cases-food-Iodine screening results

Interesting...so the AAFCO minimum for cats is 0.1% DMB, is there a DMB for dogs? (If not, maybe there should be...)

From: Jones, Jennifer L

Sent: Friday, May 4, 2018 9:46 AM

To: Rotstein, David <David.Rotstein@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>

Cc: Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>; Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>

Subject: RE: DCM cases-food-Iodine screening results

One more nutritional deficiency-Taurine low based on AAFCO's Feline Minimum for Extruded foods.

The dog consuming the product had a low whole blood Taurine level.

- Taurine = 45.5 mg/100g = 0.0455g/100g = 0.046% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB),
then $0.0455 / 0.90 = 0.05\% \text{ DMB}$, which is less than the AAFCO minimum for cats eating extruded foods (0.1% DMB.)
- Cystine = 293 mg/100g = 0.293 g/100g = 0.29% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB), then $0.293 / 0.90 = 0.33\% \text{ DMB}$
- Methionine = 358mg/100g = 0.358 g/100g = 0.36% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB),
then $0.358 / 0.90 = 0.4\% \text{ DMB}$, which is greater than the AAFCO minimum for growth & reproduction of 0.35% DMB.
The Methionine-cystine % = $0.4\% + 0.33\% = 0.73\% \text{ DMB}$, which is greater than the AAFCO minimum for growth & reproduction of 0.7% DMB.

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Jones, Jennifer L

Sent: Monday, April 23, 2018 10:32 AM

To: Rotstein, David <David.Rotstein@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>

Cc: 'Reimschuessel, Renate (Renate.Reimschuessel@fda.hhs.gov)' <Renate.Reimschuessel@fda.hhs.gov>; Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>

Subject: DCM cases-food-Iodine screening results

FYI-Iodine < 10ppm for the foods tested. Exogenous thyrotoxicosis unlikely a cause of the DCM
Multiple EONs Involved:

- 800.218
 - EON-323515
 - EON-345822

- 800.261
 - EON-350158

Jennifer L. A. Jones, DVM

Veterinary Medical Officer

U.S. Food & Drug Administration

Center for Veterinary Medicine

Office of Research

Veterinary Laboratory Investigation and Response Network (Vet-LIRN)

8401 Muirkirk Road, G704

Laurel, Maryland 20708

new tel: 240-402-5421

fax: 301-210-4685

e-mail: jennifer.jones@fda.hhs.gov

Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm>



From: [Jones, Jennifer L](#)
To: [Rotstein, David](#); [Queen, Jackie L](#); [Palmer, Lee Anne](#); [Carey, Lauren](#)
Cc: ["Reimschuessel, Renate \(Renate.Reimschuessel@fda.hhs.gov\)"](#); [Ceric, Olgica](#); [Nemser, Sarah](#)
Subject: RE: DCM cases-food-Iodine screening results
Date: Friday, May 04, 2018 9:45:00 AM
Attachments: [EON-350158-Ward-case summary-5.4.2018.doc](#)
[800.261-\(b\) \(4\)-Tau-Cys-Met.PDF](#)
[image001.png](#)
[image002.png](#)
[image003.png](#)

One more nutritional deficiency-Taurine low based on AAFCO's Feline Minimum for Extruded foods.
The dog consuming the product had a low whole blood Taurine level.

- Taurine = 45.5 mg/100g = 0.0455g/100g = 0.046% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB),
then $0.0455 / 0.90 = 0.05\% \text{ DMB}$, which is less than the AAFCO minimum for cats eating extruded foods (0.1% DMB.)
- Cystine = 293 mg/100g = 0.293 g/100g = 0.29% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB), then $0.293 / 0.90 = 0.33\% \text{ DMB}$
- Methionine = 358mg/100g = 0.358 g/100g = 0.36% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB),
then $0.358 / 0.90 = 0.4\% \text{ DMB}$, which is greater than the AAFCO minimum for growth & reproduction of 0.35% DMB.
The Methionine-cystine % = $0.4\% + 0.33\% = 0.73\% \text{ DMB}$, which is greater than the AAFCO minimum for growth & reproduction of 0.7% DMB.

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Jones, Jennifer L
Sent: Monday, April 23, 2018 10:32 AM
To: Rotstein, David <David.Rotstein@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Cc: 'Reimschuessel, Renate (Renate.Reimschuessel@fda.hhs.gov)' <Renate.Reimschuessel@fda.hhs.gov>; Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>
Subject: DCM cases-food-Iodine screening results

FYI-Iodine < 10ppm for the foods tested. Exogenous thyrotoxicosis unlikely a cause of the DCM
Multiple EONs Involved:

- 800.218
 - EON-323515

- EON-345822
- 800.261
 - EON-350158

Jennifer L. A. Jones, DVM

Veterinary Medical Officer

U.S. Food & Drug Administration

Center for Veterinary Medicine

Office of Research

Veterinary Laboratory Investigation and Response Network (Vet-LIRN)

8401 Muirkirk Road, G704

Laurel, Maryland 20708

new tel: 240-402-5421

fax: 301-210-4685

e-mail: jennifer.jones@fdg.hhs.gov

Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm>



Vet-LIRN Case Summary Document

Vet-LIRN Case Number:	800.261
EON/CC #:	EON-350158
Owner LAST Name:	(b) (6)
Vet LAST Name:	(b) (6)
Vet-LIRN Initiation Date:	3/28/2018
MedRec: Requested:	Received with Complaint
MedRec: Received:	
MedRec: Significant finding:	
Vet-LIRN Tests (planned):	<ul style="list-style-type: none"> • MSU <ul style="list-style-type: none"> ○ Iodine • (b) (6) <ul style="list-style-type: none"> ○ Cys-Met-Tau
Vet-LIRN Test Results:	<ul style="list-style-type: none"> • Iodine < 10 ppm-no suspicion of exogenous thyroid tissue • Tau
Result Interpretation:	
IF NFA, justification:	

COMPLAINT Narrative: At the time of diagnosis (b) (6), (b) (6) was a 13 year old female spayed Labrador retriever who had been maintained on a Zignature Kangaroo formula. She presented with a history of a progressive cough which, prior to presentation, became productive and she coughed up a small volume of pink foam (possible pulmonary edema). On examination she had a 2/6 left apical systolic heart murmur and on echo diagnosed with advanced dilated cardiomyopathy with severe left ventricular dilation, moderate to severe left ventricular systolic dysfunction, and moderate to severe left atrial dilation. Thoracic radiographs were suspicious for early congestive heart failure. A whole blood taurine level was submitted and was low at 168. She was treatment with furosemide, benazepril, pimobendan, spironolactone, taurine and l-carnitine and her diet was changed to Royal Canin Early Cardiac. At her recheck in 2/26/18, (b) (6) heart had improved significantly with now mild dilated cardiomyopathy with normalized left atrial dimensions, mild left ventricular dilation and low normal left ventricular systolic function. The furosemide was able to be discontinued at this time.

Signalment: (b) (6)-13 yr FS Lab

Signs: productive, progressive cough

Food Product: Zignature Kangaroo Formula

Plan:

- MRx
- Open product for Tau, Cysteine, Methionine, +/- Beta-Alanine

MRx summary:

Presenting complaint 10/27 to rDVM: developed a cough on 10/25, cough for 3-4 days, not lethargic, normal eating/drinking, no vomiting or diarrhea, worse when lying down, dog didn't cough while in clinic except for a tracheal cough when pulling on the leash → treated with hydroxyzine, doxycycline, hydrocodone → stopped all 3 drugs Monday b/c cough worsened → to ER on (b) (6) after coughing up pink tinged foam; no lethargy, continues to eat and drink; UTD on vaccines and HWP, no drugs → treat with Lasix, benazepril, vetmedin, spironolactone, Tau, L-carnitine and **vet recommended a diet change** → labwork done 11/14 → to rDVM 11/16: doing well → recheck 2/26/18: intermittent cough, related to excitement, change diet to RC Early Cardiac → on recheck improved → suspect Tau responsive DCM-mild, suspect cough secondary to bronchial or primary respiratory disease → recheck 3/13: resting RR 16 rpm, minimal coughing only when excited, since switching to cardiac food BMs are dense and tenesmus, owner is weaning dog off lasix

PE 10/27 @ rDVM: numerous lipomatous & dermal masses, no audible murmur or arrhythmia, shallow breathing

PE (b) (6) @ specialist: LS-OU, HR 100 bpm, mild periodontal disease, Gr II/VI, left apical protosystolic murmur, questionable mild inc bronchovesicular sounds bilaterally, SC mass left ventrum, mildly tense cranial abdominal palpation

PE 11/16 @ rDVM: mild underbite, H/L wnl

PE 2/26: Gr III/VI pansystolic, PMI MV, reg rhythm with S3 gallop, HR 130, BCS 6/9, hepatomegaly

PE 3/13: T 99.9F, RR 56, HR 124 bpm, Gr III/VI murmur, rest nsf

Labs: 10/27 CBC: Lym 1.01 (1.05-5.1)

-3/13: Lym 1044 (1060-4950), Plt 615 (143-448), Plt inc on direct

10/27 Chem: ALP 440 (23-212), GGT 30 (0-11), rest nsf

-11/14: Glu 51 (70-143), Glob 4.7 (2.5-4.5), ALP 621, GGT 31

-3/13: Na:K 27, ALP 2243 (5-180), GGT 117 (0-13)

(b) (6) BP 100 (based on Echo)

-2/26: 155 mg Hg, direct measurement

-3/13: 130-140 mmHg, direct measurement

11/3 Tau-blood: 168 (200-350)

3/13 UA: 1.010, pH 5

3/13 TT4: 0.8 (1-4)

Rads 10/27: generalized cardiomegaly, left atrial enlargement, slight left auricular bulge, increased sternal contact & rounded heart, dorsal tracheal deviation, prominent pulmonary vasculature with questionably mild inc interstitial opacity in caudal-dorsal lungs, suggesting early CHF/PE

(b) (6) **Echo:** severe LV hypertrophy, mild-mod MV regurgitation, mod-sev LA dilation,

mild TV regurg, mild RV & RA dilation, mod-sev lower systolic function values

-2/26: mild LV dilation, mild MV regurg, normal LA, mild TV regurg, normal RV & RA, low normal systolic functional indices of LV

(b) (6) **ECG:** normal sinus rhythm

Prior MHx: 7/2017: doing well at home-**occasionally coughs**, several SQ masses, no murmur or cough on tracheal palpation; 10/23/2017-vaccines, doing well per O, no murmur ausculted, not been getting HWP consistently,

An article about beta-alanine: <https://academic.oup.com/alcalc/article/36/1/29/138000>

If Tau & Cys/Met are normal, we may need to reconsider other MOA's causing this, unrelated to the food.

I emailed the vet to request the full MRx and see if lot/best by information available for the leftover food.

4/4/2018

JJ-Vet sent the full MRx available and does not have any leftover food. We will purchase the food for testing. A dog from a previous case without food (800.218-Hitchcock), Cocker Spaniel with Low Tau and also eating Zignature Essentials Kangaroo.

MRx added to above summary.

4/10/18

JG – Received the sample. Treat-sub1 (Zignature, Kangaroo formula)

4/11/2018

JJ-JG received the sample. I prepared the lab submission forms and will aliquot the sample today for testing.

4/12/2018

JJ-I prepared the samples and sent them to MSU for iodine screening and (b) (4) for Tau/Cys/Met screening.

5/4/2018

JJ-The MSU iodine results were < 10 ppm and not suspicious for exogenous thyroid tissue.

The (b) (4) results came back for Taurine, Cystine, and Methionine.

- Taurine = 45.5 mg/100g = 0.0455g/100g = 0.046% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB),
then $0.0455 / 0.90 = 0.05\%$ DMB, which is less than the AAFCO minimum for cats eating extruded foods (0.1% DMB.)
- Cystine = 293 mg/100g = 0.293 g/100g = 0.29% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB), then $0.293 / 0.90 = 0.33\%$ DMB
- Methionine = 358mg/100g = 0.358 g/100g = 0.36% As Is Basis
If we assume a max of 10% moisture per the label (= 90% DMB),
then $0.358 / 0.90 = 0.4\%$ DMB, which is greater than the AAFCO minimum for growth & reproduction of 0.35% DMB.
The Methionine-cystine % = $0.4\% + 0.33\% = 0.73\%$ DMB, which is greater than the AAFCO minimum for growth & reproduction of 0.7% DMB.

BLUF: Taurine was low based on the AAFCO minimum for feline extruded foods.

Certificate of Analysis

Food and Drug Administration - CVM

8401 Muirkirk Rd.
Laurel Maryland 20708 United States

Sample Name:	1-dog food	Sample:	7192972
Project ID	FDA_CVM-20180413-0004	Receipt Date	13-Apr-2018
PO Number	HHSF223201610005I HHSF22301003T	Receipt Condition	Ambient temperature
Sample Serving Size		Login Date	13-Apr-2018
Description	800.261-sub	Online Order	20

Analysis

Result

Cystine and Methionine *

Cystine	293 mg/100g
Methionine	358 mg/100g
Taurine	
Taurine	45.5 mg/100g

Method References

Testing Location

Cystine and Methionine (AAAC_S)

(b) (6)

Official Methods of Analysis of AOAC INTERNATIONAL, Method 982.30 E(a/b)

Taurine (TAUR_LC_S)

(b) (6)

Official Methods of Analysis of AOAC INTERNATIONAL, Method 999.12, AOAC International Gaithersburg, MD, USA, (Modified)

R. Schuster, "Determination of Amino Acids in Biological, Pharmaceutical, Plant and Food Samples by Automated Precolumn Derivatization and HPLC", *Journal of Chromatography*, 431:271-284, (1988) (Modified)

Henderson, J.W., Ricker, R.D. Bidlingmeyer, B.A., Woodward, C., "Rapid, Accurate, Sensitive, and Reproducible HPLC Analysis of Amino Acids, Amino Acid Analysis Using Zorbax Eclipse-AAA columns and the Agilent 1100 HPLC," Agilent Publication, 2000 (Modified)

Henderson, J.W., Books, A., "Improved Amino Acid Methods using Agilent Zorbax Eclipse Plus C18 Columns for a Variety of Agilent LC Instrumentation and Separation Goals," Agilent Application Note 5990-4547, (2010).

Testing Location(s)

Released on Behalf of (b) (6) by

(b) (6)

(b) (6)

(b) (6)



(b) (6)

These results apply only to the items tested. This certificate of analysis shall not be reproduced, except in its entirety, without the written approval of (b) (6)

* This analysis is not ISO accredited.

Printed: 01-May-2018 2:31 pm

Page 1 of 1

From: [Rotstein, David](#)
To: [Jones, Jennifer L](#); [Norris, Anne](#); [Carey, Lauren](#); [Palmer, Lee Anne](#)
Cc: [DeLancey, Siobhan](#)
Subject: RE: DCM-Follow up call?
Date: Monday, August 06, 2018 10:57:15 AM

That will work

David Rotstein, DVM, MPVM, Dipl. ACVP
CVM Vet-LIRN Liaison
CVM OSC/DC/CERT
7519 Standish Place
(b) (6) (BB)

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution, or copying is strictly prohibited. If you think you received this e-mail message in error, please e-mail the sender immediately at david.rotstein@fda.hhs.gov.

-----Original Message-----

From: Jones, Jennifer L
Sent: Monday, August 06, 2018 10:46 AM
To: Norris, Anne <Anne.Norris@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>
Cc: DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>
Subject: RE: DCM-Follow up call?

Would Wed from 4-5 work?

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421

-----Original Message-----

From: Norris, Anne
Sent: Monday, August 06, 2018 8:34 AM
To: Carey, Lauren <Lauren.Carey@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>
Cc: DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>
Subject: RE: DCM-Follow up call?

I'm interested. Best times would be this morning or Tuesday afternoon. My calendar should be up to date.

Thanks!

-----Original Message-----

From: Carey, Lauren
Sent: Monday, August 06, 2018 7:10 AM
To: Rotstein, David <David.Rotstein@fda.hhs.gov>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Palmer, Lee

Anne <LeeAnne.Palmer@fda.hhs.gov>

Cc: DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>; Norris, Anne <Anne.Norris@fda.hhs.gov>

Subject: RE: DCM-Follow up call?

I'm interested. I'm free every afternoon except today and all day Friday. Lee Anne's out for the week but I'll take notes for her.

-----Original Message-----

From: Rotstein, David

Sent: Monday, August 06, 2018 6:48 AM

To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>

Cc: DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>; Norris, Anne <Anne.Norris@fda.hhs.gov>

Subject: RE: DCM-Follow up call?

I'm interested. Vet-LIRN grants Tues and Thursday; I can do today, Wednesday, and possibly Friday.

David Rotstein, DVM, MPVM, Dipl. ACVP

CVM Vet-LIRN Liaison

CVM OSC/DC/CERT

7519 Standish Place

(b) (6) (BB)

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution, or copying is strictly prohibited. If you think you received this e-mail message in error, please e-mail the sender immediately at david.rotstein@fda.hhs.gov.

