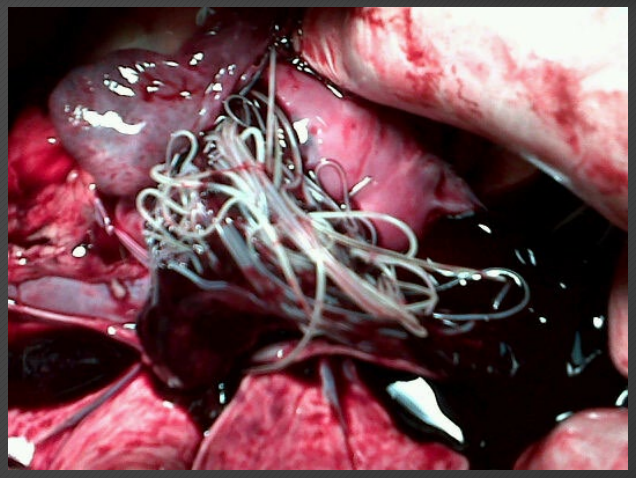
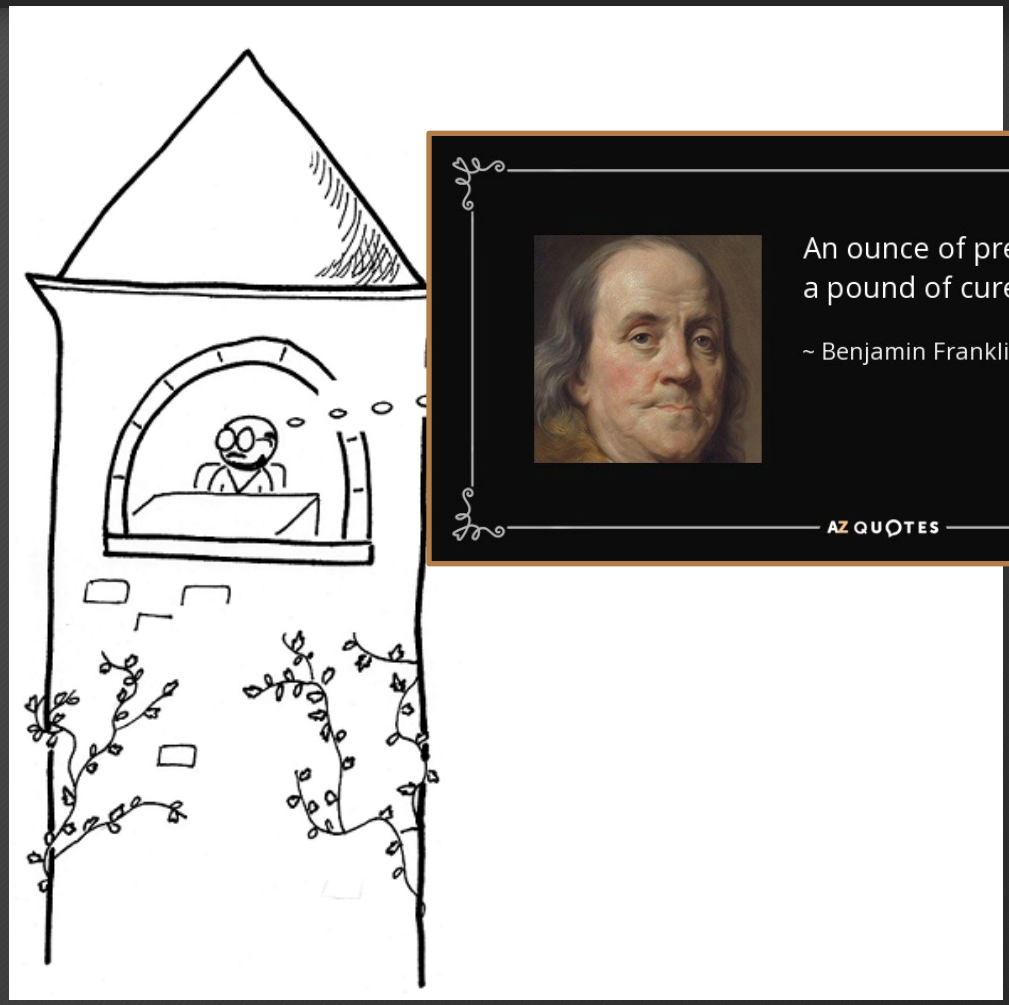
Heartworm: Biology through Prevention

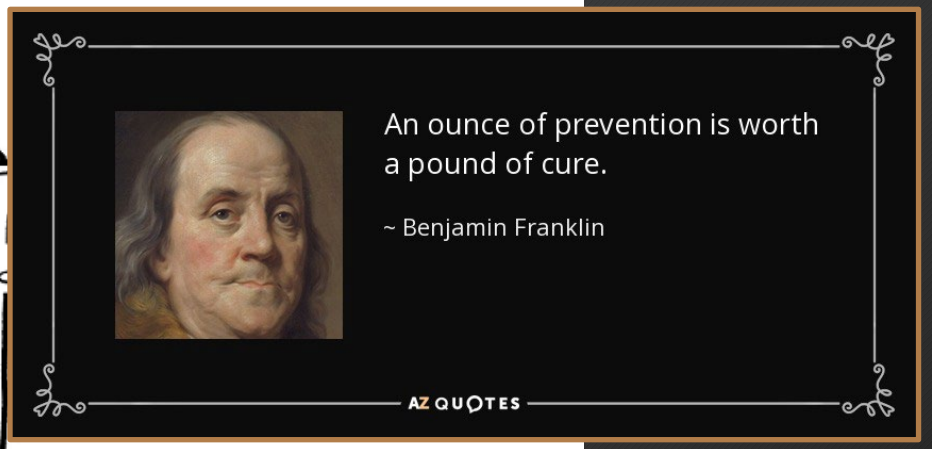


LEARNING OBJECTIVES

- Students will be able to explain the heartworm life cycle to both peers and clients
- Students will be able to describe the gross pathology associated with heartworm disease
- Students will be able to describe how heartworm is diagnosed
- Students will be able to discuss the drugs and treatment regimen for heartworm in dogs and cats

The Ivory Tower





OutLINe

- Prevalence-Dog/Cat
- Life Cycle-Dog/Cat
- Pathology-Dog/Cat
- Signs-Dog/Cat
- Diagnosis-Dog/Cat
- Treatment-Dog/Cat
- Prevention-Dog/Cat

Dirofilaria immitis Heartworm

- Hosts:
  - Dogs (canids), ferrets, CA sea lions
  - Cats (not as good a host as others listed)
- Probably the most important parasite of dogs
- Huge economic importance
  - $ Billions spent on prevention, diagnosis and treatment

WHO GETS HEARTWORMS?

AMERICAN HEARTWORM SOCIETY™ EST.1974

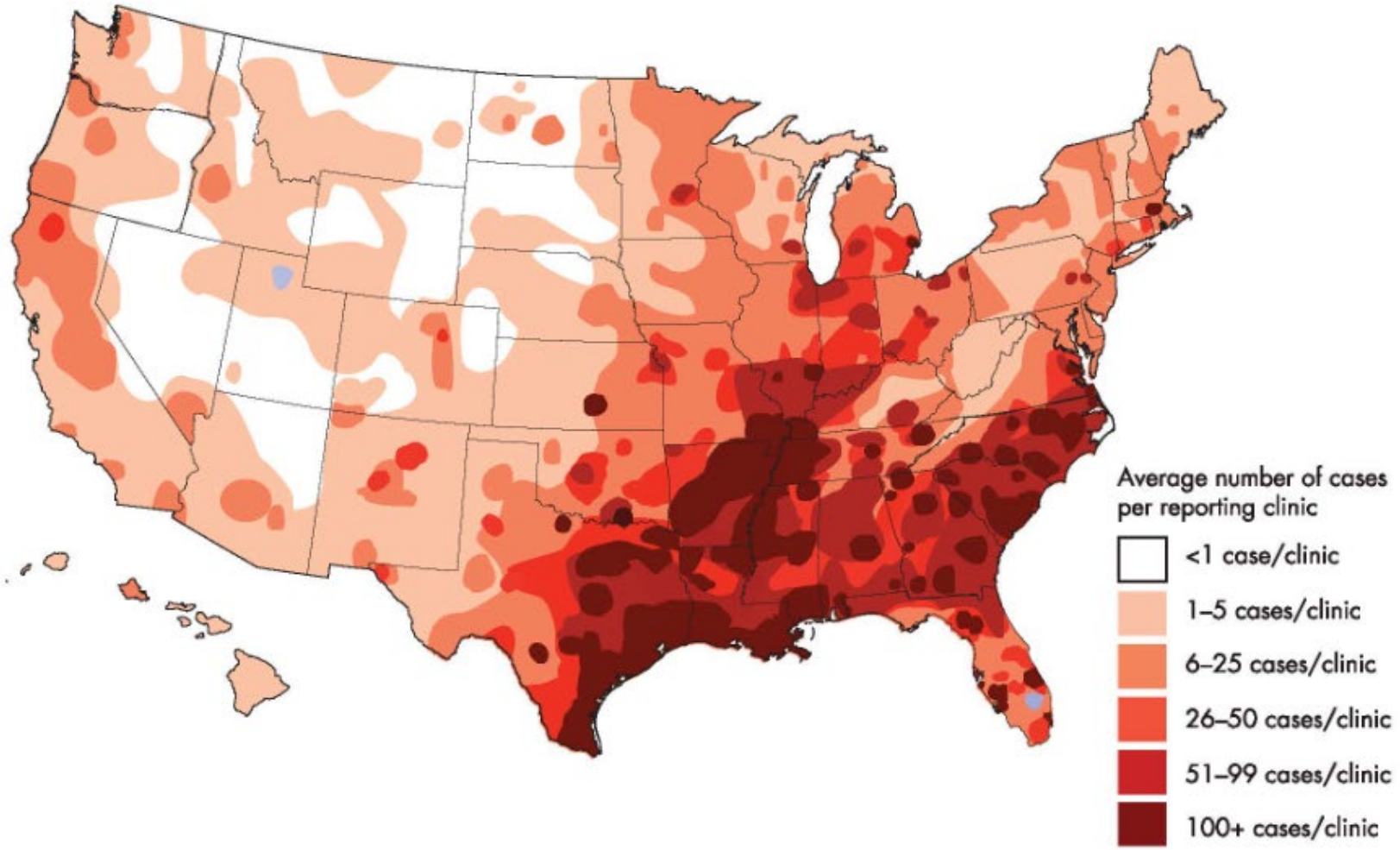
PROTECT YOUR PET FROM HEARTWORM 12 MONTHS A YEAR.
TEST FOR HEARTWORM EVERY 12 MONTHS.

www.heartwormsociety.org

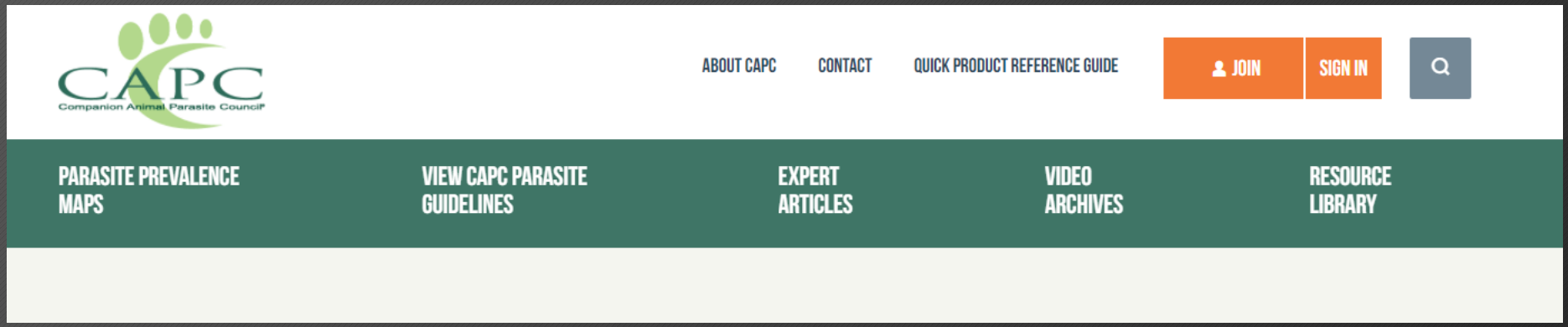
2022 HEARTWORM INCIDENCE

AMERICAN HEARTWORM SOCIETY™ EST. 1974

 The severity of heartworm incidence as shown in this map is based on the average number of cases per reporting clinic. Some remote regions of the United States lack veterinary clinics, therefore we have no reported cases from these areas.

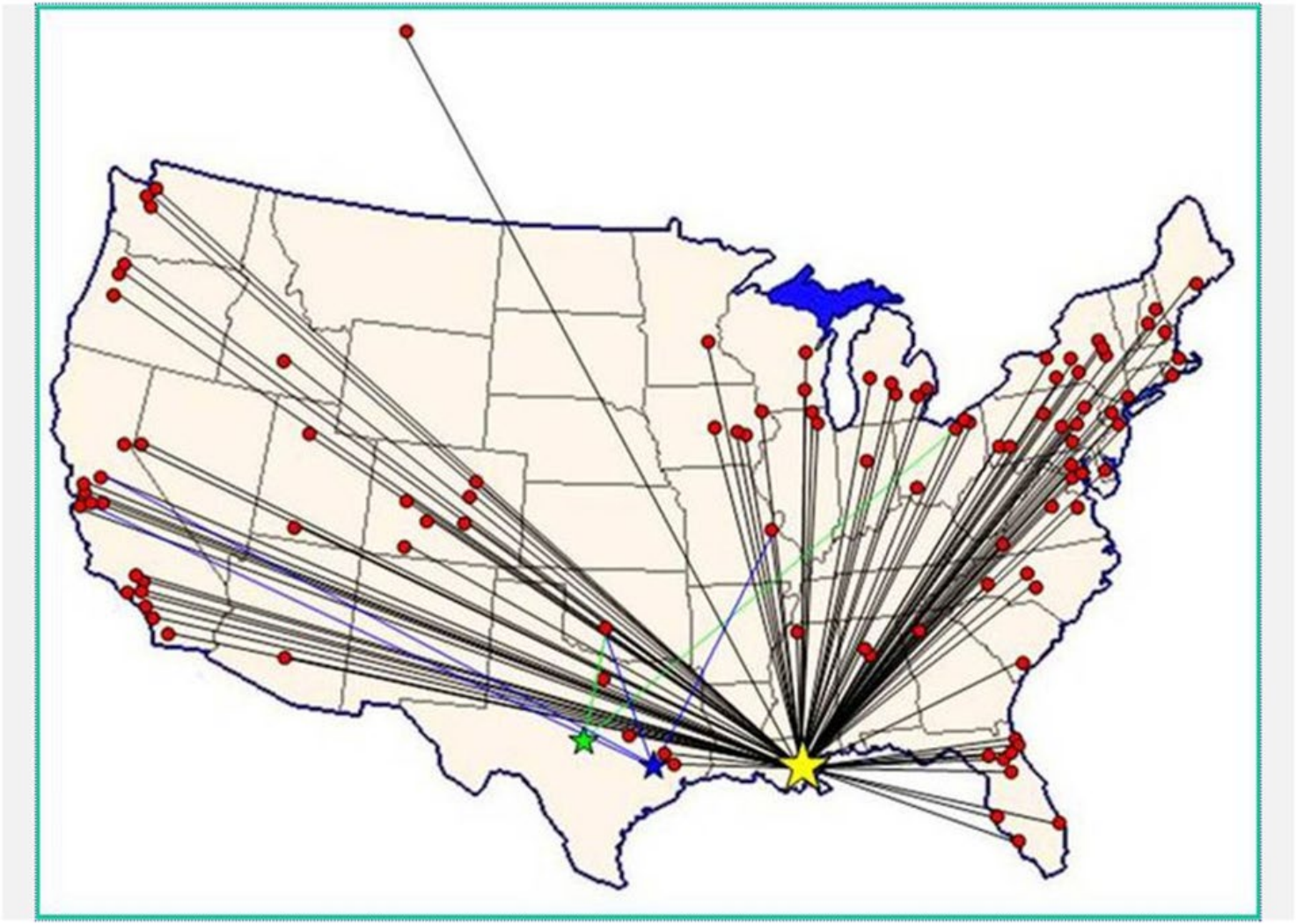


www.capcvet.org



American Heartworm Society's Photos - Wall Photos

Photo 19 of 23 Back to Album · American Heartworm Society's Photos · American Heartworm Society's Profile Previous Next




HARVEY'S IMPACTS
Into Wednesday
• Catastrophic flooding
• Damaging winds
• Isolated tornadoes
• Lengthy power outages
SHREVEPORT
HOUSTON
SAN ANTONIO
NEW ORLEANS
CORPUS CHRISTI
IMPACTS
Extreme
Moderate
Isolated
AccuWeather


IRMA
Sunday-Tuesday
• Flooding rainfall
• Coastal flooding
• Beach erosion
• Travel disruption
• Power outages
POTENTIAL IMPACTS
RALEIGH
ATLANTA
ORLANDO
AccuWeather
12:10Z 09/6/2017

Two Hurricane Harvey dogs counting on central Illinois

ost Popular

eoria Park District celebrating its 125th year with a arty

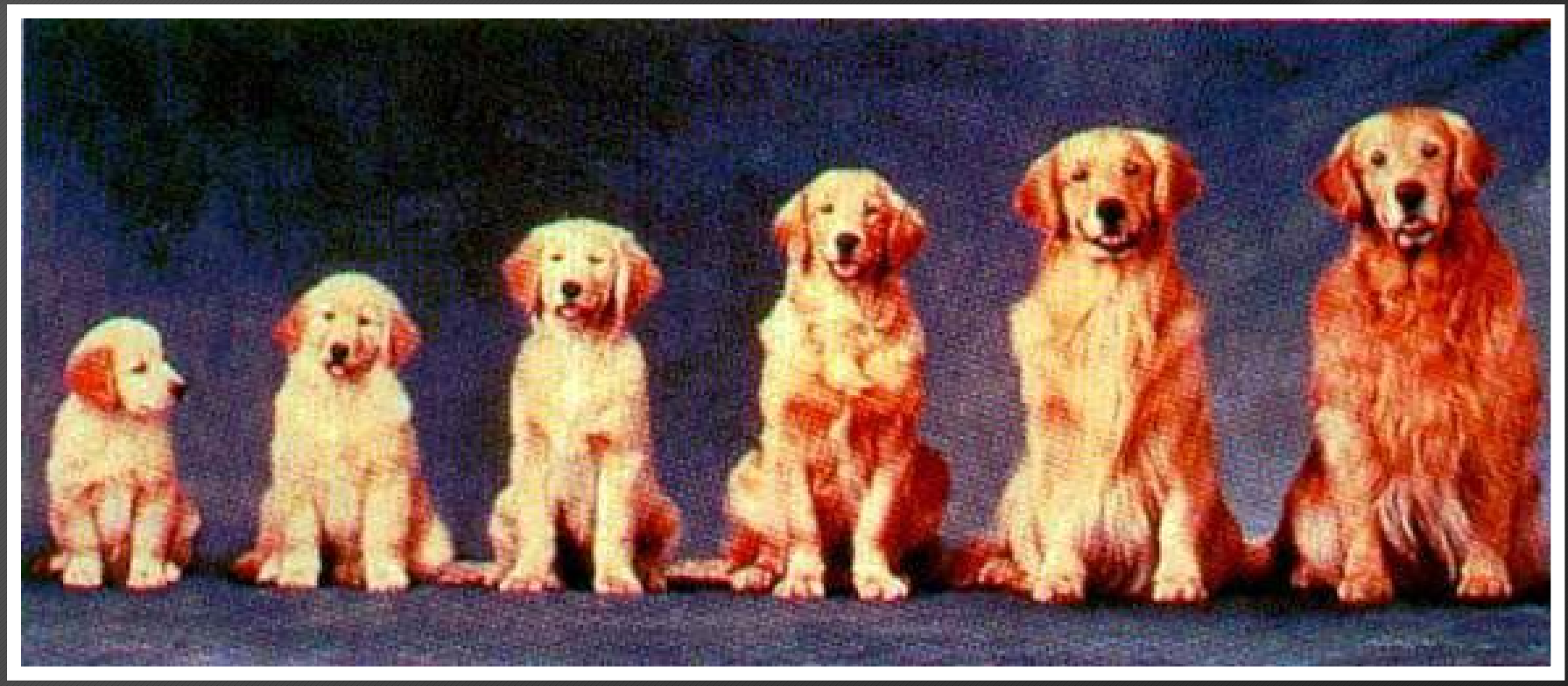
▲ HIDE CAPTION

PHOTO COURTESY OF FOSTER PET OUTREACH Ezekiel, or Zeke, a 13-week-old puppy dachshund mix, was brought to Illinois from Texas for adoption after Hurricane Harvey.

TRAVEL MAP

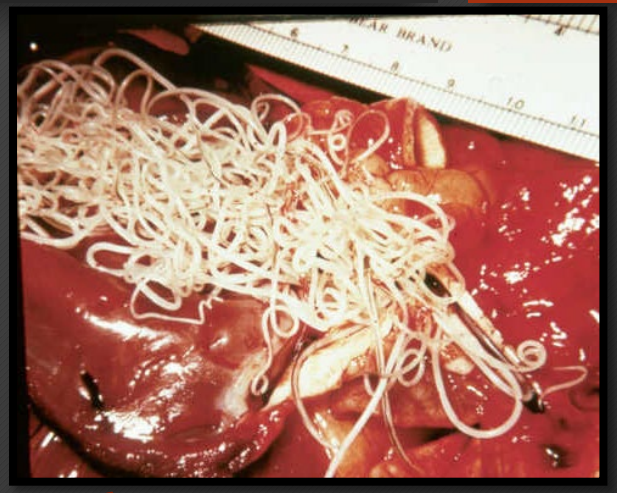
Want to find that perfect Fido-friendly vacation? Check out the FIDO Friendly Travel Map below and locate your next favorite property!

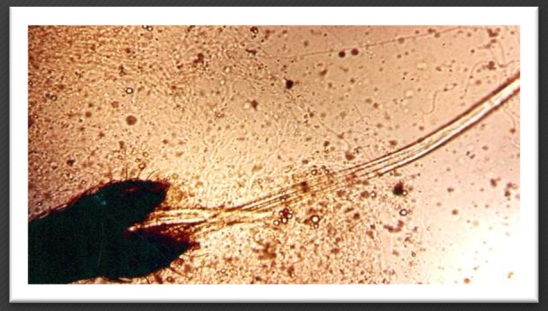
All Ages susceptible to infection



Dirofilaria immitis: Important Stages

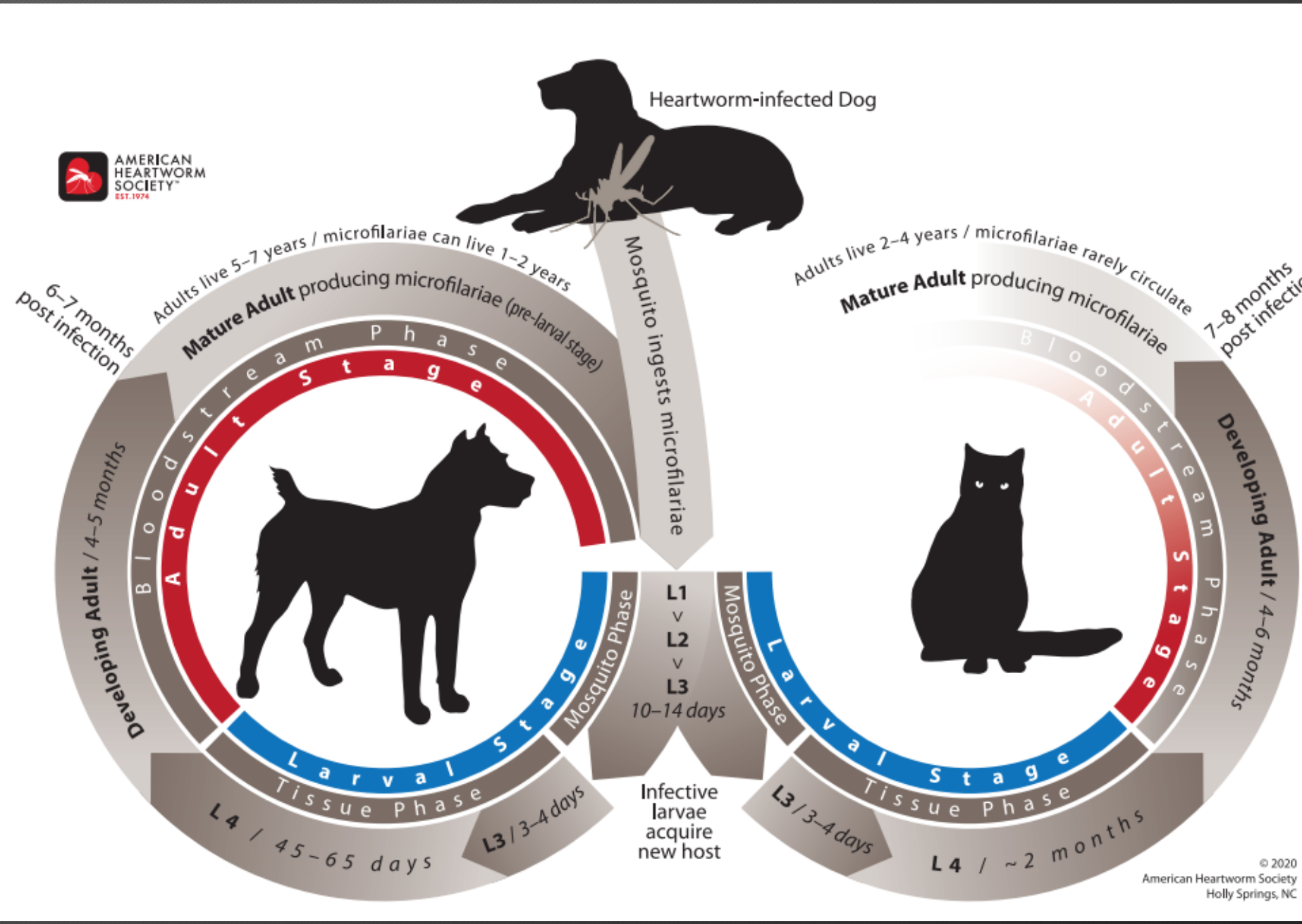
- Adult worms
  - Females 10 –12 inches
  - Males 4 – 6 inches
  - May live for 5 - 7 years in dogs
  - Pulmonary arteries
- Microfilariae (MF)
  - ~ L_1 (≥ 300 μm)
- Larvae develop in mosquito IH
  - MF to L_3
  - Infective, third-stage larvae L_3 (1 mm)
- L_3 to adult in DH





