

Updates on Adrenal Disease: GnRH AGONISTS AND GnRH VACCINE STUDIES

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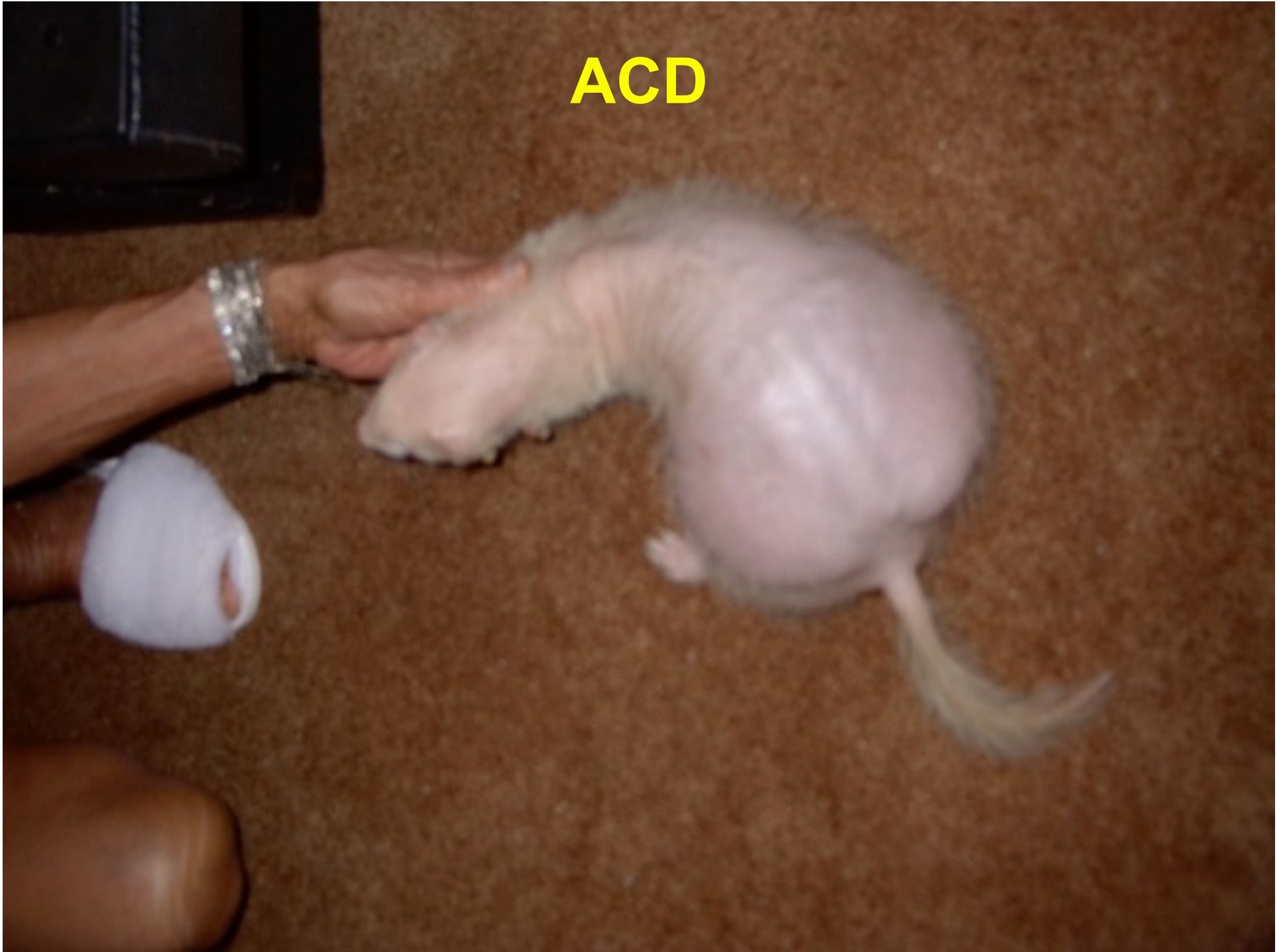
Ferret Adrenal Cortical Disease (ACD)