-----Original Message-----

From: Jones, Jennifer L

Sent: Monday, August 06, 2018 6:42 AM

To: Rotstein, David <David.Rotstein@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>

Cc: DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>; Norris, Anne <Anne.Norris@fda.hhs.gov>

Subject: FW: DCM-Follow up call?

Are you folks interested in attending? Let me know your availability this week (except Thursday).

Jennifer Jones, DVM

Veterinary Medical Officer

Tel: 240-402-5421

-----Original Message-----

From: Darcy Adin [<mailto:dbadin@ncsu.edu>]

Sent: Friday, August 03, 2018 11:29 PM

To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>

Cc: Lisa Freeman <lisa.freeman@tufts.edu>

Subject: Follow up call?

Hi Dr. Jones,

Dr. Freeman and I are wondering if your group would be willing to have another conference call as a follow-up to discuss the nutritionally based DCM cases? As you know, since the release of the FDA statement, there has been much discussion among the public and the veterinary community, and we thought it could be useful to reconvene.

Thank you for your thoughts!

Darcy

From: [Rotstein, David](#)
To: [Carey, Lauren](#); [Ceric, Olgica](#); [Jones, Jennifer L](#); [Glover, Mark](#); [Nemser, Sarah](#); [Palmer, Lee Anne](#); [Queen, Jackie L](#); [Reimschuessel, Renate](#)
Subject: Re: Facebook Taurine Deficiency Warning
Date: Monday, February 12, 2018 7:16:58 AM

Thanks Lauren

I agree the verdict is out on the cause, but gutsy to raise awareness like that!

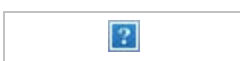
From: Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Date: February 12, 2018 at 7:10:21 AM EST
To: Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>, Glover, Mark <Mark.Glover@fda.hhs.gov>, Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>, Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>, Queen, Jackie L <Jackie.Queen@fda.hhs.gov>, Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>, Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: Facebook Taurine Deficiency Warning

FYI, I saw this posted on a veterinary hospital facebook page. Apparently the post comments were overflowing with anger because the hospital warned pet owners that grain free diets were not necessarily magical or good. People do love their "grain free."

From: [Jones, Jennifer L](#)
To: [Carey, Lauren](#); [Ceric, Olgica](#); [Glover, Mark](#); [Nemser, Sarah](#); [Palmer, Lee Anne](#); [Queen, Jackie L](#); [Reimschuessel, Renate](#); [Rotstein, David](#)
Subject: RE: Facebook Taurine Deficiency Warning
Date: Monday, February 12, 2018 7:12:00 AM
Attachments: [image001.png](#)
[image003.png](#)

Yes, unfortunately, (b) (5)? I
guess we'll see when we test...
Thanks for sharing, Lauren!

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Carey, Lauren
Sent: Monday, February 12, 2018 7:10 AM
To: Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Glover, Mark <Mark.Glover@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: Facebook Taurine Deficiency Warning

FYI, I saw this posted on a veterinary hospital facebook page. Apparently the post comments were overflowing with anger because the hospital warned pet owners that grain free diets were not necessarily magical or good. People do love their "grain free."

From: [Jones, Jennifer L](#)
To: [Freeman, Lisa](#)
Subject: RE: FDA Update Links-Live 6/27/2019
Date: Monday, July 15, 2019 7:05:00 AM
Attachments: [image005.png](#)
[image006.png](#)
[image001.png](#)
[image002.png](#)

Hi Lisa,
Yes, I absolutely have time. I'll gather my group here and send a few calendar appointments.
Thank you,
Jen

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Sent: Friday, July 05, 2019 4:02 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: RE: FDA Update Links-Live 6/27/2019

Hi Jen
It would probably make the most sense to schedule a time to chat with Darcy and me.
Do you have some time in the next couple weeks?
Thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Sent: Friday, July 05, 2019 6:50 AM
To: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Cc: Norris, Anne <Anne.Norris@fda.hhs.gov>
Subject: RE: FDA DCM Update Links-Live 6/27/2019

Hi Lisa,

No, I did not hear about any preliminary data from Bill. I'd love to read anything you're willing to share.

Thanks again,

Jen

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Sent: Thursday, June 27, 2019 11:20 AM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Cc: Norris, Anne <Anne.Norris@fda.hhs.gov>
Subject: Re: FDA DCM Update Links-Live 6/27/2019

Hi Jen. I heard rumors of something coming so thanks for letting me know. Did you hear from Bill B about our preliminary data presented at ACVIM? Let me know if you'd like to discuss
Thanks. Lisa

Sent from my iPhone

On Jun 27, 2019, at 11:14 AM, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov> wrote:

Good morning,
I wanted to let you know that FDA Consumer update about DCM when live this morning. Here are the links:

[CVM Update](#)

[Web Update – DCM Investigation](#)

[Web QA \(Updated\)](#)

[Vet-LIRN Update](#)

[DCM Complaint Spreadsheet – 1/1/14 - 4/30/19](#)

If you have any questions about the content, please direct them to:

AskCVM@fda.hhs.gov

Thank you and take care,
Jen

Jennifer L.A. Jones, DVM
Veterinary Medical Officer
U.S. Food & Drug Administration

Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
new tel: 240-402-5421
fax: 301-210-4685
e-mail: jennifer.jones@fda.hhs.gov
Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm>
<[image005.png](#)> <image006.png>

From: [Jones, Jennifer L](#)
To: ["Darcy Adin"; Freeman, Lisa](#)
Subject: RE: Follow up call?
Date: Tuesday, August 07, 2018 6:42:00 AM
Attachments: [image001.png](#)
[image003.png](#)

Absolutely, Darcy. Please do!

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Darcy Adin [mailto:dbadin@ncsu.edu]
Sent: Monday, August 06, 2018 7:33 PM
To: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Cc: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: Re: Follow up call?

Hi Jennifer

Would it be ok to invite the others who were previously involved in our call? If so, I'll ask them if they are available at that time.

Thank you!

Darcy

On Aug 6, 2018, at 6:48 PM, Darcy Adin <dbadin@ncsu.edu> wrote:

That would work for me as well. Thank you!

Darcy

On Mon, Aug 6, 2018 at 11:00 AM, Freeman, Lisa <Lisa.Freeman@tufts.edu> wrote:

That works for me

Thanks

Lisa

-----Original Message-----

From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>

Sent: Monday, August 6, 2018 10:47 AM

To: Darcy Adin <dbadin@ncsu.edu>

Cc: Freeman, Lisa <lisa.freeman@tufts.edu> Subject:

RE: Follow up call?

Good morning Darcy and Lisa,

Would you be available Wed at 4 pm?

Jen

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421

-----Original Message-----

From: Darcy Adin [mailto:dbadin@ncsu.edu]
Sent: Friday, August 03, 2018 11:29 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Cc: Lisa Freeman <lisa.freeman@tufts.edu>
Subject: Follow up call?

Hi Dr. Jones,

Dr. Freeman and I are wondering if your group would be willing to have another conference call as a follow-up to discuss the nutritionally based DCM cases? As you know, since the release of the FDA statement, there has been much discussion among the public and the veterinary community, and we thought it could be useful to reconvene.

Thank you for your thoughts!
Darcy

--

Darcy B. Adin, DVM, DACVIM (Cardiology)
Clinical Assistant Professor of Cardiology
North Carolina State University
NC State Veterinary Hospital
1060 William Moore Drive
Raleigh, NC 27607
919-513-6032

From: (b) (6)
To: [Darcy Adin](#)
Cc: [Joshua A Stern](#); [Korinn Saker](#); [Fries, Ryan C](#); [Freeman, Lisa](#); [Jones, Jennifer L](#)
Subject: Re: hold-FDA call w/ NCSU & Tufts re: DCM
Date: Tuesday, August 07, 2018 8:30:34 AM

Hi Darcy and others,

I am on vacation this week at the (b) (6) and am not sure exactly where we will be tomorrow at 4, but will do my best!

(b) (6)

On Tue, Aug 7, 2018 at 7:08 AM, Darcy Adin <dbadin@ncsu.edu> wrote:

Hi Josh, Korinn, Ryan and (b) (6),

I know it is short notice but if any of you are available to conference with Dr. Jones and her group at the FDA, we would love to have you join us tomorrow (wednesday) at 4pm EST to discuss where we are with investigations after the FDA statement release.

Thanks!
Darcy and Lisa

----- Forwarded message -----

From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Date: Mon, Aug 6, 2018 at 10:58 AM
Subject: hold-FDA call w/ NCSU & Tufts re: DCM
To: "Norris, Anne" <Anne.Norris@fda.hhs.gov>, "DeLancey, Siobhan" <Siobhan.Delancey@fda.hhs.gov>, "Rotstein, David" <David.Rotstein@fda.hhs.gov>, "Palmer, Lee Anne" <LeeAnne.Palmer@fda.hhs.gov>, "Carey, Lauren" <Lauren.Carey@fda.hhs.gov>, "Reimschuessel, Renate" <Renate.Reimschuessel@fda.hhs.gov>, "Ceric, Olgica" <Olgica.Ceric@fda.hhs.gov>, "Nemser, Sarah" <Sarah.Nemser@fda.hhs.gov>, Darcy Adin <dbadin@ncsu.edu>, Lisa Freeman <lisa.freeman@tufts.edu>

--Do not delete or change any of the following text. --

[Join Webex meeting](#)

Meeting number (access code) (b) (6)
Meeting password (b) (6)

Join by phone

+1-210-795-0506 US Toll

+1-877-465-7975 US Toll Free

[Global call-in numbers](#) | [Toll-free calling restrictions](#)

[Can't join the meeting?](#)

If you are a host, [go here](#) to view host information.

IMPORTANT NOTICE: Please note that this Webex service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

--

Darcy B. Adin, DVM, DACVIM (Cardiology)
Clinical Assistant Professor of Cardiology
North Carolina State University
NC State Veterinary Hospital
[1060 William Moore Drive](#)
[Raleigh, NC 27607](#)
919-513-6032

--

 (b) (6), DVM, DACVIM (Cardiology)
ACVIM Cardiology Secretary

From: [Freeman, Lisa](#)
To: [Jones, Jennifer L](#)
Subject: RE: Meeting to discuss ACVIM findings
Date: Tuesday, July 16, 2019 3:07:10 PM
Attachments: [image004.png](#)
[image006.png](#)

Hi Jen
I could make any of those work
Thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Sent: Tuesday, July 16, 2019 1:23 PM
To: Freeman, Lisa <Lisa.Freeman@tufts.edu>; ADIN,DARCY BRITTAİN <adind@ufl.edu>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>; Norris, Anne <Anne.Norris@fda.hhs.gov>; DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>; Peloquin, Sarah <Sarah.Peloquin@fda.hhs.gov>; Burkholder, William <William.Burkholder@fda.hhs.gov>
Subject: Meeting to discuss ACVIM findings

Good afternoon everyone,
Lisa mentioned sharing some updates on the preliminary DCM findings from work with Darcy. The work was previously presented at ACVIM. Please reply by voting on the best day and time to meet to discuss their update.
If the voting does not work, here are the dates/times.
Tues July 30 at 2pm
Mon Aug 5 at 11am
Mon Aug 12 at 1pm
Looking forward to chatting with you.
Take care,
Jen

Jennifer L. A. Jones, DVM
Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research

Veterinary Laboratory Investigation and Response Network (Vet-LIRN)

8401 Muirkirk Road, G704

Laurel, Maryland 20708

new tel: 240-402-5421

fax: 301-210-4685

e-mail: jennifer.jones@fda.hhs.gov

Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm>



From: [Freeman, Lisa](#)
To: [Jones, Jennifer L](#)
Cc: [ADIN,DARCY BRITTAIN](#)
Subject: Re: Meeting with Tufts and UFL-discuss ACVIM findings
Date: Tuesday, July 23, 2019 8:25:58 AM

Hi Jen.

Any of these work except 8/27 at 8 am

Thanks. Lisa

Sent from my iPhone

> On Jul 23, 2019, at 7:07 AM, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov> wrote:

>

> Would any of these dates work well?

> 8/13 at either 8 am or 10 am

> 8/19 at 10 am

> 8/26 at 10 am or 11 am

> 8/27 at 8 am or 10 am

>

>

> Jennifer Jones, DVM

> Veterinary Medical Officer

> Tel: 240-402-5421

>

>

> -----Original Message-----

> From: ADIN,DARCY BRITTAIN <adind@ufl.edu>

> Sent: Thursday, July 18, 2019 11:00 AM

> To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Freeman, Lisa <Lisa.Freeman@tufts.edu>

> Subject: RE: Meeting with Tufts and UFL-discuss ACVIM findings

>

> Hi Jennifer,

>

> Monday and Tuesday mornings work best for me if there are any dates where that would work for you?

>

> Thanks!

> Darcy

>

> -----Original Message-----

> From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>

> Sent: Thursday, July 18, 2019 10:30 AM

> To: Freeman, Lisa <Lisa.Freeman@tufts.edu>; ADIN,DARCY BRITTAIN <adind@ufl.edu>

> Subject: RE: Meeting with Tufts and UFL-discuss ACVIM findings

>

> Absolutely! Darcy, when are some good dates for you in August?

>

> Jennifer Jones, DVM

> Veterinary Medical Officer

> Tel: 240-402-5421

>

>

> -----Original Message-----

> From: Freeman, Lisa <Lisa.Freeman@tufts.edu>

> Sent: Thursday, July 18, 2019 10:27 AM

> To: ADIN,DARCY BRITTAIN <adind@ufl.edu>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
> Subject: RE: Meeting with Tufts and UFL-discuss ACVIM findings
>
> Hi Jen
> I'd love to have Darcy there. Could we look a little farther out for a date when she is available?
> Thanks
> Lisa
>
> Lisa M. Freeman, DVM, PhD, DACVN
> Board Certified Veterinary NutritionistTM Professor Cummings School of Veterinary Medicine Friedman School
> of Nutrition Science and Policy Tufts Clinical and Translational Science Institute Tufts University
> https://urldefense.proofpoint.com/v2/url?u=http-3A__www.petfoodology.org&d=DwlGaQ&c=sJ6xIWYx-zLMB3EPkvcnVg&r=V5a7URrvXpMRhVvlyTKAig&m=q2cdn42lylj-4kUqfSPes05nnq2fl8hE6RBLDWOVqk&s=uQ-QwXWfNT9U4KBuYqDEDHtfFvlnFDP3gEpILADaRfM&e=
>
>
>
> -----Original Message-----
> From: ADIN,DARCY BRITTAIN <adind@ufl.edu>
> Sent: Wednesday, July 17, 2019 9:18 PM
> To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
> Cc: Freeman, Lisa <Lisa.Freeman@tufts.edu>
> Subject: Re: Meeting with Tufts and UFL-discuss ACVIM findings
>
> Hi Jen,
> Unfortunately I won't be able to make the call but hopefully Dr. Freeman will be able to?
> Take care
> Darcy
>
>> On Jul 17, 2019, at 10:23 AM, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov> wrote:
>>
>> Please forward if I missed anyone. This time seemed to work well for most folks.
>>
>>
>> -- Do not delete or change any of the following text. --
>>
>>
>>
>> When it's time, join your Webex meeting here.
>>
>>
>>
>>
>>
>> Meeting number (access code): (b) (6)
>>
>> Meeting password: (b) (6)
>>
>>
>>
>>
>>
>>
>> Join<https://urldefense.proofpoint.com/v2/url?u=https-3A__fda1.webex.com_fda1_j.php-3FMTID-3Dm1e91ed293192a5751cf81fe0a878393f&d=DwMFAw&c=sJ6xIWYx-zLMB3EPkvcnVg&r=V5a7URrvXpMRhVvlyTKAig&m=818p6oias09ebW7G_x6RUT>
>> om_fda1_j.php-3FMTID-3Dm1e91ed293192a5751cf81fe0a878393f&d=DwMFAw&c=sJ6xIWYx-zLMB3EPkvcnVg&r=V5a7URrvXpMRhVvlyTKAig&m=818p6oias09ebW7G_x6RUT

