Hereditary Deafness in Dogs and Cats

Sordera Hereditaria en Perros y Gatos

Congreso Internacional de Medicina, Cirugía y Zootecnia en Perros, Gatos y otras Mascotas

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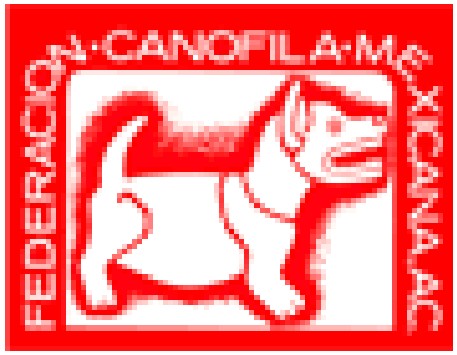
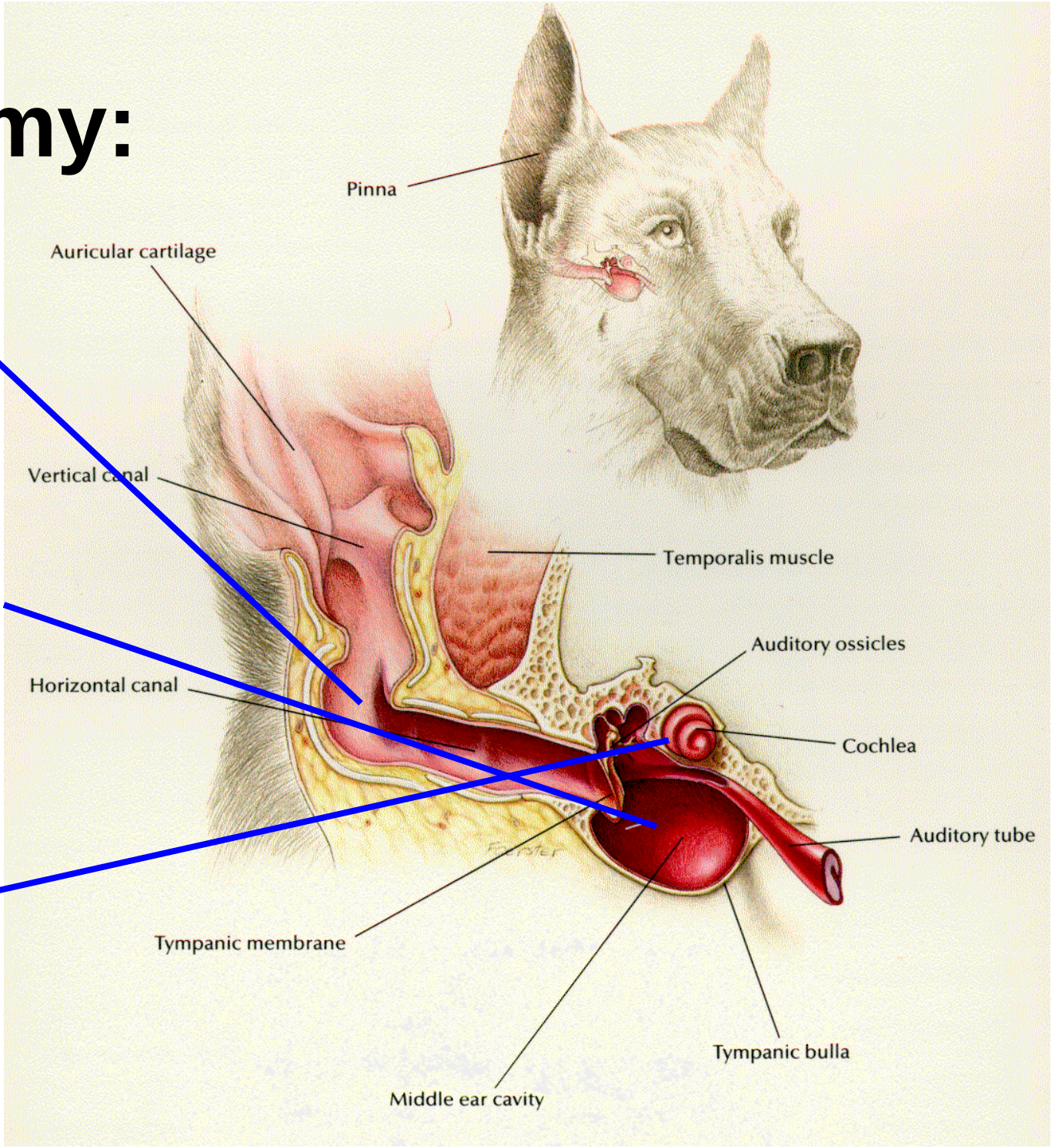