- Common (60-70%) in 2-5 year old ferrets
- Females \geq Males
- Left adrenal tumor \geq right tumor frequency
- Clinical signs are due to sex hormones
- Signs: Alopecia, swollen vulva, 30% pruritic, behavior changes, others.
- Dx: Clinical signs, sex hormones, palpate, ultrasound, exploratory surgery.
- Tx: Adrenalectomy, Lupron, Deslorelin, GnRH vaccination, melatonin

Normal Sex Hormones in Castrated Ferrets

- Estradiol < 180 pmol/L
- 17 OH Progesterone < 0.8 nmol/L
- Androstenedione < 15 nmol/L
- Dehydroepiandrosterone < 0.03 μ mol/L

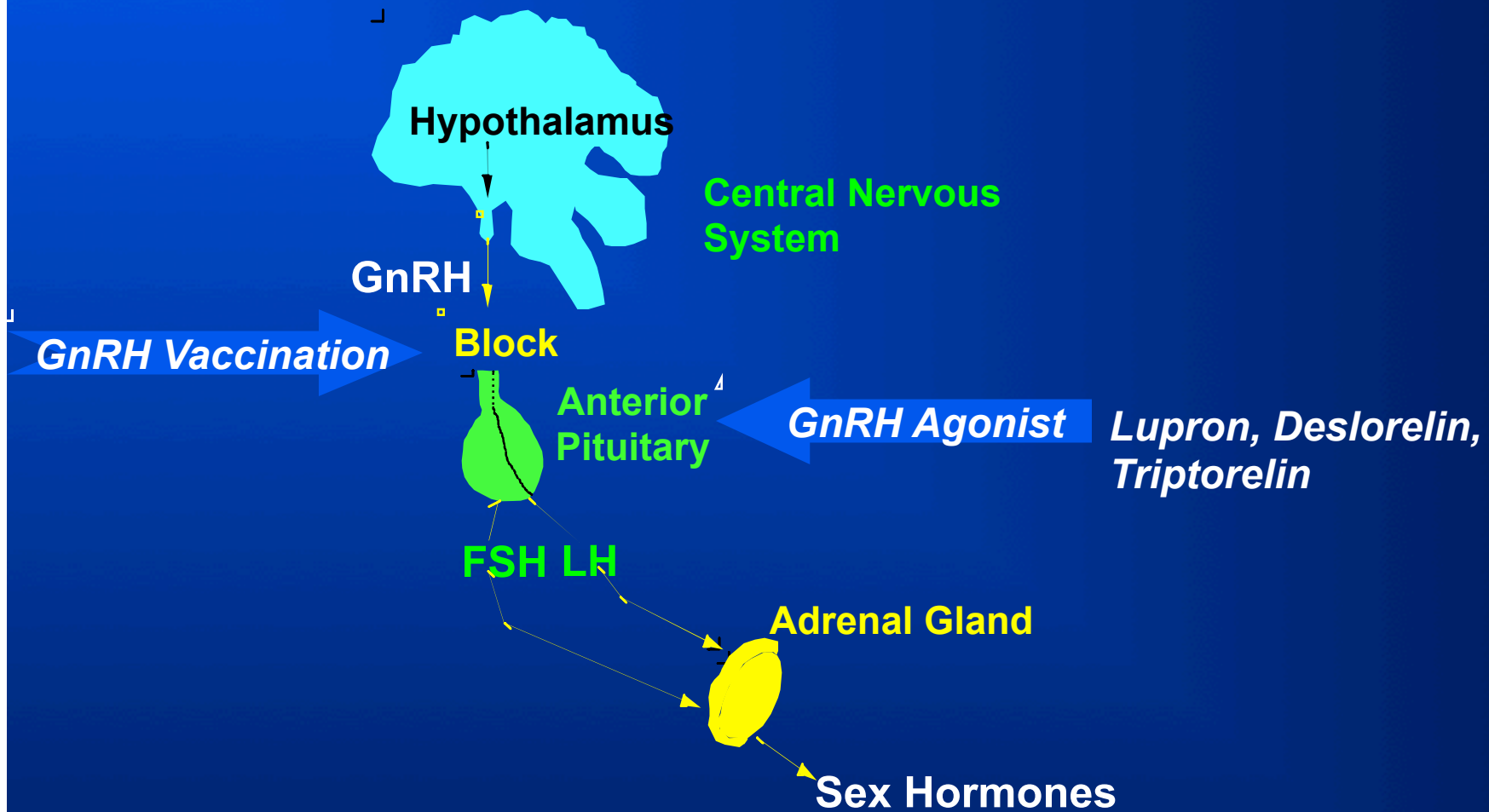
ACD



Limiting LH stimulation of the adrenal is the best way to medically treat ACD

- There is a lag-time between the rise of sex hormones and clinical signs.
- The time between the rise of LH and the stimulation of adrenal hyperplasia or tumor growth is **immediate**.
- **Long-term continuous LH suppression with minimal stimulation of adrenal LH receptors is probably the best way to medically assure minimal tumor growth.**