>> OrVjDMkiyrP9TxSrZeD0c&s=1Z05fOSrbYymRFMVCTpEpVkagDdW3BUjFDUb0L4zt0g&e=
>>>
>>
>>
>>
>>
>> Join by phone
>> Tap to call in from a mobile device (attendees only)
>> +1-210-795-0506 US Toll
>> +1-877-465-7975 US Toll Free
>> Global call-in
>> numbers<https://urldefense.proofpoint.com/v2/url?u=https-3A__fda1.webe
>> x.com_fda1_globalcallin.php-3FMTID-3Dm5dfe31deee3865c2ecbe371b84b925c3
>> &d=DwMFAw&c=sJ6xIWYx-zLMB3EPkvcnVg&r=V5a7URrvXpMRhVvlyTKAig&m=8l8p6oia
>> s09ebW7G_x6RUTOrVjDMkiyrP9TxSrZeD0c&s=V0vg6coPT-BiW7QgJ7lu9obvpfbl7Qbt
>> LivD7M9LQmQ&e=> | Toll-free calling
>> restrictions<https://urldefense.proofpoint.com/v2/url?u=https-3A__e-2D
>> meetings.verizonbusiness.com_global_pdf_Verizon-5FAudio-5FConferencing
>> -5FGlobal-5FAccess-5FInformation-5FAugust2017.pdf&d=DwMFAw&c=sJ6xIWYx-
>> zLMB3EPkvcnVg&r=V5a7URrvXpMRhVvlyTKAig&m=8l8p6oias09ebW7G_x6RUTOrVjDMk
>> iyrP9TxSrZeD0c&s=mGRi5gQiwNLfT7Oib_YoAmYq9o4RPteyYX9yoBLI2fA&e=>
>>
>>
>>
>>
>>
>>
>> Need help? Go to
>> https://urldefense.proofpoint.com/v2/url?u=http-3A__help.webex.com&d=D
>> wIGaQ&c=sJ6xIWYx-zLMB3EPkvcnVg&r=V5a7URrvXpMRhVvlyTKAig&m=q2cdn42ly1j-
>> 4kUqfSPes05nnq2f18hE6RBLDWOVqk&s=1HTkYG-gl2_tHUjfbHV36a0bvVDljyunwQqE
>> D-hFGB4&e=
>> <https://urldefense.proofpoint.com/v2/url?u=http-3A__help.webex.com&d=D
>> DwMFAw&c=sJ6xIWYx-zLMB3EPkvcnVg&r=V5a7URrvXpMRhVvlyTKAig&m=8l8p6oias09
>> ebW7G_x6RUTOrVjDMkiyrP9TxSrZeD0c&s=rA1k3wfkBJHshv4RBxaGyjT8xaJ9P9xdoDC
>> a10X4174&e=>
>>
>>
>>
>>
>>
>> <meeting.ics>

From: [Rotstein, David](#)
To: [Jones, Jennifer L](#); [Palmer, Lee Anne](#); [Carey, Lauren](#); [Peloquin, Sarah](#); [Burkholder, William](#); [Freeman, Lisa](#); [ADIN,DARCY BRITTAIN](#); [Pohl, Aurelie](#); [Norris, Anne](#); [DeLancey, Siobhan](#)
Cc: [Ceric, Olgica](#)
Subject: RE: Meeting with Tufts and UFL-discuss ACVIM findings
Date: Tuesday, August 13, 2019 8:43:06 AM
Attachments: [Histopathologic Findings – Confirmed and Non-Confirmed DCM \[Autosaved\] \[Autosaved\].pptx](#)
[image001.png](#)
[image002.jpg](#)
[image003.jpg](#)
[image004.jpg](#)
[image005.jpg](#)
[image006.jpg](#)

Please do not forward.

thanks

David Rotstein, DVM, MPVM, Dipl. ACVP
CVM Vet-LIRN Liaison
CVM OSC/DC/CERRT
7519 Standish Place
(b) (6) (BB)



This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution, or copying is strictly prohibited. If you think you received this e-mail message in error, please e-mail the sender immediately at david.rotstein@fda.hhs.gov.

-----Original Appointment-----

From: Jones, Jennifer L
Sent: Wednesday, July 17, 2019 10:19 AM
To: Jones, Jennifer L; Palmer, Lee Anne; Carey, Lauren; Rotstein, David; Peloquin, Sarah; Burkholder, William; Freeman, Lisa; ADIN,DARCY BRITTAIN; Pohl, Aurelie; Norris, Anne; DeLancey, Siobhan
Cc: Ceric, Olgica
Subject: Meeting with Tufts and UFL-discuss ACVIM findings
When: Tuesday, August 13, 2019 8:00 AM-9:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: virtual meeting

Please forward if I missed anyone.

-- Do not delete or change any of the following text. --

When it's time, join your Webex meeting here.

Meeting number (access code): (b) (6)

Meeting password: (b) (6)

Join

Join by phone

Tap to call in from a mobile device (attendees only)

+1-210-795-0506 US Toll

+1-877-465-7975 US Toll Free

[Global call-in numbers](#) | [Toll-free calling restrictions](#)

Need help? Go to <http://help.webex.com>



Histopathologic Findings – Confirmed and Non-Confirmed DCM

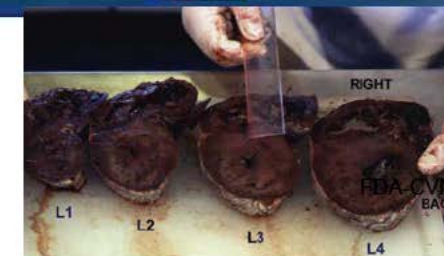
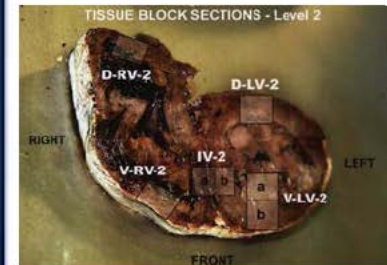
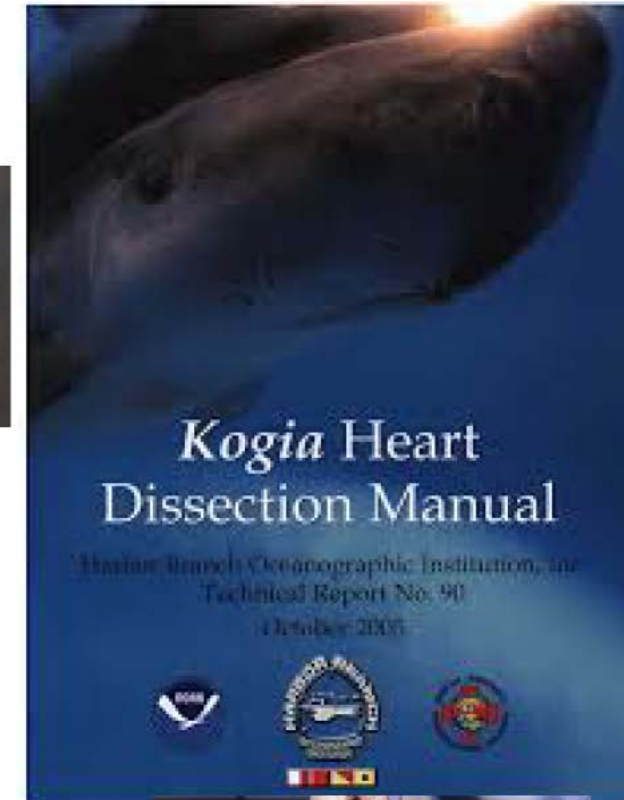
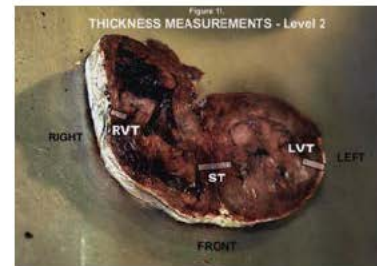
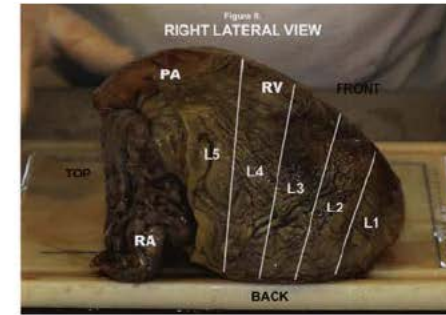


DCM & Non-DCM Cases

- Cases
 - Cases from CVCA and PFRs
 - Dogs:
 - 6 DCM based on echo
 - 3 non-DCM:
 - Sudden death
 - Endocardiosis with lung and bladder mass
 - Cardiomegaly with CHF

Plan

- Full necropsy and histopathologic evaluation
- Cardiac evaluation
 - Adapted Protocol – *Kogia* Cardiomyopathy
 - Weights and measurements
 - Histopathologic Findings
 - DCM
 - 2 types (with overlap)
 - Fatty change (infiltration)-degenerative
 - Wavy fiber -attenuation
- Grid Pathology
 - Individual
 - Population



Cardiomyopathy Types: Tidholm A and Jonsson L. 2005. Vet Pathol 42: 1-8.

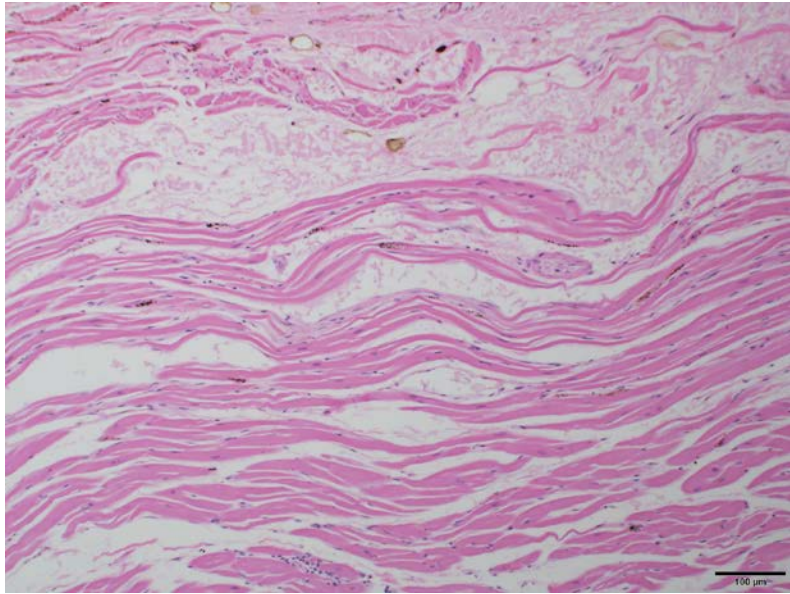
Histologic Findings

- Group:
 - Primary DCM (5/6)
 - Secondary DCM (1/6)- infectious
- Histo- Cardiac
 - Cardiomyocyte atrophy and degeneration (5/5)
 - Fatty infiltration (steatosis)(4/5)
 - Interstitial edema (3/5)
 - (mild) interstitial myocarditis (3/5)
 - Endocardiosis (5/5)
 - Fibrosis (4/5)
- Histo- Non-Cardiac (associated with cardiac disease)
 - Pulmonary edema (3/5)
 - Pulmonary fibrosis (3/5)
 - Hepatic chronic passive congestion (4/5)

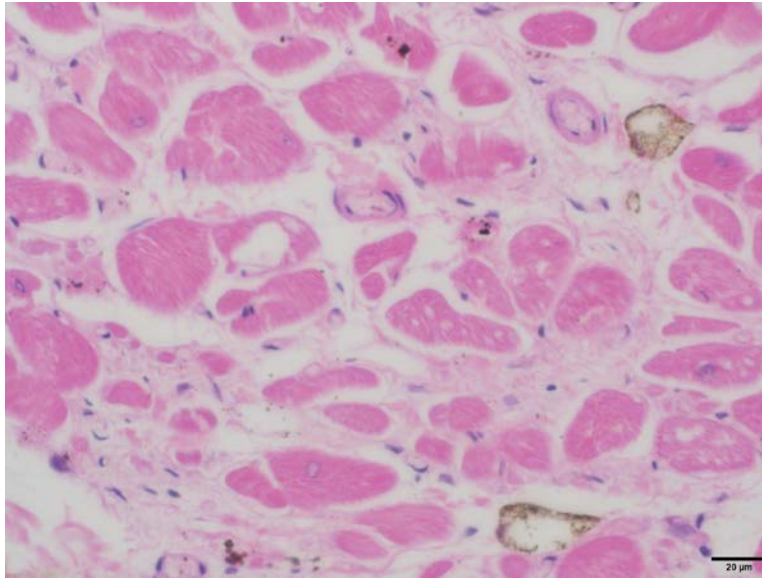
DCM: Gross



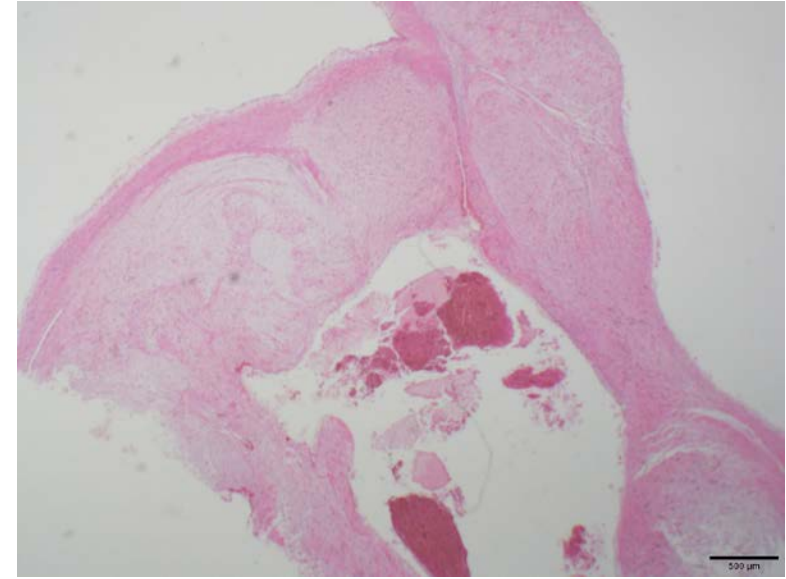




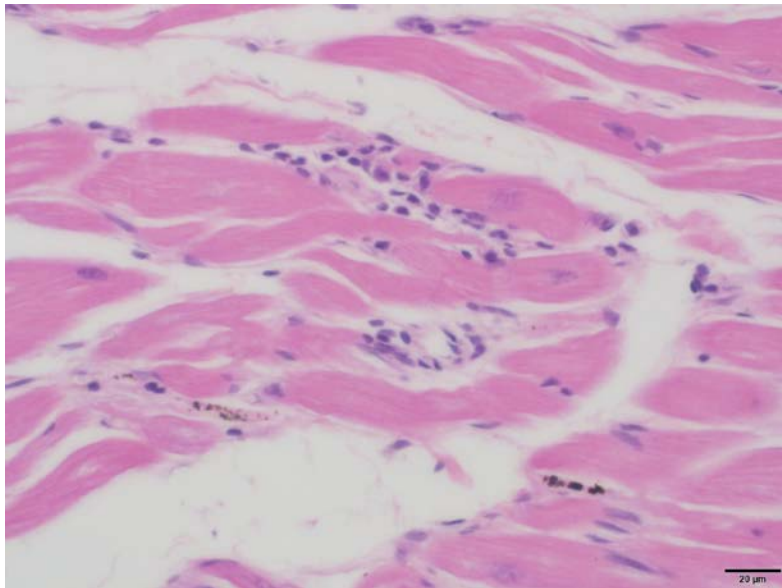
800.267-CC-092-EON-361684-Dorsal Left Ventricle Level 2 10X



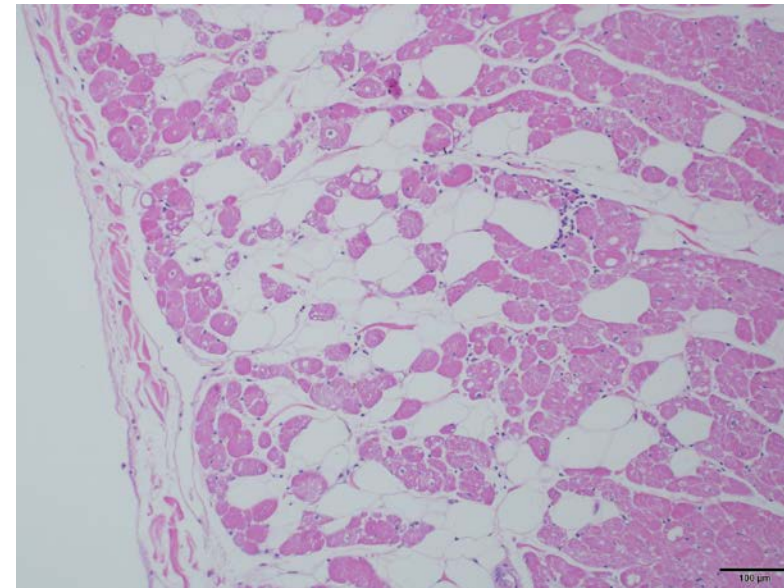
800.267-CC-092-EON-361684-Dorsal Left Ventricle Level 2 40X



800.267-CC-092-EON-361684-Left Atrioventricular Valve- 2X

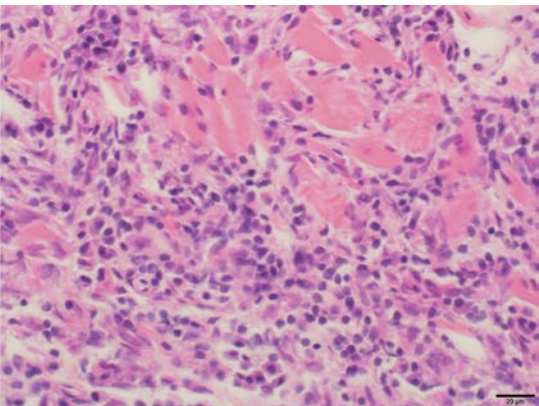
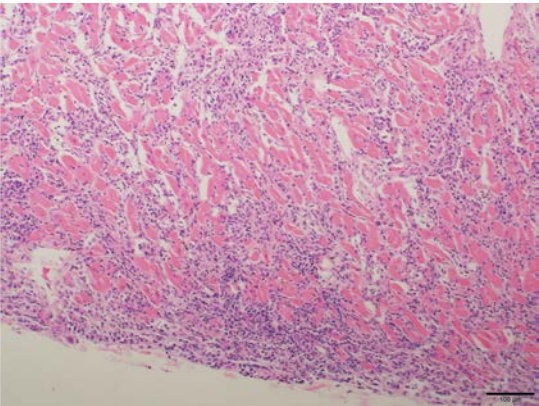