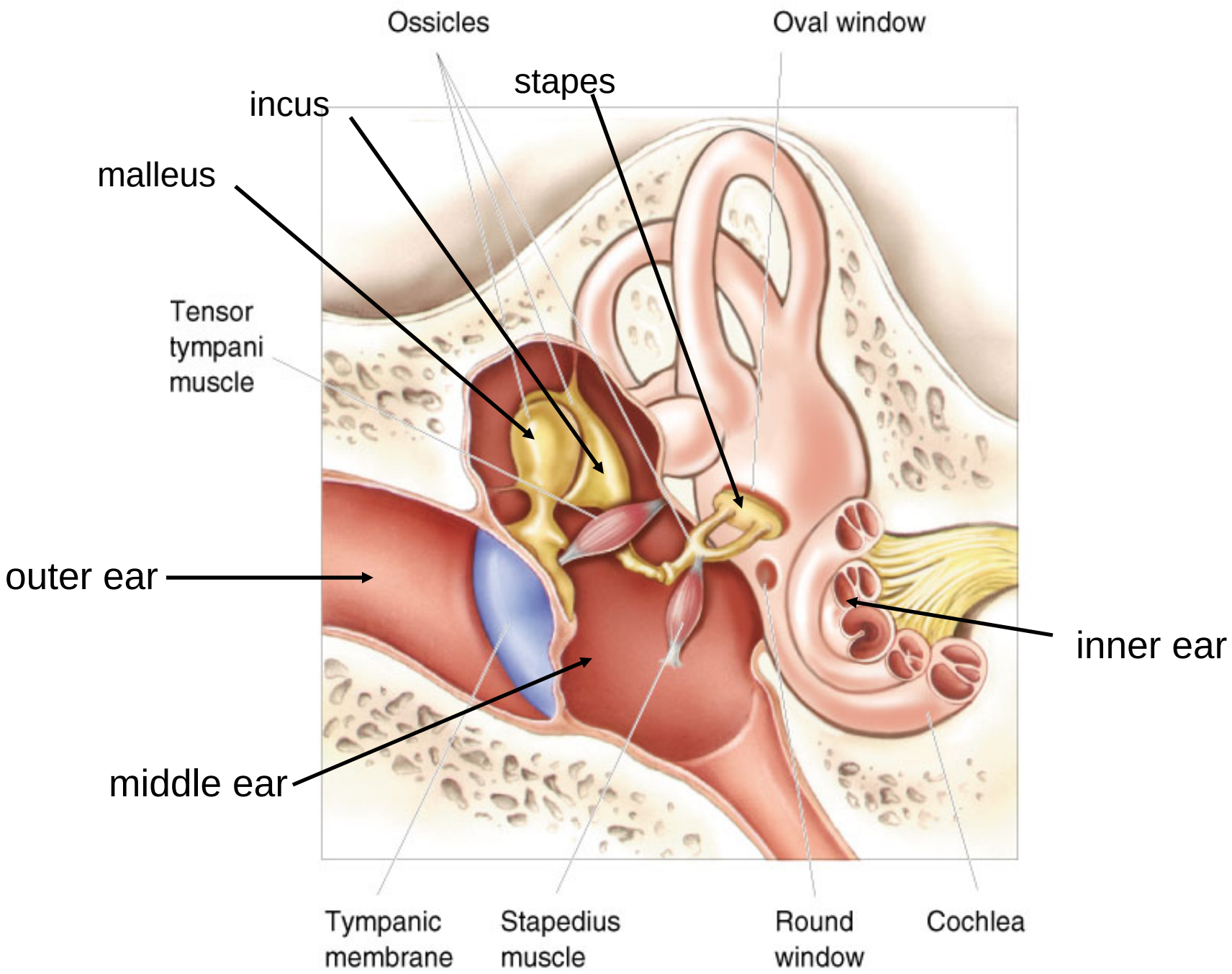
Outline

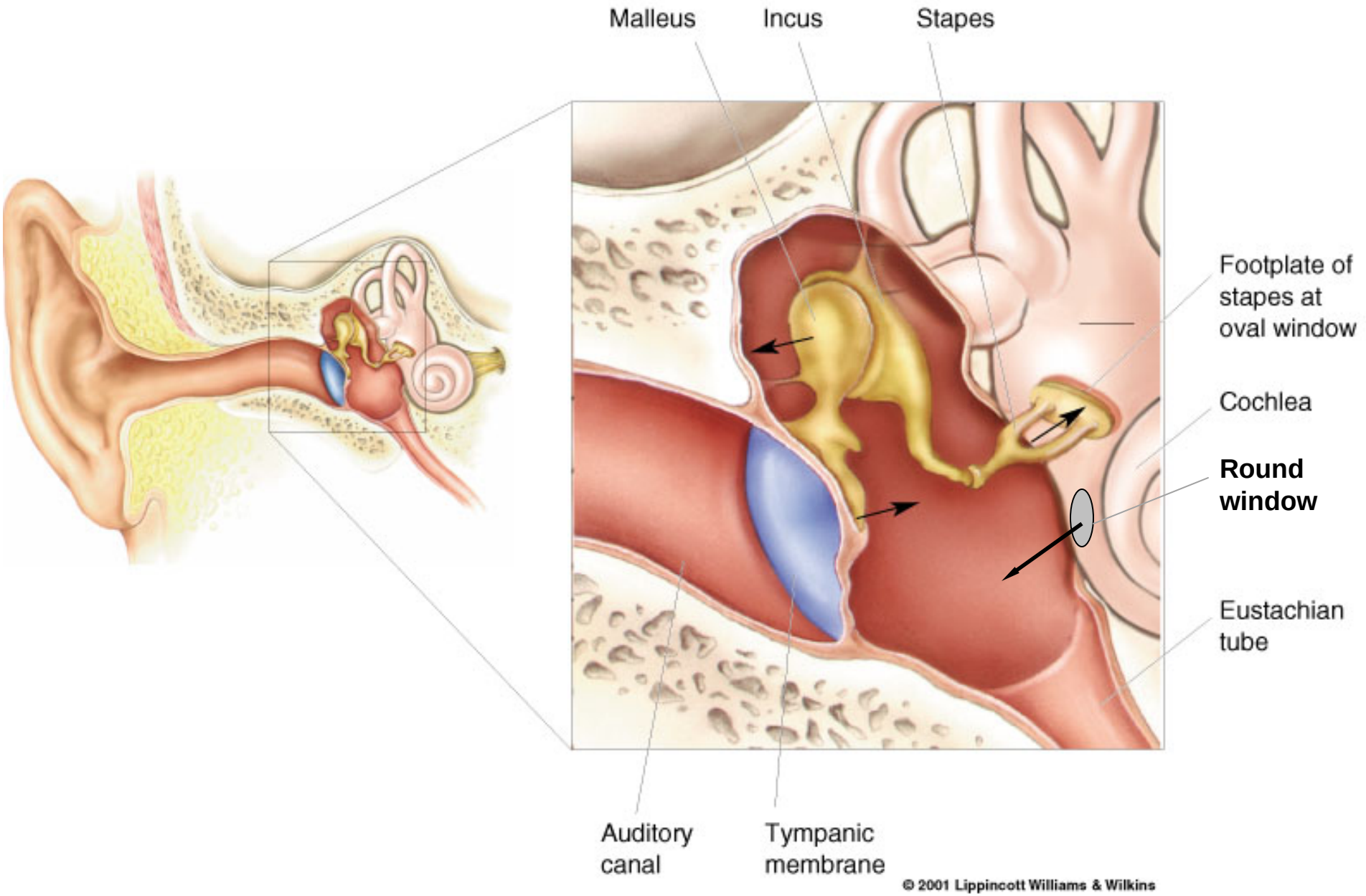
- anatomy and physiology
- forms of deafness
- hearing testing
- pigment genes and hereditary deafness
- prevalence and breeds
- genetics of deafness