Remember:

Microfilariae are not L3s


AMERICAN HEARTWORM SOCIETY
EST. 1974
Heartworm-infected Dog
Adults live 5–7 years / microfilariae can live 1–2 years
Mature Adult producing microfilariae (pre-larval stage)
6–7 months post infection
Bloodstream Phase
Adult Stage
Larval Stage
Tissue Phase
Developing Adult / 4–5 months
L4 / 45–65 days
L3 / 3–4 days
Mosquito Phase
Mosquito ingests microfilariae
L1 > L2 > L3
10–14 days
Infective larvae acquire new host
Adults live 2–4 years / microfilariae rarely circulate
Mature Adult producing microfilariae
7–8 months post infection
Developing Adult / 4–6 months
L4 / ~2 months
L3 / 3–4 days
© 2020
American Heartworm Society
Holly Springs, NC

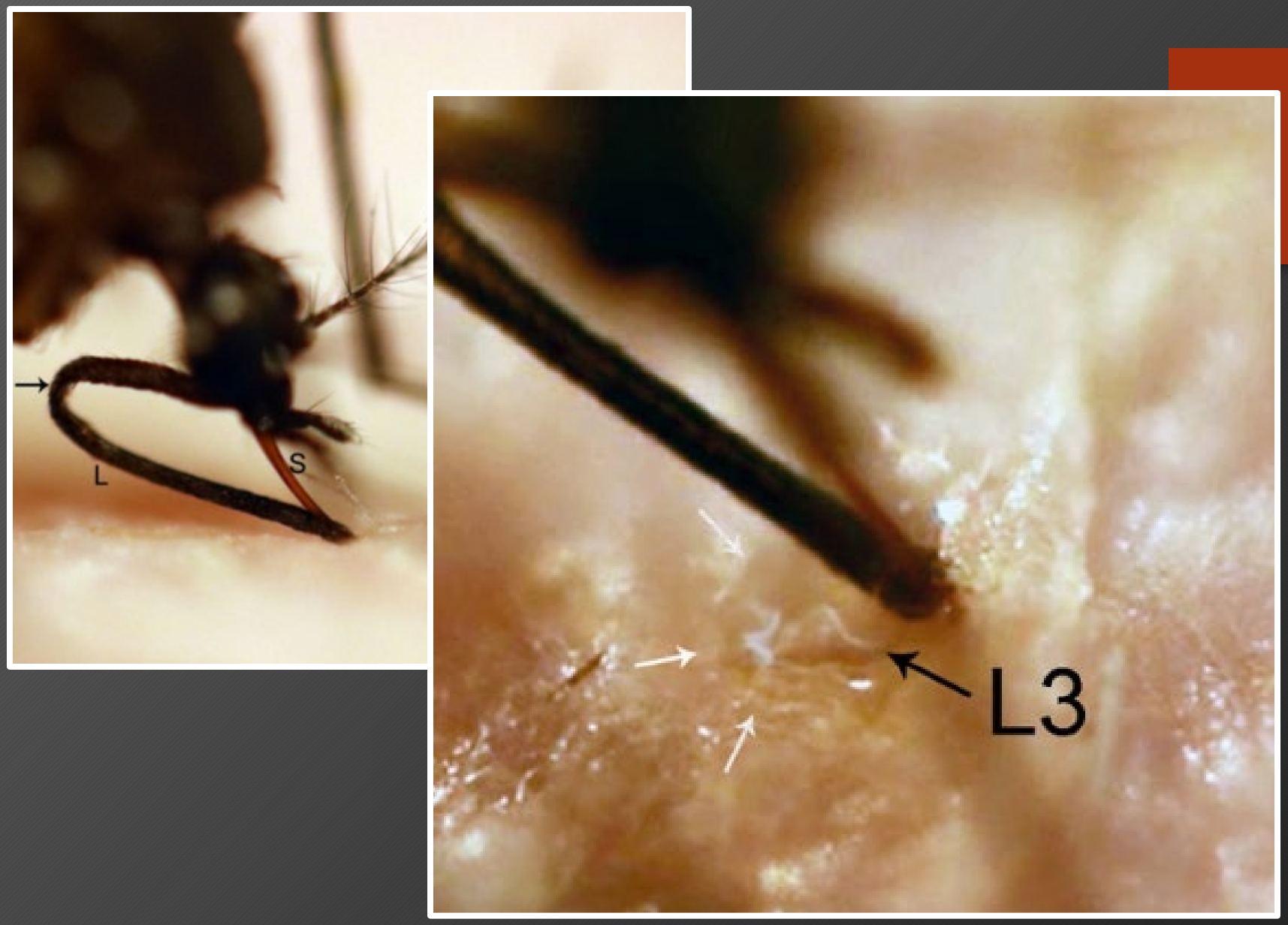
Dirofilaria immitis & Vector

http://cal.vet.upenn.edu/projects/merial/introduction/images/mosquitof.jpg


BEGIN CYCLE
INFECTED DOG
MICROFILARIA


TIME: 0
SIZE: 1.0mm
HEMOLYMPH POOL


L3 DOG
PENETRATES SKIN PUNCTURE
HEMOLYMPH POOL
MOLTS AFTER 10 DAYS



Courtesy of Dr. Steve Jones

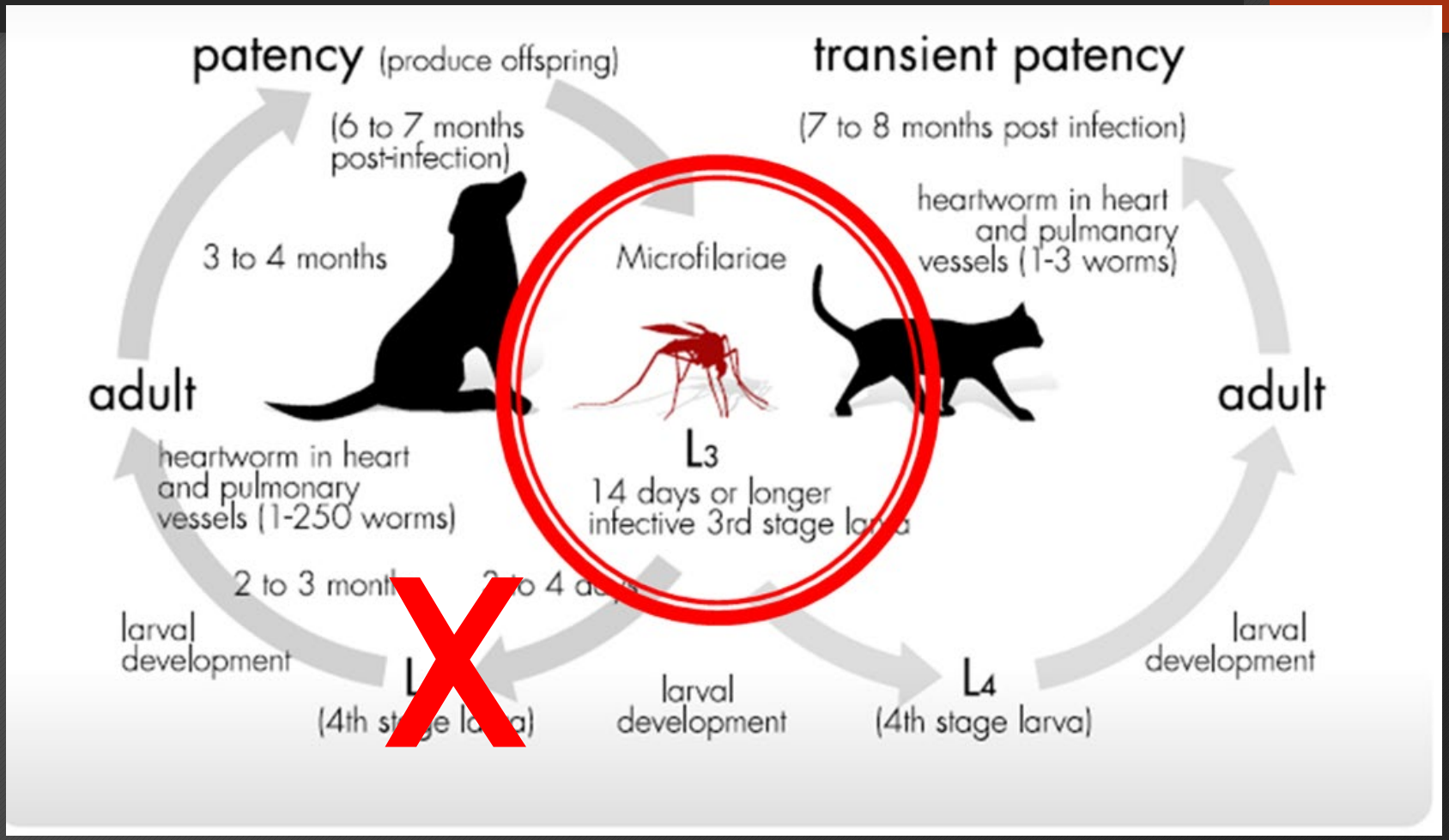
Isoxazolines

Ctenocephalides felis female

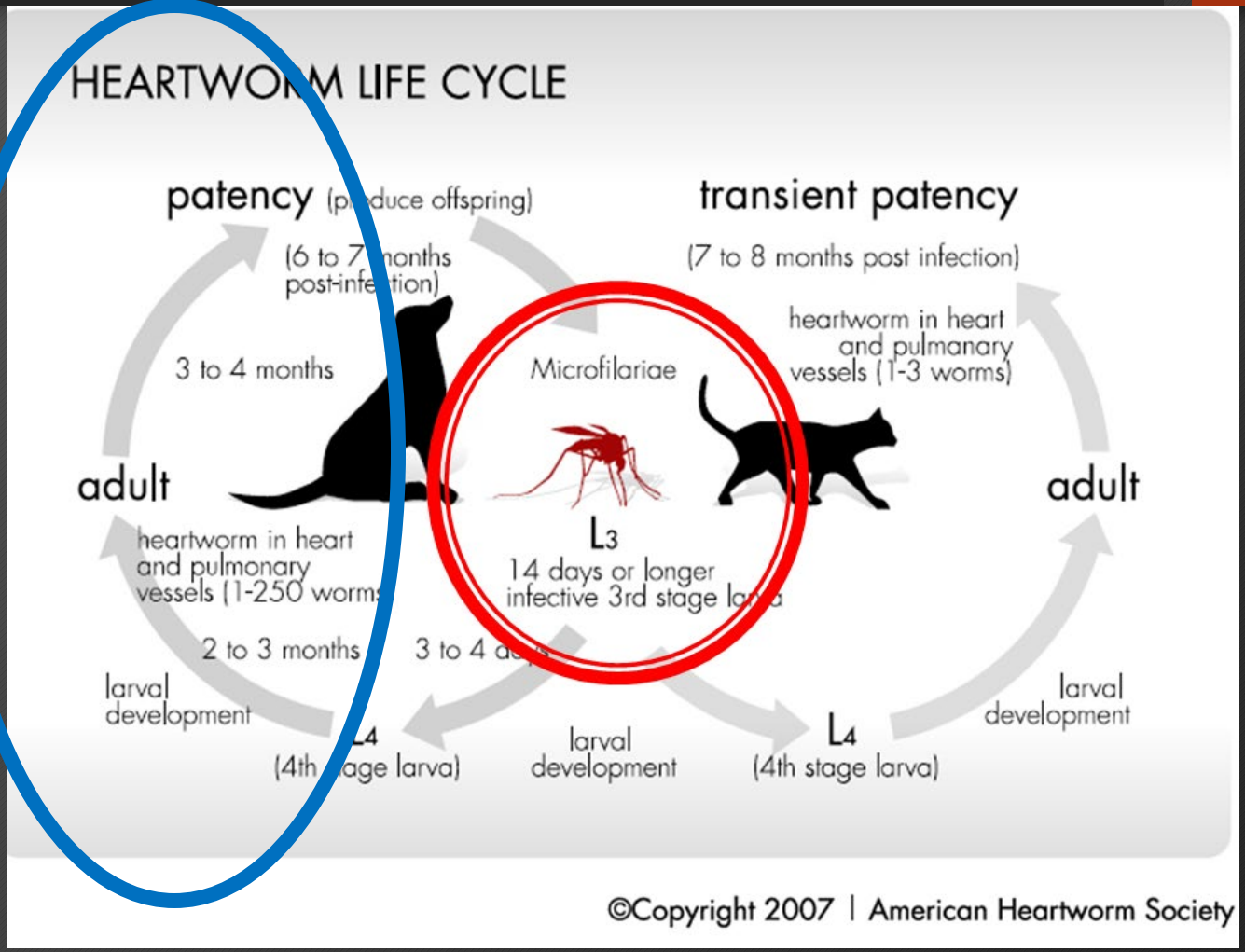
Ixodes scapularis adult female

www.capcvet.org

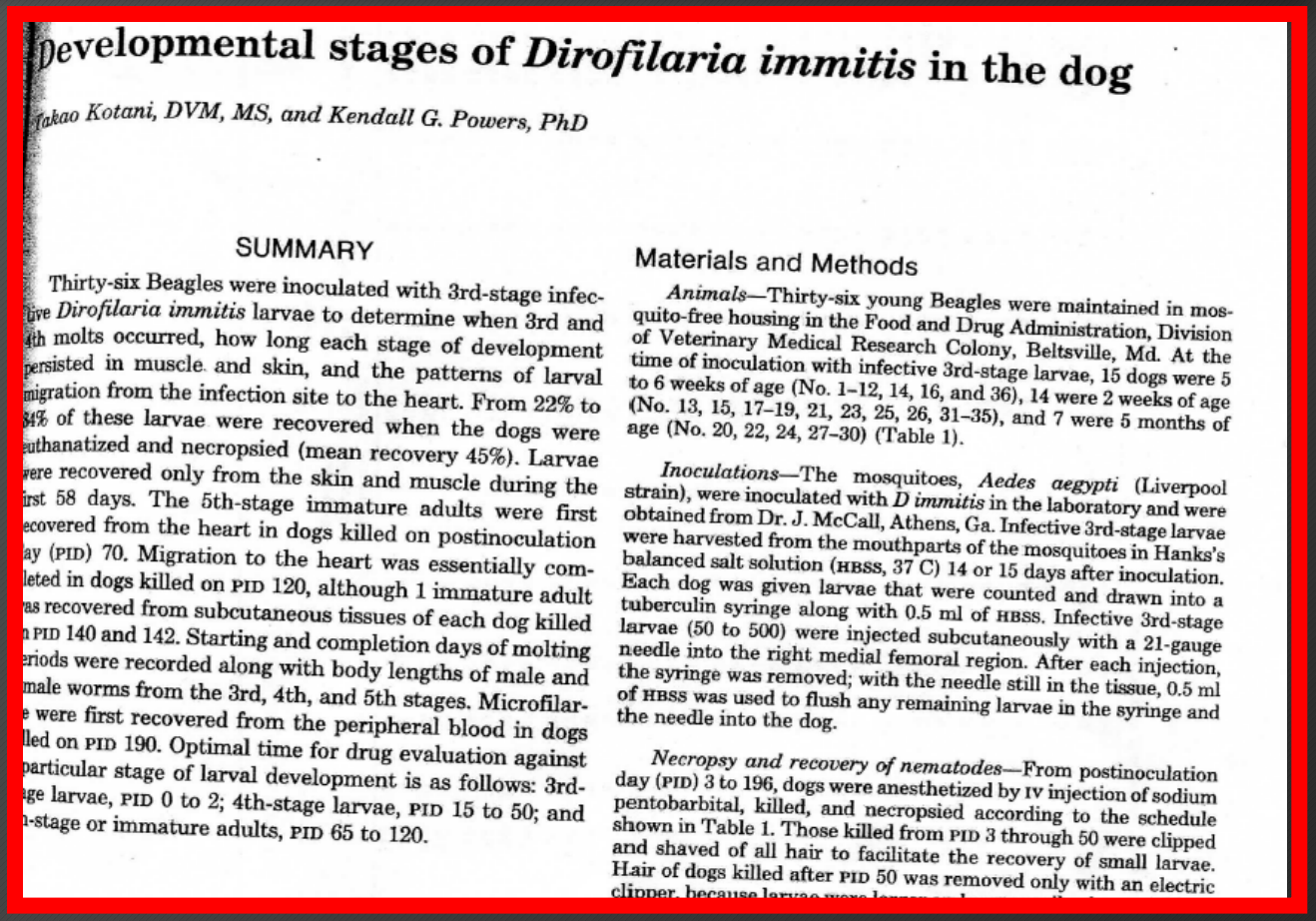
Isoxazolines decrease mosquito survival after blood feeding



Dirofilaria immitis Life Cycle



Most of what we know…



Developmental stages of *Dirofilaria immitis* in the dog

Takao Kotani, DVM, MS, and Kendall G. Powers, PhD

SUMMARY

Thirty-six Beagles were inoculated with 3rd-stage infective *Dirofilaria immitis* larvae to determine when 3rd and 4th molts occurred, how long each stage of development persisted in muscle and skin, and the patterns of larval migration from the infection site to the heart. From 22% to 34% of these larvae were recovered when the dogs were euthanatized and necropsied (mean recovery 45%). Larvae were recovered only from the skin and muscle during the first 58 days. The 5th-stage immature adults were first recovered from the heart in dogs killed on postinoculation day (PID) 70. Migration to the heart was essentially completed in dogs killed on PID 120, although 1 immature adult was recovered from subcutaneous tissues of each dog killed on PID 140 and 142. Starting and completion days of molting periods were recorded along with body lengths of male and female worms from the 3rd, 4th, and 5th stages. Microfilariae were first recovered from the peripheral blood in dogs killed on PID 190. Optimal time for drug evaluation against particular stage of larval development is as follows: 3rd-stage larvae, PID 0 to 2; 4th-stage larvae, PID 15 to 50; and 5th-stage or immature adults, PID 65 to 120.

Materials and Methods

Animals—Thirty-six young Beagles were maintained in mosquito-free housing in the Food and Drug Administration, Division of Veterinary Medical Research Colony, Beltsville, Md. At the time of inoculation with infective 3rd-stage larvae, 15 dogs were 5 to 6 weeks of age (No. 1–12, 14, 16, and 36), 14 were 2 weeks of age (No. 13, 15, 17–19, 21, 23, 25, 26, 31–35), and 7 were 5 months of age (No. 20, 22, 24, 27–30) (Table 1).

Inoculations—The mosquitoes, *Aedes aegypti* (Liverpool strain), were inoculated with *D immitis* in the laboratory and were obtained from Dr. J. McCall, Athens, Ga. Infective 3rd-stage larvae were harvested from the mouthparts of the mosquitoes in Hanks's balanced salt solution (HBSS, 37 C) 14 or 15 days after inoculation. Each dog was given larvae that were counted and drawn into a tuberculin syringe along with 0.5 ml of HBSS. Infective 3rd-stage larvae (50 to 500) were injected subcutaneously with a 21-gauge needle into the right medial femoral region. After each injection, the syringe was removed; with the needle still in the tissue, 0.5 ml of HBSS was used to flush any remaining larvae in the syringe and the needle into the dog.

Necropsy and recovery of nematodes—From postinoculation day (PID) 3 to 196, dogs were anesthetized by IV injection of sodium pentobarbital, killed, and necropsied according to the schedule shown in Table 1. Those killed from PID 3 through 50 were clipped and shaved of all hair to facilitate the recovery of small larvae. Hair of dogs killed after PID 50 was removed only with an electric clipper, because larvae were

AJVR Dec. 1982

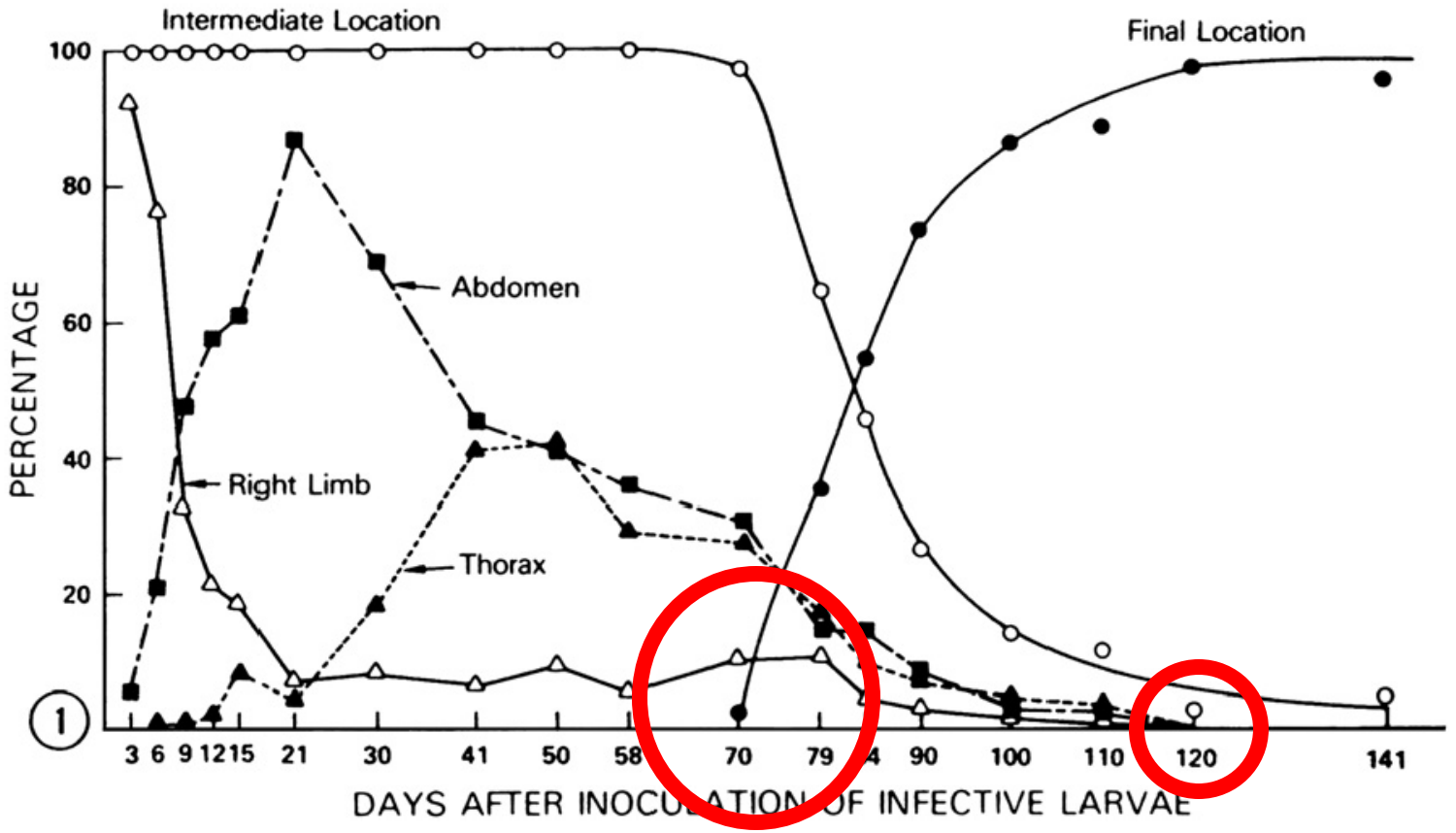
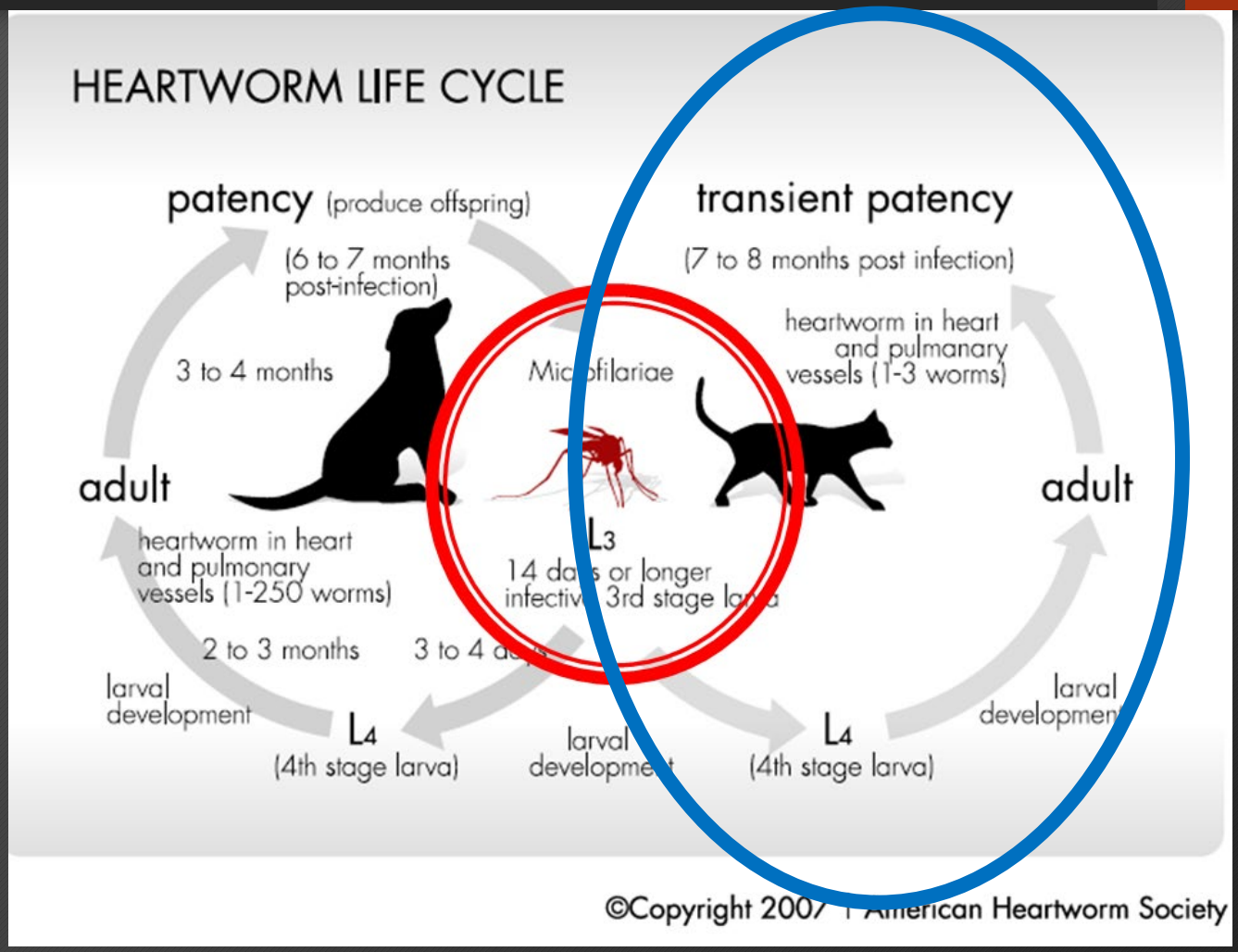


Fig. 1. Distribution and migration patterns of *D immitis* recovered from inoculated dogs, ○, total percentage of larvae recovered from the intermediate locations (subcutaneous and muscle tissues combined) throughout the body. Also included are worms from the abdominal and thoracic cavities, ρ, percentage recovered from the right hindlimb, ■, percentage recovered from the abdomen, π, percentage recovered in the thorax, ●, percentage recovered from final location (right side of the heart, pulmonary arteries, and vena cavae). (*From* Kotani T, Powers KG. Developmental stages of *Dirofilaria immitis* in the dog. Am J Vet Res 1982;43(12):2199–206; with permission.)