ACD ENDOCRINOLOGY



Concerns for Medical Management of ACD

- Various drugs and variable efficacy
- GnRH agonist is the primary Tx
- Risks: Tumor growth and necrosis, metastasis, limited other organ diagnostics and treatments, regular treatment is necessary, variable hormone control
- Tumor control questionable
- Benefits: non-invasive, few side effects, can be used for diagnostics, stabilize ferret before Sx, effective Tx for non-surgical patients,
- Cost: depends on drug used and frequency given

Clinical use of GnRH Agonist (Lupron and Deslorelin)

- < 7 days to lower hormone concentrations below pathologic concentrations
- Repeat injection or implant at the time of clinical relapse or at regular intervals.
- 4.7 mg Des implant < 5% develop large tumors
- Monitor adrenal size on a regular schedule
 - Ultrasound or Palpation
- Some ferrets are not responsive
- Some ferrets require higher doses

New Medical Treatment and Prevention of ACD

- **Deslorelin: SC implant** (available in US 2012)
 - 4.7 mg ~19 mo. duration (8-26 mo)
 - 9.4 mg --- duration ~ 2.5 years
- **GnRH vaccination: 500 µg SC once or twice in 3 years, may give life long protection against ACD**
- **Deslorelin injectable 90 day release formulation by Wildlife Pharmaceutical**

Survival Times for Medical management of ACD (Lupron and Deslorelin) verses Surgery

Survival times are similar or the same!

Des implant or Lupron: AVG= 6.0 years, MEDIAN= 6.2 years

All GnRH Agonists: AVG= 6.1 years, MEDIAN= 6.1 years

Surgery: AVG= 6.0 years, MEDIAN= 6.2 years

Medical management of ACD

Deslorelin verses Surgery

Modality	Surgery (Lennox)	Deslorelin (Wagner)
Time to relapse (months)	0-38	3-30
Range		
Average	13.55	16.48
	n=31	n=35
Time to death after treatment (months)	17.82	AVG= 25.2
	n=11	MEDIAN= 23.0
		n=34

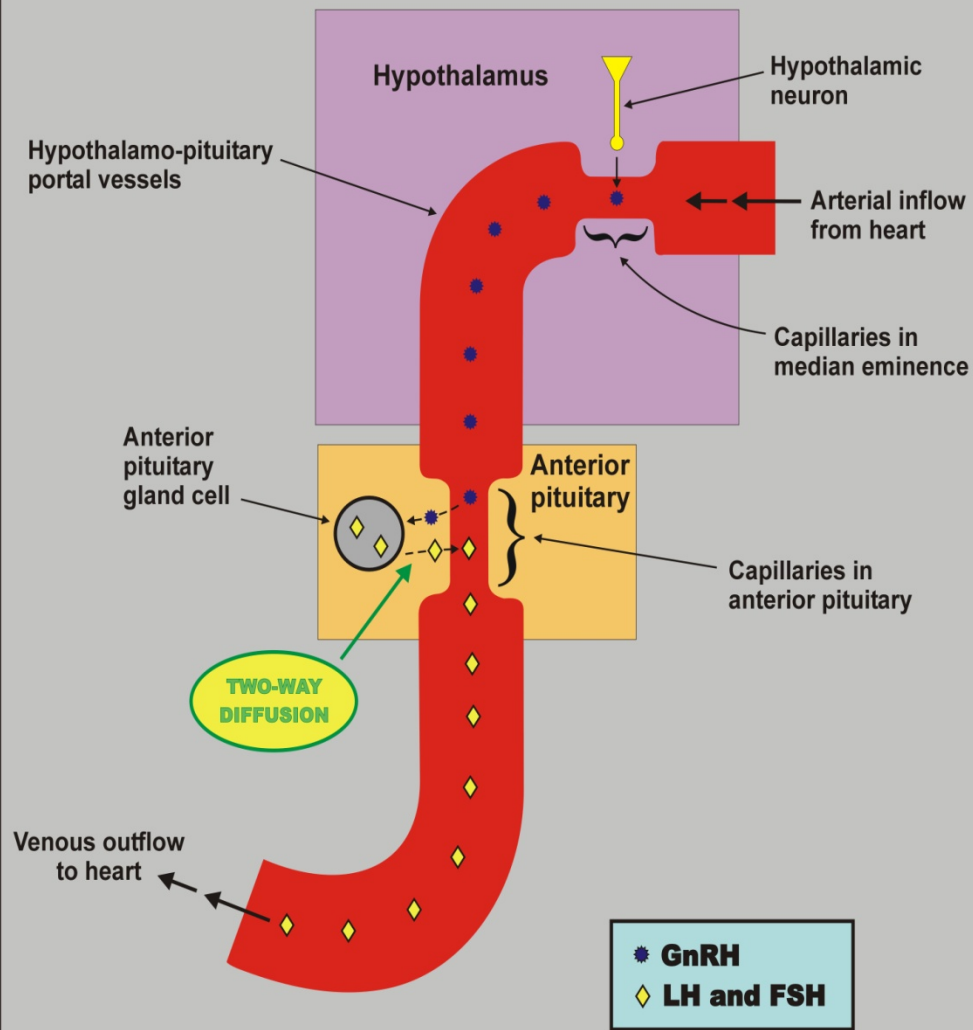
**GnRH
vaccination for
ACD treatment
or prevention
studies:
Ferret dose 500
µg IM or SC
once or twice in
3 years or once
only**