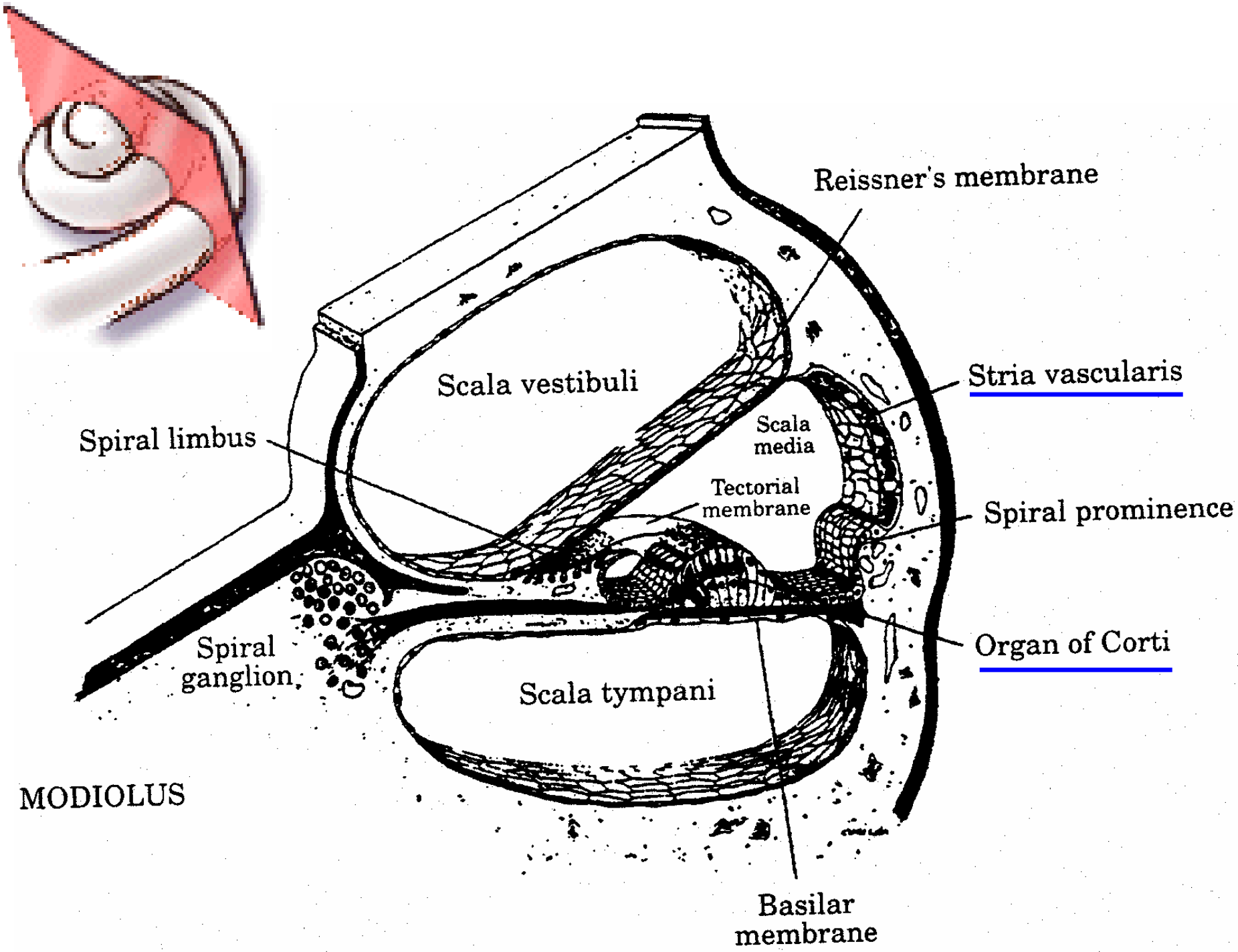
Ear Anatomy:

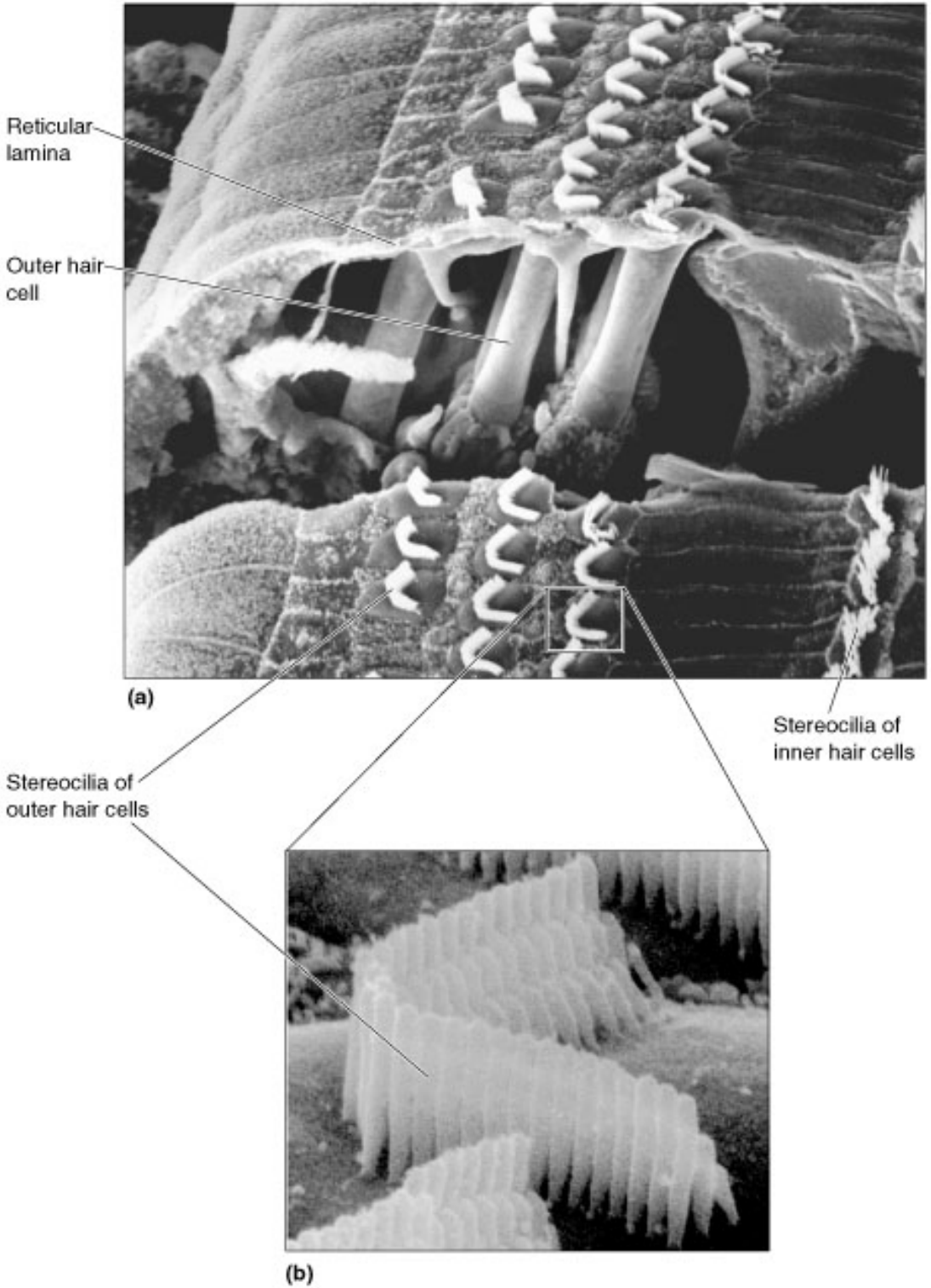
- **outer ear**
- **middle ear**
- **inner ear**




