



Appendix


Reproductive Biology 101: The Truth About Cats and Dogs

Dr. Steve Zawistowski

Reproductive Biology 101: The Truth About Dogs and Cats





Stephen Zawistowski, Ph.D., CAAB
ACCD Chair



Outline

- ▶ **Some Chemistry**
- ▶ **Some Physiology**
- ▶ **Some Endocrinology**
- ▶ **Some Anatomy**
- ▶ **Some Immunology**
- ▶ **Some Possibilities**



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Organic Chemistry

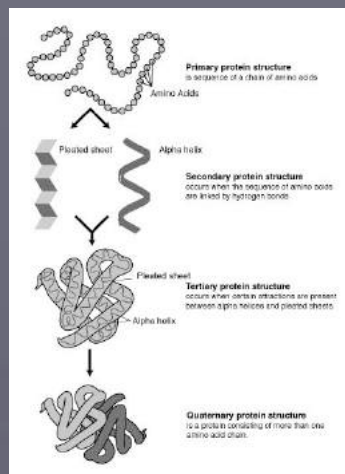
- ▶ **Molecules have shape – in three dimensions**
- ▶ **Cell membranes are complex layers of molecules**
- ▶ **Cell membrane surfaces have a topography, and receptors**

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Protein Shapes



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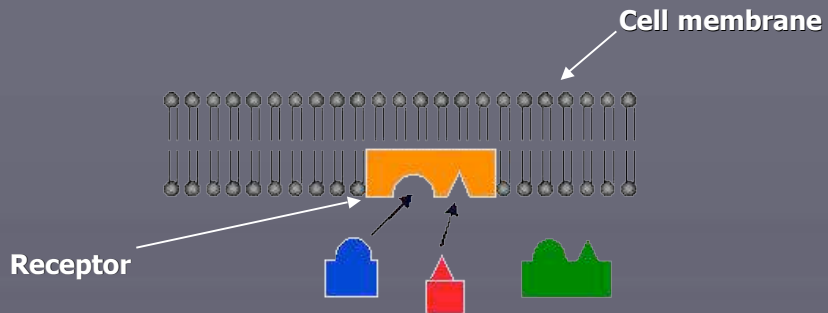


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Cells, Membranes and Receptors

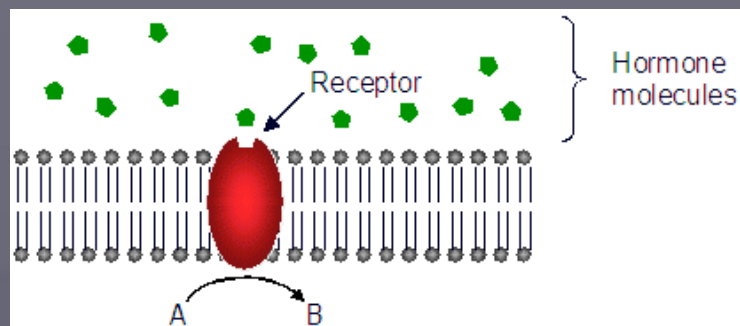


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Hormone Receptors



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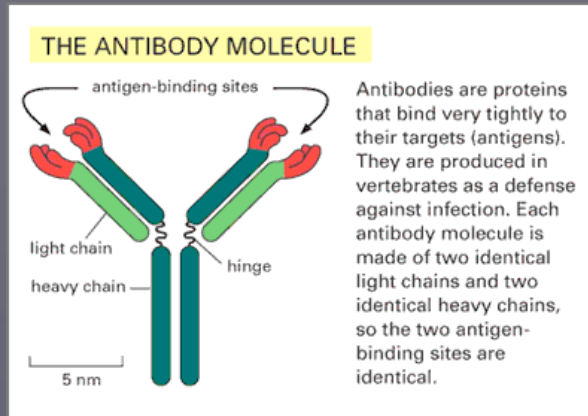


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Antibody Molecule

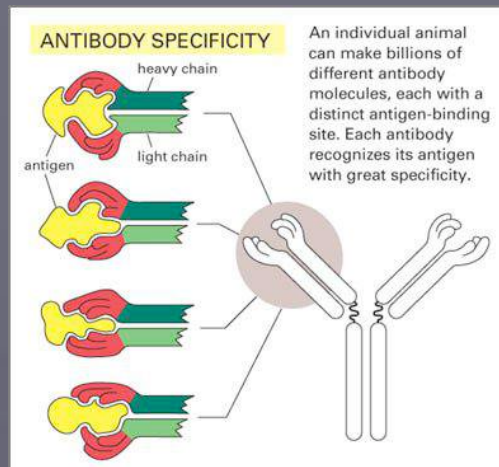


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Antibody-Antigen Binding



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Mammalian Sexual Reproduction

▶ Male

- **Gonads – Testis**
 - ▶ Seminiferous tubules – sperm
 - ▶ Interstitial cells of Leydig – testosterone (& some estrogen)

- **Gametes - Sperm**

▶ Female

- **Gonads – Ovaries**
 - ▶ Follicles – Ova
 - ▶ Corpus leuteum – postovulatory follicle produces progesterone