800.267-CC-092-EON-361684-Dorsal Left Ventricle Level 2 40X-b

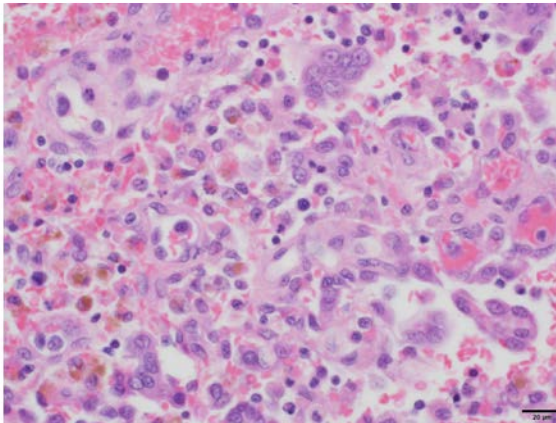
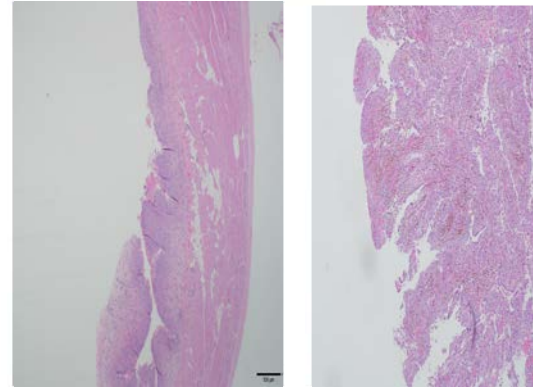
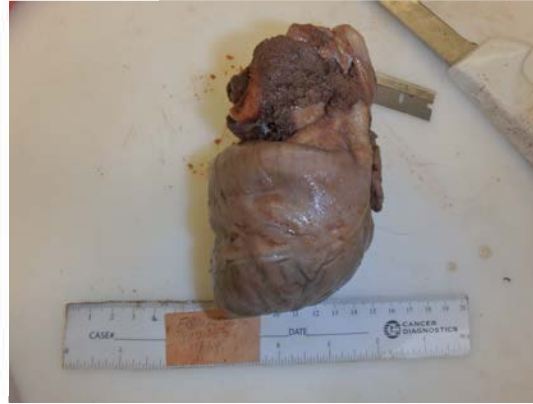


800.267-CC-191-EON-364014-Ventral Right Ventricle - 10X

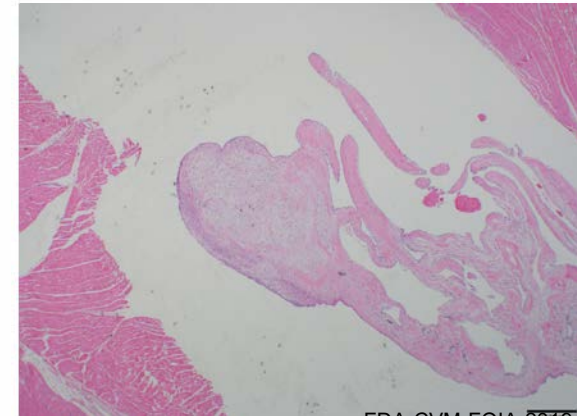
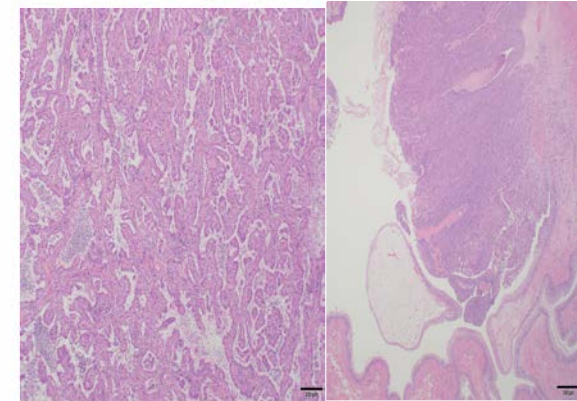
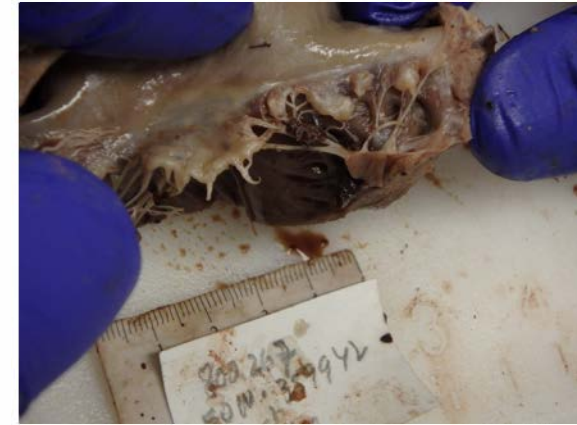
Secondary DCM & Non-DCM Cases



Secondary DCM- Myocarditis



Mesothelioma



Bronchoalveolar Carcinoma (middle photo) & Endocardiosis(lower photo)

From: [Hartogensis, Martine](#)
To: [Edwards, David](#); [Palmer, Lee Anne](#); [Burkholder, William](#); [Jones, Jennifer L](#); [Rotstein, David](#); [Carey, Lauren](#); [Norris, Anne](#); [DeLancey, Siobhan](#); [Conway, Charlotte](#)
Cc: [McDermott, Patrick](#); [Reimschuessel, Renate](#)
Subject: Weekly DCM Call with PFI :)
Date: Friday, August 17, 2018 4:02:00 PM

Hi,

I had my weekly DCM call with PFI to share our updated case numbers (thank you Lee Anne and Lauren!) with Peter Tabor. I mentioned the 94 new cases involving DCM (~92 percent labeled as grain-free).

(b) (5), (b) (4)

That's it for now and thank you all for all your help!!

Martine

Report Details - EON-351031	
ICSR:	2045676
Type Of Submission:	Initial
Report Version:	FPSR.FDA.PETF.V.V1
Type Of Report:	Adverse Event (a symptom, reaction or disease associated with the product)
Reporting Type:	Voluntary
Report Submission Date:	2018-04-12 13:26:01 EDT
Reported Problem:	<p>Problem Description: Feb 23, 2018 Patient presented to the cardiology service at (b) (6) for tachypnea. He was diagnosed with dilated cardiomyopathy and left side congestive heart failure. Whole blood taurine level was 119 (ref 200-350, critical level <150). At the time, patient consuming Zignature Kangaroo Formula and was advised to change.</p> <p>Date Problem Started: 02/22/2018</p> <p>Concurrent Medical Problem: Yes</p> <p>Pre Existing Conditions: History of swallowing disorder; on Prednisone 10mg every other day since 2015 following biopsy of nodule on larynx (granulomatous)</p> <p>Outcome to Date: Stable</p>
Product Information:	<p>Product Name: Zignature Kangaroo Formula</p> <p>Product Type: Pet Food</p> <p>Lot Number:</p> <p>Package Type: BAG</p> <p>Possess Unopened Product: No</p> <p>Possess Opened Product: No</p> <p>Product Use Information:</p> <p>Description: Owner feeding for 2-3 years prior to diagnosis.</p> <p>Last Exposure Date: 03/01/2018</p> <p>Time Interval between Product Use and Adverse Event: 3 Years</p> <p>Product Use Stopped After the Onset of the Adverse Event: Yes</p> <p>Perceived Relatedness to Adverse Event: Possibly related</p> <p>Other Foods or Products Given to the Animal During This Time Period: Yes</p> <p>Manufacturer /Distributor Information:</p> <p>Purchase Location Name: Chewy.com</p>
Animal Information:	<p>Name: (b)</p> <p>Type Of Species: Dog</p> <p>Type Of Breed: Retriever - Golden</p> <p>Gender: Male</p> <p>Reproductive Status: Neutered</p> <p>Weight: 40 Kilogram</p>

FDA-CVM-FOIA-2019-1704-001098

	Age:	6 Years
	Assessment of Prior Health:	Good
	Number of Animals Given the Product:	1
	Number of Animals Reacted:	1
	Owner Information:	Owner Information provided: Yes Contact: Name: (b) (6) Phone: (b) (6) Address: (b) (6) United States
	Healthcare Professional Information:	Practice Name: (b) (6) Contact: Name: (b) (6) Phone: (b) (6) Address: (b) (6) United States Type of Veterinarian: Referred veterinarian Date First Seen: 02/23/2018
Sender Information:	Name:	(b) (6)
	Address:	(b) (6) United States
	Contact: Phone:	(b) (6)
	Email:	(b) (6)
	Reporter Wants to Remain Anonymous:	No
	Permission To Contact Sender:	Yes
	Preferred Method Of Contact:	Email
	Reported to Other Parties:	None
Additional Documents:		
<div style="text-align: right;">FDA-CVM-FOIA-2019-1704-001099</div>		

From: [Palmer, Lee Anne](#)
To: [Hartogensis, Martine](#)
Cc: [Carey, Lauren](#); [Rotstein, David](#); [Jones, Jennifer L](#); [Burkholder, William](#)
Subject: PFI - CVM webinar and premeeting for next week - (b) (6) ...will need to miss (I had informed Nanette)
Date: Thursday, July 12, 2018 11:42:47 AM
Attachments: [Information PFI CVM Webinar on July 19 \(pre-meeting\).msg](#)
[image001.png](#)
[image002.jpg](#)
[image003.jpg](#)
[image004.jpg](#)
[image005.jpg](#)
[image006.jpg](#)
Importance: High

Hi – never good timing, but we have (b) (6) next week. I let Nanette know last week when the PFI meeting was scheduled. Understandably, she didn't want to move the meeting since it's hard to schedule. I will not be on either Tuesday or Thursday of next week for the meeting. Lauren should be well able to cover anything from our team.

Sorry to miss – thanks and good luck. Looks like an interesting set of questions from PFI...

Thanks, Lee Anne

Lee Anne M. Palmer, VMD, MPH
Team Leader HFV-242, Supervisory VMO

Center for Veterinary Medicine
OSC, Division of Veterinary Product Safety
U.S. Food and Drug Administration
Tel: 240-402-5767
Leeanne.palmer@fda.hhs.gov



From: [Milton, Nanette](#)
To: [Palmer, Lee Anne](#); [Rotstein, David](#); [McDermott, Patrick](#); [DeLancey, Siobhan](#); [Burkholder, William](#); [Hartogensis, Martine](#); [Norris, Anne](#); [Jones, Jennifer L](#); [Carey, Lauren](#)
Subject: Information: PFI & CVM Webinar on July 19 (pre-meeting)
Attachments: [PFI Questions for CVM Regarding DCM.docx](#)

Hi Nanette,

Please send the attached questions to the CVM folks attending the webinar on the 19th.

Can you set up a premeeting from CVM so we can discuss?

Also, let PFI know who will be attending from CVM.

Thanks!
Martine

From: Dana Brooks [mailto:Dana@petfoodinstitute.org <<mailto:Dana@petfoodinstitute.org>>]
Sent: Thursday, July 12, 2018 9:23 AM
To: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov <<mailto:Martine.Hartogensis@fda.hhs.gov>> >
Cc: Tabor, Peter <peter@petfoodinstitute.org <<mailto:peter@petfoodinstitute.org>> >
Subject: Information: PFI & CVM Webinar on July 19
Importance: High

Martine,

I wanted to reconfirm the webinar is scheduled for July 19. I'm sharing some questions with you in advance that may be asked by our members. These are the questions that our producer members presented to PFI as we informed them of the DCM incidents. I hope this is helpful to your team.

Please let us know who will be joining the call. We will do the same from our end.

Thank you so much,
Dana Brooks

-- Do not delete or change any of the following text. --

Join WebEx meeting <<https://fda1.webex.com/fda1/j.php?MTID=md1669c061ce203d0436a270da081f36e>>
Meeting number (access code) (b)(6)
Meeting password: (b)(6)

Join by phone
+1-877-465-7975 US Toll Free
Global call-in numbers <<https://fda1.webex.com/fda1/globalcallin.php?serviceType=MC&ED=7002862&tollFree=1>> | Toll-free calling restrictions
<https://e-meetings.verizonbusiness.com/global/pdf/Verizon_Audio_Conferencing_Global_Access_Information_August2017.pdf>

Can't join the meeting? <<https://collaborationhelp.eisco.com/article/WBX000029055>>

If you are a host, go here <<https://fda1.webex.com/fda1/j.php?MTID=m0dab1d42838e7d6c5224d9d372e353d1>> to view host information.

IMPORTANT NOTICE: Please note that this WebEx service allows audio and other information sent during the session to be recorded, which may be discoverable in a legal matter. By joining this session, you automatically consent to such recordings. If you do not consent to being recorded, discuss your concerns with the host or do not join the session.

PFI Questions for FDA CVM Regarding DCM

Questions Regarding the Language and Overall Scope of the Investigation

Is “grain-free” an adequate descriptor of the category of diets being examined?

Dr. Lisa Freeman at Tufts University indicates the incidence of DCM is associated with more than just grain-free diets: <http://vetnutrition.tufts.edu/2018/06/a-broken-heart-risk-of-heart-disease-in-boutique-or-grain-free-diets-and-exotic-ingredients/>.

Will FDA CVM consider the need for further evaluation of any link between pet food diets and incidence of DCM before deciding whether to issue a public notice?

Questions Regarding Investigation History

Can FDA CVM share more information regarding the breeds of dogs and ages involved in its observations, including information on which breeds it believes are predisposed to DCM? Also, has FDA CVM looked into the relationships between dogs exhibiting DCM to determine whether/how genetics could be playing a role in the observed cases of DCM?

Can the FDA share the details around the formal diagnoses of DCM in these dogs? Were the diagnoses based on clinical pathology blood or serum samples alone? Was there any supporting electrocardiographic data for these animals? Similarly, were the diagnoses confirmed with medical imaging data or post-mortem gross pathology/histopathology evaluations?

Can FDA CVM share the comprehensive diet histories of the impacted animals and the total dietary fiber, soluble fiber and viscous fiber content of the diets tested?

Is a nutritionist gathering diet history information as part of FDA’s investigation?

What were the protein sources and digestibility in each of these diets?

Were any (paired or whole) blood or plasma tests for taurine performed? Was any urine taurine measured before or after treatment?

In the case of the dog that improved with a diet change from one grain-free diet to another, what were the dietary taurine levels, total dietary fiber levels and digestibility percentages of the implicated and treatment diets?

In dogs whose condition improved, in addition to diet change, what level of taurine supplementation was given?

How much of the research presented at the ACVIM forum (on June 14) represents the full series of complaints that FDA CVM is investigating?

Does FDA CVM believe that other brands are implicated as well, and, if so, what are the data used by the agency to reach this conclusion?

Is there a common supplier or co-manufacturer of ingredients and/or products?

Given that not all grain-free diets are linked to an increase in DCM, has the agency evaluated other grain-free diets that share the same legume sources as the diets consumed by dogs that developed DCM?

Are there other pathologies being considered?

Research presented at ACVIM did not definitively conclude that the recently observed increase in DCM is a taurine issue (although low taurine has previously been linked to increased incidence of DCM).

What is known about the formulations, ingredient handling and processing conditions for the diets that FDA CVM considers possibly associated with DCM?

What is known about the amino acid balance in the diets containing pulses?

Questions Regarding Certain Product Attributes and the Incidence of DCM

Has FDA CVM considered whether there might be a connection between products that are not adding sufficient sources of vitamins and minerals and the incidence of DCM?

What evaluations have been done to determine the presence/absence of sufficient vitamins and minerals in any of the diets identified as linked to incidents of DCM?

Has FDA CVM considered what impact other dietary factors have on the intestinal tract in light of the tendency of many grain-free diets to contain higher levels of soluble fiber as compared to conventional diets?

If taurine is not recognized as an essential nutrient for dogs and there is no standard developed, is FDA CVM considering recommending a minimum taurine level for all dog food diets?

If a taurine requirement were to be proposed for dogs, would the requirement be based on repletion data or data shown to maintain normal blood taurine levels?

Since the whole blood taurine was normal in tested dogs that were fed a grain-free diet, is taurine supplementation through food effective?

Are the taurine dosage levels used in the treatment of DCM cases safe for long-term use?

Is FDA CVM examining the presence of certain legumes and their levels as potentially impacting the synthesis of taurine? If so, what conclusions have been drawn?

What other anti-nutrient factors may be present in legumes, tubers and other non-grain-type ingredients? Can these factors be measured in the finished product and can safe-levels be set against these?

Green peas have been a common ingredient in single animal protein source diets since the 1990s. Have there been any proposed mechanisms to explain why there is an emergence of pea- association in DCM?