Ossicles
Oval window
stapes
incus
malleus
Tensor
tympani
muscle
outer ear
inner ear
middle ear
Tympanic
membrane
Stapedius
muscle
Round
window
Cochlea


Malleus
Incus
Stapes
Footplate of stapes at oval window
Cochlea
Round window
Eustachian tube
Auditory canal
Tympanic membrane
© 2001 Lippincott Williams & Wilkins


Reissner's membrane
Stria vascularis
Scala vestibuli
Scala media
Spiral limbus
Tectorial membrane
Spiral prominence
Organ of Corti
Spiral ganglion
Scala tympani
MODIOLUS
Basilar membrane


Reticular lamina
Outer hair cell
(a)
Stereocilia of outer hair cells
Stereocilia of inner hair cells
(b)

Approximate Hearing Ranges (Hz)

human	**64-23,000**	**sheep**	**100-30,000**
dog	**67-45,000**	**rabbit**	**360-42,000**
cat	**45-64,000**	**rat**	**200-76,000**
cow	**23-35,000**	**mouse**	**1,000-91,000**
horse	**55-33,500**	**porpoise**	**75-150,000**

(See www.lsu.edu/deafness/HearingRange.html for more species)

Forms of Deafness

- **inherited* or acquired**
- **congenital* or later-onset**
- **sensorineural* or conductive**

result: eight possible combinations (i.e., <u>acquired</u> <u>later-onset</u> <u>sensorineural</u> deafness)

Definitions

- **sensorineural (nerve) deafness - loss of auditory function because of loss of cochlear hair cells or the cochlear nerve neurons they connect to**

- **conductive deafness - blockage of sound transmission through outer and/or middle ear without damage to cochlea**

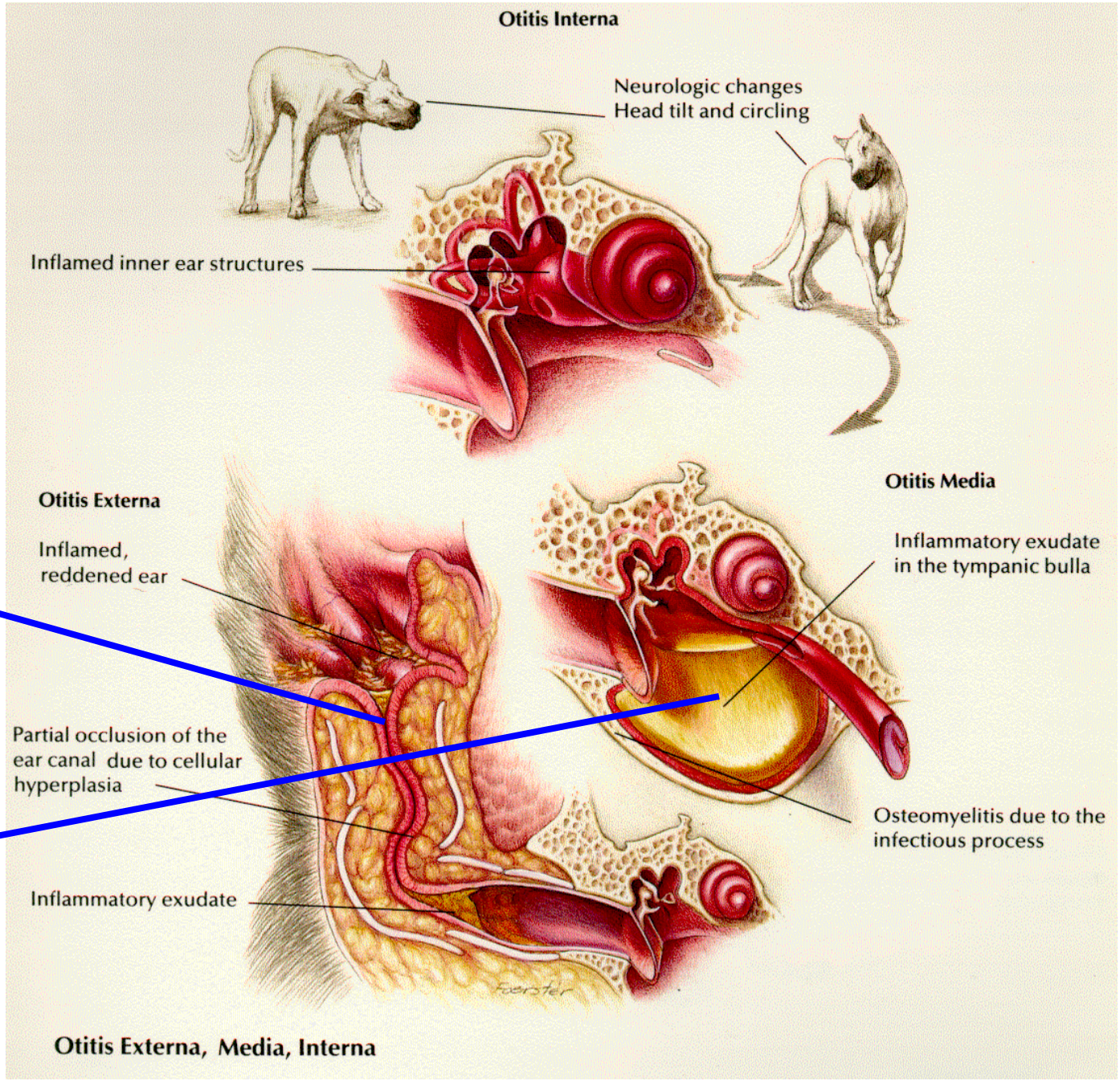
Most Common Forms of Deafness

- **hereditary congenital sensorineural**
- **acquired later-onset sensorineural**
- **acquired later-onset conductive**

