NON-SURGICAL NEUTERING IS HERE!
ARE YOU READY?

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Vice-Chairman, Board of Directors
Alliance for Contraception in Cats & Dogs
Agenda

- Introduction
- Efficacy and safety
- FDA approval research
- Expected reactions
- Treating adverse reactions
Agenda

- Long term effects
- Behavioral issues
- Administration protocol
- Identification of zinc neutered dogs
- Current use and tips for implementation
Zinc Neutering

Zinc Gluconate Neutralized by Arginine is the only FDA approved non-surgical sterilant for male dogs

A single, virtually painless injection to neuter a male dog, permanently

Courtesy Ark Sciences
Zinc Neutering Highlights

- Male dogs 3-10 months of age (older pending)
- One-time Injection into each testicle
- Safe & Effective
- Permanent and Irreversible
- Reduces Testosterone

Courtesy Ark Sciences
Key Points on Zinc Neutering

Injection Technique
- Use of Sedation
- Virtually painless
- Slow technique

Mechanism
- Blocks seminiferous tubules
- Spare Leydig cells
- Prostate atrophy

Post Injection
- Zinc & Arginine
- 1.1% treated
- Recent experience

Efficiency
- Time
- Safety
- Cost

Courtesy Ark Sciences
Efficacy

- Proven safe and effective
- 99.6% Efficacy
- FDA clinical trial: 223/224 dogs age 3 to 10 months

Courtesy Ark Sciences
How do we know zeuterin is permanent?

In Chapter 7: “Histopathologic Evaluation of the Testis in Toxicologic Testing and Risk Assessment,” of the textbook, *Histological and histopathological evaluation of the testis*, the authors discuss the histologic evaluation of the testis as an important component of many regulatory agency test protocols. They say, “Histopathologic evidence may reveal disruption in testicular tissue, particularly in the seminiferous epithelia, and may be used as the basis for regulatory action.”

How do we know Zeuterin is permanent?

End Points for Histopathologic Examination of the Seminiferous Epithelium:

- Presence of degenerating, sloughed and/or infiltrating cells
- Absence of a tubular lumen
- Absence of elongated spermatids
- Height of germinal epithelium
- Tubule diameter
- Number of spermatids/tubular cross section

How do we know Zeuterin is permanent?

Epididymis from untreated dog (100x)

Epididymis from Zeuterin treated dog (100x)

4 At 30 days post-injection

Courtesy Ark Sciences
How do we know Zeuterin is permanent?

Epididymis from untreated dog (100x)

Epididymis from Zeuterin treated dog (100x)

At 24 months post-injection

Courtesy Ark Sciences
How do we know Zeuterin is permanent?

Testicle from untreated dog (100x)

Testicle from Zeuterin treated dog (100x)$^6$

$^6$ At 24 months post-injection

Courtesy Ark Sciences
How do we know Zeuterin is permanent?

Does the testis have the capacity to reverse fibrosis?

“At the end of 24 months, the histopathology of the testis, the head of the epididymis, the body of the epididymis and the tail of the epididymis were performed to analyze the presence or absence of functioning sperm producing cells and seminiferous tubules. The histopathology showed that no normal seminiferous tubules existed and only fibrotic or nonfunctional seminiferous tubules were present throughout the testis.

It should be noted that unfortunately, or in this case fortunately, the body does not reverse fibrosis and there is no known treatment to recover the fibrotic seminiferous tubules of the testis, which renders the animal permanently sterile—a claim that the FDA has approved based on the evidence presented.”

7 Min Wang, MD
Urologist, Co-Inventor of Zeuterin
How do we know Zeuterin is safe?

"In the last twelve months, Ark Sciences veterinarians and more than a hundred other veterinarians trained by them have Zinc Neutered 1,000+ dogs in the US. Each veterinarian was trained using Ark's newly designed, hands-on training protocol. Preliminary observations are consistent with the US FDA clinical study--dogs that needed any medical attention after the procedure were found to be about 1.1% of the total. Rates of ulceration observed are 1 in 200 when protocol is followed (or when deviations are unknown) and 1 in 100 if one includes cases of known major protocol deviations (for example, injecting from the opposite side of the testicle).

A total of nine cases of scrotal ulceration reported were resolved safely either via surgery or medical management with antibiotics at the discretion of the veterinarian. Ark received reports of two apparent allergic reactions that may or may not have been unrelated to Zeuterin but were resolved safely and quickly. Statistics on minor reactions that did not need any medical management have not been compiled."