Important Life Cycle Facts- CANINE

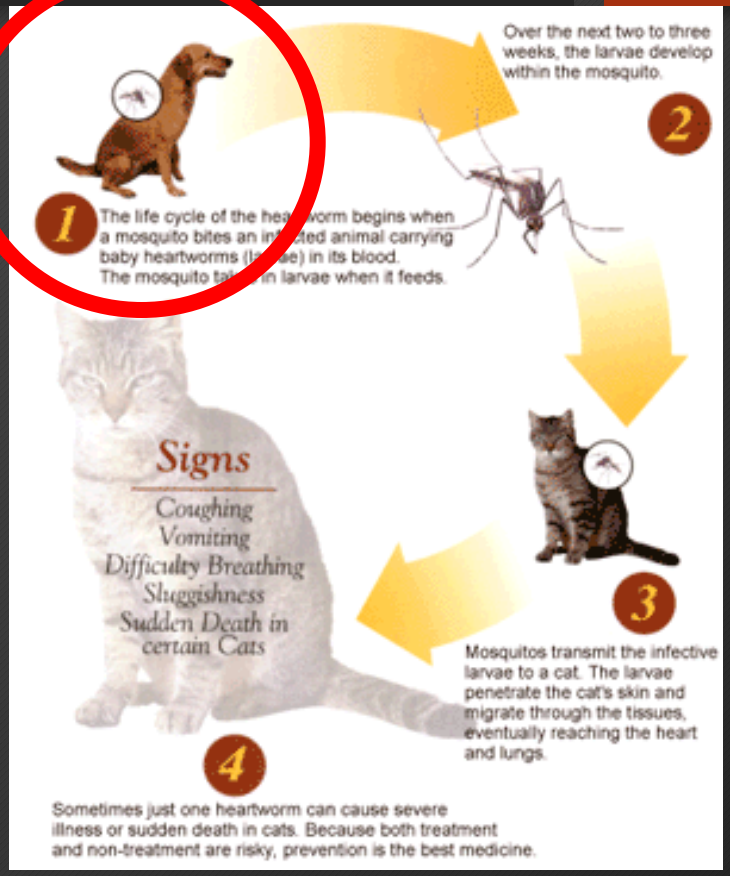
- Normal development from L1 to L3 in the **mosquito** is 10-14 days
- **L3 is the infective stage**
- By day 70 (juvenile adult stage), they are in the pulmonary vessels
  - **THIS MEANS DAMAGE CAN START.**
- **Adults by 6 months**
  - **Start producing microfilariae (the babies)**

Dirofilaria immitis Life Cycle



Life Cycle of *D. immitis* in Cats

- Life cycle the same but takes longer to complete (7-8 months)
- Adult worms do not live as long in cats (2-3 yrs) as they do in dogs (5-7 yrs)
- Cats more likely to have aberrant migration of worms
  - Aberrant migration of worms to ectopic sites (**CNS, eyes**, body cavities, arteries other than pulmonary, skin, etc.)

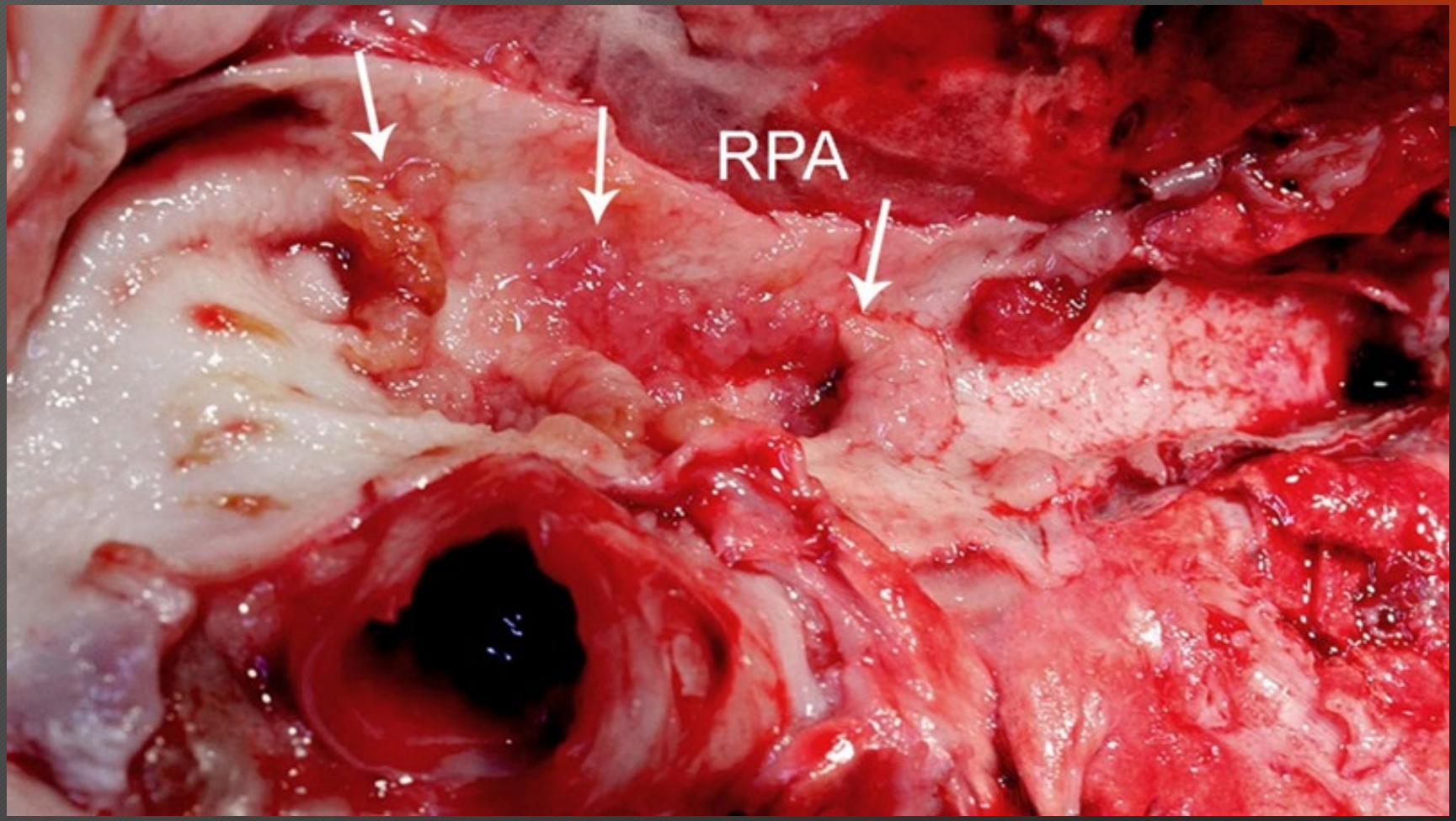


Life Cycle of *D. immitis* in Dogs vs. Cats

	Dog	Cat
Time to Adulthood	6-7 months	7-8 months
Microfilaremia	Yes	transient
Aberrant migration	Rare	Eyes, CNS
Numbers present	Few to many	<5
Lifespan	5-7 years	2-3 years

Feline HWD-Life cycle

- Few worms can cause life-threatening Dz
  - Cats usually infected with < 5 worms
  - Diagnosis more difficult
    - may be only 1 - 2 female worms present, if any
- Cats only have a transient microfilaremia
  - < 5% of infected cats are MF + at time of exam
  - **become infected from mosquitoes that have fed on infected dogs**



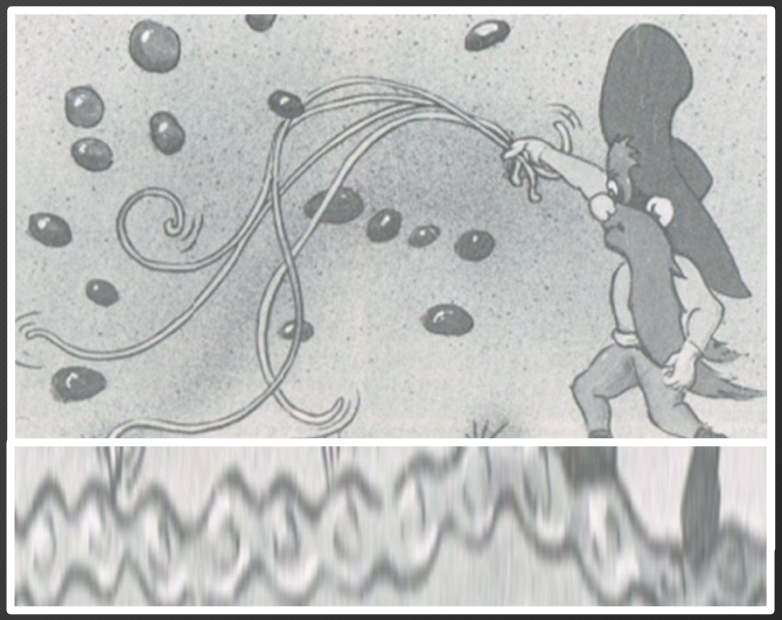
Courtesy of Dr. Steve Jones

Pathology

- Multiple organ disease
  - heart, lungs, liver, kidney
- Severity of disease can depend on:
  1. Numbers of adult worms
     - More is not better
  2. Duration of infection
     - Longer is worse
  3. Individual host response

Pulmonary arterial disease

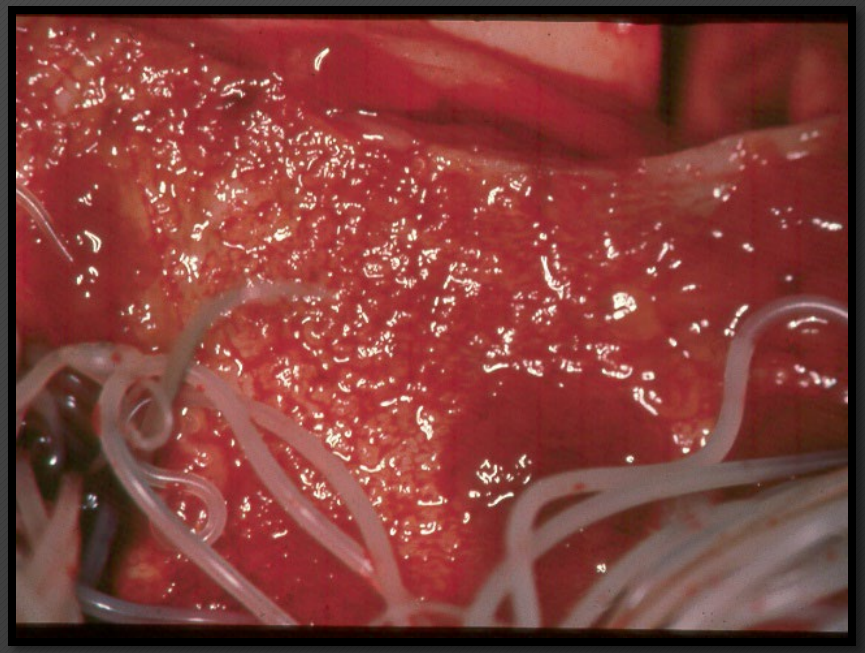
1. Inflammation
   - Endarteritis
2. Villous thickening of tunica intima
   - 1 - 3 months after worms arrive in heart



From “Heartworm Disease in Dogs and Cats” by Rawlings

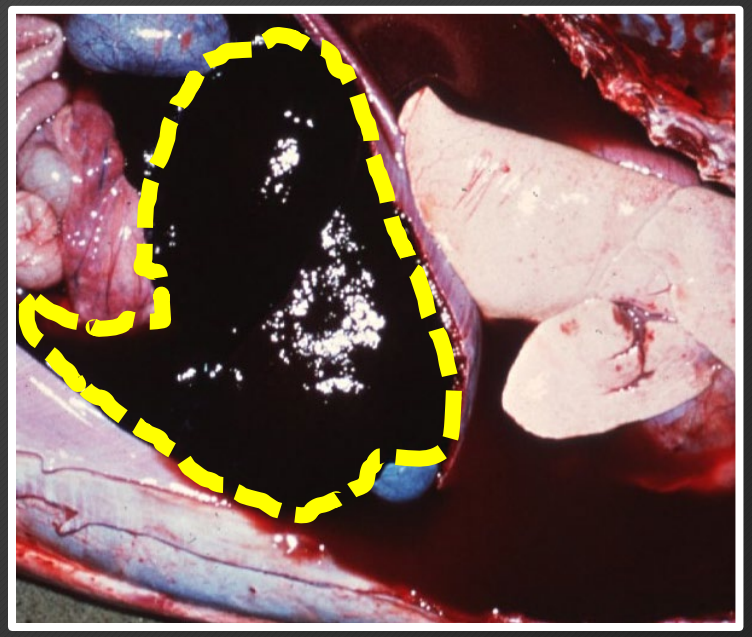
Pathology

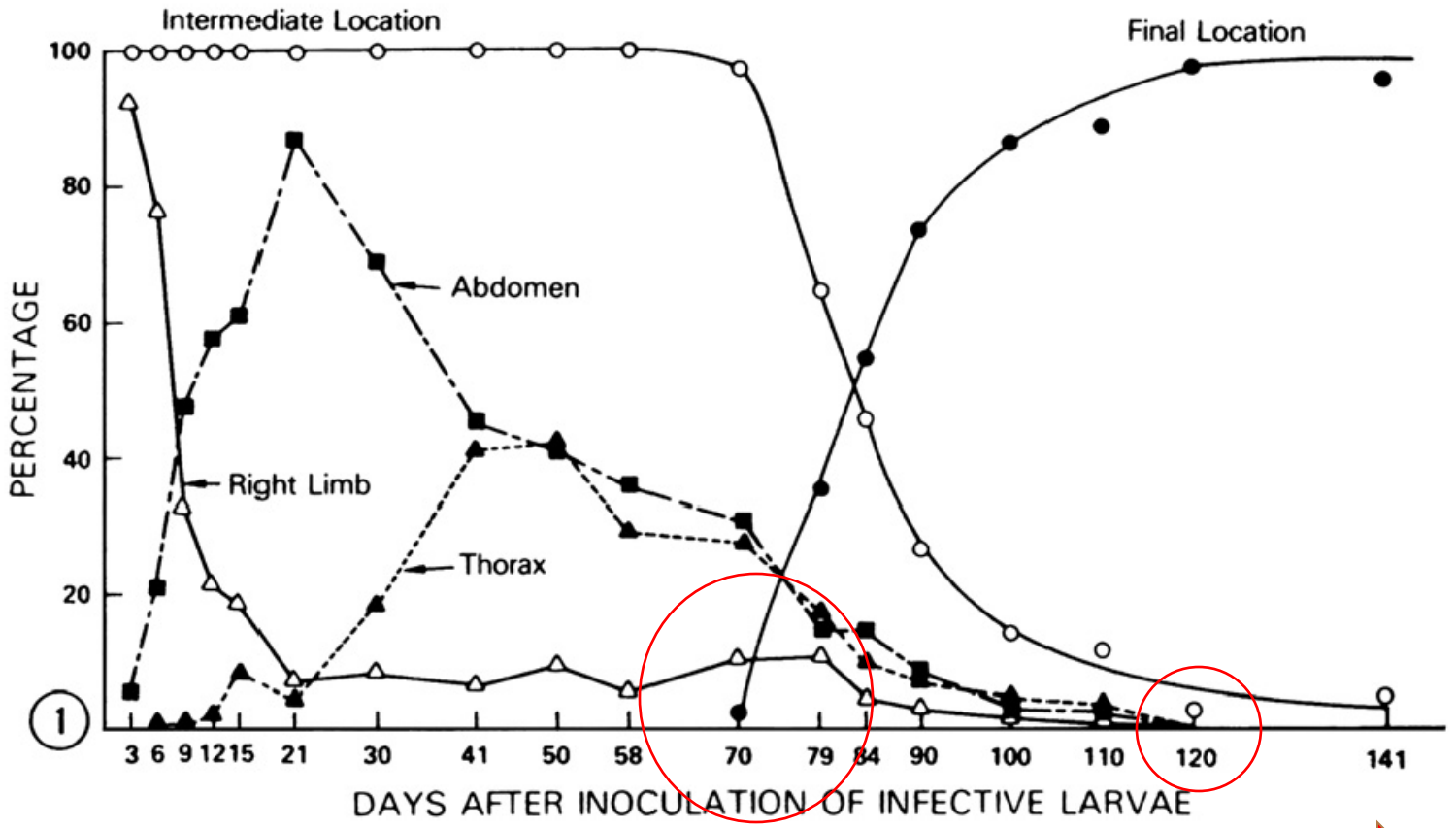
- roughened, stippled appearance
  - pathognomonic



Pathology

- Thickening of vessels
- Loss of vessel elasticity
- Leads to increased pressure
  - chronic, passive congestion and pulmonary hypertension
    - right heart enlargement
    - hepatomegaly
    - congestive heart failure -- ascites





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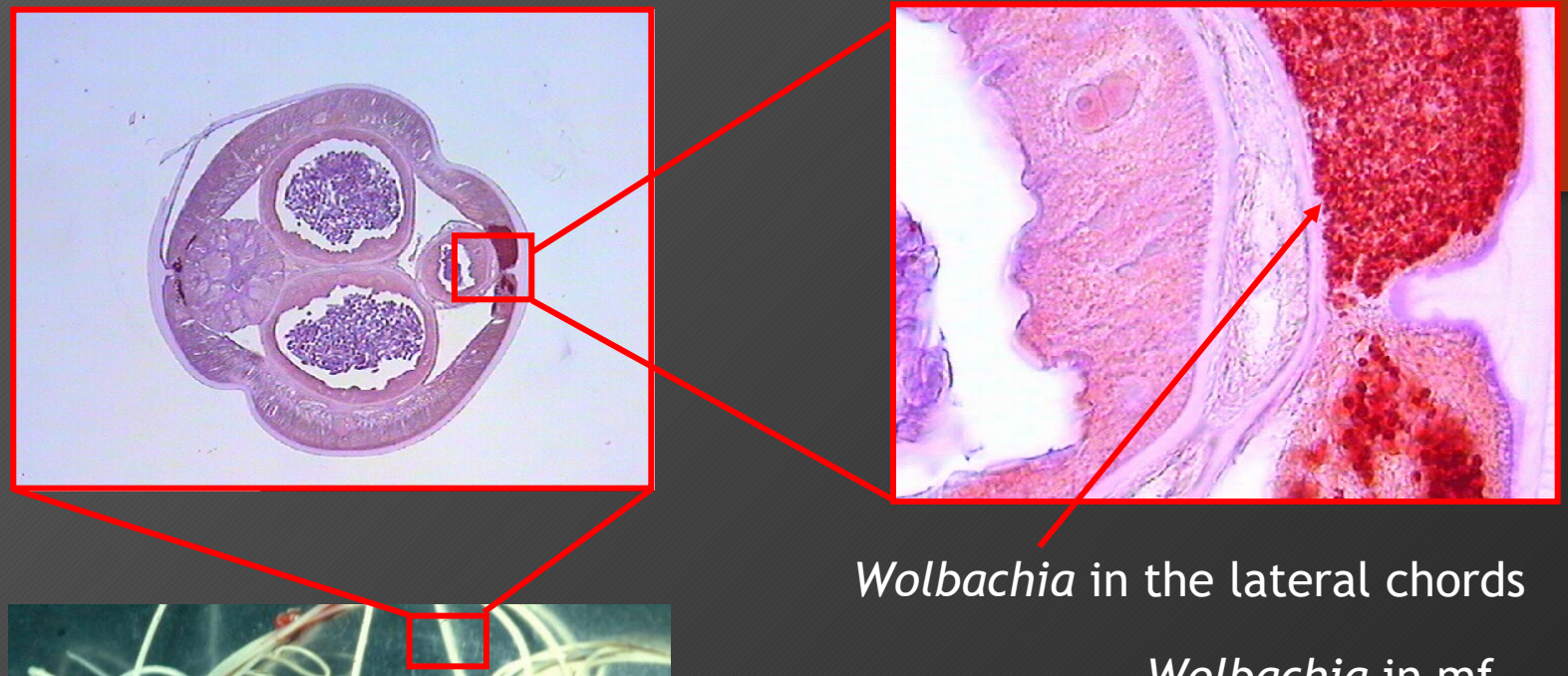
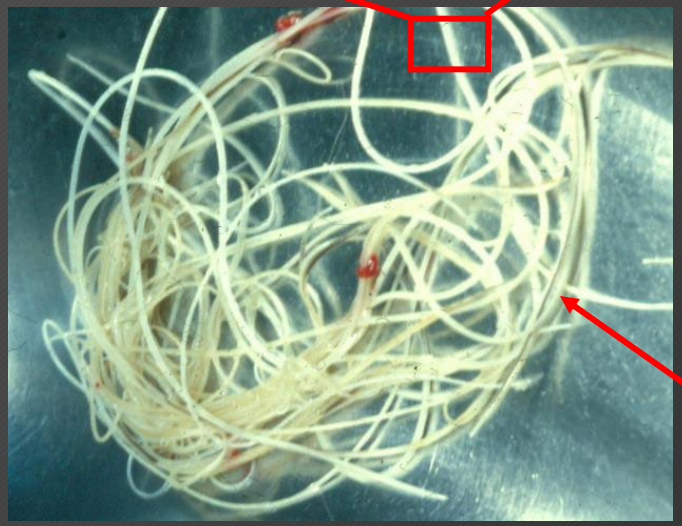
Damage

Most species of Filarioid nematodes harbour bacterial endosymbionts named *Wolbachia*

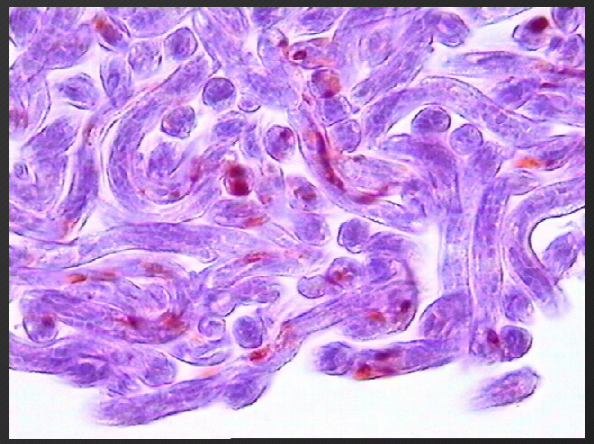


Wolbachia in the lateral chords



Dirofilaria immitis

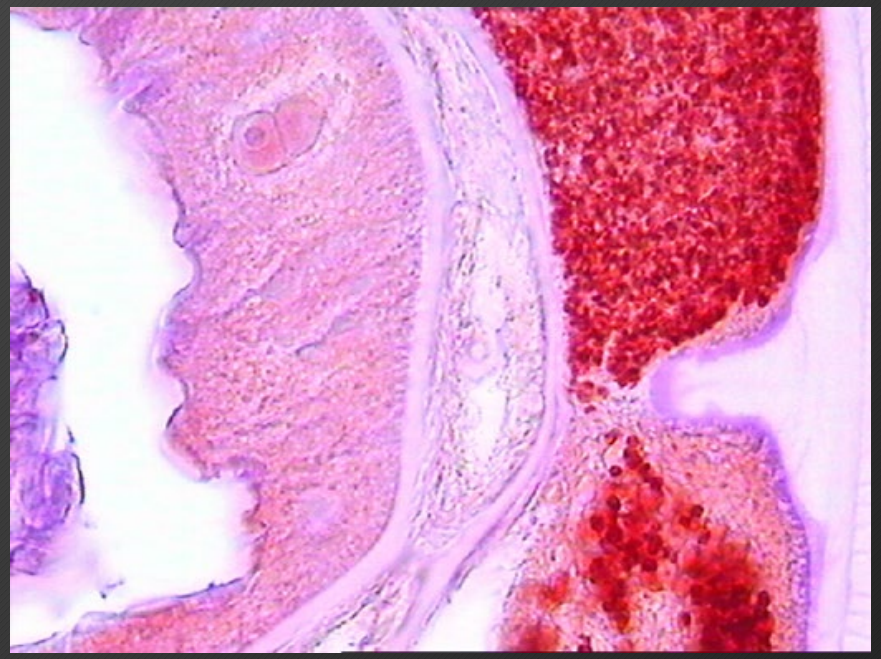
Wolbachia in mf



Immunohistology by Laura Kramer

Wolbachia: A component of inflammatory disease pathogenesis in filarial infections

- Important role in pathogenesis of filarial diseases
- *Wolbachia*-associated proteins
  - induce innate inflammatory responses by macrophages and neutrophils