Given the growing trend today toward pet food recipes that utilize novel ingredients over conventional ingredient diets (such as corn, wheat, soy, chicken, pork), is there consideration that the current generation of pet foods will require a unique set of nutrient requirements based on new knowledge of ingredient-nutrient interactions and manufacturing capabilities? What efforts would be needed to redefine nutrient requirements?

From: [DeLancey, Siobhan](#)
To: [Steven Rosenthal](#)
Cc: [Jones, Jennifer L](#)
Subject: RE: FDA-CVCA Confidentiality Agreement for signature
Date: Wednesday, July 18, 2018 6:27:59 AM
Attachments: [image001.png](#)
[image002.jpg](#)
[image003.jpg](#)
[image004.jpg](#)
[image005.jpg](#)
[image006.jpg](#)

Steve, can you give me a call at your convenience today? I should be at my desk most of the day. Right now the only time I know I'll be unavailable is 10:30-11:30.

Siobhan DeLancey, RVT, MPH
Senior Advisor for Strategic Initiatives
Center for Veterinary Medicine
U.S. Food and Drug Administration
O: 240-402-9973
M: 202-510-4177

Siobhan.DeLancey@fda.hhs.gov



From: Steven Rosenthal [mailto:steven.rosenthal@cvcavets.com]
Sent: Tuesday, July 17, 2018 10:37 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Cc: DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>
Subject: Re: FDA-CVCA Confidentiality Agreement for signature

OK Here we go - this time it is signed
Sorry for the first mishap
Steve

Steven Rosenthal DVM Dip ACVIM, Cardiology
CVCA Cardiac Care for Pets
Annapolis, Towson, Columbia, Gaithersburg, Rockville and Frederick, MD
Vienna, Leesburg, Springfield, Fairfax and Richmond, VA
Louisville, KY
[Email: steven.rosenthal@cvcavets.com](mailto:steven.rosenthal@cvcavets.com)
Visit our Website: www.cvcavets.com
"Like" our Fan Page: www.facebook.com/CVCAVETS
"Follow" us on Instagram: <https://www.instagram.com/cvcavets>

On Jul 17, 2018, at 3:32 PM, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov> wrote:

Good afternoon Steve,

(b) (5)

Jen

Jennifer Jones, DVM

Veterinary Medical Officer

Tel: 240-402-5421

[<image001.png>](#) <image004.png>

From: Jones, Jennifer L

Sent: Tuesday, July 17, 2018 10:11 AM

To: 'Steven Rosenthal' <steven.rosenthal@cvcavets.com>

Subject: RE: FDA-CVCA Confidentiality Agreement for signature

No worries. Please sign this copy. It has our office director's signature.

Jennifer Jones, DVM

Veterinary Medical Officer

Tel: 240-402-5421

[<image001.png>](#) <image003.png>

From: Steven Rosenthal [<mailto:steven.rosenthal@cvcavets.com>]

Sent: Tuesday, July 17, 2018 10:06 AM

To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>

Subject: Re: FDA-CVCA Confidentiality Agreement for signature

I guess that would be a good idea - my apologies I will send it tonight - too many things on my plate - I thought I signed it before scanning

Sent from my iPhone

On Jul 17, 2018, at 8:40 AM, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov> wrote:

Good morning Dr. Rosenthal,

Thank you for sending the agreement. I don't see a signature on the document. Can you please resend?

Thank you again,

Jen

Jennifer Jones, DVM

Veterinary Medical Officer
Tel: 240-402-5421
<[image001.png](#)> <image003.png>

From: Steven Rosenthal [<mailto:steven.rosenthal@cvcavets.com>]
Sent: Monday, July 16, 2018 10:53 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: Re: FDA-CVCA Confidentiality Agreement for signature

Here is the signed agreement
Thanks
Steve

Steven Rosenthal DVM Dip ACVIM, Cardiology
CVCA Cardiac Care for Pets
Annapolis, Towson, Columbia, Gaithersburg, Rockville and Frederick, MD
Vienna, Leesburg, Springfield, Fairfax and Richmond, VA
Louisville, KY
[Email: steven.rosenthal@cvcavets.com](mailto:steven.rosenthal@cvcavets.com)
Visit our Website: www.cvcavets.com
"Like" our Fan Page: www.facebook.com/CVCAVETS
"Follow" us on Instagram: <https://www.instagram.com/cvcavets>

On Jul 16, 2018, at 6:58 AM, Jones, Jennifer L
<Jennifer.Jones@fda.hhs.gov> wrote:

Good morning Steve,

There are a few goals with the collaboration. (b) (4), (b) (5)

(b) (4), (b) (5)

(b) (4), (b) (5) I'm happy to discuss further by phone.

Have a great week,
Jen

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421

[<image001.png>](#) [<image003.png>](#)

From: Steven Rosenthal
[\[mailto:steven.rosenthal@cvcavets.com\]](mailto:steven.rosenthal@cvcavets.com)
Sent: Sunday, July 15, 2018 8:32 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Cc: (b) (6) <(b) (6)@cvcavets.com>
Subject: Re: FDA-CVCA Confidentiality Agreement for signature

Just a quick question and then I can forward
I am no attorney so some of the language is legal mumbo jumbo
Will we as CVCA have (b) (5)
[REDACTED]

Steve

Steven Rosenthal DVM Dip ACVIM, Cardiology
CVCA Cardiac Care for Pets
Annapolis, Towson, Columbia, Gaithersburg, Rockville
and Frederick, MD
Vienna, Leesburg, Springfield, Fairfax and Richmond, VA
Louisville, KY
[Email: steven.rosenthal@cvcavets.com](mailto:steven.rosenthal@cvcavets.com)
Visit our Website: www.cvcavets.com
"Like" our Fan Page: www.facebook.com/CVCAVETS
"Follow" us on Instagram: <https://www.instagram.com/cvcavets>

On Jul 9, 2018, at 9:29 AM, Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov> wrote:

Good morning Dr. Rosenthal,
Please sign the attached confidentiality agreement. After you sign, I'll route it to our Office Director for signature. I'll send you a final version with all signatures, and we can set-up the call to discuss the case investigations.
Thank you,

Jen

Jennifer L. A. Jones, DVM

Veterinary Medical Officer

U.S. Food & Drug Administration

Center for Veterinary Medicine

Office of Research

Veterinary Laboratory Investigation and Response Network (Vet-LIRN)

8401 Muirkirk Road, G704

Laurel, Maryland 20708

new tel: 240-402-5421

fax: 301-210-4685

e-mail: jennifer.jones@fda.hhs.gov

Web: <http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm>

[<image001.png>](#) <image002.png>

<CVCA-FDA CDA-6.26.2018-Final.pdf>

Riera-Seivane, Jaime

From: Rotstein, David
Sent: Tuesday, June 18, 2019 8:01 AM
To: Hartogensis, Martine; Forfa, Tracey; Hodges, April; McCoig, Amber
Subject: Please confirm- Firm Contacts by CVM

Martine,

I wanted to confirm what I heard yesterday.

(b) (5)

(b) (5)

Thank you,

Dave

David Rotstein, DVM, MPVM, Dipl. ACVP
CVM Vet-LIRN Liaison
CVM OSC/DC/CERT
7519 Standish Place
(b) (6) (BB)



This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution, or copying is strictly prohibited. If you think you received this e-mail message in error, please e-mail the sender immediately at david.rotstein@fda.hhs.gov.

From: [Medical Records](#)
To: [Jones, Jennifer L](#)
Subject: (b) (6) records
Date: Friday, April 20, 2018 5:18:44 PM
Attachments: (b) (6) [records.pdf](#)

See Attached

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
4/12/2018	C	(b) (6)	MEDICAL COMMENTS ***ADDENDUM 4/20/2018 4/12/2018 13:26 FDA Safety Reporting Portal - Individual Case Safety Report Number (ICSR) 2045676 ADDENDUM on 4/20/2018 at 08:34:23 from (b) (6), BVSc, MRCVS, ACVIM permission signed and returned to (b) (6)
3/24/2018	P	(b) (6)	1.00 [None] of Postage (UPS) -1 Lb (POSTA) Rx #: 2863492 0 Of 0 Refills ***SHIP ONLINE ORDERS UPS ONLY!!!*** Lasix
3/24/2018	C	(b) (6)	PHARMACY NOTE TTO. Meds have been refilled
3/24/2018	P	(b) (6)	100.00 tablet of Lasix (Salix / Furosemide) 50mg Tablet (M569) Rx #: 2852561 1 Of 12 Refills Filled by: (b) (6) 1 1/2 TABLETS BY MOUTH TWO TIMES A DAY
3/22/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/22/2018 13:03 dog is restless at night, making breathing sound, but sRR is consistently at 22 bpm, so i do not think do has pulmonary edema, will try melatonin, recheck in end of april Hey His Melatonin dose is 4 or 5 mg once to three times a day. Depending on size tablet you get, a 4 mg tablet or a 5 mg tablet, then start by giving 1 tablet once day, 30 minutes before bed (b) (6)

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

(b) (6)

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
3/13/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/13/2018 10:36 SWO - Owner consented to reporting (b) (6) case to the FDA. He has been on the Zignature Kangaroo for the past 2-3 years. Treats include Milkbones and baked dog treats from pet bakery. Prior to the Zignature Kangaroo, he consumed the Acana Ranch Lamb, Natural Balance Sweet Potato and Bison, Natural Balance Sweet Potato and Fish, Zignature Trout & Salmon. He was receiving no supplements prior to his DCM diagnosis. Owner will forward me a copy of her most recent Chewy.com receipt for the Zignature. She does not have the bag anymore. I will email her for additional information. She is now feeding the Royal Canin Kangaroo and Oats.
3/1/2018	D	(b) (6)	Taurine Deficiency Final
3/1/2018	C	(b) (6)	COMMUNICATIONS WITH DOCTOR 3/1/2018 13:22 i called vet, to let them know taurine is low, she is still on kangaroo diet from Zignature, rec to change diet. The legumes in diet are most likely preventing methionine and cystine absorption, should switch to Royal Canin kangaroo and oats, i originally lm and he called back. he said he would call owner
3/1/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/1/2018 13:20 i called client to let her know taurine is low, she is still on kangaroo diet from Zignature, rec she talk to her vet at last appt, and she did to day at a recheck, and told her to wait. The legumes in diet are most likely preventing methionine and cystine absorption, should switch to Royal Canin kangaroo and oats, I will call her vet.
2/27/2018	C	(b) (6)	COMMUNICATIONS WITH CLIENT 2/27/2018 11:03 i called owner, dog is breathing better, eating fine, getting sRR 18-26, did have throat issues, does gagging, pred helped, increased pred again, continue as planned, waiting on taurine level. if normla will start enalapril
2/24/2018	L	(b) (6)	Miscellaneous results from (b) (6)

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
------	------	-------	---------

(East) Requisition ID: (b) (6) Posted Final
 Asc: (b) (6) Profile: Taurine RE: 16759 Taurine 119
 Normal Values (nmols/ml)
 Normal Range

Level			
Cat Plasma		60-120	Less than
40			
Whole Blood		300-600	Less than
200			
Dog Plasma		60-120	Less than
40			
Whole Blood		200-350	Less than
150			
TEST PERFORMED AT		(b) (4)	

2/23/2018	C	(b) (6)	PHARMACY NOTE Called (b) (6), spoke to (b) (6). Ordered Pimobendan 10 mg tiny tablets - 1 tablet two times a day, #100, 8 refills
-----------	---	---------	--

2/23/2018	D	(b) (6)	Pulmonary Edema Tentative
2/23/2018	D	(b) (6)	Taurine Deficiency Tentative Date Diagnosis made final: 03/01/18
2/23/2018	D	(b) (6)	Dilated Cardiomyopathy Tentative
2/23/2018	I	(b) (6)	Cardiology Discharge Instructions
			Dr (b) (6)
			2/23/2018

A cardiologist has evaluated (b) (6) and has diagnosed her with Dilated Cardiomyopathy (DCM). DCM means your pet has poor muscle contraction of the heart. This means the heart muscle does not pump as well as a normal dog. The heart has enlarged due to the poor muscle contraction. The change in the heart has caused fluid to form in the lungs, causing increased respiratory rate.

Please take a sleeping respiratory rate rate (sRR) at home. WHILE YOUR PET IS SLEEPING, count the number of times they breathe in over 15 seconds. Your pet should have 8 breathes or less over 15 seconds while sleeping. Do this once a day over the next 3 days, then 2 times a week thereafter.
 The free app software for iPhone and Google Play that can help with this is Cardalis

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.		
	(b) (6)	Color:	Blonde		

Date	Type	Staff	History
			<p>I have submitted blood for a taurine level. The result may not return for 2 weeks. In the mean time, please start Taurine at home, 2 gram two times a day with food. This can be purchased at any health food store. I will call in about 2 weeks with a taurine level.</p> <p>MEDICATIONS:</p> <p>Furosemide 50 mg tablets 1 1/2 tablet two times a day Furosemide: Also called Salix or Lasix. This is a diuretic and will help clear the fluid from your pet's lungs. Your pet may drink more on this medication. Side effects include electrolyte abnormalities (if they stop eating), dehydration and kidney enzyme elevations. The blood work can be done to monitor these. This medication will be probably given for the life of your pet. YOU CAN GET REFILLS OF THIS MEDICATION FROM YOUR VETERINARIAN OR HERE. THIS SIZE TABLET IS NOT AVAILABLE IN HUMAN PHARMACIES.</p> <p>Pimobendan ((b) (6)) 10 mg tiny tablets - 1 tablet two times a day Pimobendan is a phosphodiesterase inhibitor that gives increased contractility and arterial vasodilation. This will help the heart function better, allow you dog to feel better and live longer. Any medication can upset the stomach. This drug does not typically cause this, but if you see any changes, please stop the drug till you talk to a doctor here at (b) (6). PLEASE GIVE THIS MEDICATION WITH (b) (6) MEALS. Even though package insert recommends giving on empty stomach, we have adjusted the dose so that you can give with meals. Giving on empty stomach is more likely to make your pet nauseous. We will script this drug through (b) (6) Please call them in 4-5 days to order it, once we see that your dog will tolerate the drug.</p> <p>Watch for the following clinical signs and call a veterinarian if you see any of these: Excessive panting or wheezing Restlessness, unable to get comfortable Decreased appetite Lethargy/weakness, less interactive or hiding Collapse or fainting Sudden rear leg or front leg lameness Open-mouth breathing</p> <p>It has been a pleasure meeting you and caring for your (b) (6) Thank you for entrusting us with her care. If you have any further questions or problems, don't hesitate to call.</p> <p>(b) (6)</p> <p>(b) (6)</p>
2/23/2018	P	(b) (6)	30.00 tablet of Pimobendan 10mg tiny tab (cpd) (MMP0T8) Rx #: 2852563 0 Of 10 Refills

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	
Phone:	(b) (6)	Species:	Canine	Breed: Retriever, Golden
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.	Sex: Neutered Male
	(b) (6)	Color:	Blonde	

Date	Type	Staff	History
2/23/2018	P	(b) (6)	1 TABLET BY MOUTH TWO TIMES A DAY 100.00 tablet of Lasix (Salix / Furosemide) 50mg Tablet (M569) Rx #: 2852561 0 Of 12 Refills 1 1/2 TABLETS BY MOUTH TWO TIMES A DAY
2/23/2018	C	(b) (6)	CARDIAC EVALUTION - CLOSED 02/24/2018 - Cardiac Evaluation

Date of evaluation: Friday, February 23, 2018

CHIEF COMPLAINT: tachypnea

HISTORY: last 3 days has been working hard to breath. No coughing. Appetite has been poor last 2 days, usually ravenous. Energy level seems down. No cardiac medications On 1/2 10 mg pred EOD for over year, Tried thyroid medication but stopped it, did not help. Has long history of panting and swallowing disorder.