Ark Sciences Company Statement
Research Behind FDA Approval

- Twelve years of scientific research
- Dosage determination study
- Animal Safety Study
- Clinical Trial 224 dogs 3-10 months old
- Follow-up of dogs in original study

Courtesy Ark Sciences
## Adverse Reactions Observed During FDA Trial

<table>
<thead>
<tr>
<th>Local Reactions</th>
<th>No. of Dogs (n = 270)</th>
<th>Percent (%)</th>
<th>Systemic Reactions</th>
<th>No. of Dogs (n = 270)</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrotal Pain*</td>
<td>17</td>
<td>6.3%</td>
<td>Neutrophilia</td>
<td>17</td>
<td>6.3%</td>
</tr>
<tr>
<td>Scrotal Irritation</td>
<td>3</td>
<td>1.1%</td>
<td>Vomiting**</td>
<td>12</td>
<td>4.4%</td>
</tr>
<tr>
<td>Biting and Licking</td>
<td>2</td>
<td>0.7%</td>
<td>Anorexia</td>
<td>11</td>
<td>4.1%</td>
</tr>
<tr>
<td>Scrotal Swelling</td>
<td>2</td>
<td>0.7%</td>
<td>Lethargy</td>
<td>6</td>
<td>2.2%</td>
</tr>
<tr>
<td>Scrotal Irritation/Dermatitis</td>
<td>2</td>
<td>0.7%</td>
<td>Diarrhea</td>
<td>5</td>
<td>1.9%</td>
</tr>
<tr>
<td>Scrotal Ulceration</td>
<td>1</td>
<td>0.4%</td>
<td>Leukocytosis</td>
<td>2</td>
<td>0.7%</td>
</tr>
<tr>
<td>Scrotal Infection</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Scrotal Skin</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scrotal Bruising</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preputial Swelling</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scrotal Sore</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* No NSAIDs were used and most scrotal pain was reported on the first two days after injection.
** Vomiting was most commonly seen on the day of the injection, between 1 minute and 4 hours post-injection.

Courtesy Ark Sciences
Treating Adverse Reactions

- Only 1.1% of the 270 dogs in FDA Clinical Trial needed any follow up medical attention:
  - Scrotal Irritation: Apply anti-inflammatory/antibiotic ointment, possible E-collar, 2-3 days
  - Scrotal Ulceration: Antibiotics, Saline soaks, E-collar, 1-2 weeks
  - Testicle abscess/infection: Antibiotics, E-collar, 1-2 weeks
Expected Reactions

- Injection technique is critical to prevent adverse reactions

- Normal reactions include:
  - Generally non-painful swelling for 24-48 hours
  - Listlessness for the first 24 hours
  - May or may not vomit during the first 24 hours
  - Should return to normalcy within 24 hours
How do we know Zeuterin is painless?

“Pain receptors are considered to be present in the tunicae testis and it would seem reasonable to suppose that, as in other solid organs, the acute pain experienced in testicular injury is due in part to stretching of the capsule.”

30 six-month old dogs treated with Zeuterin were followed for 2 years.

2 years of routine observations and clinical evaluations.

Permanent reduction of circulating testosterone of 41-52%.

24 months post injection - necropsy concluded all vital organs normal.

Epididymides, testicles and prostate had all reduced in size.

Courtesy Ark Sciences
Long Term Effects

Zinc Neutering spares the testosterone producing function of Leydig cells, keeping the critical endocrine system intact.

Without spermatogenesis, the testosterone production goes down by 41-52%

Testosterone production remains available for other metabolic functions of the dog

Courtesy Ark Sciences
Long Term Effects of Surgical Neutering Show Benefits and Detriments

(Source: Determining the optimal age for gonadectomy of dogs and cats, Margaret V. Root Kustritz, DVM, PhD, DACT)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Substantial morbidity?</th>
<th>Specific breeds at risk?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular neoplasms</td>
<td>0.9%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BPH or prostatitis</td>
<td>75%–80% by 6 years of age</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Detriments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications of surgery</td>
<td>6.1%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prostatic neoplasms</td>
<td>0.2%–0.6%</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>TCC</td>
<td>1.0%</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>0.2%</td>
<td>Yes</td>
<td>Yes†</td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td>0.2%</td>
<td>Yes</td>
<td>Yes‡</td>
</tr>
<tr>
<td>CCL rupture</td>
<td>1.8%</td>
<td>Yes</td>
<td>Yes§</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.8%</td>
<td>No</td>
<td>YesII</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.5%</td>
<td>No</td>
<td>Yes¶</td>
</tr>
</tbody>
</table>