GnRH Vaccination for ACD

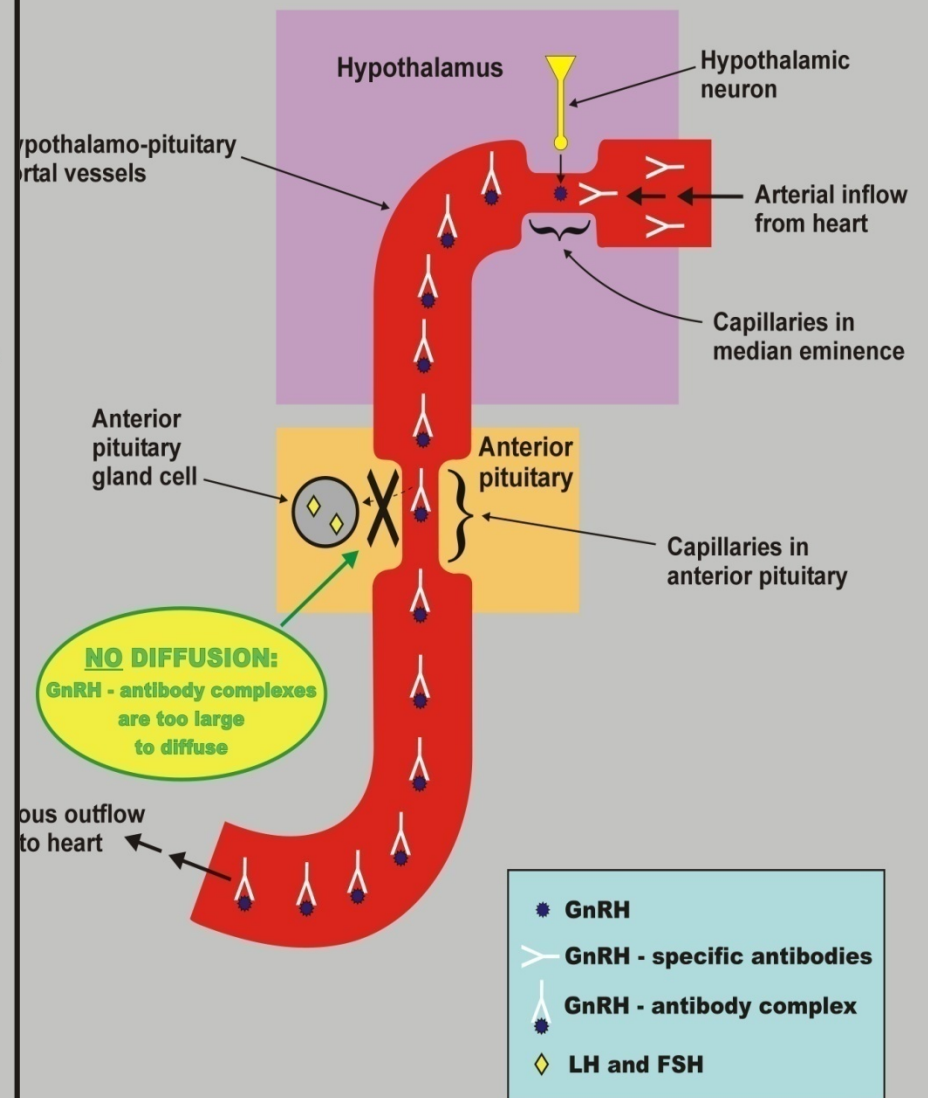
- GnRH is a small peptide hormone secreted from the hypothalamus in the brain and controls release of FSH and LH from the pituitary.
- Antibody to GnRH interferes with its biological action and reduces secretion of FSH and LH.
- GnRH vaccination is effective in both sexes.
- Slower clinical response than GnRH agonists