- **Gametes – Ova (eggs)**



Reproductive Control

Hypothalamus



Pituitary Gland



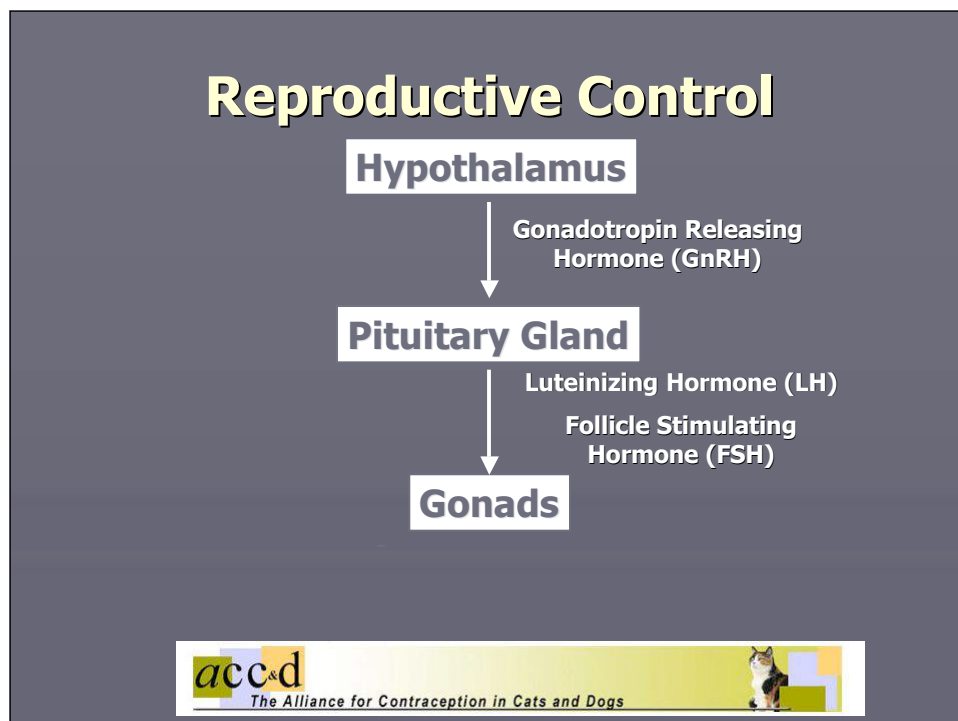
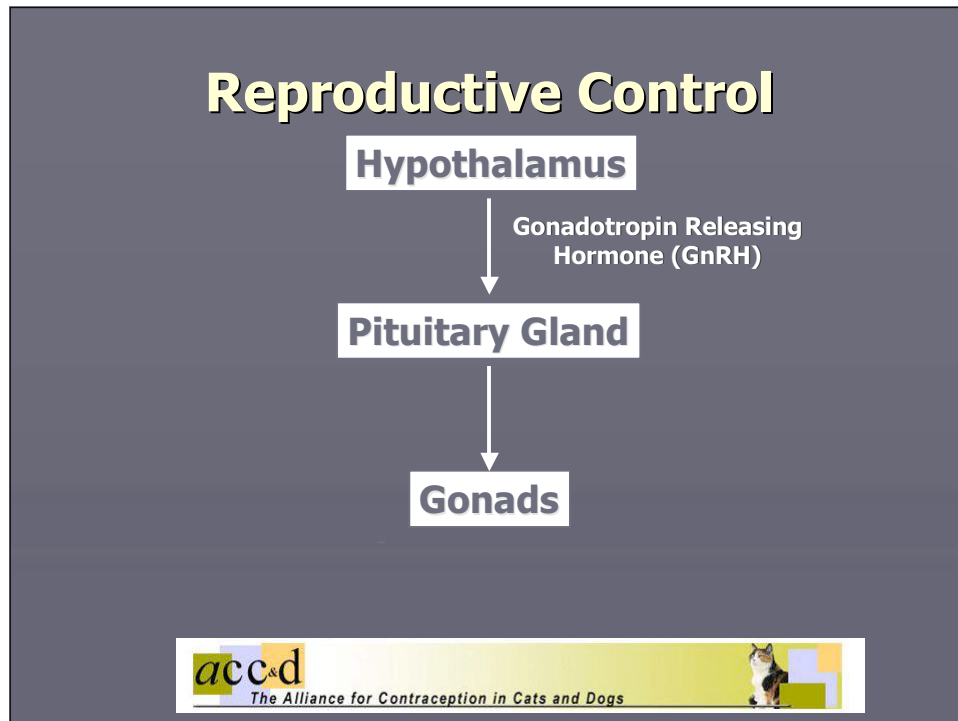
Gonads