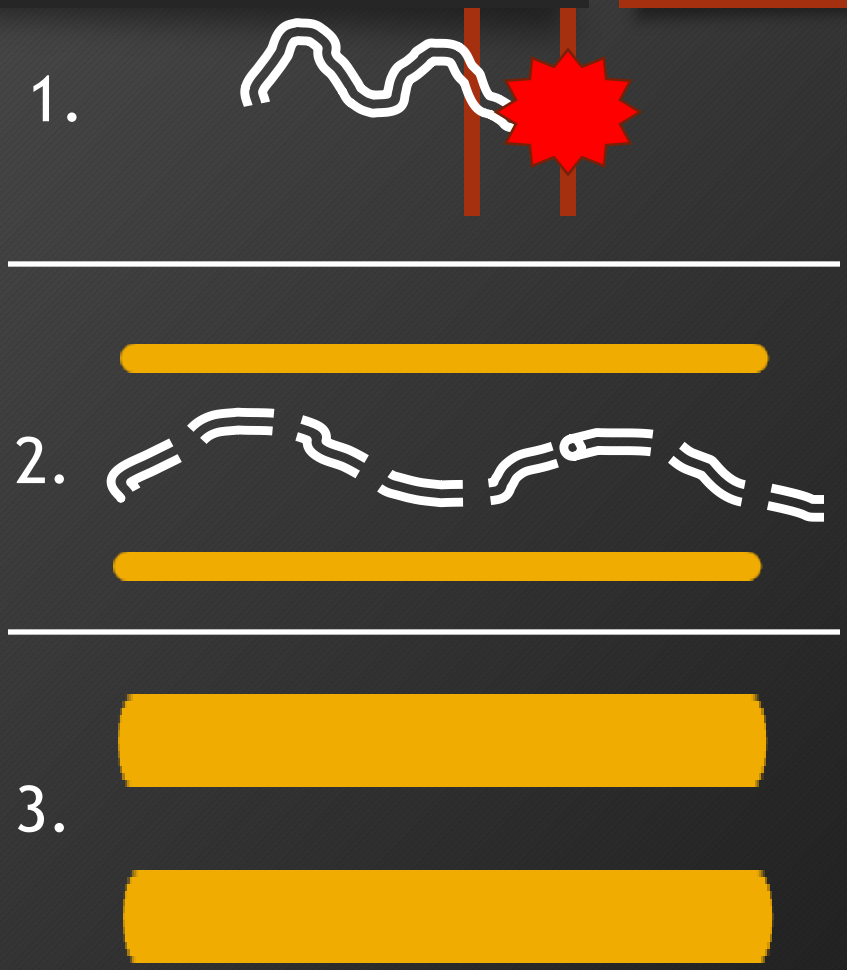
Feline HWD: Pathophysiology

- 3 stages of Disease

1. Worms reach lung blood vessels (3 – 4 months post infection) they induce an acute inflammatory response

2. When mature worms begin to die the degenerating worms induce pulmonary inflammation and thromboembolism

3. Chronic respiratory disease



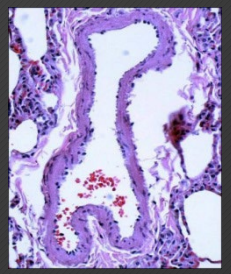
Feline HWD: Pathophysiology Step 1

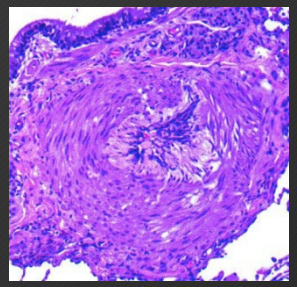
- Soon after worms reach the pulmonary blood vessels (3 – 4 months post infection) they induce an acute inflammatory response

Normal

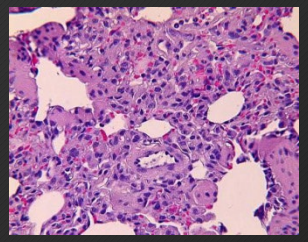
HW-positive (early stage)

Pulmonary Artery





Alveolus



Feline HWD: Pathophysiology Step 1

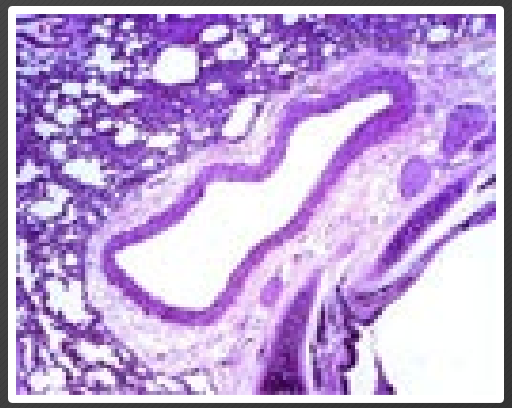
- Now referred to as HARD
  - "heartworm-associated respiratory disease"
  - DDx asthma
- Disease caused by immature worms is most common and important in cats

Feline HWD: Pathophysiology Step 2

- When mature worms begin to die the degenerating worms induce pulmonary inflammation and thromboembolism
  - Acute lung injury
  - Sudden death

Pulmonary Artery

Normal



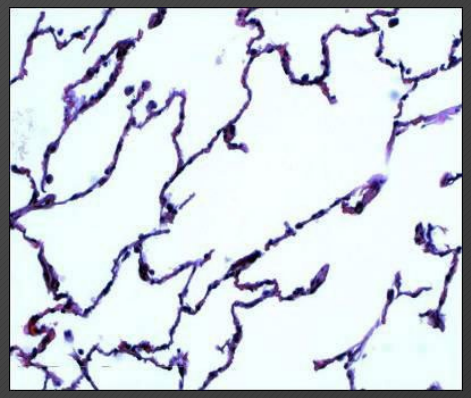
HW-positive

Feline HWD: Pathophysiology Step 3

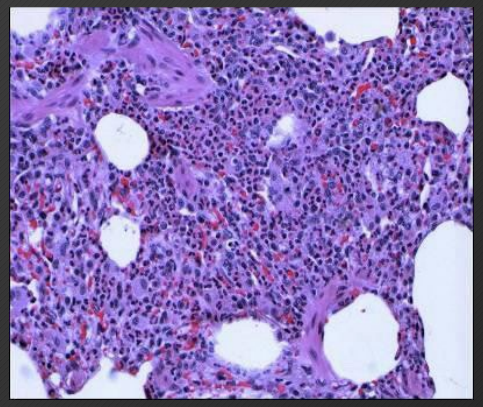
- Chronic respiratory diseases
  - Due to permanent lung injury
    - hyperplasia of alveolar cells

Alveolus

Normal

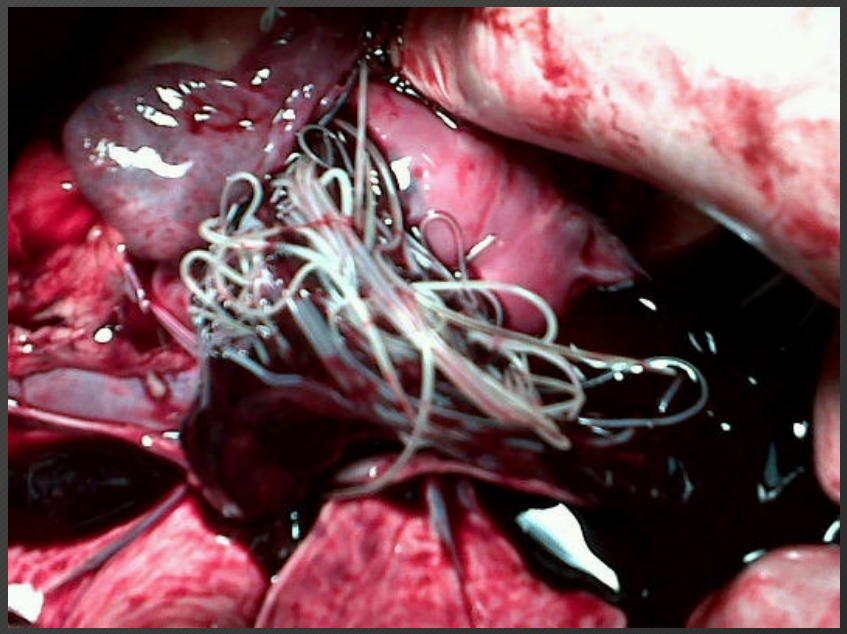


HW-positive (adult HW-chronic)

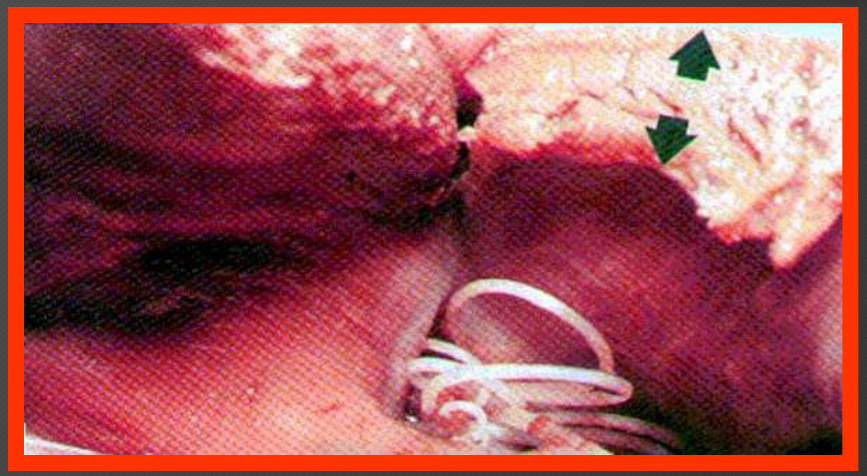


Manifestation of Pathology

- Clinical signs
  - Acute
    - Caval Syndrome

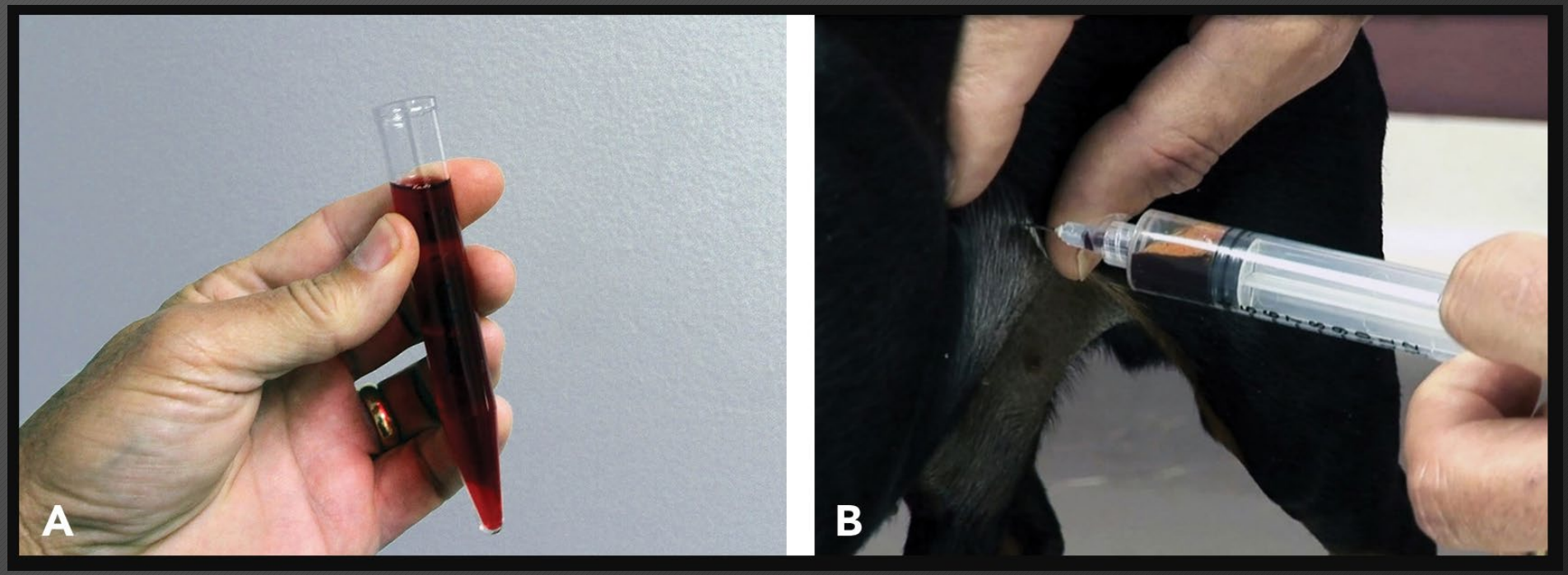


Caval Syndrome



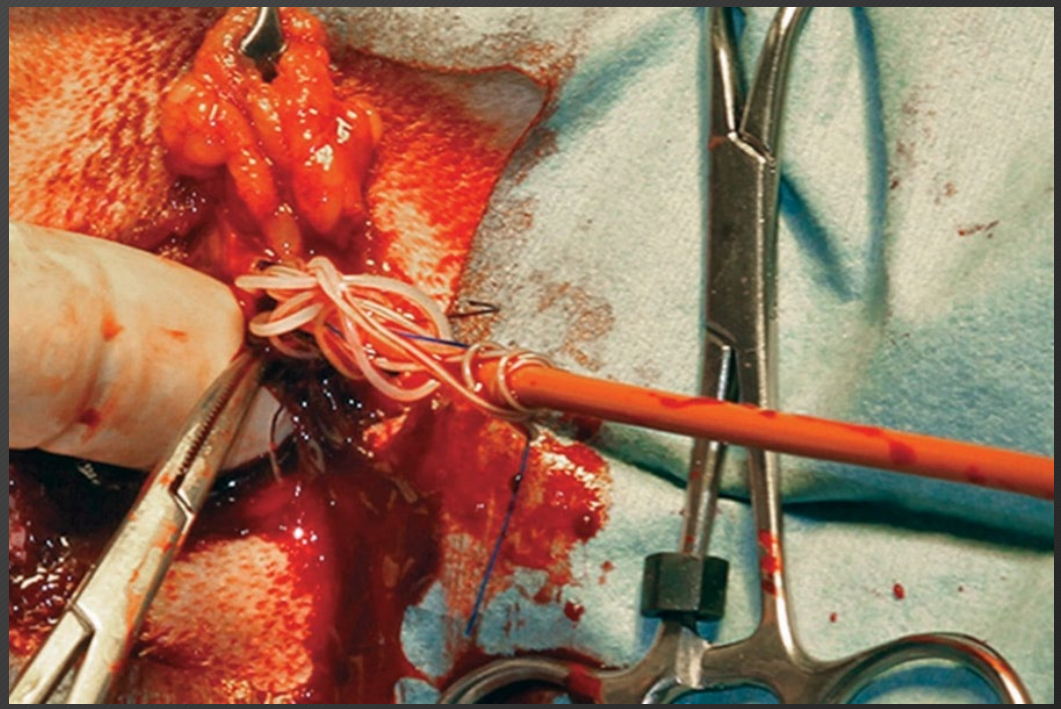
- Large numbers of worms
  - obstruct blood flow through tricuspid valve
- Rapid onset
- Death usually within 12 - 72 hours

Caval Syndrome-Hemoglubinuria



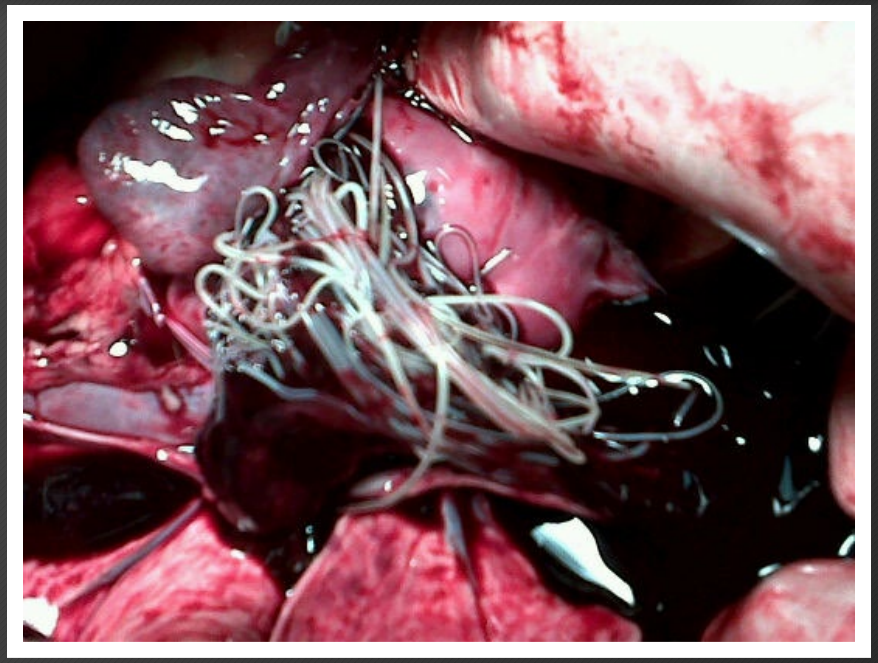
Caval Syndrome

- Poor candidates for treatment
- TOC = surgical removal of worms via jugular vein

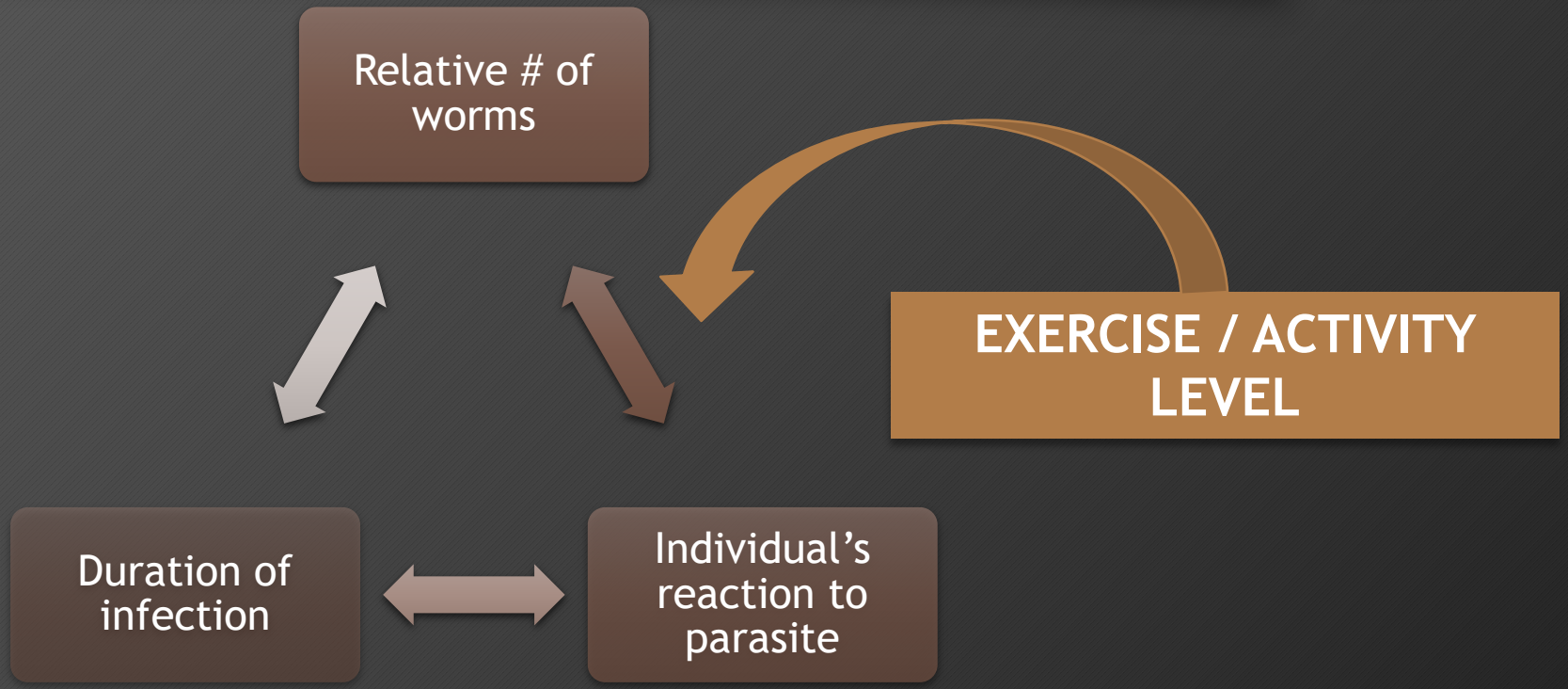


Manifestation of Pathology

- Clinical signs
  - Acute
    - Caval Syndrome
  - **Chronic**



Determinants of Clinical Consequences



Courtesy of M. Ames

Assessing the patient

- History, PE, exercise tolerance
- Immunodiagnosis/+/- test for MF
- Serum Chemistry/Hematology
  - Liver Function
- UA
- Radiography
- Cardiac US and ECG


INSIDE HEARTWORM DISEASE IN DOGS
Early infection
A FEW WORMS
COUGH
TIRED
DECREASED APPETITE
WEIGHT LOSS
FATIGUE
Advanced disease
MANY WORMS
CAN'T EXERCISE
LABORED BREATHING
FAST HEART RATE
ANEMIA
FAINTING
HEART FAILURE
SWOLLEN BELLY
DEATH
Damage can be lifelong and treatment costly.
Prevention is safe and affordable.
PROTECT 12 MONTHS A YEAR • TEST EVERY 12 MONTHS
AMERICAN HEARTWORM SOCIETY™
EST. 1974


INSIDE HEARTWORM DISEASE IN CATS
Immature worm infection
COUGH
WHEEZE
NAUSEA
VOMITING
LOSS OF APPETITE
LETHARGY
Adult worm infection
CONFUSION
PALPITATIONS
LABORED BREATHING
SEVERE ANXIETY
BLINDNESS
SEIZURES
SUDDEN DEATH
There's NO approved treatment for heartworm infection in cats!
Prevention is the only option.
PROTECT 12 MONTHS A YEAR • TEST EVERY 12 MONTHS
AMERICAN HEARTWORM SOCIETY™
EST. 1974

Chronic Heartworm Disease-Signs

- May be asymptomatic
- Symptomatic
  - **mild to moderate**
    - chronic cough
    - dyspnea
    - decreased exercise tolerance
  - **moderate to severe**
    - syncope
    - hemoptysis
  - **severe**
    - congestive heart failure

Summary of Clinical Signs- CANINE

Summary of Clinical Signs of Canine Heartworm Disease

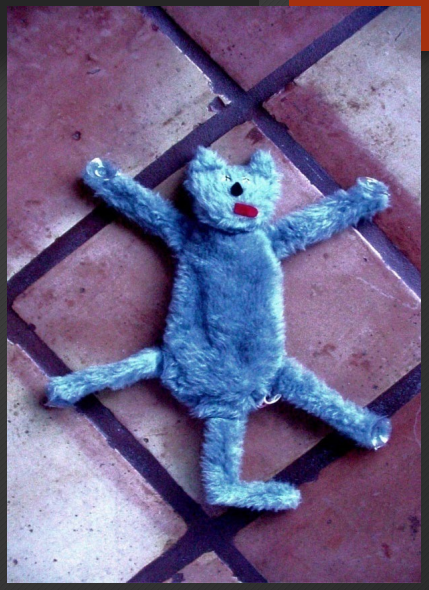
Early infection	Class 1	No signs
Mild disease	Class 1	Cough
Moderate disease	Class 2	Cough, exercise intolerance, abnormal lung sounds
Severe disease	Class 3	Cough, exercise intolerance, dyspnea, abnormal heart and lung sounds, enlarged liver (hepatomegaly), syncope (temporary loss of consciousness from reduced blood flow to the brain, ascites (fluid accumulation in the abdominal cavity), death
Caval Syndrome	Class 4	Sudden onset of severe lethargy and weakness accompanied by hemoglobinemia and hemoglobinuria

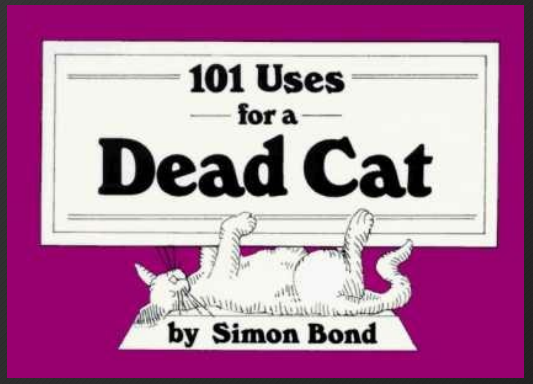
Feline HWD
Clinical Presentation

- About 33% of all cases reported in cats housed totally indoors
  - Are they really indoors?
  - No such thing as an outdoor-only mosquito

Feline HWD Clinical Signs

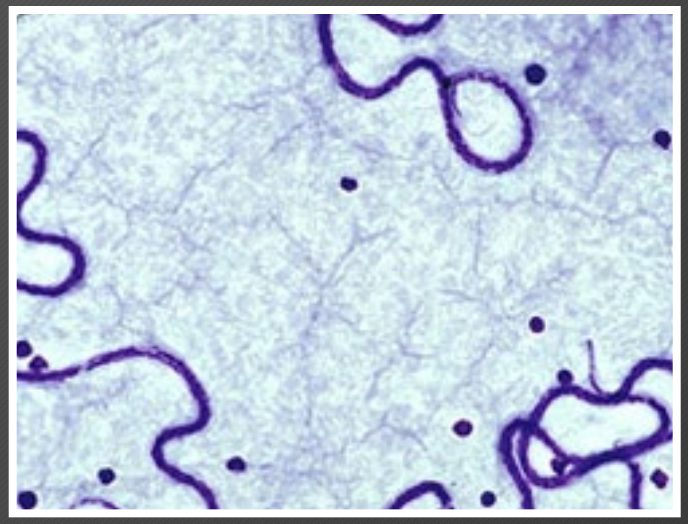
- Infected cats can be asymptomatic
  - Some infected cats have severe disease
- Common signs with chronic disease:
  - coughing, dyspnea
  - vomiting unrelated to eating
  - lethargy, anorexia, weight loss
  - systolic heart murmur
- Infrequent signs – acute disease
  - respiratory distress, hemoptysis
  - ataxia, seizures, blindness
  - sudden death