GonaCon™ Untreated



After Vander et al. 1998

GonaCon™ Treated



After Vander et al. 1998

9 Ferrets GnRH Vaccination for ACD Tx Study: 500 ug IM

(Wagner, Miller and Finkler unpublished data)

Response 2 mo Post	Response > 2 mo		GnRH titer @ 2 mo 32,000 is effective
100%	100%		128,000
80%	90%		32,000
100%	100%		128,000
100%	100%		128,000
80%	100%		32,000
20%	80%		8,000
40%	60%	slow tail growth	32,000
100%	100%		128,000
0%	0%		ND to 1 (ND=non-
			detectable)

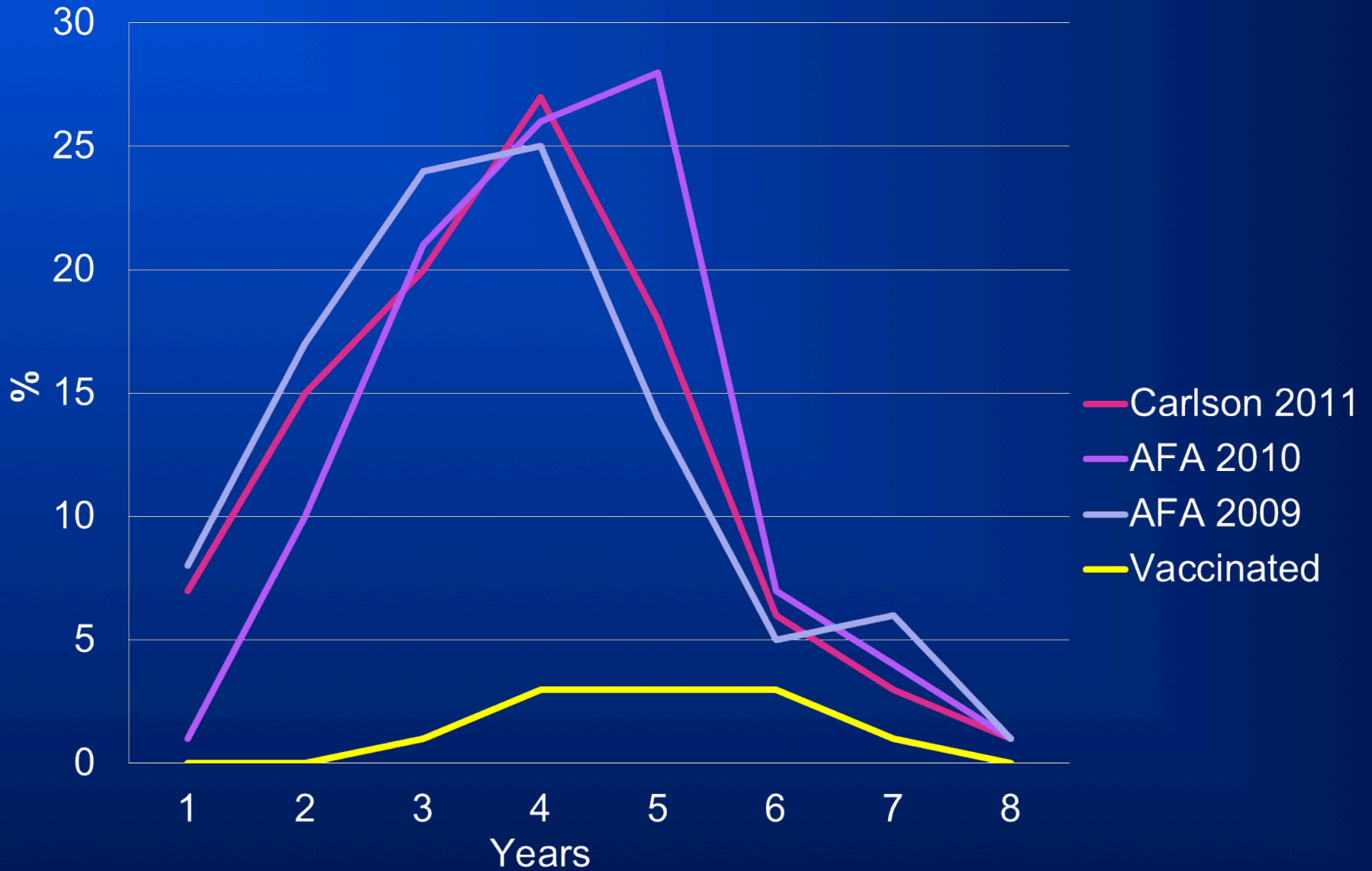
ACD Treatment Study with GnRH vaccine

- **50 ferrets with ACD, 25 given vaccine SC and 25 given IM**
- **IM caused some large vaccine granulomas but most ferrets did well**
- **Favorable response with 80-100% resolution of clinical signs**