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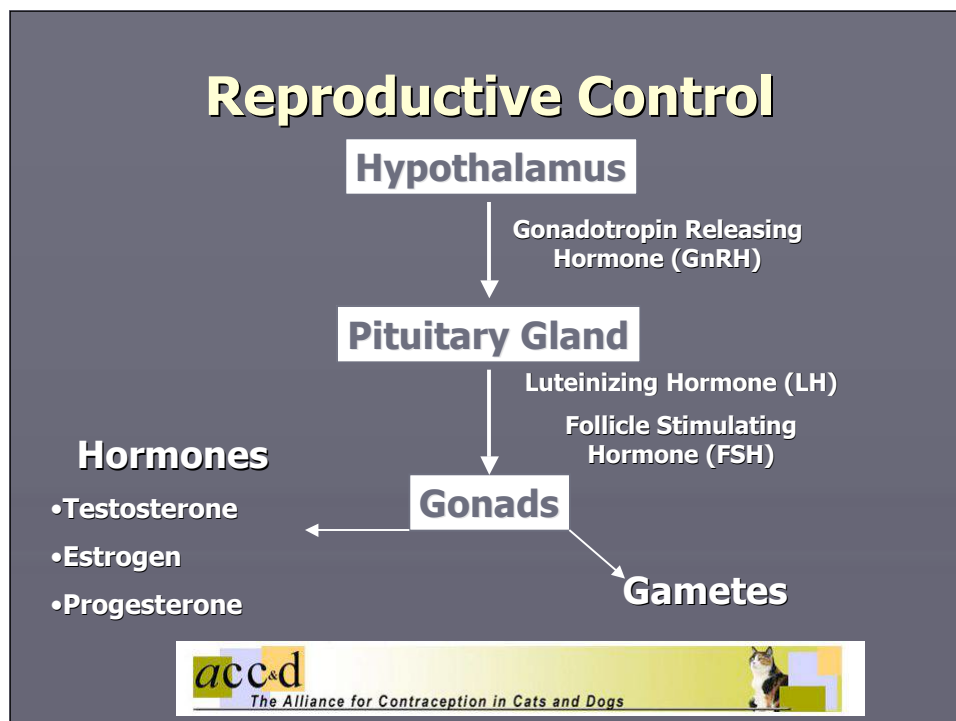
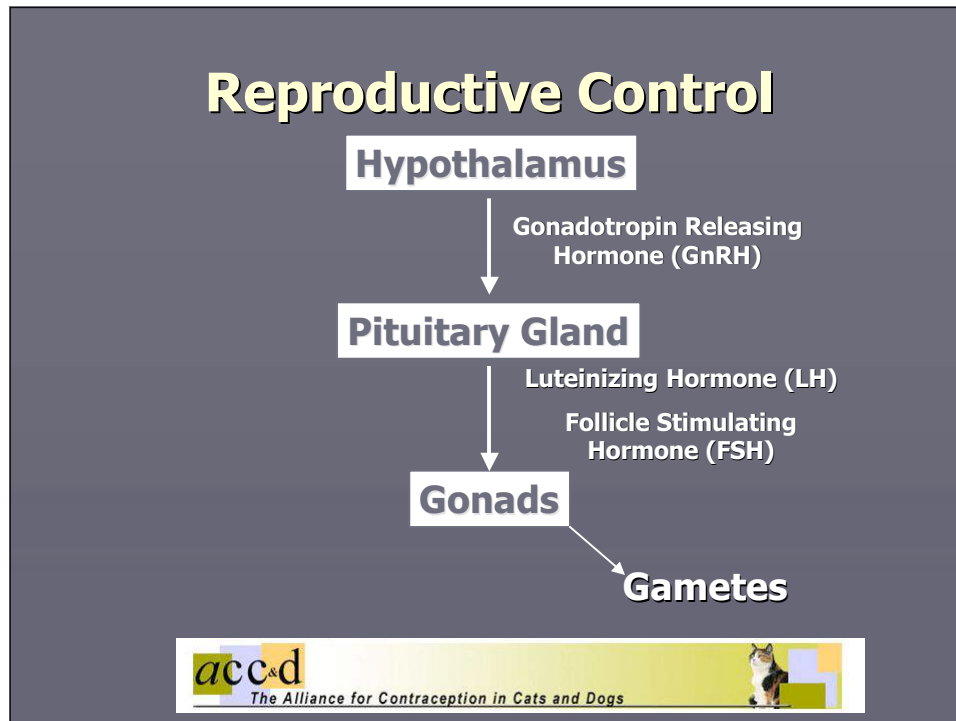
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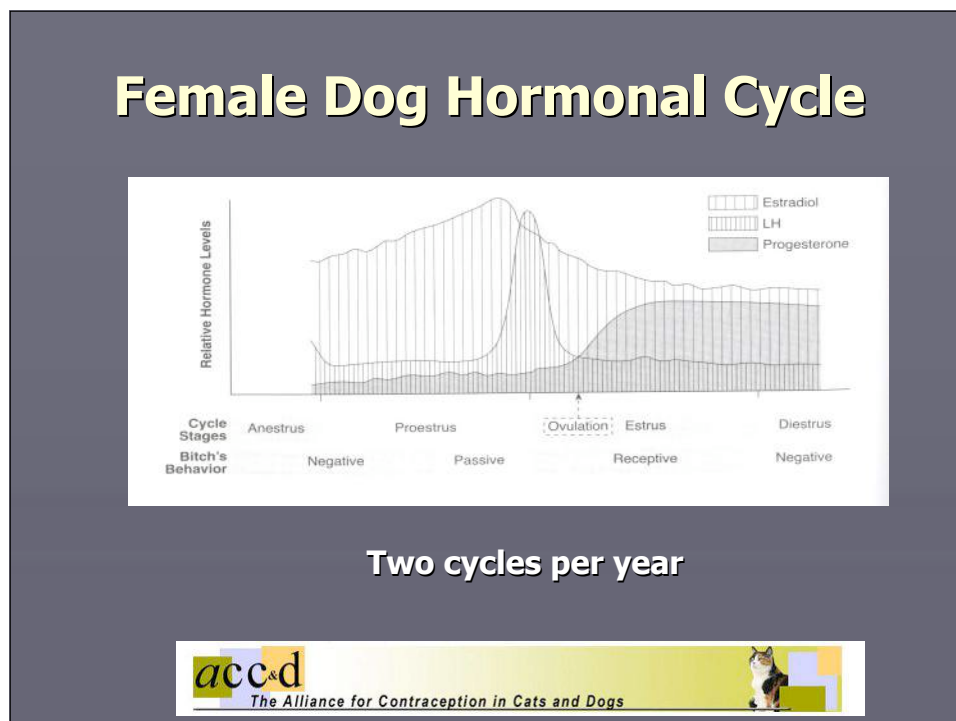
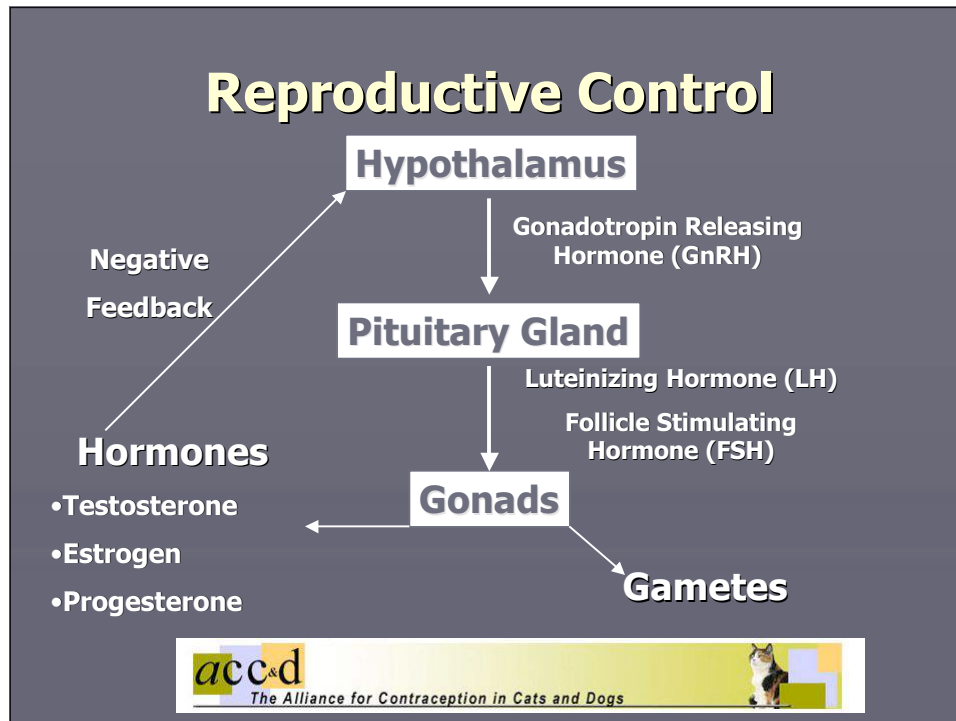
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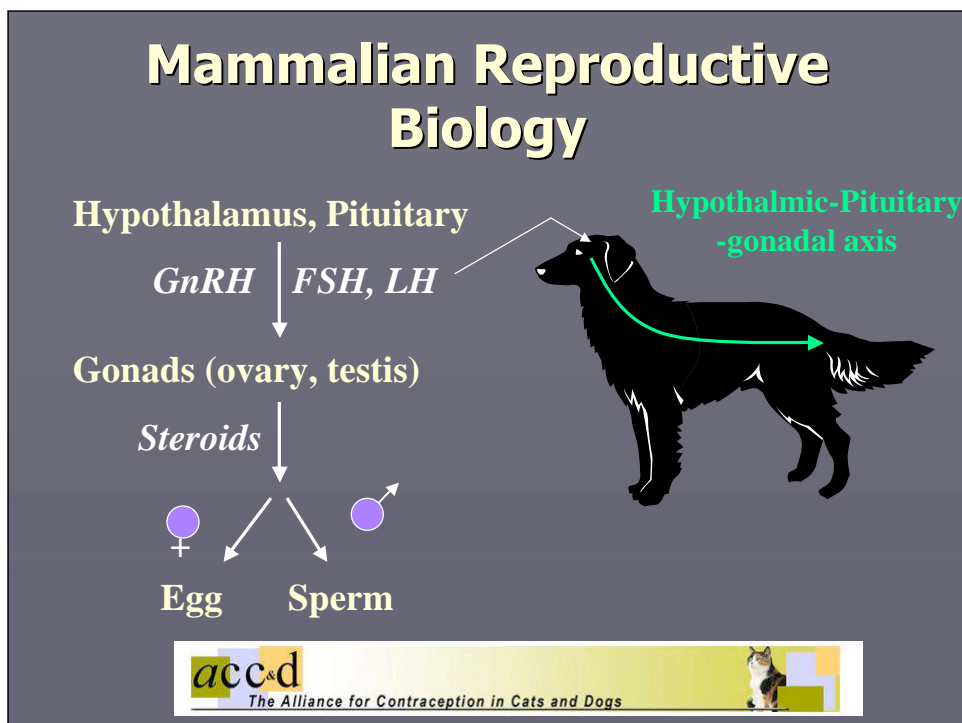
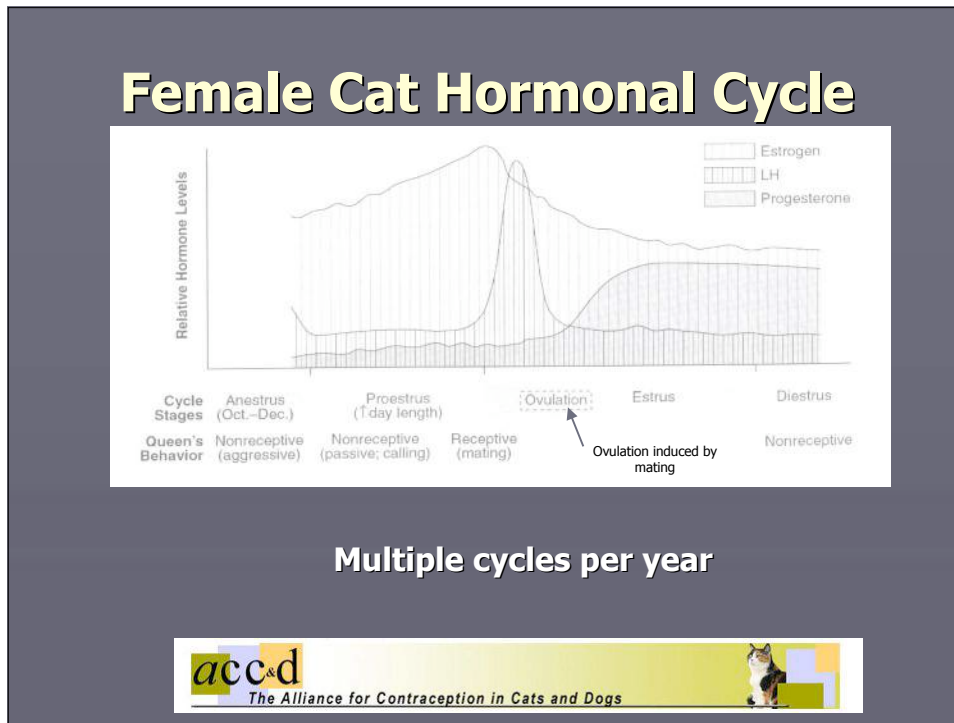
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Mammalian Reproductive Biology - Contraception