Infectious causes of conductive deafness:

otitis externa

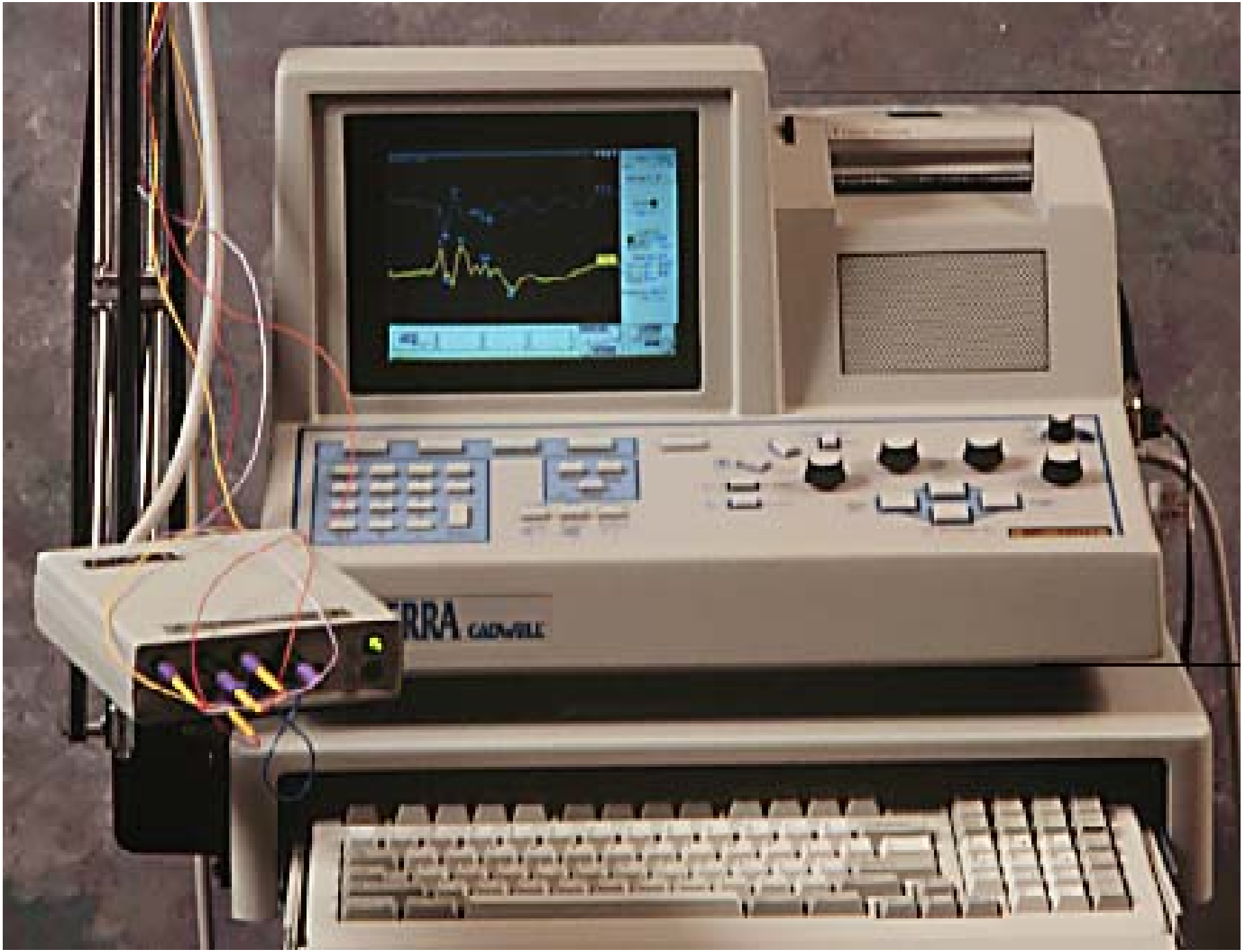
otitis media



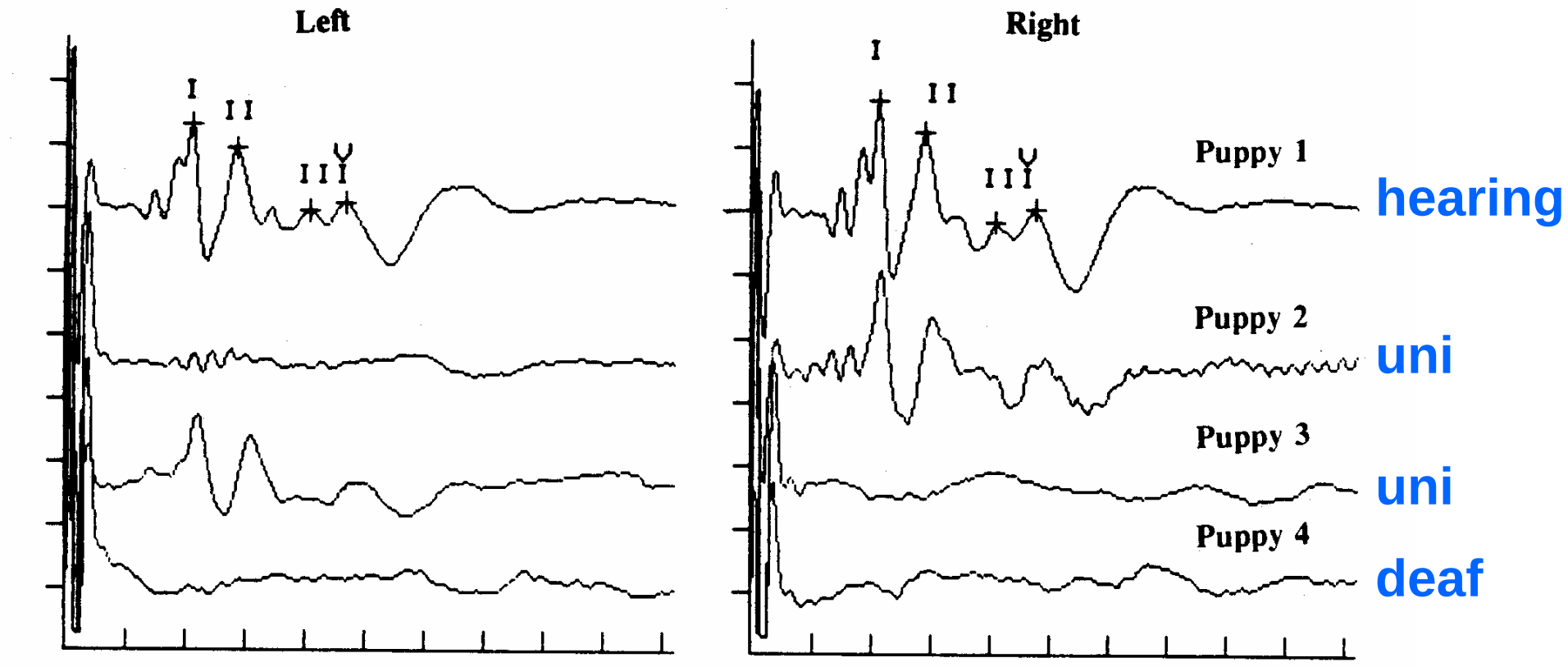
Hearing Testing

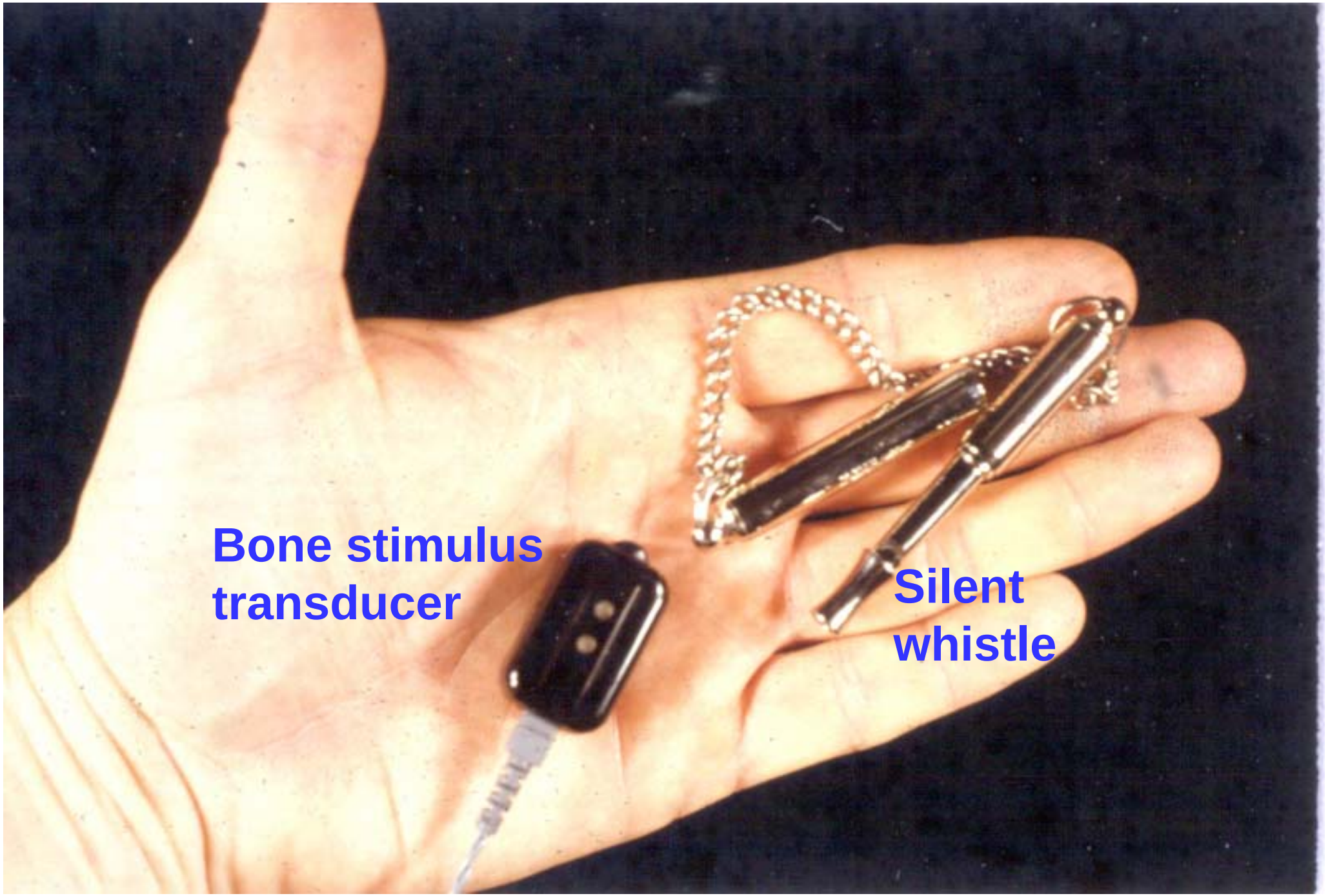
- **behavioral testing - sound stimuli produced outside of the animal's visual field**
  - **cannot detect unilateral deafness**
  - **animals quickly adapt to testing**
  - **stimuli detected through other sensory modalities**

- **electrodiagnostic testing - brainstem auditory evoked response (BAER, BAEP, ABR)**
  - **objective, non-invasive**
  - **detects unilateral deafness**
  - **limited availability**