- **6 ferrets had only a partial or no response**
- **Clinical response was not as good as GnRH agonists**

ACD GnRH Vaccine Prevention Study

- 125 normal ferrets vaccinated at 1-3 years of age
- Vaccinated either twice in 3 years or once
- 11 of 125 (9%) ferrets have developed ACD over all age groups
- Comparison group: Most ferrets develop ACD between 3-5 years of age. 60-70% develop ACD before death.
- 30-40% of comparison group never develop ACD
- Serum for GnRH titers at time 0, 1-3 mo. post vaccination and then at signs of ACD

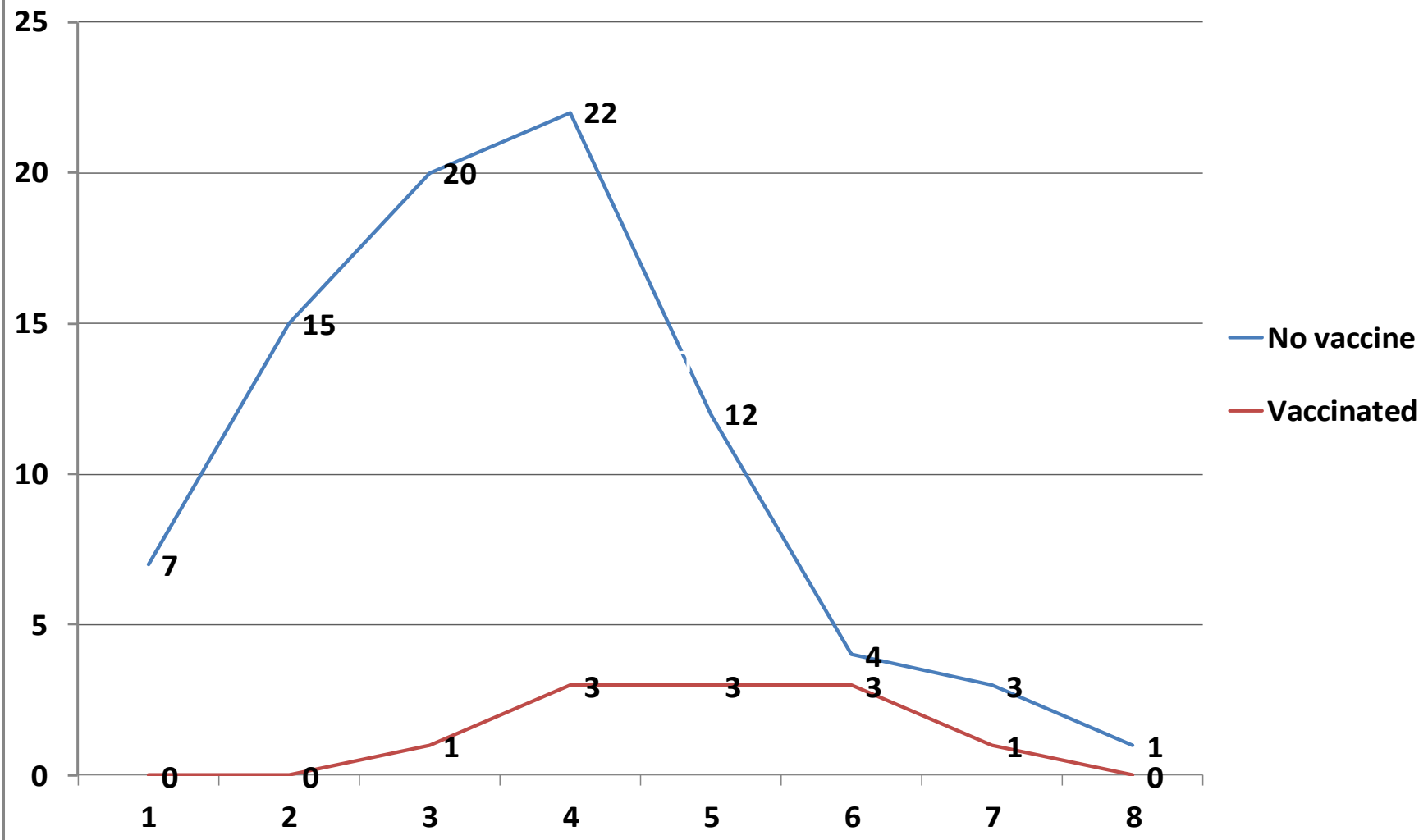
**% of ACD by age in CONTROL GROUP:
118 ferrets Carlson data 2011, 120 ferrets AFA data 2010
and 100 ferrets AFA data 2009**