Physical restraint



Mammalian Reproductive Biology - Contraception



**Surgical:
Spay or Neuter**

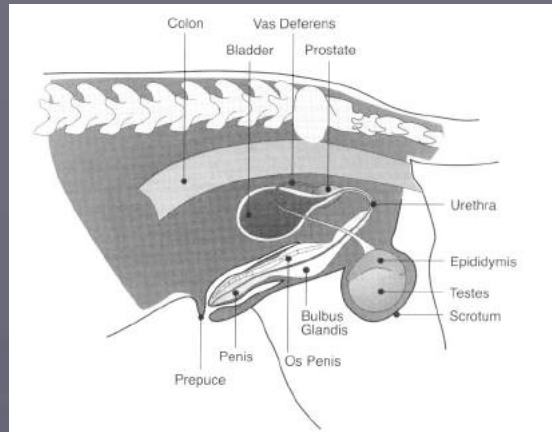


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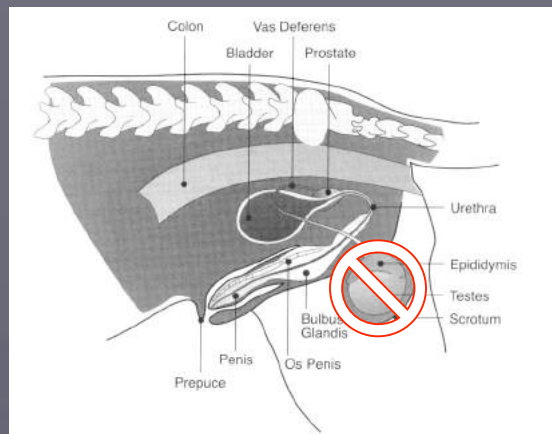
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Male Dog Reproductive System