* Airedale Terrier, Beagle, Collie, Scottish Terrier, Shetland Sheepdog, West Highland, White Terrier, and Wire Fox Terrier.
† Doberman Pinscher, Great Dane, Irish Setter, Irish Wolfhound, Rottweiler, and Saint Bernard.
‡ Boxer, English Setter, German Shepherd Dog, Golden Retriever, Great Dane, Labrador Retriever, Pointer, Poodle, and Siberian Husky.
§ Akita, American Staffordshire Terrier, Chesapeake Bay Retriever, German Shepherd Dog, Golden Retriever, Labrador Retriever, Mastiff, Neapolitan Mastiff, Newfoundland, Poodle, and Saint Bernard.
II Beagle, Cairn Terrier, Cavalier King Charles Spaniel, Cocker Spaniel, Dachshund, Labrador Retriever.

JAVMA, Vol 231, No. 11, December 1, 2007
Does Zinc Neutering Change Behavior?

Behavior changes may be observed after zinc neutering:

“My observation as an Animal Caretaker for the dogs is that the male dogs treated with Zinc Gluconate are much calmer than as compared to the intact male dogs.”
– FDA Clinical Trial, Progeny Testing and Sexual Behavior Study

“Max stopped urine marking and now sits on my lap”
– Dee Ann, Dog Owner

“Tank stopped digging the garden and became cuddly”
– Kari, Dog Owner

Observations during the FDA study resulted in this statement:

“As with surgical castration, secondary male characteristics (roaming, marking, aggression, or mounting) may be displayed.”

Courtesy Ark Sciences
What Do We Really Know about the Behavioral Effects of Surgical Neutering in Dogs?

Courtesy Dr. James Serpell
What We Think We Know

(Quotes from websites of veterinary clinics, humane societies, trainers & animal shelters)

“Spaying and neutering makes pets better, more affectionate companions.”

“Unsterilized animals often exhibit more behavior and temperament problems than do those who have been spayed or neutered.”

“Female dogs, like males, have an increased risk of aggression if left intact.”

“Unneutered dogs are often more aggressive and territorial (urine marking, fighting), but these traits should not be confused with loyalty and protection of their home and family.”

“Altered pets are less aggressive toward other dogs and cats, are less likely to urine mark and wander, and generally have better personalities.”

Courtesy Dr. James Serpell
But........

- N= 122.
- Quasi-random sample derived from veterinary clinic records of male dogs castrated in previous 6-12 months.
- Most dogs castrated for behavior problems (expectation effects).
- No control group (unsterilized); no way to determine if reported effects were due to surgery.
- Retrospective phone survey; owners were asked to remember dog’s behavior prior to surgery and compare with post-surgical behavior.
- Owners given three choices: Behavior increased; behavior stayed the same; behavior decreased.

<table>
<thead>
<tr>
<th>Behavior</th>
<th>% Decrease</th>
<th>% No change</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Mounting</td>
<td>41%</td>
<td>58%</td>
<td>1%</td>
</tr>
<tr>
<td>Roaming</td>
<td>40%</td>
<td>58%</td>
<td>2%</td>
</tr>
<tr>
<td>Inter-male Aggression</td>
<td>57%</td>
<td>39%</td>
<td>4%</td>
</tr>
<tr>
<td>Aggression to familiar people</td>
<td>9%</td>
<td>87%</td>
<td>4%</td>
</tr>
<tr>
<td>Aggression to unfamiliar people</td>
<td>22%</td>
<td>74%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinating inside</td>
<td>69%</td>
<td>31%</td>
<td>0%</td>
</tr>
</tbody>
</table>


Courtesy Dr. James Serpell
Original Evidence (summarized)

• Neutering has some positive effects on sexual mounting, roaming, urine-marking, and aggression directed toward other (intact) male dogs.

• But it has minor–negligible effects on all other aspects of behavior.