GnRH Vaccine ACD Prevention Study

- 125 active ferrets on study 6/11
Avg age = 4.0
- 11 ferrets developed ACD on study
Avg age = 5.0
- 35 ferrets finished study
Avg age = 6.2
- Many ferrets lost to follow-up

Preliminary Data (125 vaccinated): ACD Prevention Study with GnRH vaccine.



GnRH Vaccine ACD Prevention Study

- **Vaccinated ferrets that developed ACD had mild clinical signs and often did not develop severe alopecia.**
- **Some of these ACD ferrets maintained high GnRH titers but developed adrenal signs.**
- **Vaccinated ferrets responded well to GnRH agonists**
- **11 of the ferrets that developed ACD on study averaged 5 years of age. Non-vaccinated ferrets average age of ACD onset is 3.5 years of age.**

ACD Prevention and Treatment Studies with GnRH vaccine

- **Treatment studies are completed**
- **125 ferrets are enrolled in prevention study**
- **The vaccine looks promising as a prevention vaccine and has some utility as a treatment modality.**
- **Best medical treatment for ACD still seems to be Deslorelin implants or Lupron.**
- **ACD prevention will be the ultimate goal for practitioners**

Wildlife Pharmaceutical Inc. 10 mg Deslorelin SR

- **Clinical trials using a 90 day slow release polygalactin deslorelin injectable for ferret ACD treatment.**
- **This formulation is designed to produce therapeutic blood concentrations of deslorelin for up to 90 days.**
- **Preliminary results show variable control of ACD but similar to 1 month Lupron Depot.**
- **Drug release profile may be the problem.**
- **0-6 month ACD control duration, N=50**

Future ACD Treatments

- Improved surgical techniques, **nothing really new**
- Improved GnRH analog delivery
- LH-RH antagonists
- Improved use of hormone blocker and receptor drugs, **new drugs, questionable efficacy**
- Anti-neoplasia drugs---**Palladia has eliminated ACD signs in some ferrets!**
- Anti-angiogenesis approach, **doesn't seem to work**
- GnRH immunization, **shows promise**
- LH – Receptor immunization, **needs work**
 - Saxena BB, et al. Effect of immunization with bovine LH on cat ovarian function. AJVR 2003; 64: 292-298.
- Genetics: breeding or genetic manipulation
 - Yazawa M. Adenoviral vector that expresses canine p53 gene in dogs with MGT. AJVR 2003; 64: 880-887.