Testing

- Microfilaria



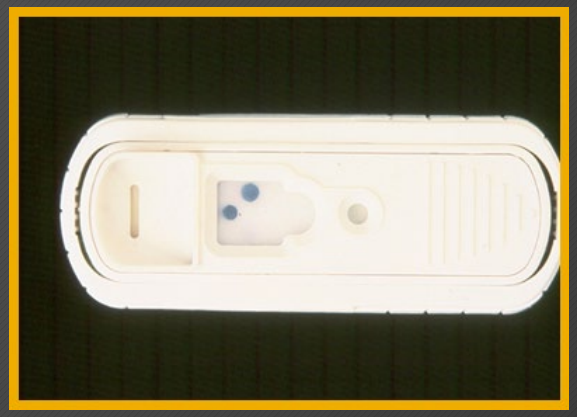
- Antigen

Immunodiagnosis of HW Infections
Adult Heartworm Antigen Kits

- **DETECTS FEMALE UTERINE ANTIGEN**
- Highly sensitive and specific for infections
- **CAN DETECT AS EARLY AS 6 MONTHS**
- Detects only infections with female worms
  - single sex infections w/ only males not detected
  - does not detect prepatent infections (< 5 mo.)
  - older worms produce more antigen
- Can be used to determine effectiveness of adulticidal treatment

Types of Immunodiagnostic Tests

- **ELISA**



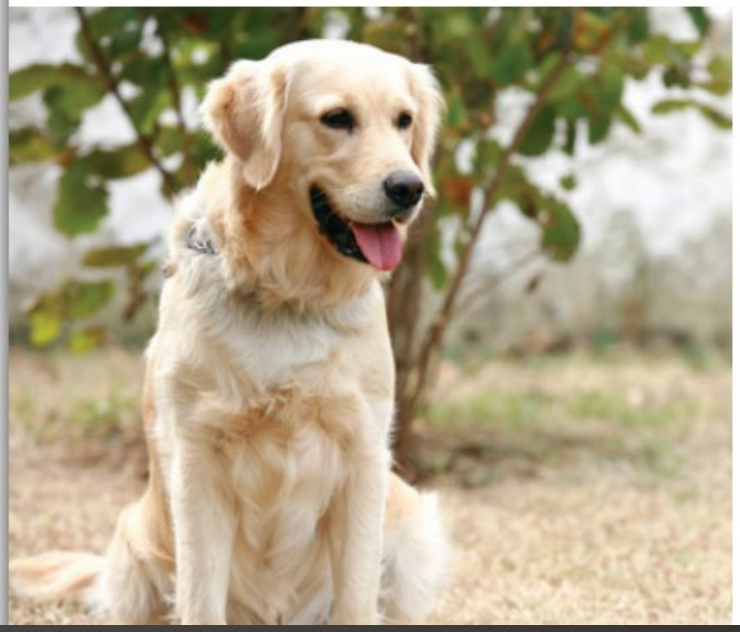
- Immunochromatographic (lateral flow)
  - uses colored gold colloidal particles tagged to monoclonal antibodies to visualize the presence of adult worm Ag

Pet-side heartworm screening you don't have to second-guess

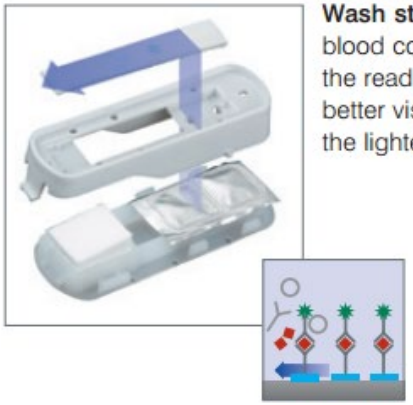
You have plenty of options for point-of-care heartworm assays. But only the SNAP® Heartworm RT, SNAP® 3Dx® and SNAP® 4Dx® Plus tests deliver:

- Highest sensitivity of all rapid assay tests
- Most effective detection of low worm-burden infections
- Reference laboratory ELISA technology with a pet-side test

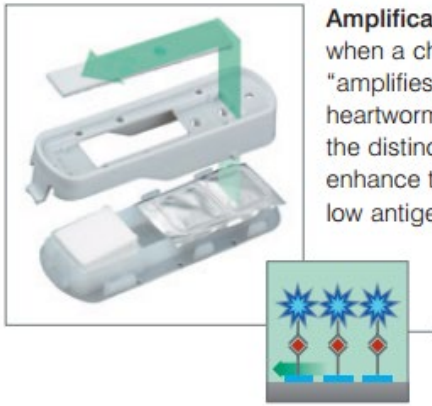
With unmistakable blue-dot results in minutes, IDEXX SNAP tests help you send more clients home with accurate answers and the trust that you're doing everything in your power to care for their pets.



The SNAP tests are the only heartworm assays that use gold-standard laboratory technology on an in-house platform. Two unique features give the ELISA method better performance:



Wash step removes unbound blood components and clears the read window, allowing better visualization of even the lightest positive results.

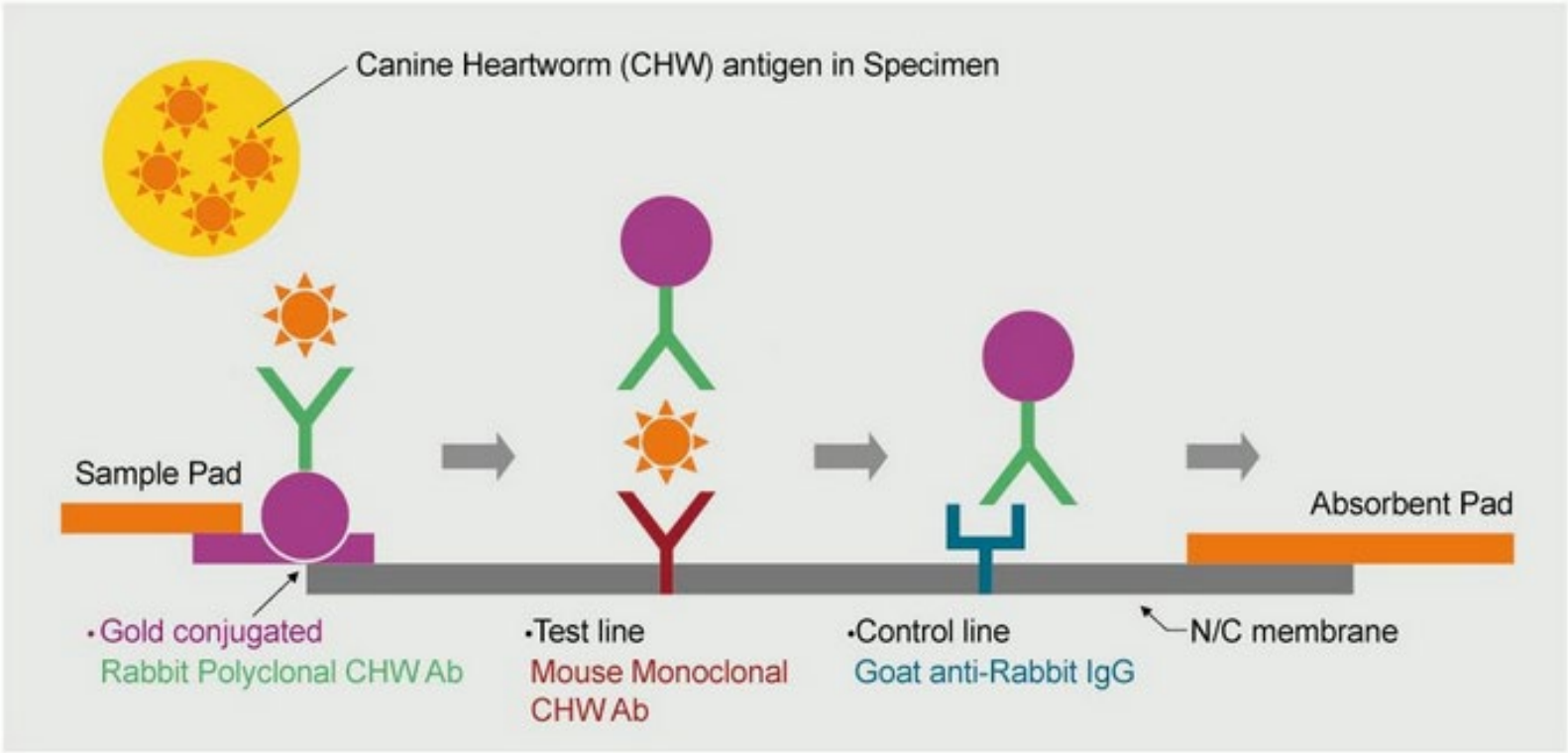


Amplification step occurs when a chemical reaction "amplifies" the presence of heartworm antigen, generating the distinct blue color to further enhance the ability to detect low antigen samples.

https://www.idexx.com/pdf/en_us/smallanimal/snap/heartworm/snap-heartworm-accuracy-brochure.pdf

Lateral flow

- **Principle of Rapid test kit:**



http://www.danscottandassociates.com/files/Files/back1%20copy.jpg

Feline HWD – Immunodiagnosis Antigen Tests

- Same tests available as for dogs but much less sensitive
  - Few females
- Positive test=diagnostic
- Negative test is not definitive
  - Pursue other methods of diagnosis

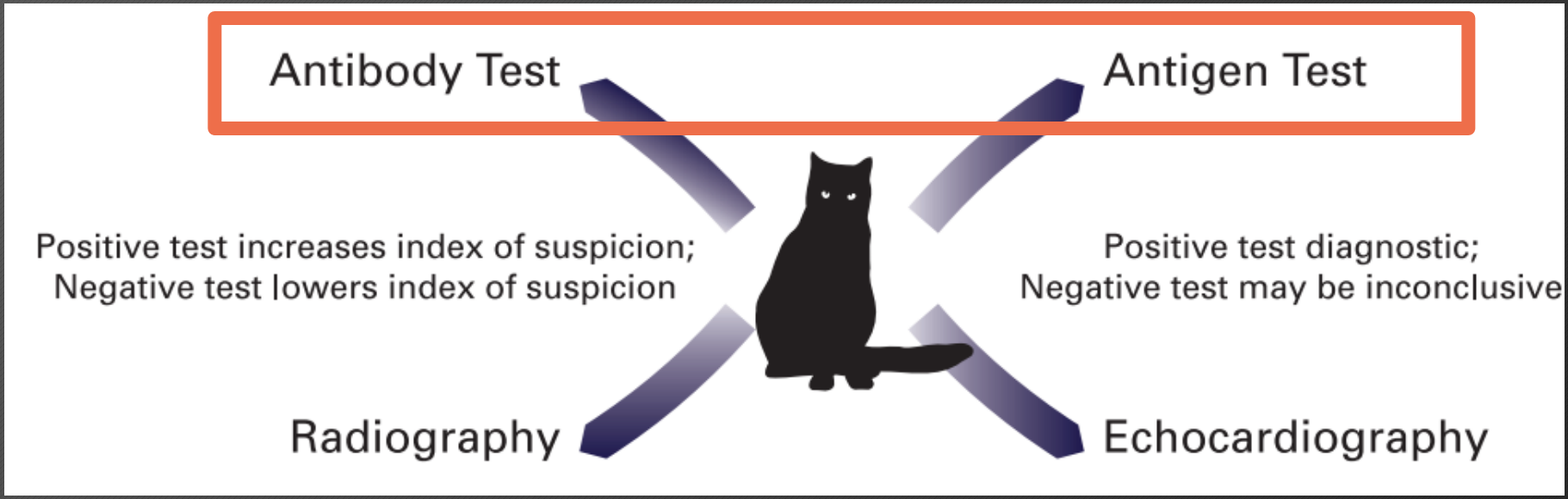
Feline HWD – Immunodiagnosis
Antigen Tests

- Low sensitivity of Ag tests in cats is due mainly to:
  - low worm burden, few females
  - single-sex (male) infections
  - young infections

Feline HWD – Immunodiagnosis
Antibody Tests

- Highly sensitive
  - detect infections by 2 -3 months PI
- BUT -- titers remain high for extended periods after death of worms
- Positive test indicates a cat has been infected
  - NOT -- that it has adult worms in the heart and lungs
- Negative test strongly suggests that cat is not infected and has not been infected recently

HW testing in cats-Summary

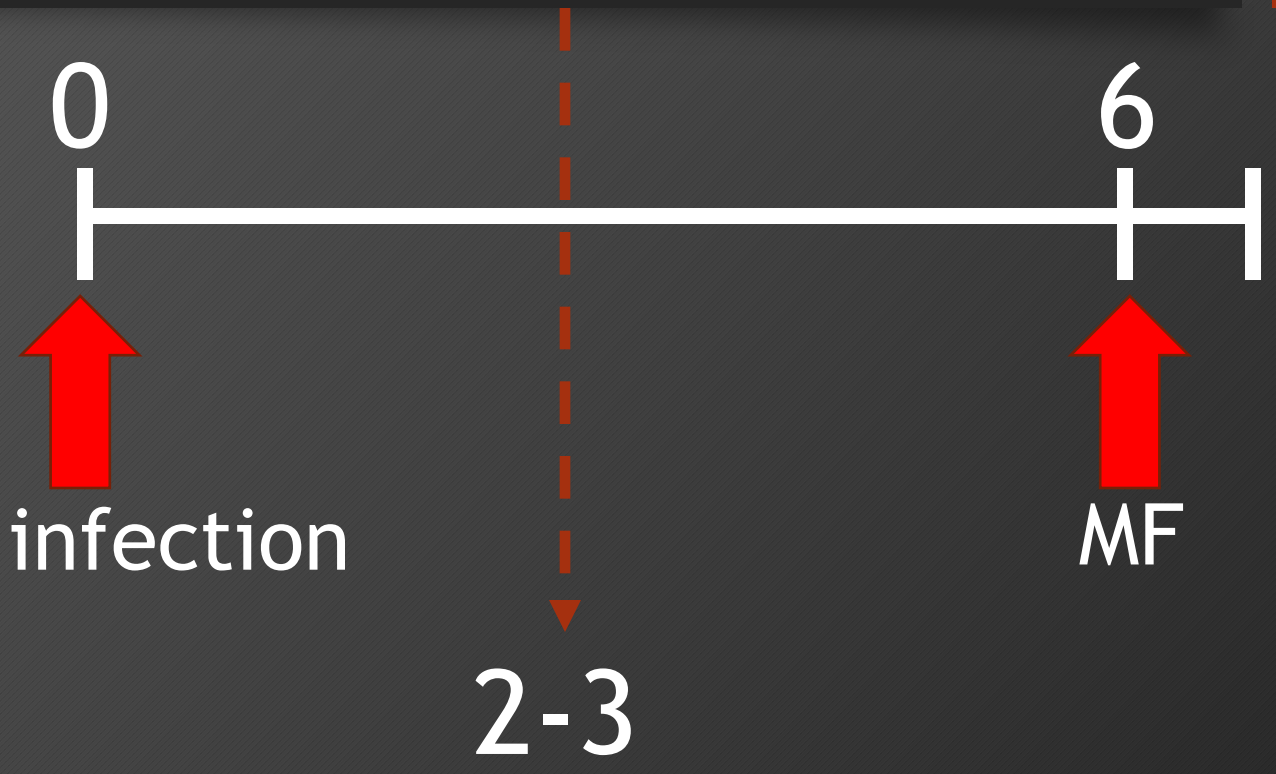


Combining results from Ag and Ab tests achieves greater sensitivity than using either test alone

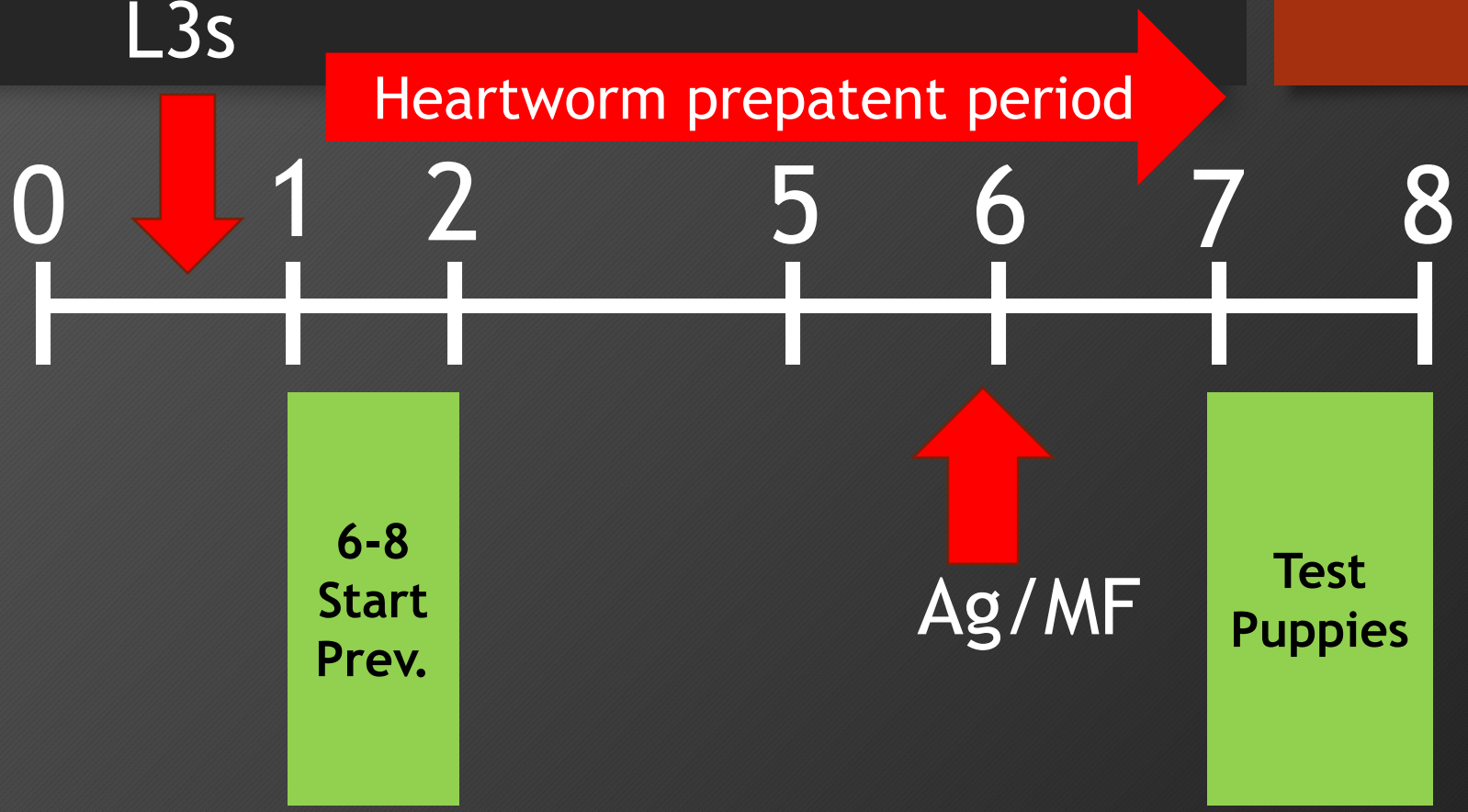
When should I test?-CANINE

- **Practically, you are going to test at 6 months**

YOU Won't detect infection during the prepatent time

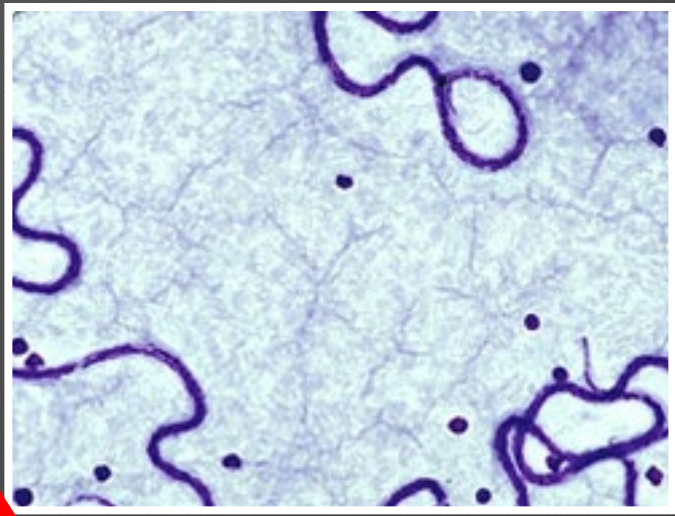


When should I test puppies?



Testing

- Microfilaria



- Antigen

Why MF test?

- Confirms (+) Ag test
- Identifies reservoir of infection

Diagnosis: Detection of microfilariae

- Examination of blood for MF
  - direct smear - detects ~75% of patent infections
  - concentrations techniques
    - Knott test
  - Must differentiate MF of *D. immitis* and *A. reconditum*

Diagnosis: Detection of microfilariae

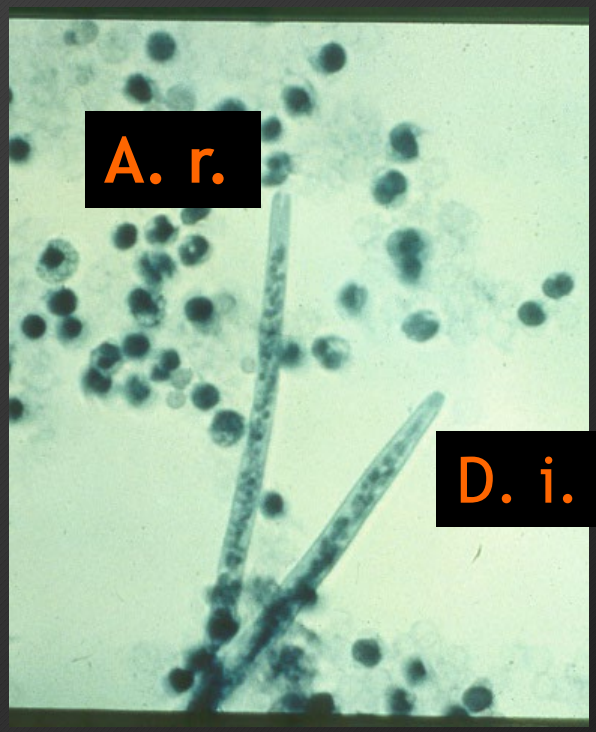
Why does this not matter in a cat?

Acanthocheilonema (Dipetalonema) reconditum

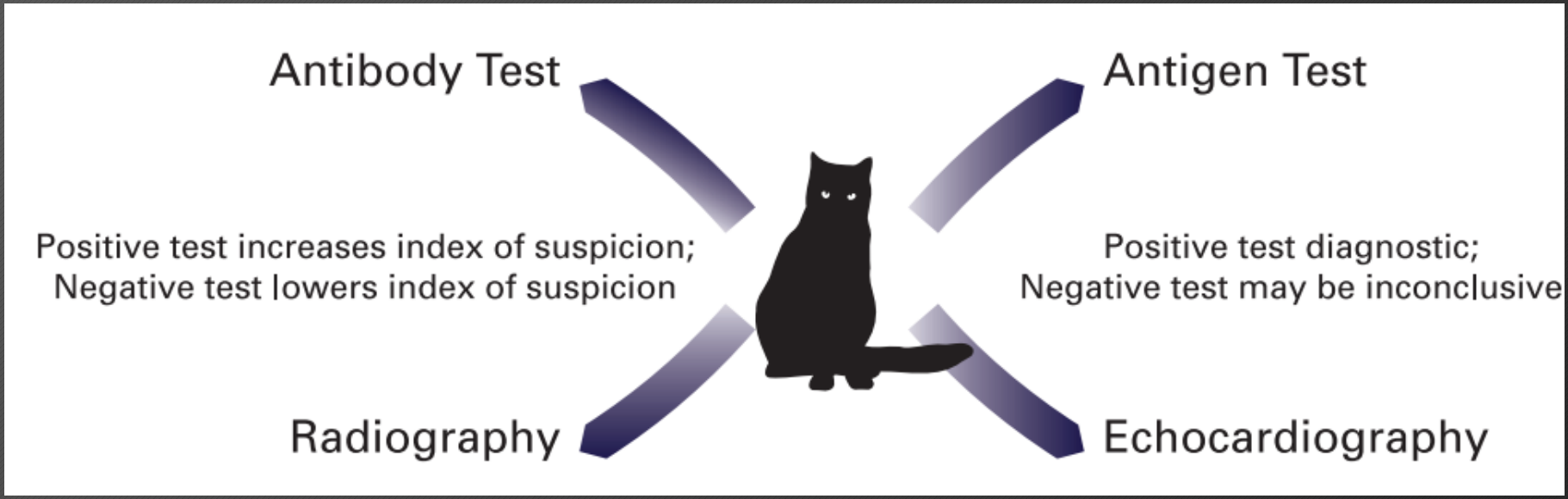
- Adult worms in subcutaneous tissue
- Microfilariae in blood
- Transmitted by fleas
- Nonpathogenic
- Major importance
  - Must differentiate MF of *D. immitis* and *A.* (*D.*) *reconditum*

Identification of MF

	D. immitis	*A. reconditum*
Length (microns)	286-340 (usually >300)	258-292 (always < 300)
Shape of anterior end	tapered	blunt (broom handle)
Number present	few to many	usually few
Movement (direct smear)	stationary	progressive