PHYSICAL EXAM: BAR. HR = 120, regular rhythm, no murmur, gallop noted, pulses normal and synchronous. Mild tachypnea but panting, when rests lying down, still tachypnea. Normal bronchovesicular sounds bilaterally, no crackles or wheezes ausculted. BCS 5/9 PCS 0/4

ECHOCARDIOGRAM 2/23/18: BW 40 kg BSA 1.14

IVSd: 10 mm LVIDd: 64 mm LVPWd: 9 mm EPSS 21 mm
IVSs: 14 mm LVIDs: 52 mm LVPWs: 11 mm %FS: 19 % Pa: 21 mm
Ao: 24 mm LAD: 43 mm LA:Ao ratio 1.79 LA max: 48 mm LLAD: 56 mm
RWT = IVSd+LVPWd/LVIDd = 0.30, LVID long 90 mm, Sphericity index 1.41 (Lax/Sax,<1.65=increased sphericity).
Norm LA:Ao < 1.7, Normal LLAD < 42.93 mm, LVIDdn = 2.16 (N<1.73), LIVDsn = 1.63 (N<1.4)
MV E vel: 132, MV Dec T:89, MV A vel: 67, IVRT:71 ms, E:A 1.97 (N 1-2)E:IVRT 1.86 (N<2.5) Ea 10 E:Ea 13.2 (N<14.5)
Pa distensibility (mm): 11.7 - 5 = 57 %, PEP/ET = 96/170 = 0.56, > 0.4 is abnormal, with myocardial failure
Tricuspid peak flow velocity 3.2 m/s, gradient 41 mmHg, acceleration time 88 ms, PAET 177 ms, ratio = 0.50
(ratio greater than 0.30 is considered normal)
100% spec for PH if AT< 45 ms +/-or AT:ET < 0.25, 100% spec for Normal if AT>64 ms +/-or AT:ET > 0.42
Grey zone for predicting: AT <58 ms (Se 88%, Sp 80%), AT:ET < 0.31 (Se 73% and Sp 87%)

COMMENTS: dilated LV with poor systolic function. Left atrial enlargement. Large EPSS. Moderate MR and TR. Reduce aortic and pulmonic flows. no pleural or pericardial effusion

DIAGNOSIS/PROBLEM LIST: dilated cardiomyopathy (DCM), left side congestive heart failure (LCHF)

SUMMARY: The dilated cardiomyopathy may be related to diet and taurine deficiency. There have been personal communications amongst cardiologist of a rash of cases of Golden Retrievers on grain free and/or kangaroo diets that have taurine deficiency cardiomyopathy. We pulled a whole blood level taurine today and started 2 grams of taurine BID. I also started furosemide and pimobendan as below. If taurine deficiency

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	
Phone:	(b) (6)	Species:	Canine	Breed: Retriever, Golden
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.	Sex: Neutered Male
	(b) (6)	Color:	Blonde	

Date	Type	Staff	History
------	------	-------	---------

cardiomyopathy, this could be reversible. It could take 2 months to see echo changes, but dog may feel better within a month. Recheck echocardiogram in 2 months. We should recheck a taurine level in 2 weeks. They will most likely do that with (b) (6).

MEDICATIONS:

Furosemide 50 mg tablets 1 1/2 tablet two times a day

Pimobendan ((b) (6)) 10 mg tiny tablets - 1 tablet two times a day

Taurine at home, 2 grams two times a day with food.

2/23/2018	V	(b) (6)	Feb 23, 2018 01:06 PM Staff: (b) (6) ----- Weight : 40.00 kilograms room 14
2/23/2018	CK	(b) (6)	CHF poss, setup by rdvm Reason for Visit: Consult Date Patient Checked Out: 02/23/18 Practice TF
2/23/2018	CB	(b) (6)	Callback - Call Client Back (CB) ---- Note from (b) (6) on 2/23/2018 at 15:51:32 ---- Called (b) (6), spoke to (b) (6). ---- Note from (b) (6), BVSc, MRCVS, ACVIM on 2/23/2018 at 15:06:34 ---- Pimobendan ((b) (6)) 10 mg tiny tablets - 1 tablet two times a day, #100, 8 refills

2/22/2018	TC	(b) (6)	RECORDS FROM RDVM/LDVM (see attachment) - TENTATIVE 2/22/2018 14:47 rDVM records attached. - Attachment(s)
-----------	----	---------	---

3/10/2017	C	(b) (6)	COMMUNICATIONS WITH CLIENT 3/10/2017 10:26 updated owner regarding (b) (6) - recommending trial of soloxine. can be low from pred. but worth a try. can consider fluoro study in future. called into rdvm thyrotab 0.8 mg bid ; recheck t4 4 hours post pill in a month
-----------	---	---------	---

3/8/2017	L	(b) (6)	Endocrinology results from (b) (6) (b) (6) Requisition ID: (b) (6) Posted Final
----------	---	---------	--

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.		
	(b) (6)	Color:	Blonde		

Date	Type	Staff	History
------	------	-------	---------

Test	Result	Reference Range
TSH	<0.03 ng/mL	0 - 0.60
Asc n:	(b) (6)	Profile: TSH

3/7/2017 C (b) (6) RADIOLOGY REVIEW - CLOSED 03/08/2017
The right lateral views of the neck and thorax obtained today have been reviewed.
There are no significant abnormalities in the extra-thoracic soft tissues, visible skeletal structures, pleural space, pulmonary parenchyma and vessels, cardiovascular structures, mediastinum, and cranial abdomen.
An endoscopic evaluation may be considered for further investigation of the previously diagnosed arytenoid nodule.

This review was written by: (b) (6), DVM, DACVR, DACVS

3/7/2017 V (b) (6) Mar 7, 2017 04:21 PM Staff: (b) (6)

Weight : 41.40 kilograms

3/7/2017 CK (b) (6) recheck for (b) (6)
Reason for Visit: Recheck
Date Patient Checked Out: 03/07/17 Practice TF

3/7/2017 C (b) (6) IM PHYSICAL EXAM NEW
3/7/2017 10:10

Chief Complaint: reevaluation of hard swallowing; upper airway noise

History: (b) (6) was originally evaluated in 2015 for hard swallowing, gagging. A laryngeal exam at that time revealed a nodule on the larynx which was biopsied as granulomatous. He has been on low dose prednisone since. Owner still notices hard swallowing and sometimes regurgitation. He also has upper airway noise when sleeping- breathes through nose and no nasal discharge. Occasional hoarse bark. No diarrhea, no pu/pd. He has gained weight. In 2015 a myasthenia titer was negative. Diet includes zignature kangaroo. unsure of current dose of pred 1 tab in morning and sometimes 1/2 tab at night unsure what strength

Previous Medical Problems:

(b) (6)

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.		
	(b) (6)	Color:	Blonde		

Date	Type	Staff	History
------	------	-------	---------

Medications/Supplements:

Current Diet:

- Frequency:

- Amount:

Subjective:

Mentation: Quiet, Alert, Responsive

Objective Findings

Temperature: 101.8 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec.

Hydration Status: normal

Pain Score: /4

Weight: 41.4 kilograms

Body Condition Score/Muscle Score: 8/9/

Oropharyngeal: Normal

Eyes/Ears: fundic normal

Integument: Normal

Peripheral Lymph Nodes: Normal size

Cardiovascular/Respiratory: heart ausculted normal; lungs clear; occasionally hard swallowing in the room

Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful.

Urogenital: Normal

Musculoskeletal/neurologic: normal ambulation; weak gag; hard swallowing during exam

Rectal: Normal

Diagnostics:

Lab Work: see below

Radiographic Findings: Thoracic radiograph unremarkable- no megaesophageous, lateral laryngeal radiograph normal

Other Diagnostics:

Problems/Differential Diagnoses/Assessment:

Hard swallowing- rule out esophageal motility disorder, laryngeal / pharyngeal dysfunction , other types of neuromuscular condition; Low T4 consider secondary to chronic pred, hypothyroidism. Can consider trial of soloxine and recheck after a month. Other diagnostics to consider would be a fluoroscopy study of (b) (6) swallowing.

Treatment:

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

Plan/Recommendations:

3/7/2017 L	Hematology results from (b) (6) Requisition
ID: (b) (6)	Posted Final
Test	Result Reference Range
HCT	45 % 36 - 60
HGB	14.9 g/dL 12.1 - 20.3
MCHC	33 g/dL 30 - 38
WBC	19.6 10 ³ /uL H 4.0 - 15.5
Bands	0 % 0 - 3
RBC	6.1 10 ⁶ /uL 4.8 - 9.3
MCV	73 fL 58 - 79
MCH	24.3 pg 19 - 28
ABS BASO	0 /uL 0 - 150
Platelet C	128 10 ³ /uL L 170 - 400
Platelet E	ADEQUATE
Neutrophil	91 % H 60 - 77
Lymphocyte	6 % L 12 - 30
Monocytes	3 % 3 - 10
Eosinophil	0 % L 2 - 10
Basophils	0 % 0 - 1
Absolute N	17836 /uL H 2060 - 10600
Absolute L	1176 /uL 690 - 4500
Absolute M	588 /uL 0 - 840
Absolute E	0 /uL 0 - 1200
Ascن:	(b) (6) Profile: Complete Blood Count

Platelet count reflects the minimum number due to platelet clumping.

3/7/2017 L	Chemistry results from (b) (6) Requisition
ID: (b) (6)	Posted Final
Test	Result Reference Range
ALB	3.8 g/dL 2.7 - 4.4
ALKP	48 IU/L 5 - 131
ALT	33 IU/L 12 - 118
AMYL	461 IU/L 290 - 1125
AST	15 IU/L 15 - 66
BUN/UREA	19 mg/dL 6 - 31
Ca	10.0 mg/dL 8.9 - 11.4
Chloride	109 mEq/L 102 - 120
CHOL	209 mg/dL 92 - 324
CK	67 IU/L 59 - 895
CREA	0.2 mg/dL L 0.5 - 1.6
GGT	2 IU/L 1 - 12

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

GLU	72 mg/dL	70 - 138
Mg	1.9 mEq/L	1.5 - 2.5
PHOS	4.6 mg/dL	2.5 - 6.0
Potassium	4.5 mEq/L	3.6 - 5.5
Sodium	148 mEq/L	139 - 154
TBIL	0.2 mg/dL	0.1 - 0.3
TP	6.6 g/dL	5.0 - 7.4
TRIG	32 mg/dL	29 - 291
GLOB	2.8 g/dL	1.6 - 3.6
A/G Ratio	1.4	0.8 - 2.0
B/C Ratio	95 H	4 - 27
Na/K Ratio	33	27 - 38

3/7/2017 L

Endocrinology results from (b) (6)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Test Result Reference Range
 T4 0.6 ug/dL L 0.8 - 3.5
 Asc: (b) (6) Profile: Total T4

The Total T4 result is less than 1.0 mcg/dl. A Free-T4 by equilibrium dialysis may be helpful in supporting the diagnosis of hypothyroidism in patients demonstrating clinical signs compatible with hypothyroidism. Please contact Customer Service for this additional testing.

3/7/2017 L

Miscellaneous results from (b) (6)
 (East) Requisition ID: (b) (6) Posted Final
 Asc: (b) (6) Profile: Superchem
 RE: 1045 PrecisionP 50 U/L 24 - 140
 Pancreatitis is unlikely, but a normal PrecisionPSL result does not completely exclude pancreatitis as a cause for gastrointestinal signs.
 RE: 11067 Comment
 Hemolysis 1+ No significant interference.

3/6/2017 C

(b) (6) COMMUNICATIONS WITH CLIENT
 3/6/2017 12:55
 (b) (6) confirmed appt w/ gr @ 330 on 3/7
 (6)

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
2/26/2017	C	(b) (6)	COMMUNICATIONS WITH CLIENT 2/26/2017 10:15 (b) (6) to confirm 3:30 pm (b) (6) appt tomorrow
2/23/2017	TC	(b) (6)	RECORDS FROM RDVM/LDVM (see attachment) - TENTATIVE 2/23/2017 20:36 Records from (b) (6) - Attachment(s)
2/23/2017	C	(b) (6)	COMMUNICATIONS WITH DOCTOR 2/23/2017 17:18 SW (b) (6) of (b) (6) to request updated records from 5/3/15 forward be faxed
2/20/2016	C	(b) (6)	RECEPTION ACTIONS NOTE faxed ref letters and labs to (b) (6) per o's req
9/28/2015	C	(b) (6)	OUTSIDE PHARMACY RX ***ADDENDUM 10/2/2015 - Closed Sep 30/2015 Rx #: 0172 Prescribing doctor: (b) (6) Pharmacy prescription called in to: (b) (6) Pharmacy Phone #: (b) (6) Pharmacy Fax #: (b) (6) Medication: Doxycycline 100mg Quantity and Unit of Measure: #56 # of Refills: none Rx Instructions: 2t po q12h Is this medication a controlled substance?

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates,
 I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended,
 R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 11 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
			Additional Comments: faxed ADDENDUM on 10/1/2015 at 21:11:18 from (b) (6) Re-faxed as per request of (b) (6). ADDENDUM on 10/2/2015 at 11:27:39 from (b) (6) they only have 200mg tablets ADDENDUM on 10/2/2015 at 13:26:23 from (b) (6) Owner said (b) (6) charged more than Target, refaxing script to Target fax # (b) (6).
9/28/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 9/28/2015 13:29 (b) (6) was good for 2 months, then small flair up, then went away again for a few months. last time, we discussed repeat abx treat may not be helpful. discussed that we can repeat abx treatment as it worked for such a long period of time. discussed dual treatment for bartonella vs considering doxycycline and niacinamide. will try doxy/niacinamide and recheck 2 wks. will rx doxy to local rdvm, niacinamide 500 mg PO q 8 hr to get at local health store (OTC)
6/1/2015	C	(b) (6)	OUTSIDE PHARMACY RX - Closed Jun 04/2015 Rx #: PIYM90115000055 Prescribing doctor: (b) (6) Pharmacy prescription called in to: Target Pharmacy Pharmacy Phone #: (b) (6) Pharmacy Fax #: Medication: Doxycycline 100 mg Quantity and Unit of Measure: #60/ 100 mg # of Refills: 0 Rx Instructions: Give 2 tab PO q 12hr Is this medication a controlled substance? Yes No Additional Comments: Called into Target Pharmacy in (b) (6)

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.		
	(b) (6)	Color:	Blonde		

Date	Type	Staff	History
6/1/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 6/1/2015 16:05 within the last 3 days stopped doing the neck movement/episodes that he was having. still sounds congested. when he barks there sounds like there is something in there. would continue abx for bartonella unless we are planning to rescope him. owner needs refill of doxycycline. will touch base in 1-2 wks.
5/17/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/17/2015 10:26 swo and asked how (b) (6) is doing, owner said she started ab's yesterday and so far he is doing well, owner will recheck in one week
5/15/2015	C	(b) (6)	OUTSIDE PHARMACY RX - Closed May 17/2015 Rx #: 0042 Prescribing doctor: (b) (6) Pharmacy prescription called in to: (b) (6) Pharmacy Phone #: n/a Pharmacy Fax #: (b) (6) Medication: Enrofloxacin 136mg Quantity and Unit of Measure: 45 # of Refills: 0 Rx Instructions: Give 1.5 tab (204mg) po q 24hr Is this medication a controlled substance? Additional Comments: Faxed to (b) (6)
5/15/2015	C	(b) (6)	OUTSIDE PHARMACY RX Rx #: 90115000043

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.		
	(b) (6)	Color:	Blonde		

Date	Type	Staff	History
------	------	-------	---------

Prescribing doctor: (b) (6)

Pharmacy prescription called in to: Target- (b) (6)

Pharmacy Phone #: (b) (6)

Pharmacy Fax #:

Medication: Doxycycline 100mg

Quantity and Unit of Measure: #60

of Refills: 0

Rx Instructions: Give 2 tab PO q12hr

Is this medication a controlled substance? No

Additional Comments:

5/15/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT ***ADDENDUM 5/15/2015 5/15/2015 16:27 SWO per (b) (6), cost of bartonella test is \$342 which is something she can do via tech appt. or if O would prefer (b) (6) is OK with treating with AB's w/o testing. O wanted to know how long the course of AB's would be- per (b) (6) it would be a 2-4 week course. O also wanted to know if there is a chance of needing another course of AB's after the initial 2-4wk course, per (b) (6) P would not go on another course of AB's at that point. O would like go to skip blood test due to cost and try treating with AB's first. Would like called into Target Pharmacy in (b) (6) ADDENDUM on 5/15/2015 at 18:45:06 from (b) (6) called O, there are two medications- one is only veterinary can call into (b) (6) animal hospital and the other can be called into target in (b) (6). O OK with this plan. Called doxy into target pharm and rx to be faxed to (b) (6) animal hospital.
-----------	---	---------	--

5/12/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/12/2015 14:50 called owner with results. granulomatous inflammation. can be infectious, inflammatory or immune mediated disease. discussed type of inflammation present, there is concern for possible infectious organism. discussed bartonella and that this can be difficult to diagnose. discussed triple blood draw and
-----------	---	---------	---

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 14 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.	Color:	Blonde
	(b) (6)				

Date	Type	Staff	History
------	------	-------	---------

performing PCR and serology. discussed infectious disease CE and the recommendations for testing for bartonella. will look into cost for tests and then take it from there. this may not be the cause for his signs. discussed whether inflammation causes dysfunction or dysfunction started first. may need steroids or doxepin. will be in touch with owner as soon as i can get pricing information. last night he had the worst night. couldn't lay down. panting like crazy.

5/12/2015 C

(b) (6)

IM TREATMENT NEW
5/12/2015

Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion

nodule on vocal fold with asymmetry of arytenoid function: granulomatous inflammation

consider infectious disease screening; however due to length of time this has been doing on this is considered less likely. Consider treatment with anti-inflammatory doses of prednisone for possible immune mediated vs sterile inflammation

if no improvement with either abx therapy, anti-inflammatory to possibly immunosuppressive steroid therapy, consider doxepin

Treatment: no treatment implemented today

Recommended Follow-up Care: looking into pricing for bartonella testing. will recheck/touch base with owner when this is available; may go to local rDVM for testing due to proximity

5/8/2015 L

Miscellaneous results from (b) (6)

(b) (6) Requisition ID: (b) (6) Posted Final
Ascn: (b) (6) Profile: Histopathology, Full Written
Report

RE: 7801 History:

Nodule on glottal opening. Episodes since he was 9 months old.