Male Dog Reproductive System



Neuter

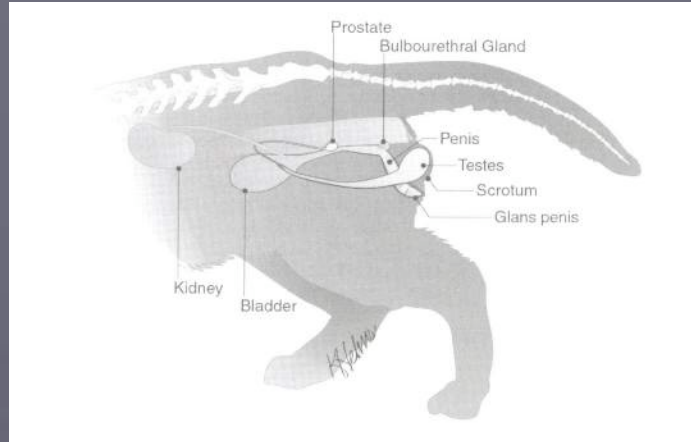


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Male Cat Reproductive System

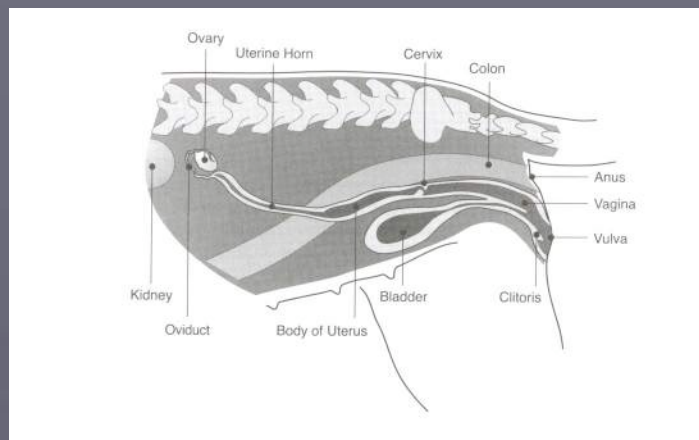


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Female Dog Reproductive System



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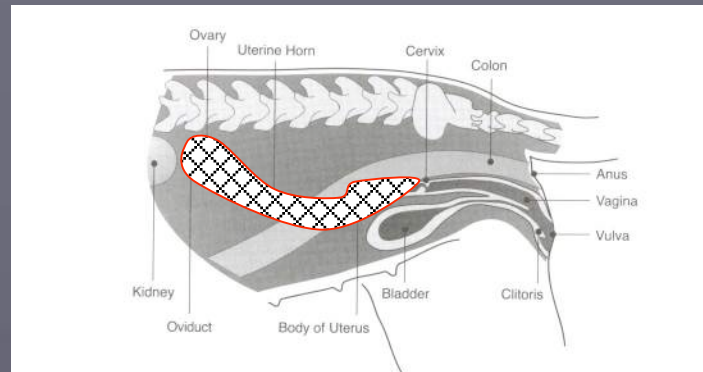


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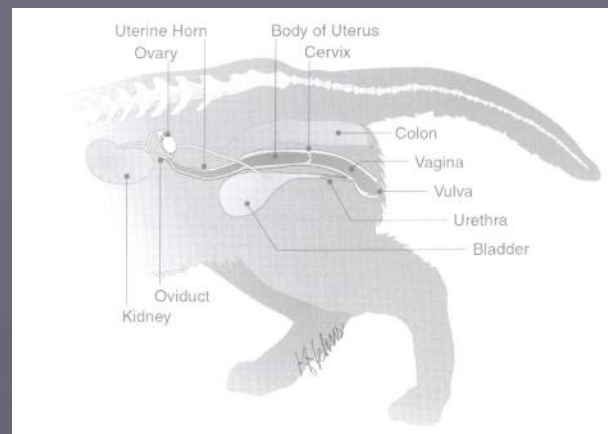
Female Dog Reproductive System



Spay



Female Cat Reproductive System



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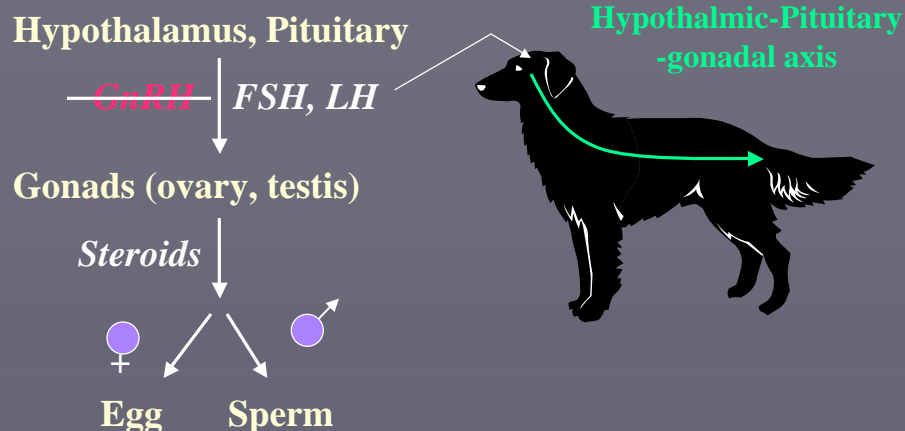
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Three General Approaches to Non-Surgical Contraception

- 1) Immunocontraception: Vaccinate against reproductive hormones, proteins
- 2) Drugs: GnRH agonists, antagonists to suppress GnRH action
- 3) Chemical sterilization: Zinc gluconate