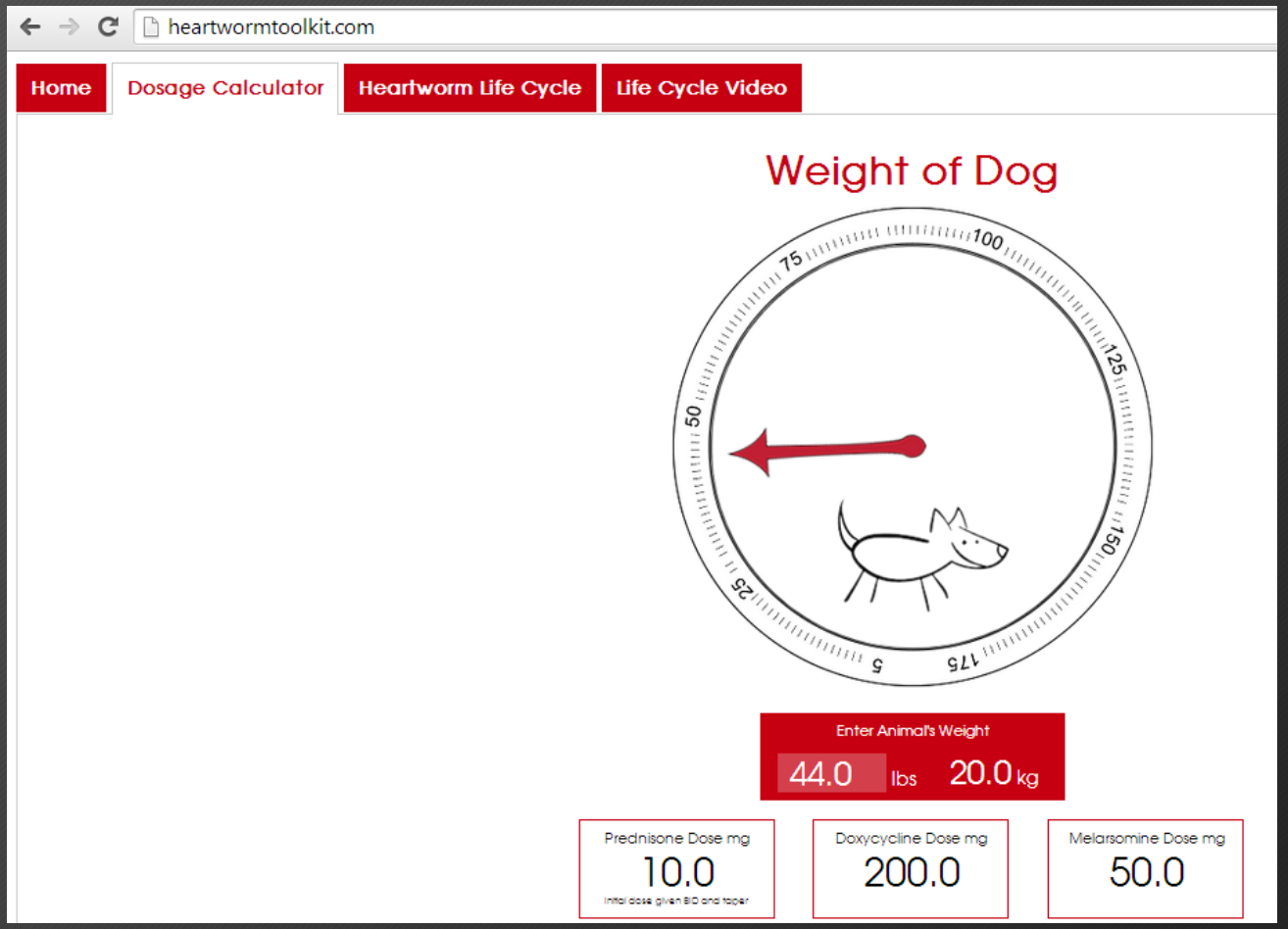
HW testing in cats-Summary



Combining results from Ag and Ab tests achieves greater sensitivity than using either test alone


Highlights of the
Canine Guidelines for the
Prevention, Diagnosis, and Management of Heartworm Infection
(*Dirofilaria immitis*)
in Dogs
Revised 2024

Keeping it all straight



Enter Animal's Weight

44.0 lbs 20.0 kg

Prednisone Dose mg	Doxycycline Dose mg	Melarsomine Dose mg
10.0	200.0	50.0
Initial dose given BID and taper		

Create a Treatment Plan

Treatment Plan

Start Date: Today

☑ **January 14, 2025**

In a dog diagnosed and verified as heartworm positive, either by:

• Positive antigen (Ag) test verified with microfilaria (MF) test, OR if no MF are detected,
• Confirm with a second Ag test with a new sample on a different type of testing platform

1. Administer appropriate heartworm preventive (monthly [topical or oral] or injectable)
– If MF are detected, pre-treat with antihistamine and glucocorticosteroids, if not already on prednisone, to reduce risk of anaphylaxis
– Observe for at least 8 hours for signs of reaction
2. Administer doxycycline 10 mg/kg BID for 28 consecutive days
• Reduces pathology associated with dead heartworms
• Disrupts heartworm transmission
3. Begin activity restriction—the more pronounced the signs, the more rigid the activity restriction
4. Administer an EPA- or FDA-approved ectoparasiticide product designed for use in dogs that has demonstrated mosquito-killing activity

If the dog is symptomatic in addition to the items above:

• Stabilize with appropriate therapy and nursing care
• Prednisone prescribed at a tapering dose of 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg every other day (EOD) for the 3rd and 4th weeks

☑ **February 13, 2025**

Communicate with the client to ensure:

1. Completion of the full course of doxycycline
2. Administration of heartworm preventive (unless injectable heartworm preventive was administered on day 0)
3. Administration of an EPA- or FDA-approved ectoparasiticide product designed for use in dogs that has demonstrated mosquito-killing activity

Melarsomine dihydrochloride (Diroban®/Immiticide®)

https://www.zoetisus.com/products/dogs/diroban/index.aspx?gclid=Cj0KCQjw9O6HBhCrARIsADx5qCSFXGXkD0UZBfGvdzj8GiWoJYvY3D0BgNAeO_L7JA9BkIBMCD3h3L8aAsgsEALw_wcB

https://www.midwestvetsupply.com/item/466.47000.3/Immiticide-Sterile-Powder-with-Sterile-Water-for-Injection-5-ct/

PREADULTICIDE EVALUATION

Summary of Clinical Signs of Canine Heartworm Disease

Early infection	Class 1	No signs
Mild disease	Class 1	Cough
Moderate disease	Class 2	Cough, exercise intolerance,
		from reduced blood flow to the brain, ascites (fluid accumulation in the abdominal cavity), death
Caval Syndrome Class 4		Sudden onset of severe lethargy and weakness accompanied by hemoglobinemia and hemoglobinuria

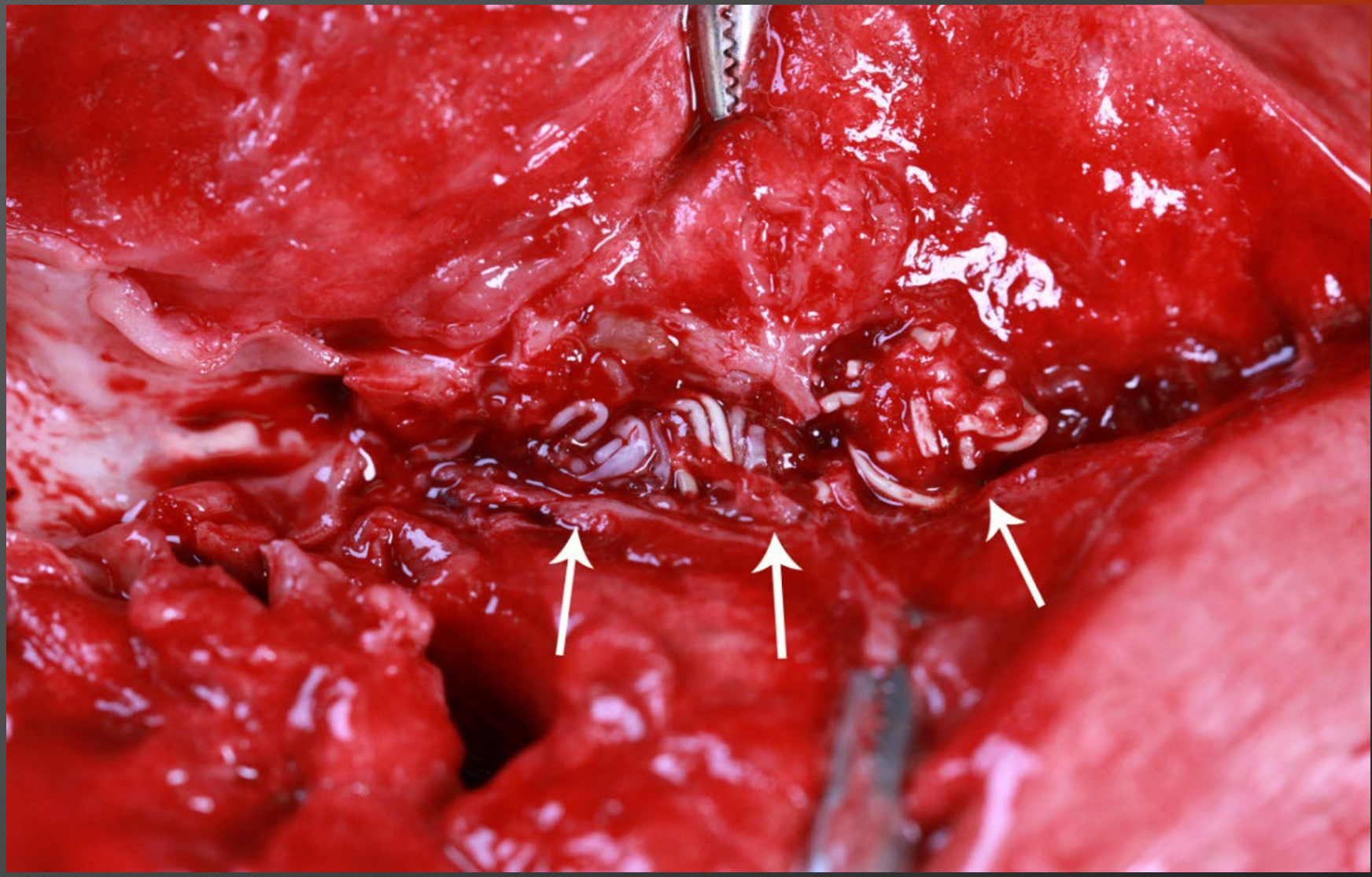
o_o

o o

Pulmonary thromboembolism (PTE) after treatment

x x

⁀



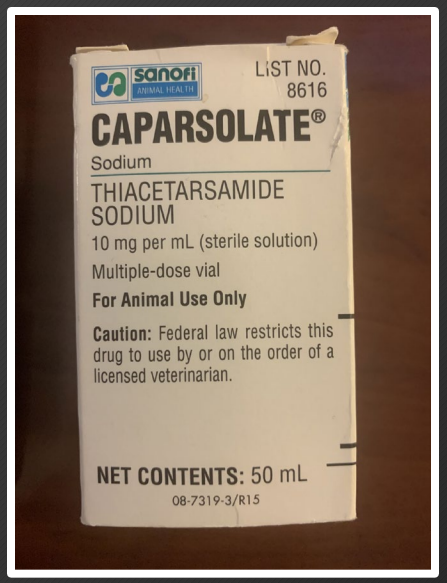
Courtesy of Dr. Steve Jones

Pulmonary Thromboembolism

- More worms, more pathology
- Clinical Signs of embolism = fever, cough, hemoptysis
- Usually evident within 7-10 days but may occur for up to 4 weeks post-Tx

No Known Tests Are Predictive For When Thromboembolism Will Occur

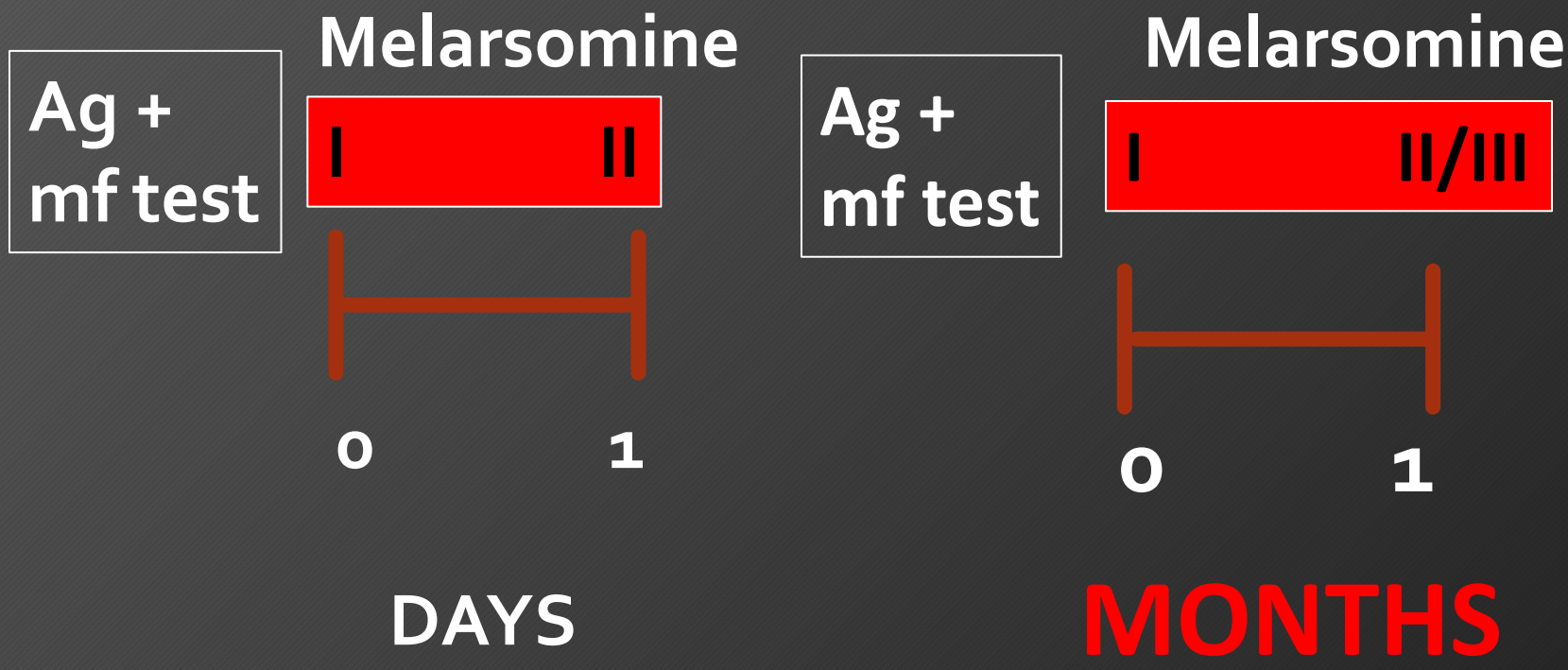
- PTE and adulticide therapy
  - pulmonary damage
  - inevitable consequence of successful adulticide therapy
  - The potential reason people have become scared of adulticide therapy



Adulticide Therapy

- Melarsomine dihydrochloride (Immiticide®/Diroban®)
  - standard 2-dose regimen
    - 2 IM injections, each at 2.5 mg/kg, 24 hr apart
  - 3-dose regimen dogs
    - 1 injection at 2.5 mg/kg, 1 month later give 2 dose regimen
    - increase in safety and efficacy with 3-dose regimen
    - **RECOMMENDED**
- Repeat HW Ag test at 9 months after treatment to confirm treatment success
  - AHS recommended

The 2-dose vs. 3-dose protocol



Efficacy and Safety of 3-Dose Schedule for Melarsomine

- Standard 2-dose regimen
  - Kills >90% of adult worms and 4-month-old larvae
- Alternate or 3-dose regimen
  - First dose kills ~50% of worms
    - Diminishes degree of insult to pulmonary vasculature and tissue
  - Remaining 2 doses 1-2 months later gives ~99% efficacy on adult worms
- **BOTTOM LINE: 3-DOSE KILLS MORE WORMS**

2-dose

2-dose

3-dose

5 worms
Still alive

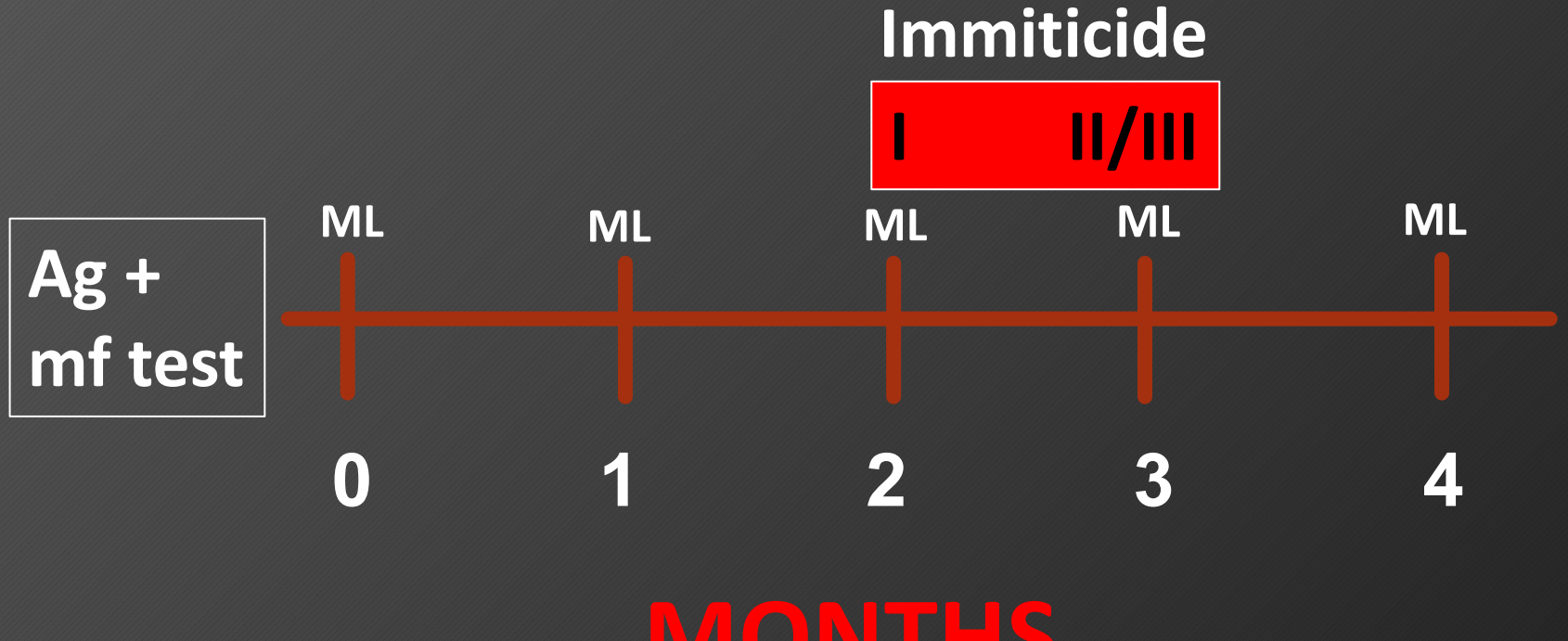
Current Rec'd of AHS For Improving Safety of Heartworm Treatment

- Use 3-injection protocol for all heartworm infections
- Start ML preventive at time of diagnosis prior to melarsomine Tx
  - Prevent further infection
- Per AHS guidelines

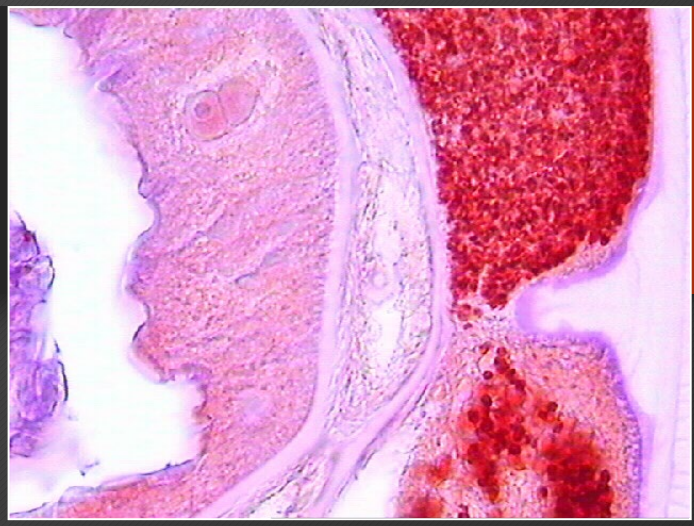
AMERICAN HEARTWORM SOCIETY
ESTABLISHED 1974

Heartworm Treatment Summary

But it is not that simple…

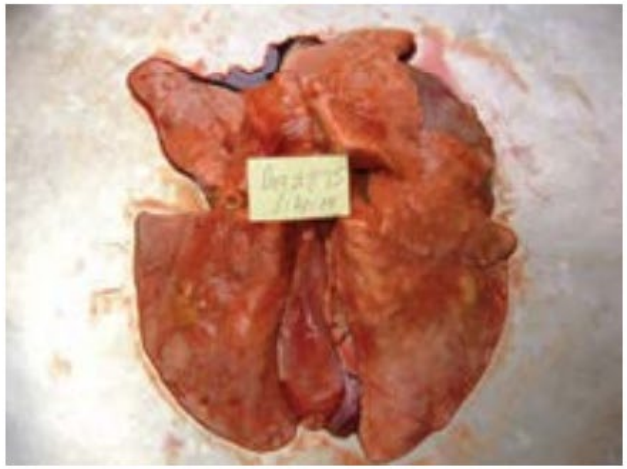


Doxycycline



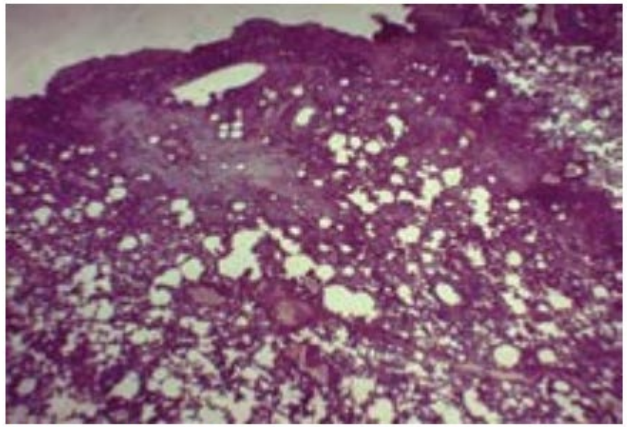
- *Wolbachia*
  - Endosymbiont of filarial worms
- Potentially reduces risk of thromboembolism (Kramer et al. Vet Para. **176** pp. 357-360)
- For 28 days prior to adulticide treatment
- 10 mg/kg BID for 28 days

AMERICAN HEARTWORM SOCIETY
EST. 1974

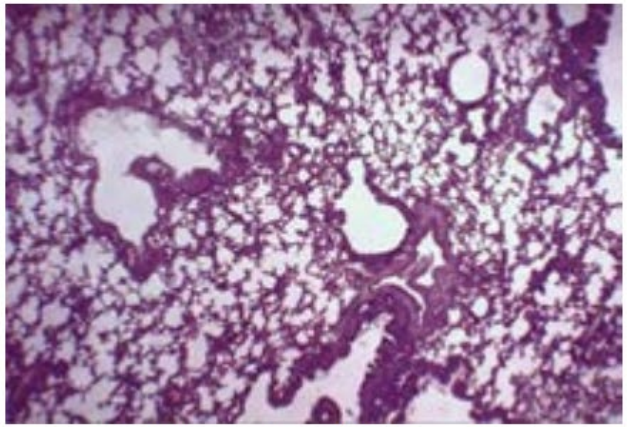


Melarsomine only

Ivermectin / Doxycycline / Melarsomine



Melarsomine only

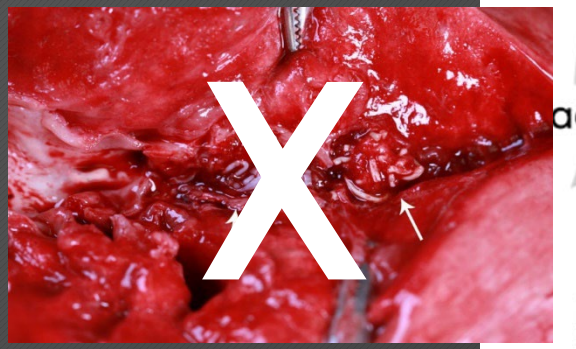


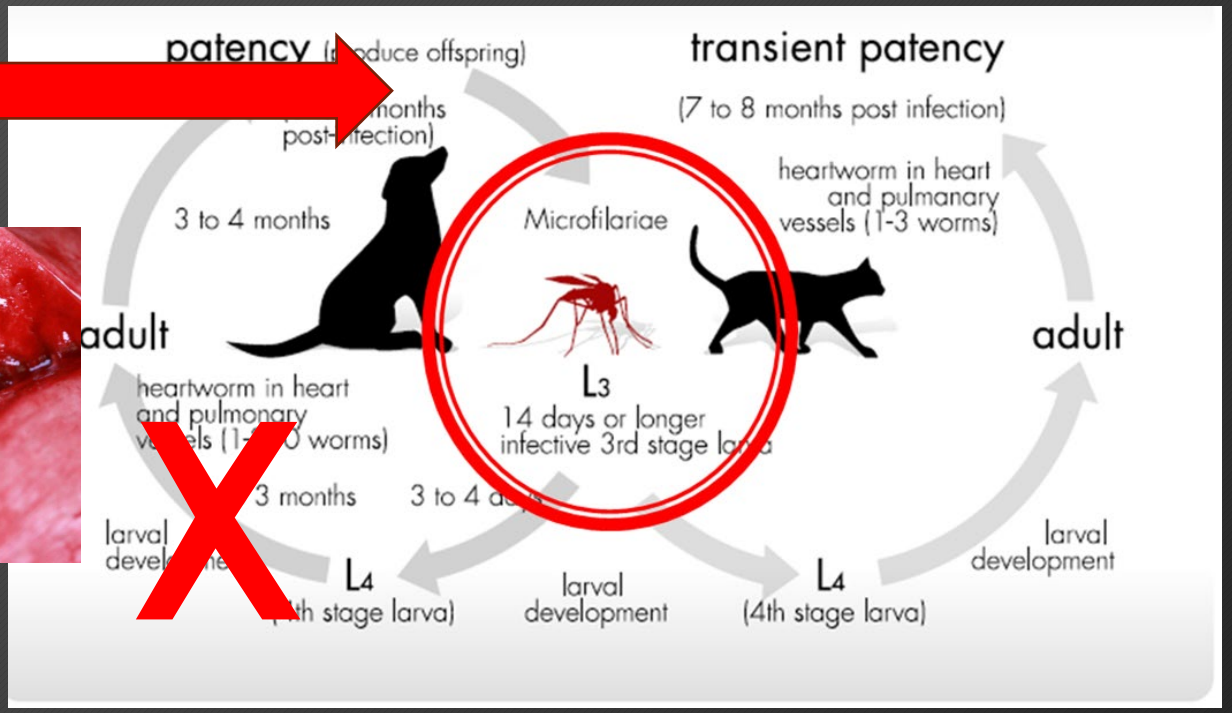
Ivermectin / Doxycycline / Melarsomine

Figure 8. Pulmonary pathology associated with the death of heartworms in experimentally infected heartworm-positive dogs pretreated with ivermectin and doxycycline prior to receiving melarsomine injections. Photographs courtesy of John McCall, PhD and Laura Kramer, DVM, PhD.