Courtesy Dr. James Serpell
More Recent Study

Used data collected via a validated online survey (C-BARQ©) to compare the reported incidence of behavioral problems among spayed/neutered versus intact dogs.
SPAYED/NEUTERED DOGS ARE MORE AGGRESSIVE TOWARD PEOPLE AND OTHER DOGS

Bonferroni corrected p value: 0.0016
Mann-Whitney U test

Dog-directed Aggression/Fear
- **FEMALE**: n=247, n=672
- **MALE**: n=276, n=542

Owner-directed Aggression
- **FEMALE**: n=283, n=766
- **MALE**: n=353, n=638

Courtesy Dr. James Serpell

*** p < 0.0001
** p < 0.001

INTACT
SPAYED/NEUTERED
SPAYED/NEUTERED DOGS ARE MORE FEARFUL AND SENSITIVE TO HANDLING

Mann-Whitney U test

* p < 0.0001

Courtesy Dr. James Serpell
Behavior Conclusions

• Surgical neutering may reduce specific male hormone-dependent behaviors (e.g. sexual mounting, roaming, urine-marking, and aggression directed toward other (intact) males) in dogs that have already learned these behaviors.

• Surgical spay/neuter may increase other undesirable behaviors (e.g. owner-directed aggression, touch sensitivity, fearfulness, etc.) in otherwise behaviorally normal dogs.

• Definitive conclusions will require prospective, controlled studies.

Courtesy Dr. James Serpell
Zeuterin Administration

Measure the testicular width

Gently cleanse and disinfect the scrotum
Zeuterin Administration

Pass the needle from the cranial aspect of the testicle, just ventral to the head of the epididymis

Position the needle along the long axis of the testicle in the center of the testicular parenchyma

Courtesy Dr. Brenda Griffin
Zeuterin vs. Neutersol
What has changed?

Injection technique modified – strict adherence to protocol is important to minimize potential adverse reactions

- Three 28 gauge needles, ½ to 1 inch length
- 1 needle to draw solution – 2 needles to inject
- Timed injection (slow)
Zeuterin vs. Neutersol

What has changed?

Injection technique modified – strict adherence to protocol is important to minimize potential adverse reactions

- Do not aspirate prior to injecting
- Wait when done injecting prior to withdrawal
- Do not massage the testicles after injecting
Zeuterin Administration

Ark Sciences refresher training video available online at:

http://www.youtube.com/watch?feature=player_detailpage&v=S-vUyMfIORA

Courtesy Ark Sciences
How Do We Identify a Zinc Neutered Dog?

**Microchipping**
- Microchip tracking companies will record the Zinc Neutered status of dog

**Tattooing**
- A “Z” tattoo between the genitals and inner thigh is the standard sign for zinc neutering

**Unique Collar Tag**
- Every dog is given a unique identification number collar tag with the website address to verify neutering status

Courtesy Ark Sciences
Real World Zinc Neutering Around the Globe

- **Mexico** – 10,000 dog field trial to establish scale & efficacy
- **Japan** – U.S. Army Veterinary Corp’s earthquake disaster response
- **Guatemala** – Veterinarians Without Borders
- **Peru** – Project by Arkansas University
- **Dominican Republic** – Animal Balance and Global Alliance for Rabies Control

Courtesy Ark Sciences
Real World

Training

Measurement

Injection

Courtesy Ark Sciences
Zinc Neutering in Shelters

“Humane organizations throughout the United States can’t surgically sterilize homeless cats and dogs fast enough to control their numbers, and developing countries with dangerous feral dog populations—such as China and India—fare even worse.”

September 2009 issue of Science, “A cure for euthanasia?”
Zeuterin Training in United States

Courtesy Ark Sciences
Zeuterin Use in the United States

- A sample of locations using Zeuterin after training:
  - Texas: Wichita Falls, Dallas, McAllen
  - Oregon: Bend, Portland
  - California: SF SPCA, San Jose Animal Care
  - Florida: Fort Lauderdale
  - North Carolina: SNAP-NC, Raleigh
  - Kansas: Spay/Neuter Kansas City

Courtesy Ark Sciences
Changing Perception

Evidence-based decision making

- Conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.
- De-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research.
Implementing Zeuterin

Training
- Experience
- Certification
- Refresher

Communication
- Clients
- Ark Veterinarians
- Media

Organizational Readiness
- Client support
- Follow Up
- Data capture

Community Readiness
- Local veterinarians
- City agencies
- Rescue and Welfare groups

Courtesy Ark Sciences
Zinc Gluconate Neutralized by L-Arginine is the only FDA Approved Non-surgical Sterilant

A single, virtually painless injection to sterilize a male dog, permanently.
“The greatness of a nation and its moral progress can be judged by the way its animals are treated.”

Mahatma Gandhi
For more information:

www.arksciences.com

Or

http://www.acc-d.org/Esterilisol