Mammalian Reproductive Biology - Contraception

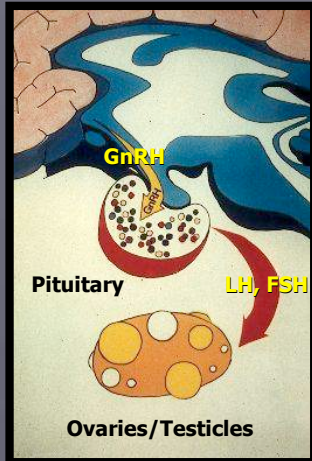


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Interfering with Hypothalamic-pituitary-gonadal Axis Prevents Sperm and Egg Production



GnRH Interference :

- **Drugs** - blocks GnRH receptor/activity
- **Vaccines** - antibodies neutralize GnRH

Result:

Lack of LH and FSH needed for production of eggs and sperm

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Mammalian Reproductive Biology - Contraception

Hypothalamus, Pituitary

GnRH → FSH, LH

Gonads (ovary, testis)

Steroids

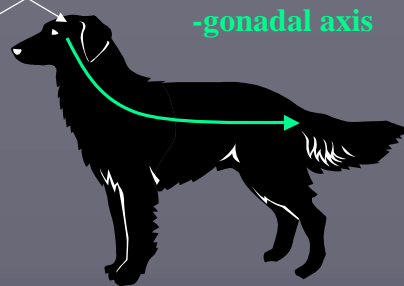
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Egg