Episodes are described as extending his neck repeatedly and gagging/choking and swallowing. (b) (6) would swallow hard repeatedly and

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 15 of 30

Date: 4/20/2018 5:17
PM

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.	Color:	Blonde
	(b) (6)				

Date	Type	Staff	History
			<p>have continual lip licking with a stridorous noise when breathing. He licks the air. He will intermittently vomit, but not with every episode. He has been treated with sucralfate, Cerenia and Pepcid. The Cerenia seems to help, but does not completely resolve the signs.</p> <p>-</p> <p>Received: Multiple fragments - all processed. RE: 601 Biopsy DESCRIPTION/MICROSCOPIC FINDINGS/COMMENTS:</p> <p>Sections of fragments of an ulcerated inflammatory mass lesion affecting the glottal region are examined. This lesion is composed of collagen bundles and fibroblasts arranged haphazardly among moderate numbers of capillaries. There are moderate numbers of neutrophils in the stroma. There also is mild edema. No neoplasia or infectious organisms are seen.</p> <p>MICROSCOPIC FINDINGS: Chronic-active, proliferative and granulomatous, inflammation</p> <p>PROGNOSIS: Good</p> <p>COMMENT: No neoplasia or infectious organisms are seen. These proliferative inflammatory lesions are common. Most of these lesions develop secondary to ruptured ducts of submucosal glands but some are a reaction to a small penetrating foreign body. Excision usually is curative.</p> <p>PATHOLOGIST:</p> <p>PATHOLOGIST: (b) (6) DVM, PhD, DIPLOMATE ACVP email: (b) (6) .com, ph: (b) (6)</p>
5/7/2015	I	(b) (6)	For your pet's safety, he/she was intubated for the anesthetic. You may notice

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 16 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
5/7/2015	I	(b) (6)	<p>some coughing for the next couple of days. This is normal due to a small amount of irritation to the throat from the endotracheal tube. If the coughing seems excessive please contact our office.</p> <p>(b) received an anesthetic. Please keep him confined until full recovery. Restrict water intake to small amounts at a time for the next 12-24 hours. Restrict food intake to small amounts also; 1/3 of the normal ration this evening. Because the anesthetic can lower his body temperature, keep him where it is warm and dry. Today's oropharyngeal exam revealed a small white nodule, irregular on the left medial aspect, mid way up vocal fold. with suspected kissing lesion on the right aryepiglottic fold; Assymetry to the left and right arytenoid with seemingly inappropriate function of the left with collapse towards midline; both arytenoids were able to abduct when inspiring but were asymmetrical when this was occurring. edematous and swollen corniculate tubercle bilaterally; prominent tonsils which were erythematous and out of crytps</p> <p>- nodule on vocal fold with assymetry of arytenoid function: r/o: pharyngeal or laryngeal dysfunction secondary to inflammation, neurogenic or infiltrative</p>
5/7/2015	C	(b) (6)	<p>COMMUNICATIONS WITH CLIENT</p> <p>5/7/2015 14:10</p> <p>called owner post procedure. discussed scope findings. and discussed possible causes for findings. no treatment recommended until results available. okay to d/c at 5 pm.</p>
5/7/2015	C	(b) (6)	<p>ENDOSCOPIC EVALUATION</p> <p>Upper Gastrointestinal: oropharyngeal exam: small white nodule, irregular on the left medial aspect, mid way up vocal fold. with suspected kissing lesion on the right aryepiglottic fold; Assymetry to the left and right arytenoid with seemingly inappropriate function of the left with collapse towards midline; both arytenoids were able to abduct when inspiring but were asymmetrical when this was occurring. edematous and swollen corniculate tubercle bilaterally; prominent tonsils which were erythematous and out of crytps</p> <p>Lower Gastrointestinal:</p> <p>Bronchoscopy:</p> <p>Rhinascopy:</p> <p>Cystoscopy:</p>

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

(b) (6)

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
<p>Other:</p> <p>Biopsies: 3 biopsies obtained with minimal bleeding</p> <p>Culture/Sensitivity:</p> <p>Visual Inspection: suspected dysfunction of the left arytenoid with nodule present on the left vocal fold.</p> <p>Initial Recommendations: consider doxepin 100 mg PO q 12 hr pending biopsy results.</p>			
5/7/2015	C	(b) (6)	<p>IM TREATMENT NEW 5/7/2015</p> <p>Internal Medicine Assessment (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion</p> <p>nodule on vocal fold with assymetry of arytenoid function: r/o: pharyngeal or laryngeal dysfunction secondary to inflammation, neurogenic or infiltrative</p> <p>Treatment: no treatment today</p> <p>Recommended Follow-up Care: pending biopsies consider doxepin 100 mg PO q 12 hr</p>
5/7/2015	C	(b) (6)	<p>IM PHYSICAL EXAM Chief Complaint:</p> <p>History: (b) (6) presented for endoscopic evaluation - prior hx: (6)</p> <p>(b) (6) is a 3 yo MN golden retriever presenting for further evaluation of episodes that he has been having since he was 9 months old. He was evaluated in May 2014 and lab work and u/s were performed but did not elucidate the cause of his episodes. He was additionally evaluated by (b) (6) and the owner was told the problem was likely neurological but may not be treatable. The owner says the episodes are becoming more frequent and lasting longer. The episodes are described as extending his neck repeatedly and gagging/choking and swallowing. The owner showed a video at the consult and this behavior was witnessed where (b) (6) would swallow hard (6)</p>

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.		
	(b) (6)	Color:	Blonde		

Date	Type	Staff	History
------	------	-------	---------

repeatedly and have continual lip licking with a stridorous noise when breathing. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is initiated by drinking and occurred in the exam room after drinking water. Eating is not as much of a trigger. He is eating dry food which the owner waters down. The owner has not tried canned food. She doesn't think that the episodes are related to consistency. He does not have episodes when active and out/about. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. On the evening of an episode he will snore when sleeping. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He is eating well. He seems to be acting normally otherwise. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.

Significant Physical Exam Findings: Mentation: BAR
Temperature: 102.4 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec.
Hydration Status: adequate
Weight: 36.6 kilograms
Body Condition Score: 7/9
Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum;
normal cervical palpation
Eyes/Ears: clear OU; fundic exam WNL OU; clean AU
Integument: full coat; no ectoparasites
Peripheral Lymph Nodes: Normal size
Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic
Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful.
Urogenital: neutered male; no prepuce d/c
Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed.

Lab Work: Chemistry: BUN: 11, Creat: 1.4 - NSF
CBC: HCT: 46.9%, WBC: 8.14, neut: 4.10, PLT: 57k

Radiographic Findings: CHIEF COMPLAINT/HISTORY: 5/3/2015. Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure.

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

FINDINGS: Three views of the thorax are available for review.

No significant abnormalities are present in the extra-thoracic soft tissues, skeletal structures, pleural and mediastinal spaces, pulmonary and cardiovascular structures, as well as in the visible cranial abdomen.

SUMMARY/CONCLUSIONS:

1. Normal thorax with no evidence of megaesophagus.

5/7/2015 L

Chemistry results from (b) (6)		In-clinic
Laboratory Requisition ID: (b) (6)		Posted
Test	Result	Reference Range
ALB =	3.2 g/dL	2.3 - 4.0
ALKP =	73 U/L	23 - 212
ALT =	31 U/L	10 - 125
AMYL =	744 U/L	500 - 1500
BUN/UREA =	11 mg/dL	7 - 27
Ca =	9.4 mg/dL	7.9 - 12.0
Chloride =	112 mmol/L	109 - 122
CHOL =	257 mg/dL	110 - 320
CREA =	1.4 mg/dL	0.5 - 1.8
GGT <	< 0 U/L	0 - 11
GLU =	97 mg/dL	74 - 143
LIPA =	1120 U/L	200 - 1800
PHOS =	4.0 mg/dL	2.5 - 6.8
Potassium =	4.7 mmol/L	3.5 - 5.8
Sodium =	153 mmol/L	144 - 160
TBIL =	0.3 mg/dL	0.0 - 0.9
TP =	6.0 g/dL	5.2 - 8.2
GLOB =	2.8 g/dL	2.5 - 4.5
ALB/GLOB =	1.1	
BUN/CREA =	8	
Na/K =	33	
OSM calc =	303 mmol/kg	

PCV=49% TS= 6.8g/dl (serum norm)

5/7/2015 V

(b) (6)

May 7, 2015 10:20 AM Staff: (b) (6)

Weight : 36.60 kilograms

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

Temperature : 102.4
 Pulse : 100
 Respiration : pant
 mm pk, crt <2s

5/7/2015 L

Hematology results from (b) (6) In-clinic
Laboratory Requisition ID: (b) (6) Posted Final

Test	Result	Reference Range
HCT =	46.9 %	37.3 - 61.7
HGB =	16.3 g/dL	13.1 - 20.5
MCHC =	34.8 g/dL	32.0 - 37.9
WBC =	8.14 K/uL	5.05 - 16.76
NEUT =	4.10 K/uL	2.95 - 11.64
%NEUT =	50.4 %	
EOS =	0.71 K/uL	0.06 - 1.23
%EOS =	8.7 %	
PLT *	* 57 K/uL L	148 - 484
Retics =	21.5 K/uL	10.0 - 110.0
%Retics =	0.3 %	
RBC =	6.94 M/uL	5.65 - 8.87
MCV =	67.6 fL	61.6 - 73.5
MCH =	23.5 pg	21.2 - 25.9
RDW =	18.1 %	13.6 - 21.7
MPV -	--.-- fL	8.7 - 13.2
PDW -	--.-- fL	9.1 - 19.4
PCT -	--.-- %	0.14 - 0.46
LYMPHS =	2.88 K/uL	1.05 - 5.10
%LYMPHS =	35.4 %	
MONOS =	0.43 K/uL	0.16 - 1.12
%MONOS =	5.3 %	
BASO =	0.02 K/uL	0.00 - 0.10
%BASO =	0.2 %	

5/7/2015 C FAC RADIOLOGY REPORT - FINAL 05/07/2015
 RADIOGRAPHIC REPORT

CHIEF COMPLAINT/HISTORY: 5/3/2015. Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure.

FINDINGS: Three views of the thorax are available for review.

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 21 of 30

Date: 4/20/2018 5:17
 PM

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
------	------	-------	---------

No significant abnormalities are present in the extra-thoracic soft tissues, skeletal structures, pleural and mediastinal spaces, pulmonary and cardiovascular structures, as well as in the visible cranial abdomen.

SUMMARY/CONCLUSIONS:

1. Normal thorax with no evidence of megaesophagus.

5/7/2015	CK	(b) (6)	Drop off for procedure w/ (b) (6) - CXR, chem III, CBC Reason for Visit: Medicine Procedure Date Patient Checked Out: 05/07/15 Practice TF
----------	----	---------	--

5/6/2015	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/6/2015 11:48 Spoke to O and confirmed (b) (6) procedure for tomorrow. Dropping off between 9:30 -10am. Told O no food after midnight and no water after 6am tomorrow. O knows she will not speak to (b) (6) at drop off. She thanked me for calling.
----------	---	---------	---

5/3/2015	C	(b) (6)	IM TREATMENT NEW 5/3/2015 Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, epiglottal entrapment, epiglottal retroversion, primary GI disease unlikely, neuro disease -functional problem vs focal seizure recommend further evaluation including thoracic radiographs, sedated oral exam and endoscopy +/- fluoroscopy and esophagram. Treatment: no treatment implemented Recommended Follow-up Care: to return Thursday for further evaluation - chemistry, CBC thoracic radiographs, oral exam and endoscopy
----------	---	---------	--

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	
Phone:	(b) (6)	Species:	Canine	Breed: Retriever, Golden
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.	Sex: Neutered Male
	(b) (6)	Color:	Blonde	

Date	Type	Staff	History
5/3/2015	C	(b) (6)	<p>IM PHYSICAL EXAM</p> <p>Chief Complaint:</p> <p>History: (b) (6) is a 3 yo MN golden retriever presenting for further evaluation of episodes that he has been having since he was 9 months old. He was evaluated in May 2014 and lab work and u/s were performed but did not elucidate the cause of his episodes. He was additionally evaluated by (b) (6) and the owner was told the problem was likely neurological but may not be treatable. The owner says the episodes are becoming more frequent and lasting longer. The episodes are described as extending his neck repeatedly and gagging/choking and swallowing. The owner showed a video at the consult and this behavior was witnessed where (b) (6) would swallow hard repeatedly and have continual lip licking with a stridorous noise when breathing. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is initiated by drinking and occurred in the exam room after drinking water. Eating is not as much of a trigger. He is eating dry food which the owner waters down. The owner has not tried canned food. She doesn't think that the episodes are related to consistency. He does not have episodes when active and out/about. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. On the evening of an episode he will snore when sleeping. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He is eating well. He seems to be acting normally otherwise. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.</p> <p>Significant Physical Exam Findings: Mentation: BAR Temperature: 101.7 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec. Hydration Status: adequate Weight: 36.7 kilograms Body Condition Score: 7.9 Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum; normal cervical palpation Eyes/Ears: clear OU; fundic exam WNL OU; clean AU Integument: full coat; no ectoparasites Peripheral Lymph Nodes: Normal size Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic</p>

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6) Phone: (b) (6) Address: (b) (6) (b) (6)	Patient: (b) (6) Species: Canine Age: 6 Yrs. 2 Mos. Color: Blonde	Breed: Retriever, Golden Sex: Neutered Male
---	--	--

Date	Type	Staff	History
			Abdominal Palpation: There was no obvious mass or organomegaly, and the abdomen was non-painful. Urogenital: neutered male; no prepuce d/c Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed. Lab Work: none performed today Radiographic Findings: none performed today
5/3/2015	CK	(b) (6)	Reason for Visit: Recheck Date Patient Checked Out: 05/03/15 Practice TF
11/21/2014	C	(b) (6)	COMMUNICATIONS WITH CLIENT 11/21/2014 13:54 SWO - Myasthenia gravis test was negative, and so the next step for (b) (6) would be an esophageal scope to determine the cause for his clinical signs. Owner thankful, will call and schedule with (b) (4) after thanksgiving.
11/14/2014	CK	(b) (6)	swallowing issues Reason for Visit: Consult Date Patient Checked Out: 11/14/14 Practice TF
5/31/2014	C	(b) (6)	IM TREATMENT NEW 5/31/2014 Internal Medicine Assessment (b) (6) is a 2 yo MN golden retriever with usual episodes of swallowing and what appears to be "air sucking" behavior. ddx include laryngeal, pharyngeal disease, esophageal disease, primary GI disease, neuro disease -functional problem vs focal seizure Chemistry - NSF CBC - NSF T4: WNL No evidence of endocrine or metabolic disease based on screening labs.