RRA CADWELL

Brainstem Auditory Evoked Response

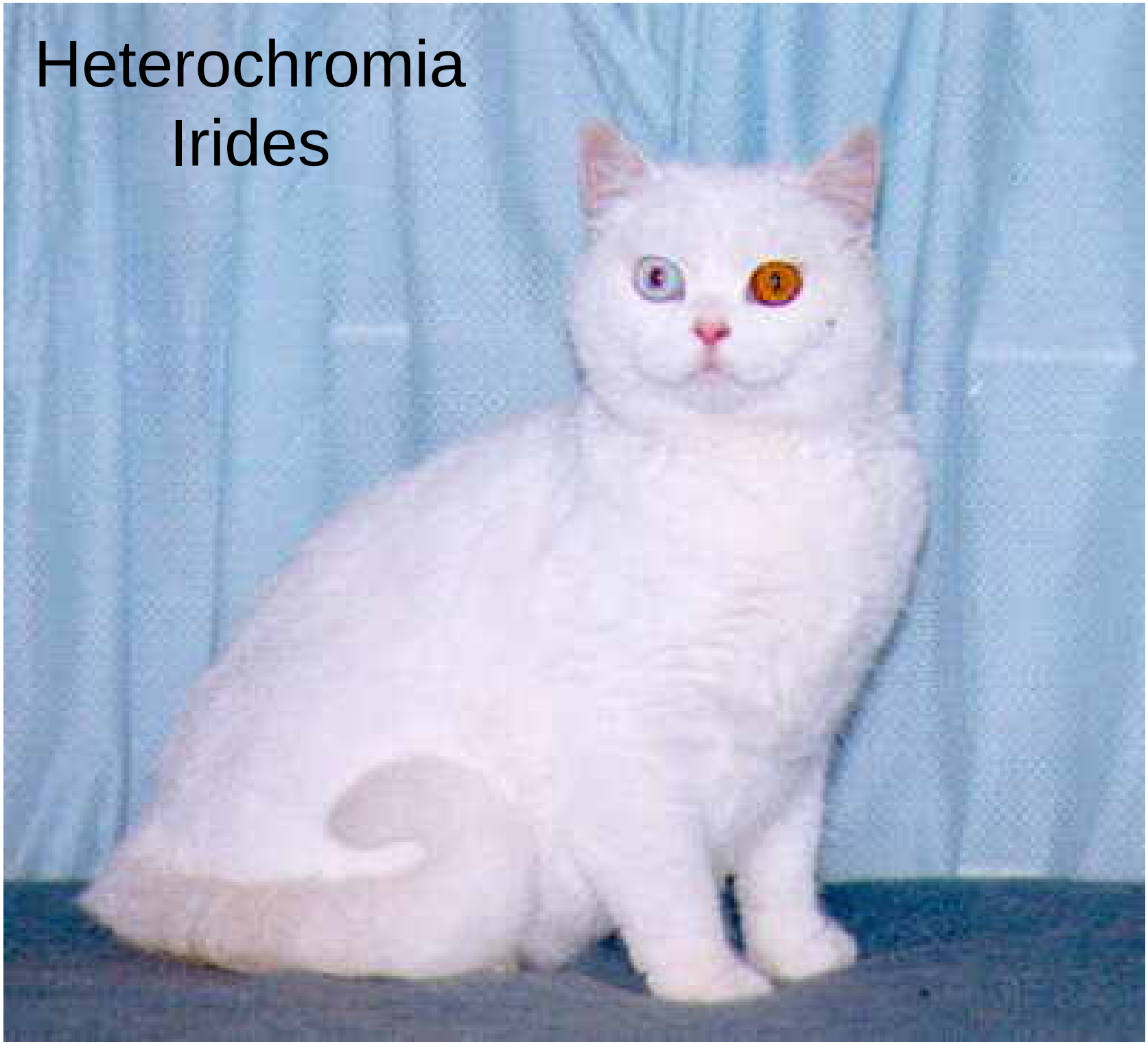



Bone stimulus transducer
Silent whistle

Hereditary Congenital Sensorineural Deafness

- **usually** linked to the genes responsible for white
  - Dog – Recessive alleles of the piebald (**s**) gene: Irish spotting (s^i), piebald (s^p), extreme-white piebald (s^w)
  - Dog – Dominant allele of the merle (**M**) gene
  - Cat – Dominant allele of the white (**W**) gene
- deafness develops at 3-4 weeks of age when the blood supply to the cochlea (stria vascularis) degenerates
- degeneration is thought to result from an absence of pigment cells (melanocytes) which normally help maintain the ionic concentrations of K^+ and Na^+
- other pigmentation effects are frequently seen


Demi Azure


Heterochromia
Irides

Dog Breeds With Congenital Deafness

- reported in over 85 dog breeds
- prevalence (unilateral & bilateral) highest in:
  - Dalmatian (n=5,333) 30%
  - white bull terrier (n=346) 20%
  - English setter (n=3,656) 8%
  - English cocker spaniel (n=1,247) 6%
  - Australian cattle dog (n=296) 15%
  - Jack Russell terrier (n=56) 16%*
  - Catahoula leopard dog (n=78) 63%*

(prevalence unknown for most breeds)