♂

Sperm

Hypothalamic-Pituitary-gonadal axis



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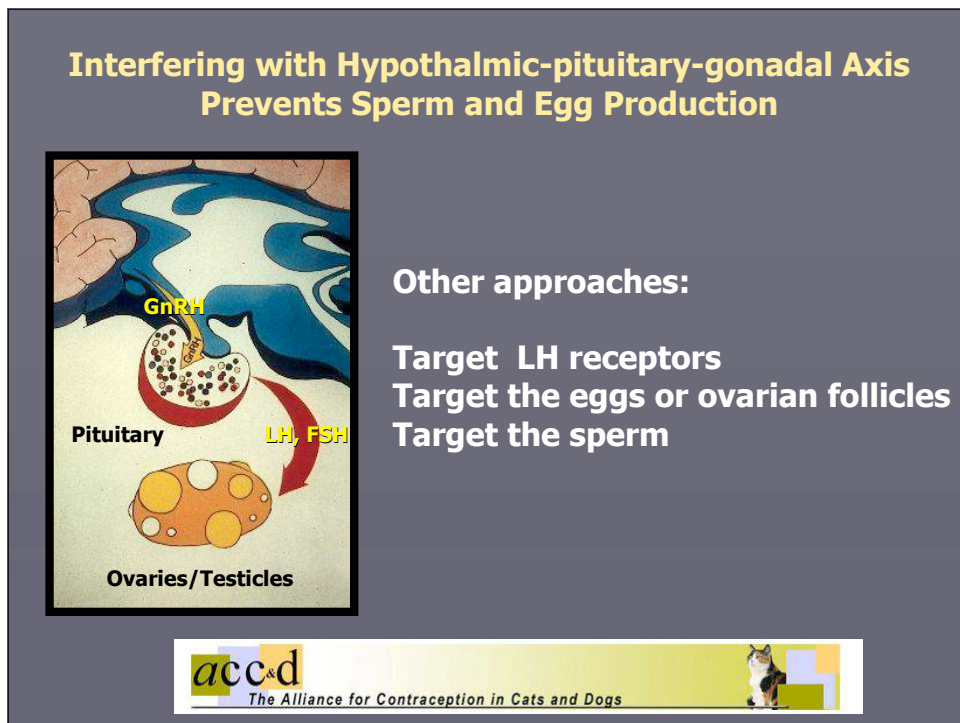
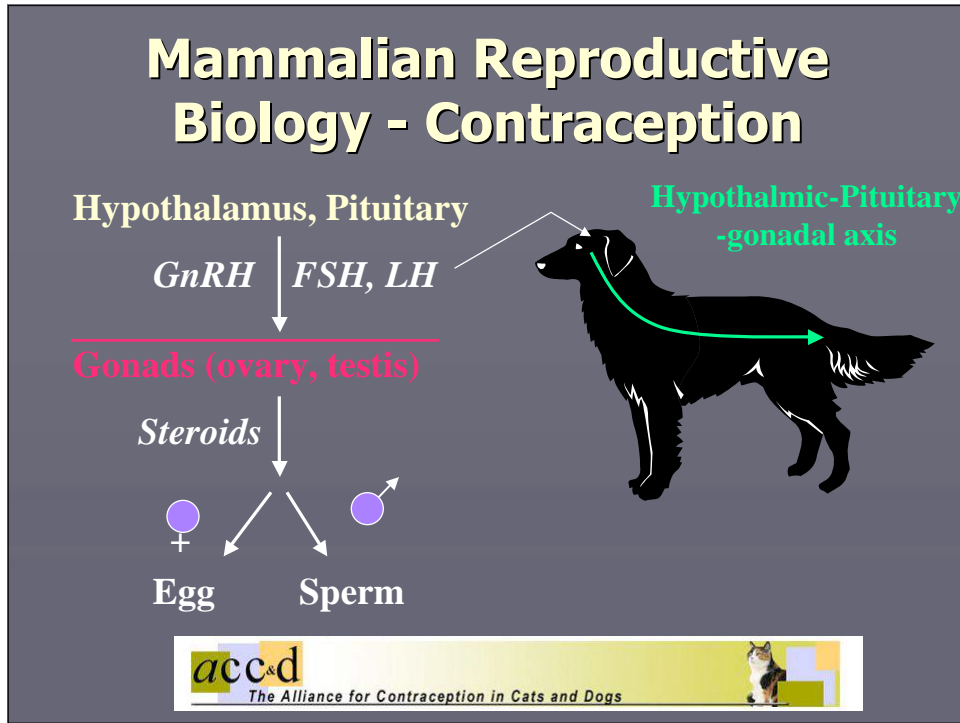
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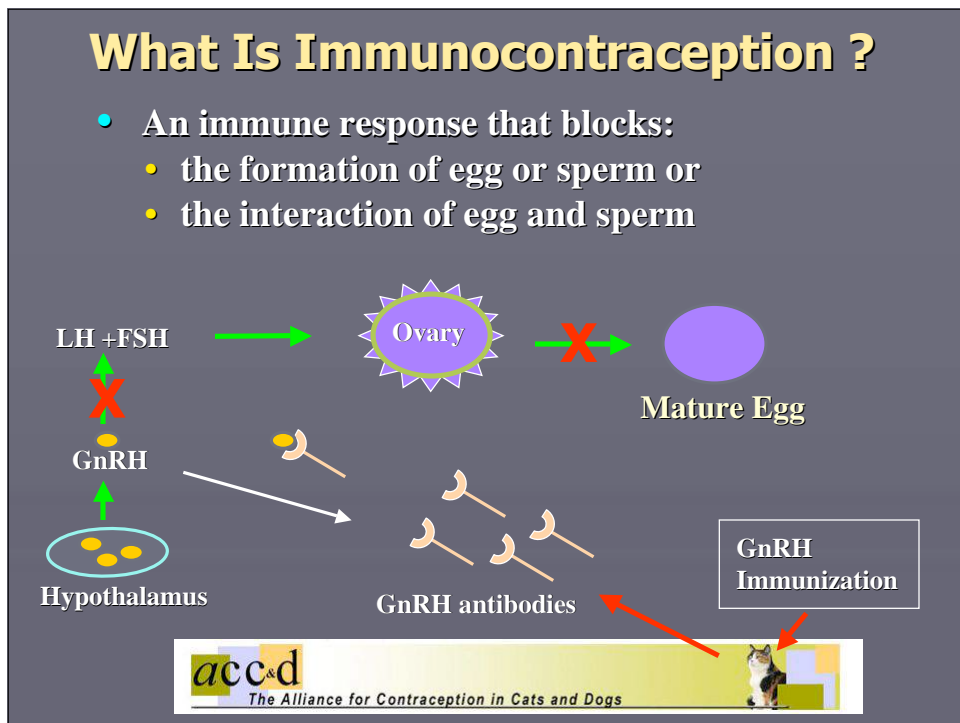
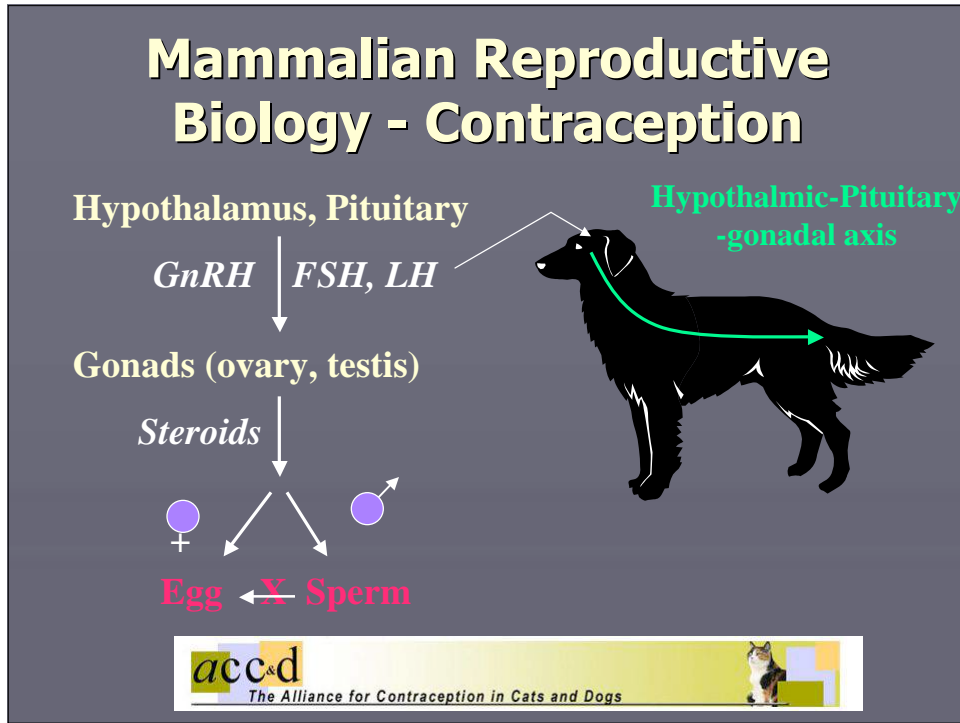
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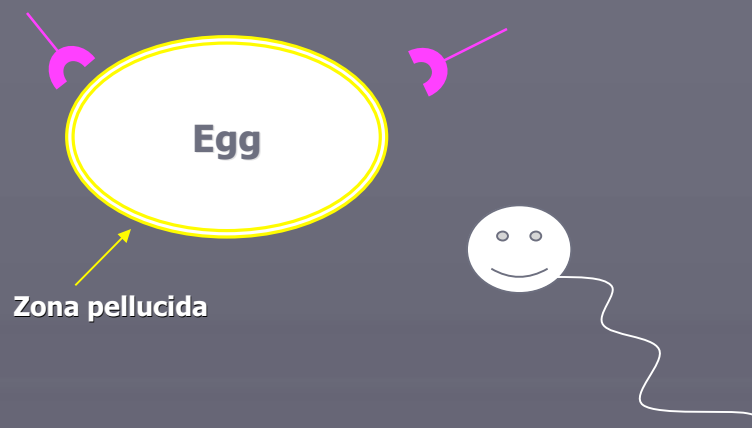
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Synthesize Vaccine to ZP (using ZP from pigs)

- ▶ ZP molecular structure is similar in mammalian species
- ▶ Extract from pig ovaries
- ▶ “Vaccinate” females to generate an immune response to ZP
- ▶ Antibodies inhibit sperm penetration of ZP to fertilize egg