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

Treatment: no treatment implemented at this time

Recommended Follow-up Care: recheck after owner discusses steps with insurance company - to consider chest radiographs, neuro consult, sedated oral exam and endoscopy

5/31/2014	C	(b) (6)	<p>COMMUNICATIONS WITH CLIENT</p> <p>5/31/2014 11:29</p> <p>Spoke with owner and relayed that blood results are all normal. owner would like to speak with insurance prior to scheduling appt. next steps could be to get neuro consult, sedated oral exam and endoscopy</p>
-----------	---	---------	--

5/31/2014	L		<p>Hematology results from (b) (6) Requisition</p> <table border="1"> <thead> <tr> <th>ID:</th> <th>(b) (6)</th> <th>Posted</th> <th>Final</th> <th></th> </tr> </thead> <tbody> <tr> <td>Test</td> <td></td> <td>Result</td> <td></td> <td>Reference Range</td> </tr> <tr> <td>HCT</td> <td></td> <td>46 %</td> <td></td> <td>36 - 60</td> </tr> <tr> <td>HGB</td> <td></td> <td>15.9 g/dL</td> <td></td> <td>12.1 - 20.3</td> </tr> <tr> <td>MCHC</td> <td></td> <td>34.6 g/dL</td> <td></td> <td>30 - 38</td> </tr> <tr> <td>WBC</td> <td></td> <td>8.1 10³/uL</td> <td></td> <td>4.0 - 15.5</td> </tr> <tr> <td>Bands</td> <td></td> <td>0 %</td> <td></td> <td>0 - 3</td> </tr> <tr> <td>RBC</td> <td></td> <td>6.3 10⁶/uL</td> <td></td> <td>4.8 - 9.3</td> </tr> <tr> <td>MCV</td> <td></td> <td>73 fL</td> <td></td> <td>58 - 79</td> </tr> <tr> <td>MCH</td> <td></td> <td>25.2 pg</td> <td></td> <td>19 - 28</td> </tr> <tr> <td>Platelet C</td> <td></td> <td>158 10³/uL L</td> <td></td> <td>170 - 400</td> </tr> <tr> <td>Platelet E</td> <td></td> <td>ADEQUATE</td> <td></td> <td>ADEQUATE -</td> </tr> <tr> <td>Neutrophil</td> <td></td> <td>49 % L</td> <td></td> <td>60 - 77</td> </tr> <tr> <td>Lymphocyte</td> <td></td> <td>46 % H</td> <td></td> <td>12 - 30</td> </tr> <tr> <td>Monocytes</td> <td></td> <td>4 %</td> <td></td> <td>3 - 10</td> </tr> <tr> <td>Eosinophil</td> <td></td> <td>1 % L</td> <td></td> <td>2 - 10</td> </tr> <tr> <td>Basophils</td> <td></td> <td>0 %</td> <td></td> <td>0 - 1</td> </tr> <tr> <td>Absolute N</td> <td></td> <td>3969 /uL</td> <td></td> <td>2060 - 10600</td> </tr> <tr> <td>Absolute B</td> <td></td> <td>0 /uL</td> <td></td> <td>0 - 150</td> </tr> <tr> <td>Absolute L</td> <td></td> <td>3726 /uL</td> <td></td> <td>690 - 4500</td> </tr> <tr> <td>Absolute M</td> <td></td> <td>324 /uL</td> <td></td> <td>0 - 840</td> </tr> <tr> <td>Absolute E</td> <td></td> <td>81 /uL</td> <td></td> <td>0 - 1200</td> </tr> </tbody> </table> <p>Ascn: (b) (6) Profile: CBC</p> <p>Platelet count reflects the minimum number due to platelet clumping.</p>	ID:	(b) (6)	Posted	Final		Test		Result		Reference Range	HCT		46 %		36 - 60	HGB		15.9 g/dL		12.1 - 20.3	MCHC		34.6 g/dL		30 - 38	WBC		8.1 10 ³ /uL		4.0 - 15.5	Bands		0 %		0 - 3	RBC		6.3 10 ⁶ /uL		4.8 - 9.3	MCV		73 fL		58 - 79	MCH		25.2 pg		19 - 28	Platelet C		158 10 ³ /uL L		170 - 400	Platelet E		ADEQUATE		ADEQUATE -	Neutrophil		49 % L		60 - 77	Lymphocyte		46 % H		12 - 30	Monocytes		4 %		3 - 10	Eosinophil		1 % L		2 - 10	Basophils		0 %		0 - 1	Absolute N		3969 /uL		2060 - 10600	Absolute B		0 /uL		0 - 150	Absolute L		3726 /uL		690 - 4500	Absolute M		324 /uL		0 - 840	Absolute E		81 /uL		0 - 1200
ID:	(b) (6)	Posted	Final																																																																																																														
Test		Result		Reference Range																																																																																																													
HCT		46 %		36 - 60																																																																																																													
HGB		15.9 g/dL		12.1 - 20.3																																																																																																													
MCHC		34.6 g/dL		30 - 38																																																																																																													
WBC		8.1 10 ³ /uL		4.0 - 15.5																																																																																																													
Bands		0 %		0 - 3																																																																																																													
RBC		6.3 10 ⁶ /uL		4.8 - 9.3																																																																																																													
MCV		73 fL		58 - 79																																																																																																													
MCH		25.2 pg		19 - 28																																																																																																													
Platelet C		158 10 ³ /uL L		170 - 400																																																																																																													
Platelet E		ADEQUATE		ADEQUATE -																																																																																																													
Neutrophil		49 % L		60 - 77																																																																																																													
Lymphocyte		46 % H		12 - 30																																																																																																													
Monocytes		4 %		3 - 10																																																																																																													
Eosinophil		1 % L		2 - 10																																																																																																													
Basophils		0 %		0 - 1																																																																																																													
Absolute N		3969 /uL		2060 - 10600																																																																																																													
Absolute B		0 /uL		0 - 150																																																																																																													
Absolute L		3726 /uL		690 - 4500																																																																																																													
Absolute M		324 /uL		0 - 840																																																																																																													
Absolute E		81 /uL		0 - 1200																																																																																																													

5/31/2014	L		<p>Chemistry results from (b) (6) Requisition</p>
-----------	---	--	---

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

ID: (b) (6)	Posted	Final	
Test	Result		Reference Range
ALB	3.5 g/dL		2.7 - 4.4
ALKP	42 U/L		5 - 131
ALT	28 U/L		12 - 118
AMYL	515 U/L		290 - 1125
AST	20 U/L		15 - 66
BUN/UREA	14 mg/dL		6 - 31
Ca	11.1 mg/dL		8.9 - 11.4
Chloride	109 mEq/L		102 - 120
CHOL	298 mg/dL		92 - 324
CK	40 U/L L		59 - 895
CREA	1.2 mg/dL		0.5 - 1.6
GGT	6 U/L		1 - 12
GLU	91 mg/dL		70 - 138
LIPA	428 U/L		77 - 695
Mg	1.7 mEq/L		1.5 - 2.5
PHOS	4.0 mg/dL		2.5 - 6.0
Potassium	4.8 mEq/L		3.6 - 5.5
Sodium	145 mEq/L		139 - 154
TBIL	0.1 mg/dL		0.1 - 0.3
TP	5.9 g/dL		5.0 - 7.4
TRIG	113 mg/dL		29 - 291
GLOB	2.4 g/dL		1.6 - 3.6
A/G Ratio	1.5 Ratio		0.8 - 2.0
B/C Ratio	12 Ratio		4 - 27

5/31/2014 L Endocrinology results from (b) (6)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Test Result Reference Range
 T4 1.6 ug/dL 0.8 - 3.5
 Asc: (b) (6) Profile: Total T4

5/31/2014 L Miscellaneous results from (b) (6)
 (b) (6) Requisition ID: (b) (6) Posted Final
 Asc: (b) (6) Profile: Superchem
 RE: 1050 Na/K Ratio 30
 RE: 11067 Comment
 Hemolysis 1+. No significant analyte interference.

5/30/2014 C (b) (6) ULTRASOUND REPORT NEW

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History
------	------	-------	---------

Referring Vet: Hospital:

ULTRASONOGRAPHIC FINDING: # of
Films:
Written: 5/30/2014

Liver The liver appeared diffusely normal; the liver margins were smooth.
Gallbladder The gall bladder appeared normal-the visible biliary tree is not dilated.
Spleen The spleen appeared normal.
Right Kidney The right kidney had good corticomedullary distinction; Smooth capsule; there were no nephroliths and the renal pelvis was not dilated. The right kidney measured: 6.73 cm
Left Kidney The left kidney had good corticomedullary distinction, Smooth capsule; there were no nephroliths and the renal pelvis was not dilated. The left kidney measured: 6.55 cm
Urinary Bladder The urinary bladder appeared normal; no urolith or masses seen.
Right Adrenal The right adrenal was normal size and shape measuring: 0.45 cm
Left Adrenal The left adrenal was normal size and shape measuring: 0.54 cm
Stomach The stomach appeared normal and empty of ingesta
Small Intestines The small intestine appeared normal in layering and thickness measuring 0.51 - duodenum
Colon The colon appeared normal.
Pancreas The pancreatic region appeared normal.
Lymph Nodes There was no obvious mesenteric or sublumbar lymphadenopathy.
Prostate Appeared small and symmetrical for a neutered male.
Uterus
Testicles Not visualized - neutered.
Ovaries

Additional Comments: There was no free fluid noted. There were no overt abnormalities noted to explain patient's clinical signs.

5/30/2014	C	(b) (6)	IM TREATMENT NEW 5/30/2014
-----------	---	---------	-------------------------------

Internal Medicine Assessment: (b) (6) is a 2 yo MN golden retriever with usual episodes of swallowing and what appears to be "air sucking" behavior. ddx include

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 27 of 30

Date: 4/20/2018 5:17 PM

FDA-CVM-FOIA-2019-1704-001137

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	
Phone:	(b) (6)	Species:	Canine	Breed: Retriever, Golden
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.	Sex: Neutered Male
	(b) (6)	Color:	Blonde	

Date	Type	Staff	History
			<p>laryngeal, pharyngeal disease, esophageal disease, primary GI disease, neuro disease -functional problem vs focal seizure</p> <p>Treatment: no treatment implemented at this time</p> <p>Recommended Follow-up Care: pending lab results; consider fluroscopy, sedated oral exam and endoscopy with neuro exam prior.</p>

5/30/2014 C (b) (6) IM PHYSICAL EXAM NEW
5/30/2014 22:58

Presenting Complaint:

History: (b) (6) is a 2 yo MN golden retriever presenting for episodes that the owner describes as extending his neck repeatedly and gagging/choking. The owner initially thought he had a hard time breathing. He licks the air. These episodes can occur anytime of day or night. It is not associated with eating or drinking specifically but does occur after drinking. He seems to have episodes when lying down or the owner will wake up and he will be doing this behavior. When he has an episode, (b) (6) heads to the front door to go outside and eat grass. He will intermittently vomit but not with every episode. He has no diarrhea. He used to have diarrhea until his diet was switched to natural balance fish and sweet potato. He has been treated with sucralfate, cerenia and pepcid. The cerenia seems to help but doesn't completely resolve the signs. These episodes seemed to start when (b) (6) was 9 mo old and has been progressively more frequent. The last 1-2 weeks he's having daily signs. He has no travel history. He is currently not receiving any medication. He receives flea and tick prevention. He has no other medical problems reported.

Mentation: BAR

Temperature: 102 Pulse: 100 Respiration: panting MM: Pink/CRT < 1 sec.

Hydration Status: adequate

Weight: 37.3 kilograms

Body Condition Score: 7.9

Oropharyngeal: minimal dental disease; no lesions noted; normal nasal planum; normal thyroid palpation

Eyes/Ears: clear OU; fundic exam WNL OU; clean AU

Integument: full coat; no ectoparasites

Peripheral Lymph Nodes: Normal size

Cardiovascular/Respiratory: no murmur, no arrhythmia, ssp, normal bv sounds, eupneic

Abdominal Palpation: There was no obvious mass or organomegaly, and the

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

(b) (6)

Page 28 of 30

Date: 4/20/2018 5:17 PM

Patient History Report

Client: (b) (6)	Patient: (b) (6)	
Phone: (b) (6)	Species: Canine	Breed: Retriever, Golden
Address: (b) (6)	Age: 6 Yrs. 2 Mos.	Sex: Neutered Male
(b) (6)	Color: Blonde	

Date	Type	Staff	History																		
			abdomen was non-painful. Urogenital: neutered male; no prepuce d/c Musculoskeletal/neurologic: Normal ambulation 4; weak gag; remaining CN WNL; CP WNL; A complete neurologic and orthopedic exam was not performed. Rectal: Normal Lab Work: cbc, superchem, T4 pending to (b) (4) Radiographic Findings: none performed																		
5/30/2014	I	(b) (6)	(b) has unusual signs that appear to be a lot of swallowing air. At this time it is not clear why this is happening; however, our plans to further evaluate this include lab work to rule out metabolic abnormalities, GI malabsorption or thyroid problems. These tests are pending and I will call you when results are available. The next steps would include a neurology consultation, sedated oral exam followed by endoscopy to evaluate his clinical signs +/- chest radiographs.																		
5/30/2014	V	(b)	May 30, 2014 12:26 PM Staff: (b) ----- Weight : 37.30 kilograms																		
5/30/2014	V		May 30, 2014 12:26 PM -----																		
5/30/2014	CK	(b) (6)	Consult for possible scope Reason for Visit: Consult Date Patient Checked Out: 05/30/14 Practice TF																		
5/30/2014	L	(b) (6)	Chemistry results from (b) (6) Services Requisition <table><tr><td>ID: (b) (6)</td><td>Posted</td><td>Final</td></tr><tr><td>Test</td><td>Result</td><td>Reference Range</td></tr><tr><td>COBALAMIN</td><td>442 ng/L</td><td>284 - 836</td></tr><tr><td>FOLATE</td><td>6.9 ug/L</td><td>4.8 - 19.0</td></tr><tr><td>Asc: (b) (6)</td><td></td><td></td></tr><tr><td>SS</td><td>MN CANINE</td><td></td></tr></table>	ID: (b) (6)	Posted	Final	Test	Result	Reference Range	COBALAMIN	442 ng/L	284 - 836	FOLATE	6.9 ug/L	4.8 - 19.0	Asc: (b) (6)			SS	MN CANINE	
ID: (b) (6)	Posted	Final																			
Test	Result	Reference Range																			
COBALAMIN	442 ng/L	284 - 836																			
FOLATE	6.9 ug/L	4.8 - 19.0																			
Asc: (b) (6)																					
SS	MN CANINE																				
5/29/2014	C	(b) (6)	COMMUNICATIONS WITH CLIENT 5/29/2014 11:08 swo confirmed 5/30 apt at 1130																		

B: Billing, C: Med note, CB: Call back, CK: Check-in, CM: Communications, D: Diagnosis, DH: Declined to history, E: Examination, ES: Estimates, I: Departing instr, L: Lab result, M: Image cases, P: Prescription, PA: PVL Accepted, PB: problems, PP: PVL Performed, PR: PVL Recommended, R: Correspondence, T: Images, TC: Tentative medl note, V: Vital signs

Patient History Report

Client:	(b) (6)	Patient:	(b) (6)	Breed:	Retriever, Golden
Phone:	(b) (6)	Species:	Canine	Sex:	Neutered Male
Address:	(b) (6)	Age:	6 Yrs. 2 Mos.		
	(b) (6)	Color:	Blonde		

Date	Type	Staff	History
5/27/2014	C	(b) (6)	RECEPTION ACTIONS NOTE Receved fax from (b) (6). Placed in box under "(b) (6)"
5/27/2014	C	(b) (6)	RECEPTION ACTIONS NOTE ***ADDENDUM 5/27/2014 recv'd fax from (b) (6) and (b) (6) in black bx under (b) (6). ADDENDUM on 5/27/2014 at 12:49:24 from (b) (6) Recv'd fax from (b) (6). Placed in black box under (b) (6)

B:Billing, C:Med note, CB:Call back, CK:Check-in, CM:Communications, D:Diagnosis, DH:Declined to history, E:Examination, ES:Estimates, I:Departing instr, L:Lab result, M:Image cases, P:Prescription, PA:PVL Accepted, PB:problems, PP:PVL Performed, PR:PVL Recommended, R:Correspondence, T:Images, TC:Tentative medl note, V:Vital signs

From: [Jones, Jennifer L](#)
To: ["Freeman, Lisa"](#)
Subject: RE: as promised
Date: Wednesday, August 08, 2018 5:15:00 PM
Attachments: [image001.png](#)
[image003.png](#)

Thank you!

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421



From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Wednesday, August 08, 2018 4:43 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: as promised

Hi Jennifer

Below are the WSAVA guidelines and also my blog that expands on the quality control measures.

<https://www.wsava.org/WSAVA/media/Arpita-and-Emma-editorial/Selecting-the-Best-Food-for-your-Pet.pdf>

<http://vetnutrition.tufts.edu/2016/12/questions-you-should-be-asking-about-your-pets-food/>

Also, I think I sent the attached to you before but resending in case.

Thanks

Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

From: [Conway, Charlotte](#)
To: [Edwards, David](#)
Subject: FW: DCM Plan
Date: Tuesday, June 04, 2019 1:55:00 PM
Attachments: [DCM Project Plan.docx](#)

fyi

From: Forfa, Tracey
Sent: Tuesday, June 04, 2019 12:22 PM
To: Steinberg, Nadine <Nadine.Steinberg@fda.hhs.gov>; DeLancey, Siobhan <Siobhan.Delancey@fda.hhs.gov>; Norris, Anne <Anne.Norris@fda.hhs.gov>; Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Cc: Dewitt, Susan J <Susan.Dewitt@fda.hhs.gov>; Cepeda, Sandra <Sandra.Cepeda@fda.hhs.gov>; Murphy, Jeanette <Jenny.Murphy@fda.hhs.gov>; Conway, Charlotte <Charlotte.Conway@fda.hhs.gov>
Subject: DCM Plan

(b) (5)

Thank you!!!

DCM Plan

(b) (5)

(b) (5)

From: Cepeda, Sandra
To: Palmer, Lee Anne
Cc: Hartogensis, Martine
Subject: RE: Copy of DCM Complaint File - 4-24-2019.xls FOR REDACTION
Date: Thursday, April 25, 2019 9:44:10 AM
Attachments: [image001.png](#)
[image002.jpg](#)
[image003.jpg](#)
[image004.jpg](#)
[image005.jpg](#)
[image006.jpg](#)

Good morning Lee Anne – We'll start working on this.

I can convert it to PDF.

Thanks!
Sandra

From: Palmer, Lee Anne
Sent: Thursday, April 25, 2019 9:18 AM
To: Cepeda, Sandra <Sandra.Cepeda@fda.hhs.gov>
Cc: Hartogensis, Martine <Martine.Hartogensis@fda.hhs.gov>
Subject: Copy of DCM Complaint File - 4-24-2019.xls FOR REDACTION

Hi Sandra – the Center has request we prepare a file of DCM complaints for webposting (b) (5)

[REDACTED]
[REDACTED]. If not, just let me know what you prefer.

Thank you so much!

Lee Anne

Lee Anne M. Palmer, VMD, MPH
Team Leader HFV-242, Supervisory VMO

Center for Veterinary Medicine
OSC, Division of Veterinary Product Safety
U.S. Food and Drug Administration
Tel: 240-402-5767
Leeanne.palmer@fda.hhs.gov