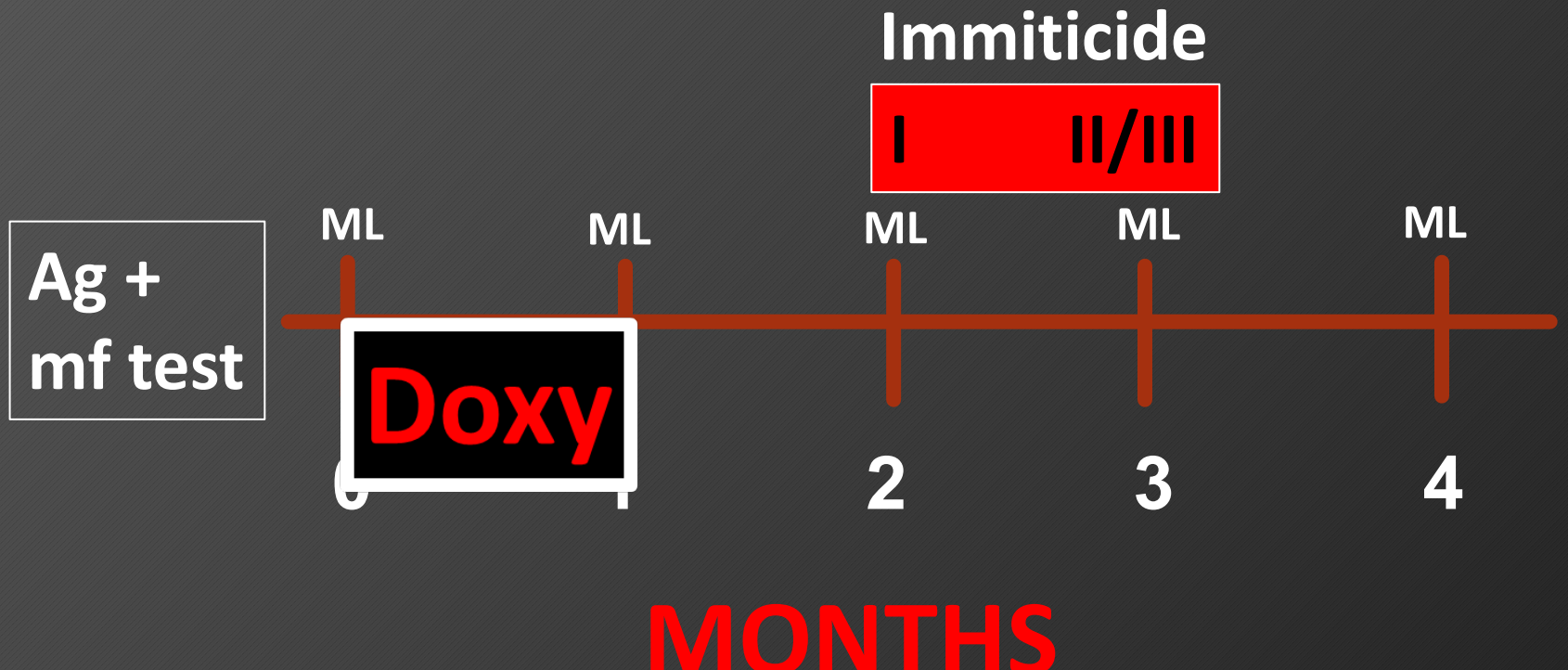
Doxy prevents HW development in subsequent hosts

DOXY

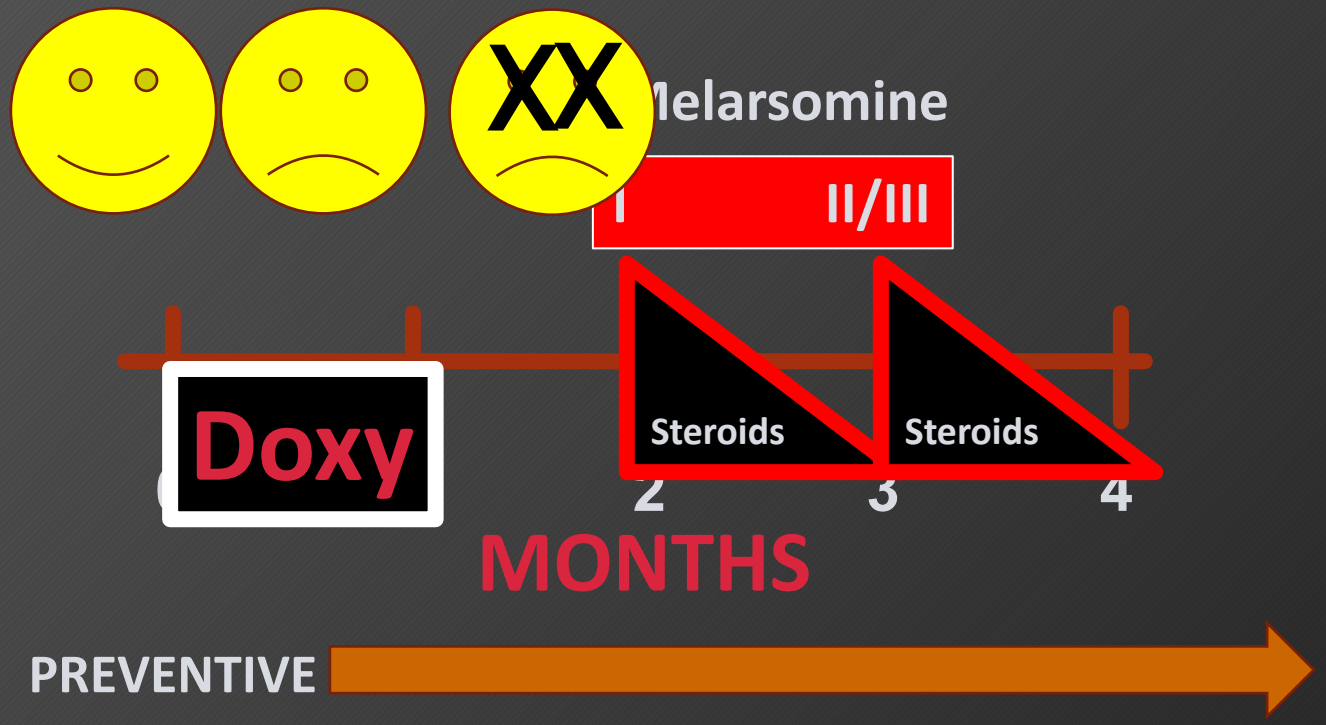




Heartworm Treatment Summary



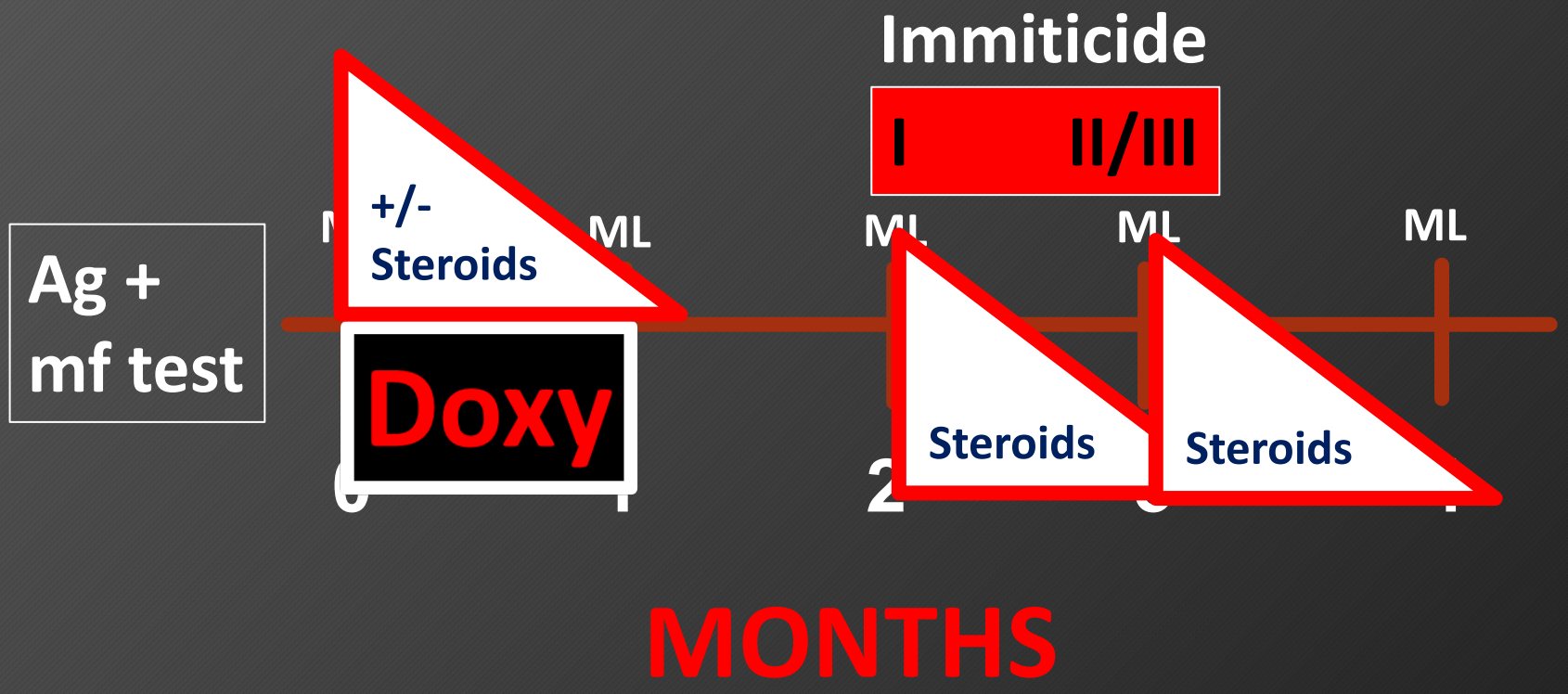
Why the extra month?



Other medications

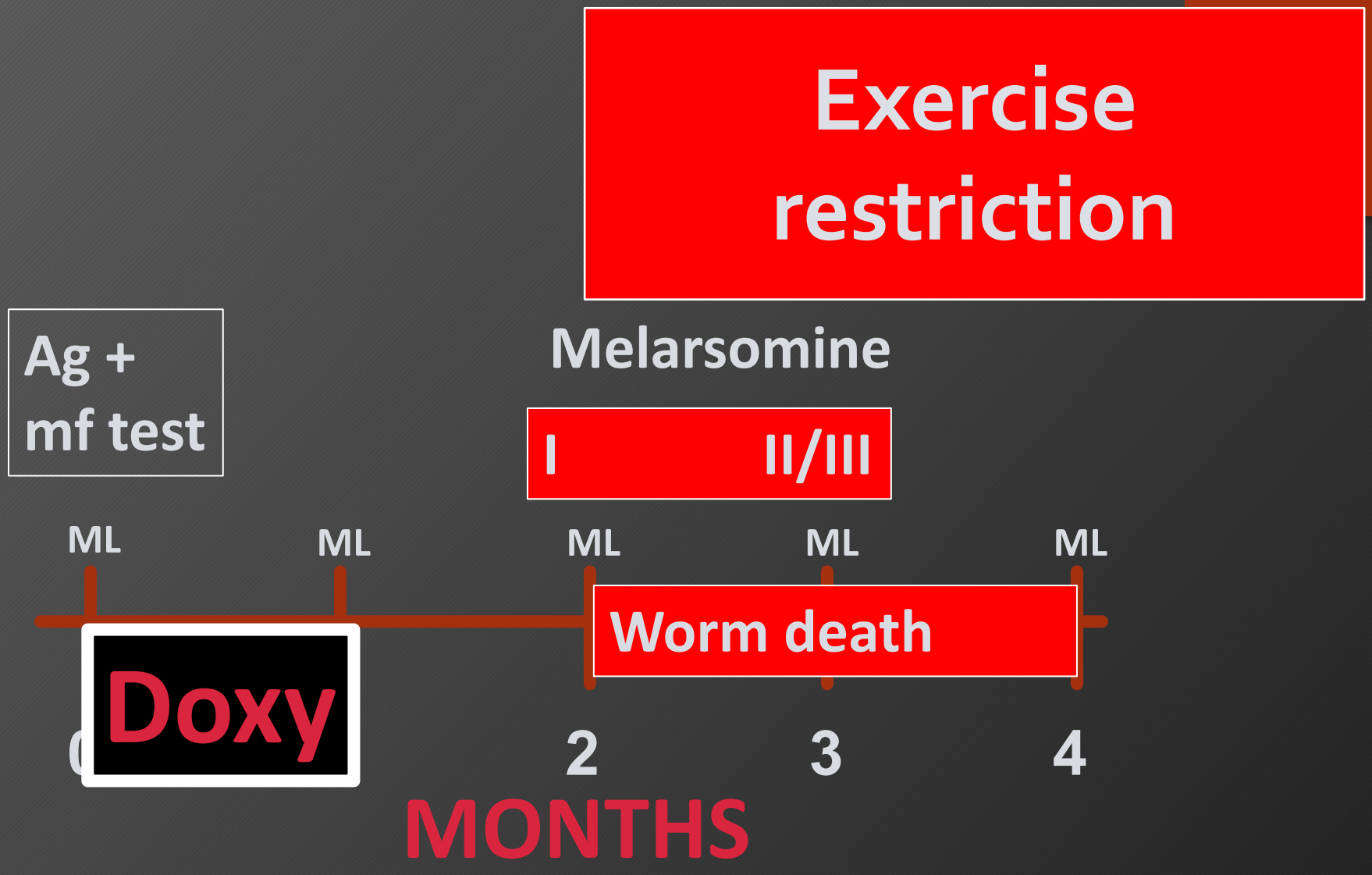
- Herbal medicines
  - None are effective
- NSAIDs/Aspirin
  - Not recommended
- Steroids
  - Prednisone
    - 0.5 mg/kg BID for 1st week
    - 0.5 mg/kg SID for 2nd week
    - 0.5 mg/kg q48 h for 1-2 weeks

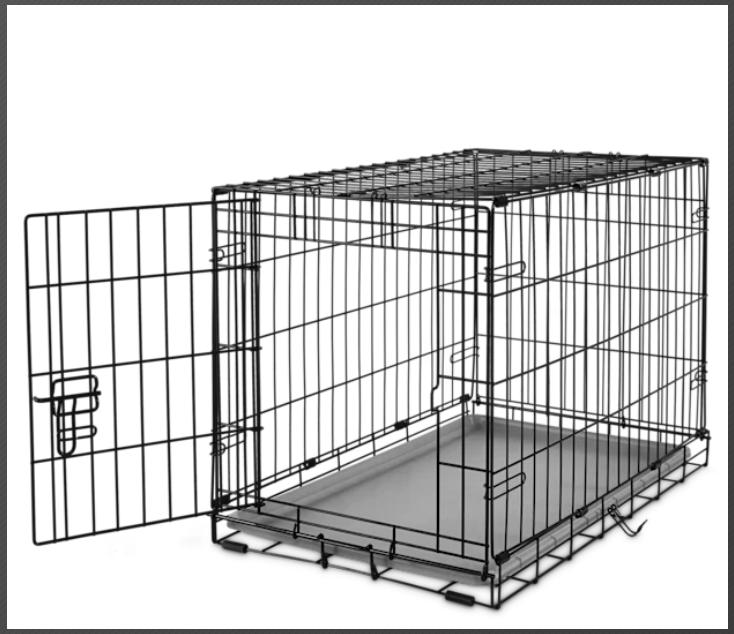
Heartworm Treatment Summary



EXERCISE RESTRICTION

- Diagnosis
  - Reduced activity
- Treatment
  - After 1st dose
  - 6-8 weeks post-Tx
  - Total of 10-12 weeks


Exercise restriction
Ag + mf test
Melarsomine
I
II/III
ML
ML
ML
ML
ML
Worm death
Doxy
0
2
3
4
MONTHS



Microfilaricidal Therapy

- Drugs
  - Labelled microfilaricide
    - Topical Moxidectin/Imidicloprid
- Monitor dogs closely after 1st dose for systemic side effects
  - most rxns are transient
  - severe shock is possible
  - Keep in hospital after treatment

Table 2. AHS-Recommended Heartworm Management Protocol

Day	Treatment
0	**In a dog diagnosed and verified as heartworm positive, either by:** • Positive antigen (Ag) test verified with microfilaria (MF) test, OR if no MF are detected, • Confirm with a second Ag test with a new sample on a different type of testing platform 1. Administer appropriate heartworm preventive (monthly [topical or oral] or injectable) – If MF are detected, pre-treat with antihistamine and glucocorticosteroids, if not already on prednisone, to reduce risk of anaphylaxis – Observe for at least 8 hours for signs of reaction 2. Administer doxycycline 10 mg/kg BID for 28 consecutive days • Reduces pathology associated with dead heartworms • Disrupts heartworm transmission 3. Begin activity restriction—the more pronounced the signs, the more rigid the activity restriction 4. Administer an EPA- or FDA-approved ectoparasiticide product designed for use in dogs that has demonstrated mosquito-killing activity **If the dog is symptomatic in addition to the items above:** • Stabilize with appropriate therapy and nursing care • Prednisone prescribed at a tapering dose of 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg every other day (EOD) for the 3rd and 4th weeks
30	**Communicate with the client to ensure:** 1. Completion of the full course of doxycycline 2. Administration of heartworm preventive (unless injectable heartworm preventive was administered on day 0) 3. Administration of an EPA- or FDA-approved ectoparasiticide product designed for use in dogs that has demonstrated mosquito-killing activity
31–59	A one-month wait period after administration of doxycycline but before administration of melarsomine is currently recommended
60	1. Administer heartworm preventive (unless injectable heartworm preventive was administered on day 0) 2. Administer 1st (of 3) melarsomine injections, 2.5 mg/kg intramuscularly (IM) a. Monitor for post-injection anaphylaxis b. Prescribe appropriate pain control 3. Prescribe a tapering dose of prednisone of 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg EOD for the 3rd and 4th weeks 4. Start rigid activity restriction (or maintain if started on day 0): cage restriction, on-leash when taken outside to eliminate 5. Administer an EPA- or FDA-approved ectoparasiticide product designed for use in dogs that has demonstrated mosquito-killing activity
90	1. Administer heartworm preventive (unless injectable heartworm preventive was administered on day 0) 2. Administer 2nd (of 3) melarsomine injection, 2.5 mg/kg intramuscularly (IM) a. Monitor for post-injection anaphylaxis b. Prescribe appropriate pain control 3. Prescribe a tapering dose of prednisone of 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg every other day (EOD) for the 3rd and 4th weeks 4. Administer an EPA- or FDA-approved ectoparasiticide product designed for use in dogs that has demonstrated mosquito-killing activity
91	1. Administer 3rd (of 3) melarsomine injection into the opposite epaxial muscle from the injection site on day 90, 2.5 mg/kg intramuscularly (IM) a. Monitor for post-injection anaphylaxis b. Prescribe appropriate pain control 2. Continue rigid activity restriction for the next 6–8 weeks: cage restriction, on-leash when taken outside to eliminate
120	1. Quantitatively test (e.g., Modified Knott Test) for presence of MF regardless of patient's MF-status on day 0 • If positive, treat with a microfilaricide and retest every 4 weeks until no MF detected. If MF persist, additional testing for resistance should be considered 2. Continue a year-round heartworm and mosquito prevention program as described under Prevention 3. Gradual return to normal activity over the next 4 weeks
365	Resume annual HW-screening protocol (9 months after last melarsomine injection) • Antigen test • Microfilaria test If still Ag-positive, re-treat with 28 days of doxycycline followed by 2 injections (2.5 mg/kg IM each) of melarsomine 24 hours apart • Monitor for post-injection anaphylaxis • Prescribe appropriate pain control • Prescribe a tapering dose of prednisone of 0.5 mg/kg BID 1st week, 0.5 mg/kg SID 2nd week, 0.5 mg/kg for the 3rd and 4th weeks • Institute and maintain strict activity restriction for 6–8 weeks: cage restriction, on-leash when using yard

Managing Interruptions in Scheduled Treatment

Situations may arise where there is an interruption in a scheduled treatment. If the clinic environment necessitates that a delay occurs in any stage of treatment, practitioners may question 1) how to resume the treatment protocol; and 2) whether the protocol itself should be re-started. The following recommendations address these potential questions with the dearth of scientific data that is currently available.

Scenario A: A dog diagnosed and confirmed to have heartworms has been started on heartworm preventive and prescribed doxycycline; however, administration of the first melarsomine injection must be delayed. How long can the practitioner wait before administering melarsomine without having to repeat doxycycline?

Answer: If doxycycline was administered at a dose of at least 5 mg/kg BID for 4 weeks, **and consistent heartworm prevention was administered throughout the elapsed time frame**, there is no need to repeat doxycycline until 6 months has passed.

Scenario B: A dog has been pre-treated with a monthly heartworm preventive and doxycycline and received the first melarsomine injection, but the second and third melarsomine injections are delayed. How long can the practitioner wait before administering the second and third injections?

Answer: In such cases, practitioners can delay the second and third injections for up to 6 months. However, the second and third injections MUST be given within a 24-hour period when the adulticide treatment is resumed. **Again, the dog must be maintained on a preventive without interruption**.

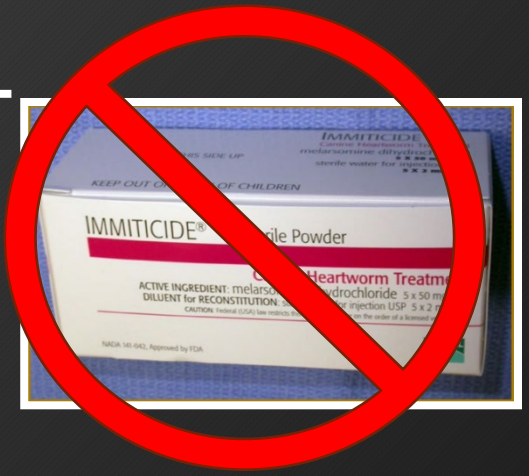
365	Resume annual HW-screening protocol (9 months after last melarsomine injection) • Antigen test • Microfilaria test If still Ag-positive, re-treat with 28 days of doxycycline followed by 2 injections (2.5 mg/kg IM each) of melarsomine 24 hours apart

2 doses melarsomine

9 months post treatment=positive

Feline HWD Treatment

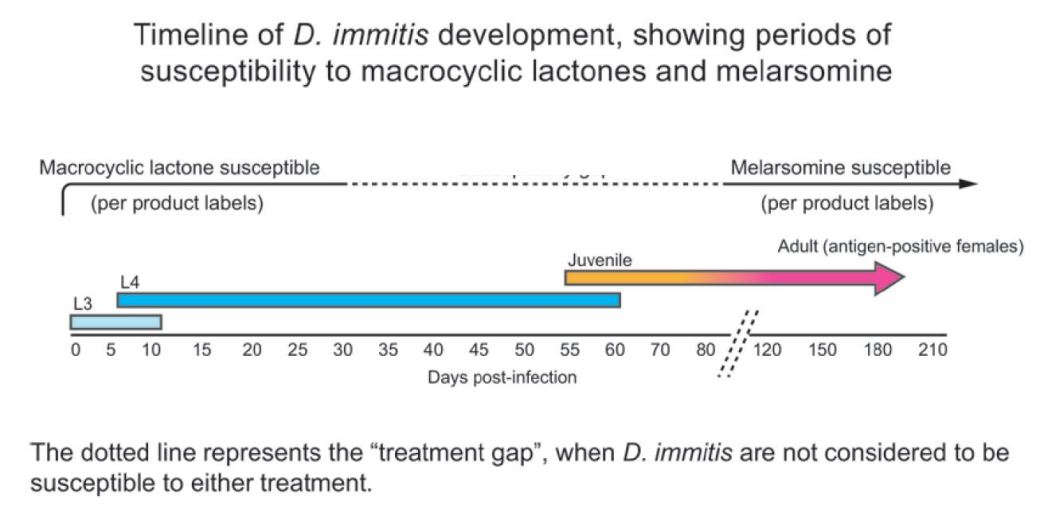
- NO satisfactory treatments
  - arsenical drugs are highly toxic in cats
- Severely affected cats have poor prognosis
- Prophylaxis with monthly ML
- Steroids




Percentage of Pet Owners
Who Regularly Administer a
Heartworm Prevention Product
59%
5%
Dog Owners
Cat Owners

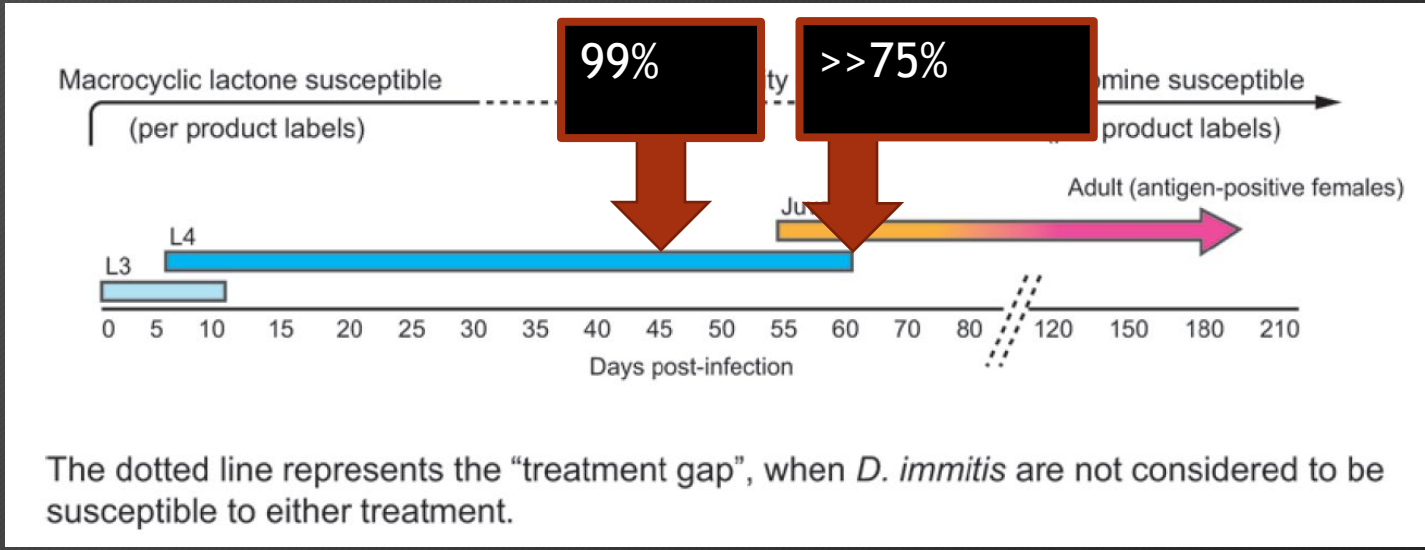
Heartworm Prophylaxis

- Monthly ML treatments kill L3 and L4 stages with virtually 100% efficacy
  - **THIS STRATEGY IS DESIGNED TO ALLOW THE DOG TO BECOME INFECTED AND THE PREVENTIVES THEN KILLS ALL RECENTLY ACQUIRED WORMS**



Heartworm Prophylaxis

- **RECOMMENDED YEAR ROUND**
- HW transmission season < than mosquito season
  - mosquitoes will be around both before and after transmission begins and ceases

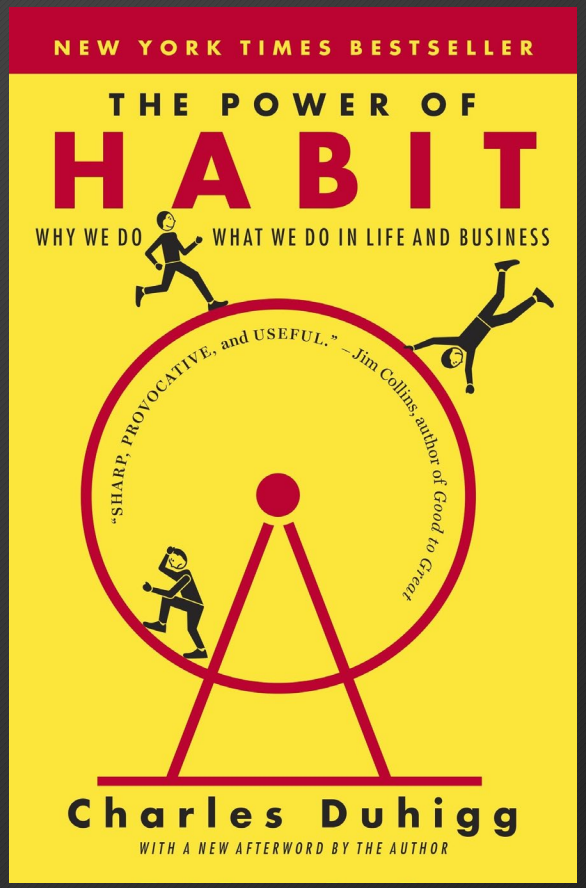


The dotted line represents the "treatment gap", when *D. immitis* are not considered to be susceptible to either treatment.