PZP Immunocontraception: Porcine zona pellucida

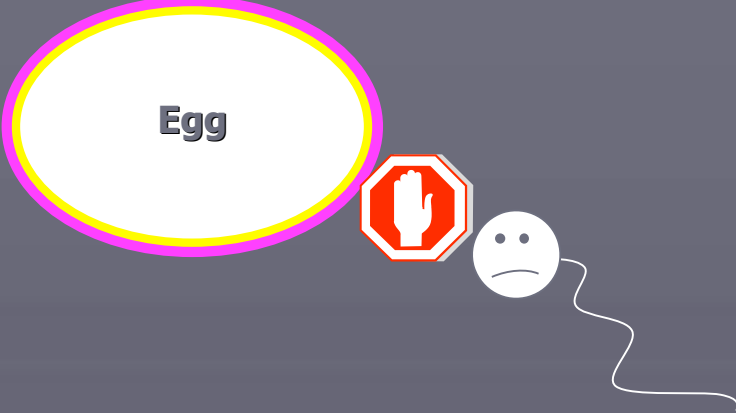


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PZP Immunocontraception: Porcine zona pellucida



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Products on the Market

Zinc gluconate - Neutersol™ (PHI, Inc.)
Permanent; male dogs 3-10 months old
Approved by the FDA
Currently not available

Deslorelin implant - Suprelorin® (Peptech)
Temporary (6-12 months); male dogs
Approved in Australia, New Zealand
Under development for Europe, USA



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Research Stage Technology

Vaccines

Zona pellucida (f)

Luteinizing hormone receptor (f,m)

Novel oocyte, sperm proteins (f,m)

GnRH (f,m) - GonaCon™ - (USDA)

Drugs

GnRH agonists and antagonists (m,f)

Chemical sterilants

VCD - ovarian follicle destruction (f)
(Senestech)

GnRH-toxin conjugate (Gonex)



Questions?



GLOSSARY

ablation – removal of a part (usually by cutting).

agonist – a drug that has affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances (e.g., a GnRH agonist binds to and stimulates GnRH receptors on the pituitary gland).

antagonist – a drug that binds to a cell's receptor without eliciting a biological response and that can prevent the naturally occurring substance from binding, therefore blocking the normal biological response (e.g., a GnRH antagonist will block the GnRH receptor on the pituitary gland, preventing the binding of GnRH).

antibody – an immunoglobulin that is made by white blood cells in response to exposure to an antigen.

antigen – a substance that is administered to an animal to elicit an immune response (usually refers to a protein substance).

benign prostatic hypertrophy (BPH) – enlargement of the prostate that is not cancerous; commonly seen in older dogs and men.

castration – technically, removal of either the ovaries of females or the testicles of males, but commonly used only for males, and synonymous with neuter.

cDNA – complementary DNA, which defines the DNA coding sequence of the gene and can be used to define the amino acid sequence of the protein.

down-regulation – used in this report to mean the reduction of the number of receptors or the activity of those receptors, which results in a desensitization to the substance that binds the receptor (e.g., GnRH no longer causes its biological action when the receptors on the pituitary gland cells are down-regulated).

estrus – also known as “heat,” the time during which a female animal is ovulating and receptive to breeding by a male; it is characterized by specific hormonal and behavior changes in the female.

fecundity – ability to produce offspring rapidly and in large numbers.

fertilization – the act of rendering eggs capable of further development by contact with sperm.

follicle stimulating hormone (FSH) – one of the hormones of the anterior pituitary that stimulates the growth of ovarian follicles in females and stimulates spermatogenesis in males.

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gonadotropin releasing hormone (GnRH) – the hormone that is produced in the brain, released in a pulsatile manner, and stimulates the pituitary gland to release luteinizing hormone and follicle stimulating hormone. It is a small ten amino acid peptide.

gonadotroph – specific cells in the pituitary gland that have receptors that bind GnRH; these cells then synthesize and secrete the gonadotrophins (luteinizing hormone and follicle stimulating hormone).

good manufacturing practice (GMP) – the list of practices to be followed in manufacturing pharmaceutical products to meet worldwide regulatory requirements.

heat – also known as estrus (see *estrus*).

histopathology – a study of the microscopic appearance of tissues to look for any pathological changes caused by an illness, toxin, or drug treatment.

hypothalamus – an area of the brain that controls crucial body functions, such as hormone release, water balance, body temperature, sleep and food intake. Its importance in the reproductive system is that the neurons that produce GnRH are located in the hypothalamus.

immunocontraception – causing an animal to become infertile by injecting it with an antigen that causes it to mount an immune response to some component of the reproductive system, such as eggs, zona pellucida, sperm or GnRH.

INAD –investigational new animal drug; used as an abbreviation for the paperwork that is filed to start the process for regulatory approval of a new animal drug by the FDA Center for Veterinary Medicine.

luteinizing hormone (LH) – one of the hormones of the anterior pituitary that acts to cause ovulation of mature follicles and the secretion of estrogen in females, and stimulates the testes to produce testosterone in males.

luteinizing hormone releasing hormone (LHRH) – another name for gonadotropin releasing hormone (GnRH).

NADA – new animal drug approval; refers to the final approval by the FDA's Center for Veterinary Medicine to market a new drug.

negative feedback – the condition of maintaining a constant output of a system by exertion of an inhibitory control on a key step in the system by a product of that system.

neuter – common term usually used to mean removal of the testicles of male animals.

oligonucleotide – a relatively small fragment of DNA (usually about 2-20 bases).

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ovariectomy – surgical removal of the ovaries.

ovariohysterectomy – surgical removal of the ovaries and uterus; generally referred to as spaying when referring to female companion animals.

palpation – the act of feeling with the hand to determine the consistency of the parts under the skin and the outline of organs and structures.

pituitary gland – a gland located at the base of the brain that, under influence from the brain, releases a number of important hormones that regulate body function (thyroid gland, gonads, adrenal gland and other endocrine organs).

receptor – a specific molecule on the surface or within the cell that recognizes and binds with other specific molecules, such as hormones.

serum chemistry – used in this report to mean the various serum biochemistry measurements that are standard for evaluation of health or disease.

spay – when used in reference to dogs and cats, spay means ovariohysterectomy, or surgical removal of the uterus and ovaries; when used in reference to cattle, spay means surgical removal of the ovaries.

subcutaneous – under the skin.

zona pellucida – a transparent, non-cellular layer or envelope of uniform thickness surrounding an oocyte (egg).

Adapted from Contraception and Fertility Control in Animals by Rhodes and Moldave, 2002.