Heartworm Prophylaxis

Think 12

- **RECOMMENDED YEAR ROUND**
- Adherence
- Company Guarantees
  - Require proof of purchase



Macrocyclic lactones-Dogs

- Oral
  - Ivermectin
  - Milbemycin oxime
  - Moxidectin
- Topical
  - Moxidectin
  - Selamectin

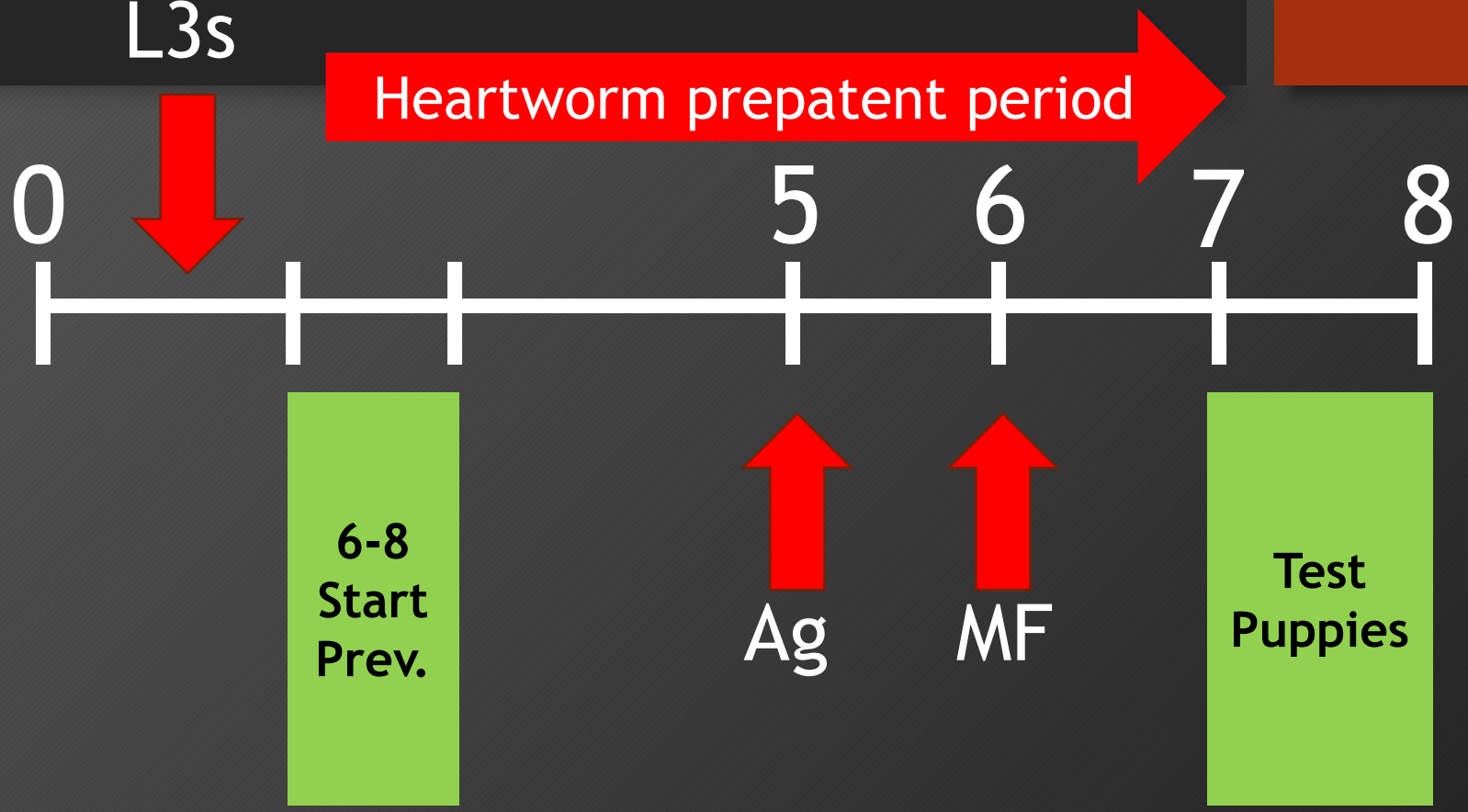
PREVENTIVES FOR DOGS		*Dirofilaria immitis*		Other Parasites Treated in Addition to Heartworm										
Drug	**Trade Name(s)**	Tissue Stages (Larvae)	Circulating Microfilariae	Fleas	Ticks	Hookworms	Roundworms	Whipworms	Tapeworms	Ear Mites	Sarcoptic Mange Mites	Minimum Age/ Weight	Safe to Use During Breeding/ Lactation	Food Allergen Considerations
Oral Administration (monthly tablets and chews)														
Ivermectin + pyrantel pamoate	**HEARTGARD® Plus** (*Boehringer Ingelheim*) **Tri-Heart® Plus** (*Merck*)	X				X[a]	X[b]					6 weeks/ no minimum weight	Yes	Beef
	Iverhart Plus® (*Virbac*)	X				X[a]	X[b]							Pork liver
Ivermectin + pyrantel pamoate + praziquantel	**Iverhart Max®** (*Virbac*) **IMECTRO®** (*Ceva*)	X				X[a]	X[b]		X[h]			8 weeks/ 6 lbs	Not evaluated	Pork liver Artificial beef
Milbemycin oxime	**Interceptor®** (*Elanco*), **MilbeGuard®** (*Ceva*) **Milbehart™** (*Virbac*)	X				X[c]	X[b]	X[d]				4 weeks/ 2 lbs	Yes	Beef
Milbemycin oxime + praziquantel	**Interceptor® Plus** (*Elanco*)	X				X[c]	X[b]	X[d]	X[f]			6 weeks/ 2 lbs	Not evaluated	Chicken
Milbemycin oxime + lufenuron	**Sentinel® Flavor Tabs** (*Merck*)	X		X[j]		X[c]	X[b]	X[d]				6 weeks/ 2 lbs	Yes	Artificial beef Pork/soy
Milbemycin oxime + lufenuron + praziquantel	**Sentinel® Spectrum®** (*Merck*)	X		X[j]		X[c]	X[b]	X[d]	X[f]			6 weeks/ 2 lbs	Not evaluated	Beef
Milbemycin oxime + spinosad	**Trifexis®** (*Elanco*)	X		X[n]		X[c]	X[b]	X[d]				8 weeks/ 5 lbs	Use with caution	Artificial beef Pork liver/ hydrolyzed soy
Moxidectin + afoxolaner + pyrantel	**NEXGARD® PLUS** (*Boehringer Ingelheim*)	X		X[n]	X[k]	X[o]	X[b]					8 weeks/ 4 lbs	Not evaluated	None
Moxidectin + sarolaner + pyrantel pamoate	**Simparica® Trio** (*Zoetis*)	X		X[k]	X[l]	X[m]	X[b]					8 weeks/ 2.8 lbs	Not evaluated	Pork
Injectable Administration (every 6 or 12 months)														
Moxidectin	**ProHeart® 6** (*Zoetis*)	X				X[o]						6 months/ 5 lbs	Yes	
	ProHeart® 12 (*Zoetis*)	X				X[o]						12 months/ 5 lbs	Yes	
Topical Administration (monthly spot-on)														
Moxidectin + imidacloprid	**Advantage Multi®** (*Elanco*), **IMOXI™** (*Votoquinol USA*), **Midamax®** (*Norbrook*), **PARASEDGE™ Multi** (*Virbac*)	X	X	X[n]		X[p]	X[q]	X[d]			X[r]	7 weeks/ 3 lbs	Not evaluated	
Selamectin	**Revolution®** (*Zoetis*), **Paradyne®** (*Vethical*), **Senergy™** (*Virbac*), **Selarid™** (*Norbrook*), **Revolt™** (*Aurora*)	X		X[s]	X[t]					X[s]	X[r]	6 weeks/ no minimum weight	Yes	

Injectable moxidectin

Recommended Year-round

PREVENTIVES FOR CATS		*Dirofilaria immitis*		Other Parasites Treated in Addition to Heartworm								
Drug	**Trade Name(s)**	**Tissue Stages (Larvae)**	**Circulating Microfilariae**	**Fleas**	**Ticks**	**Hookworms**	**Roundworms**	**Tapeworms**	**Ear Mites**	**Minimum Age/Weight**	**Safe to Use During Breeding/ Lactation**	**Food Allergen Considerations**
Oral Administration (monthly tablets and chews)												
Milbemycin oxime	**Interceptor®** (*Elanco*), **MilbeGuard®** (*Ceva*) **Milbehart™** (*Virbac*)	X				X[c]	X[e]			6 weeks/ 1.5 lbs	Not evaluated	Beef
Topical Administration (monthly spot-on; Bravecto PLUS is every 2 months)												
Moxidectin + imidacloprid	**Advantage Multi®** (*Elanco*), **IMOXI™** (*Vetoquinol USA*), **PARASEDGE™ Multi** (*Virbac*), **Midamox™ for Cats** (*Norbrook*)	X		X[n]		X[s]	X[t]		X[u]	9 weeks/ 1.5 lbs	Not evaluated	
Moxidectin + fluralaner	**Bravecto® PLUS** (*Merck*)	X		X[n]	X[v]	X[s]	X[t]			6 months/ 2.6 lbs	Not evaluated	
Esafoxolaner + eprinomectin + praziquantel	**NEXGARD® COMBO** (*Boehringer Ingelheim*)	X		X[n]	X[4]	X[g]	X[e]	X[5]		8 weeks/ 1.8 lbs	Not evaluated	
Selamectin	**Revolution®** (*Zoetis*), **Paradyne®** (*Vethical*), **Revolt™** (*Aurora*) **Senergy™** (*Virbac*), **Selarid®** (*Norbrook*),	X		X[k]		X[m]	X[e]		X[u]	8 weeks/ no minimum weight	Yes	
Selamectin + sarolaner	**Revolution® PLUS** (*Zoetis*)	X		X[k]	X[2]	X[m]	X[e]		X[u]	8 weeks/ 2.8 lbs	Not evaluated	

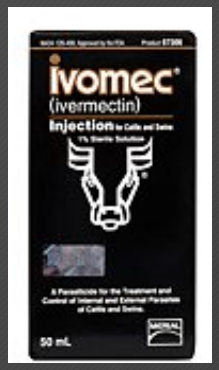
When should I test puppies?

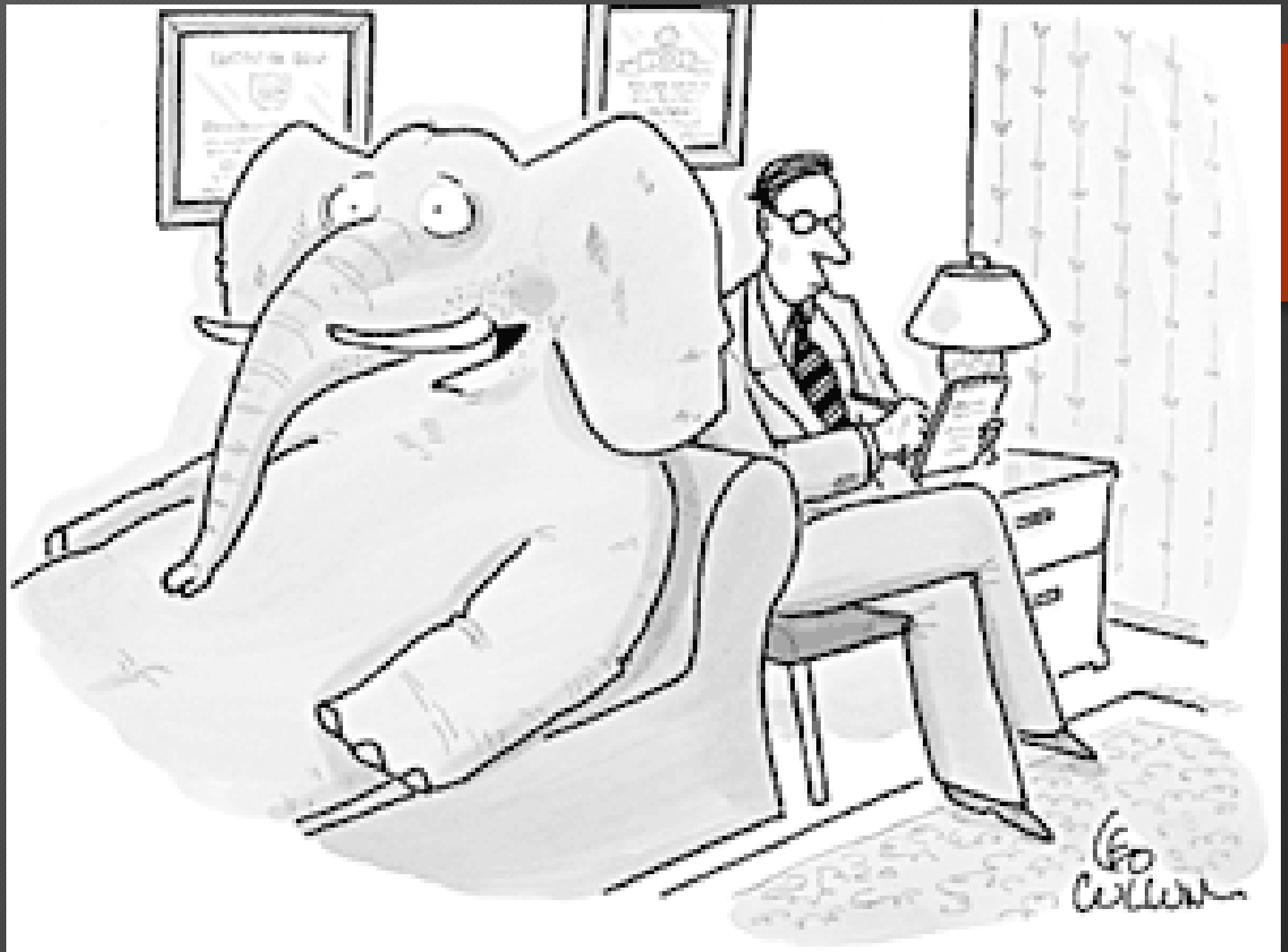


Puppy age in months

Macrocyclic lactones and collies

- Sensitivity first seen with high doses of IVM
  - 16x prophylactic dose
  - Seen with other MLs
- Often seen with concentrated livestock preparations





"I'm right there in the room, and no one even acknowledges me."

ALTERNATIVE THERAPIES

Long-term Macrocyclic Lactone Administration

Diagnosis, Prevention, and Management of Heartworm (*Dirofilaria immitis*) Infection in Dogs

AMERICAN HEARTWORM SOCIETY
ESTABLISHED 1974

Preamble

These recommendations are based on the latest information presented at the 2007 Triennial Symposium of the American Heartworm Society (AHS), new research and additional clinical experience. Guidelines for diagnosis, treatment and prevention of heartworm infection in cats are contained in a separate document.

Highlights

Diagnostics: AHS recommends annual testing for canine heartworms.

Chemoprophylaxis: AHS recommends year-round administration of chemoprophylactic drugs to prevent heartworm disease, increase compliance and control pathogenic and/or zoonotic parasites.

Adulticide therapy: AHS recommends use of the "alternate (three-injection) protocol" for treatment of heartworm disease in both symptomatic and asymptomatic dogs.

- **NOT RECOMMENDED!**

Monthly Prophylaxis As Adulticidal Treatment- "Slow-kill"

- Monthly administration of macrocyclic lactone
  - Prophylactic dosages for multiple months
  - Surviving worms appear to be moribund
  - Different time periods in different studies.
- Disadvantages

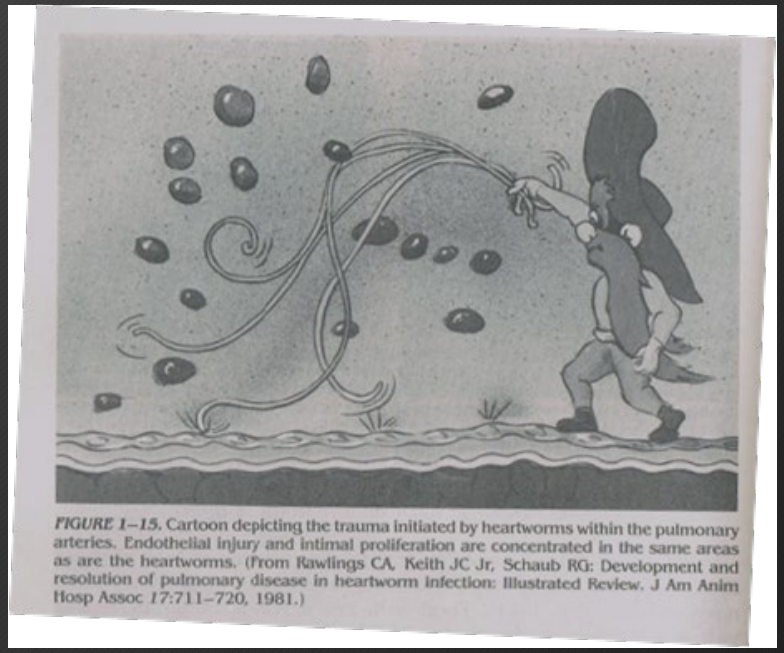


FIGURE 1–15. Cartoon depicting the trauma initiated by heartworms within the pulmonary arteries. Endothelial injury and intimal proliferation are concentrated in the same areas as are the heartworms. (From Rawlings CA, Keith JC Jr, Schaub RG: Development and resolution of pulmonary disease in heartworm infection: Illustrated Review. J Am Anim Hosp Assoc *17*:711–720, 1981.)


Exercise restriction
Ag + mf test
Melarsomine
I
II/III
ML
ML
ML
ML
ML
Worm death ????????
Doxy
0
2
3
4
MONTHS

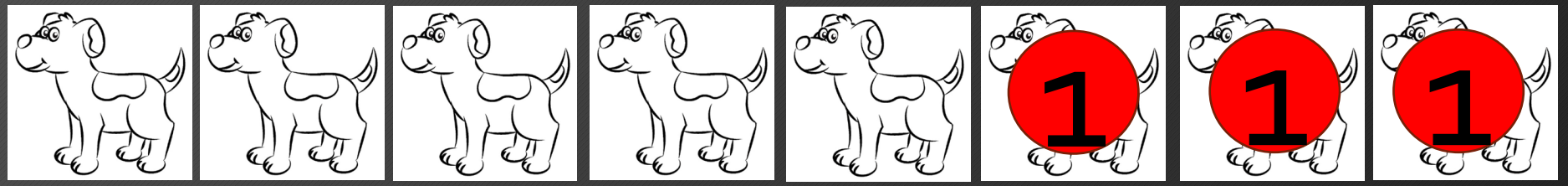
Savadelis *et al. Parasites & Vectors* (2017) 10:245
DOI 10.1186/s13071-017-2190-9

Parasites & Vectors

RESEARCH Open Access

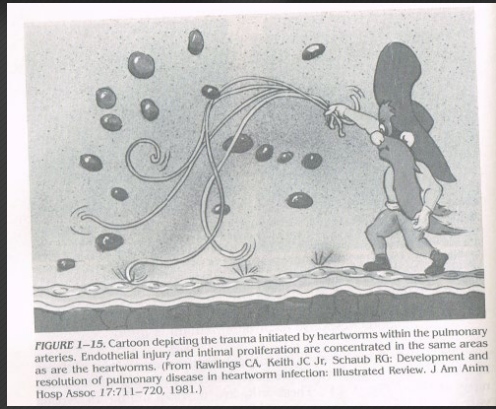
Assessment of parasitological findings in heartworm-infected beagles treated with Advantage Multi® for dogs (10% imidacloprid + 2.5% moxidectin) and doxycycline

Molly D. Savadelis[1*], Cameon M. Ohmes[2], Joe A. Hostetler[2], Terry L. Settje[2], Robert Zolynas[2], Michael T. Dzimianski[1†] and Andrew R. Moorhead[1†]



However, if you decide to…

- Realize damage to dog is occurring
- Get owner consent
- Older worms take longer to die
- Could take a year or two
- Restrict exercise
- Examine at minimum every 4-6 months
  - Until confirmed negative
- Do not use:
  - Dogs with clinical signs
  - Very active dogs



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Educa

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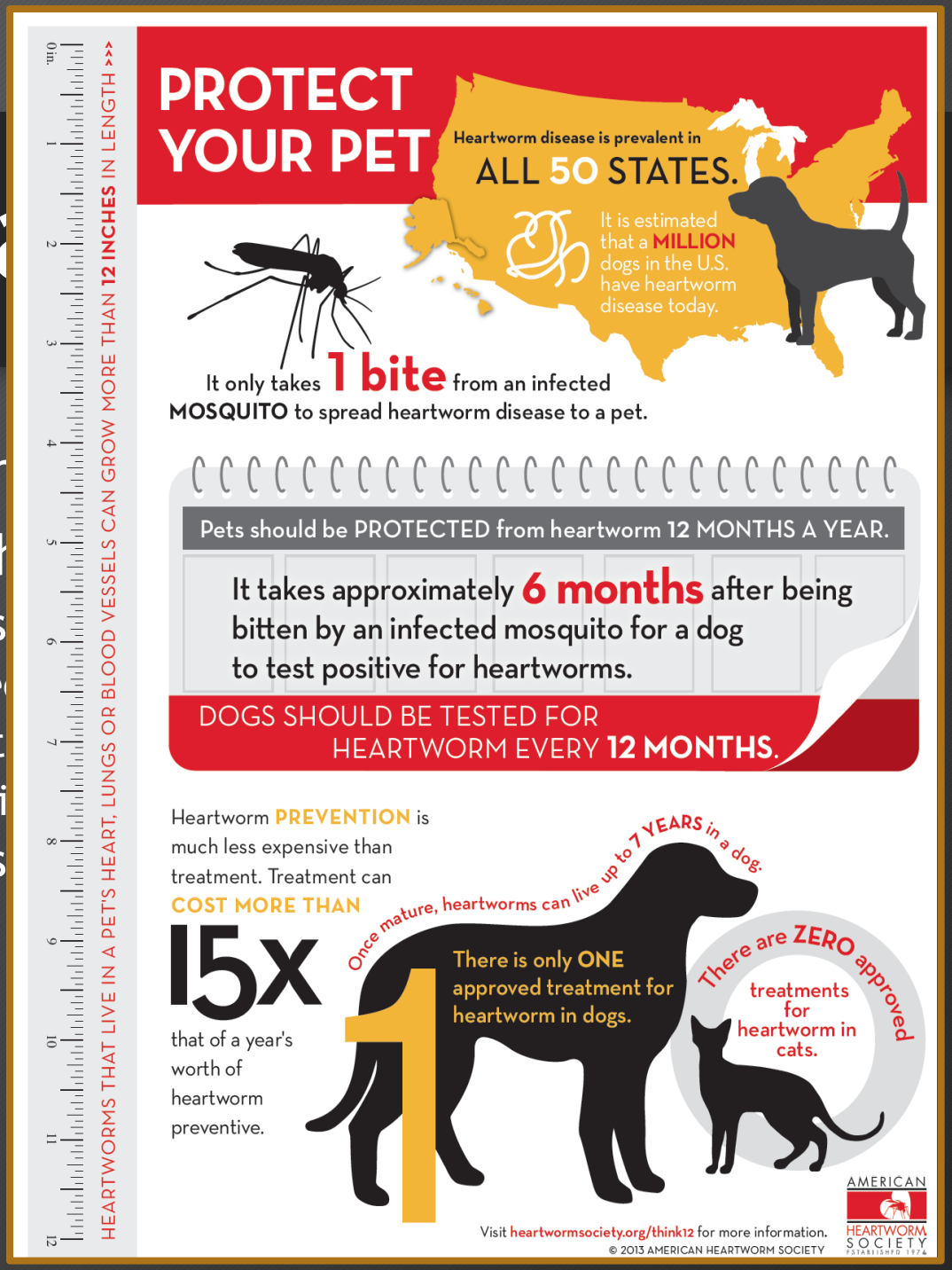
- Give the h
  - Emphas
    - Che
    - By t
    - Duri
  - Emphas



Summary

- Follow AHS protocols
- Always consider the patient