Cat Breeds With White Gene

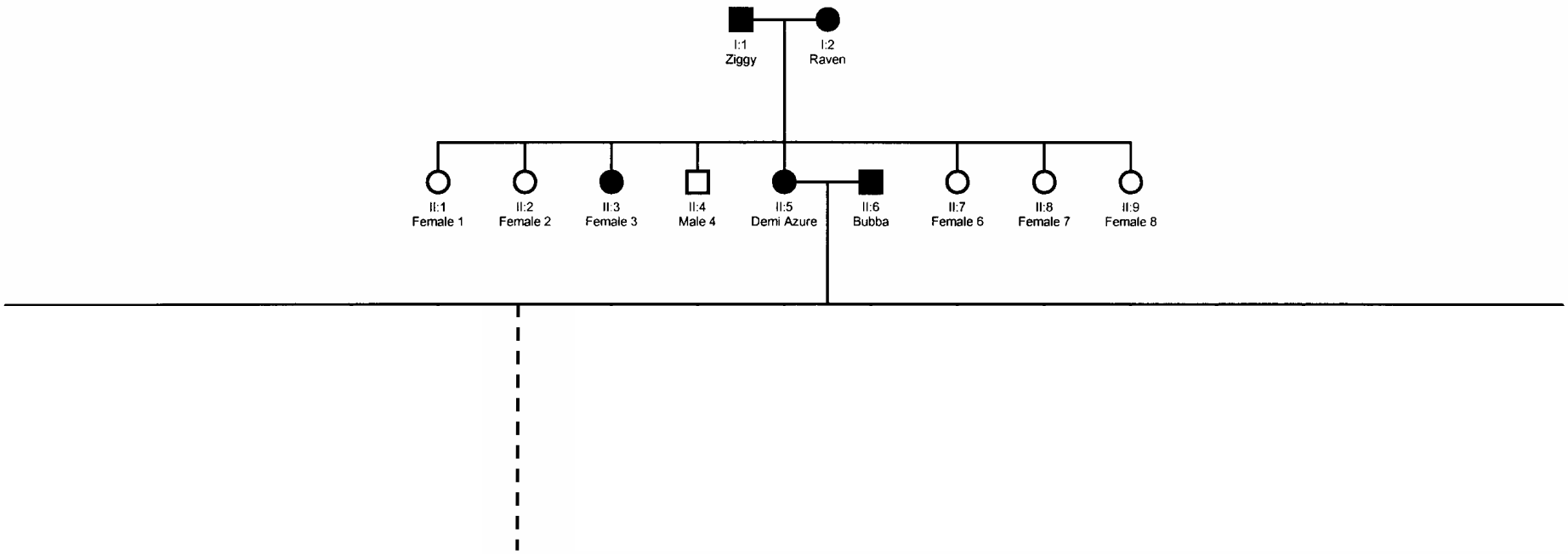
- **W is present in at least 17 cat breeds**
- **prevalence data (unilateral & bilateral) is unknown for most breeds**
  - **DSH and DHL white cats 50-96%**
  - **white Norwegian Forest, Maine coon, and Turkish angora cats 11-18%**
    (data from owner surveys – likely underestimates)

Genetics of Congenital Deafness

- Doberman – simple autosomal recessive; vestibular dysfunction, not pigment-associated
- “nervous” pointer deafness – dogs bred for anxiety research studies - simple autosomal recessive?
- pigment-associated deafness - ?
  - merle gene (M) – dominant gene; homozygous dogs may have additional health problems
  - piebald gene (s) – recessive gene, but all white dogs in the breed are homozygous – deafness likely due to a single locus with modifier genes – NOT simple autosomal recessive
  - white gene (W) – dominant gene

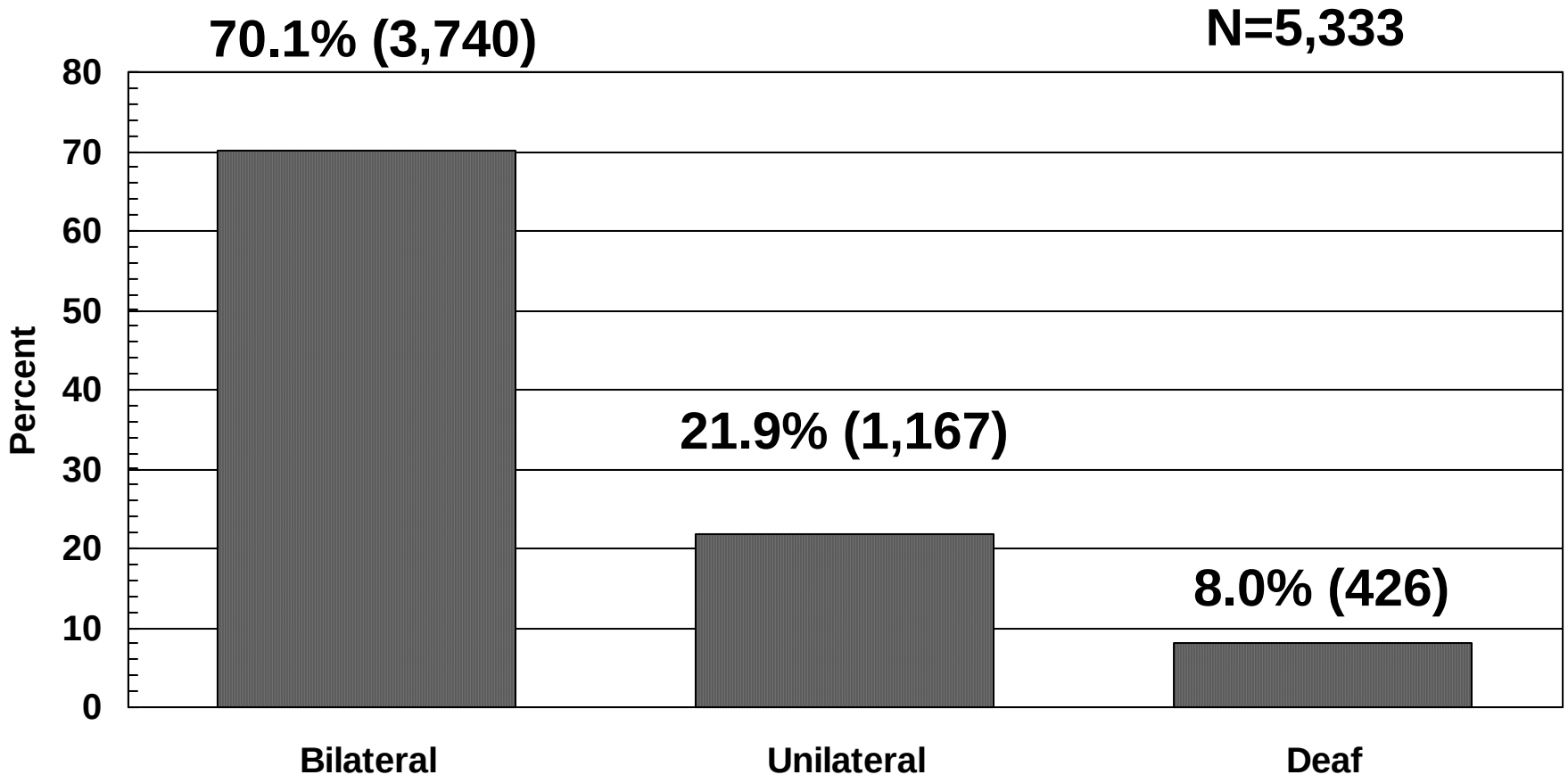
Piebald Gene

Demi Azure Pedigree

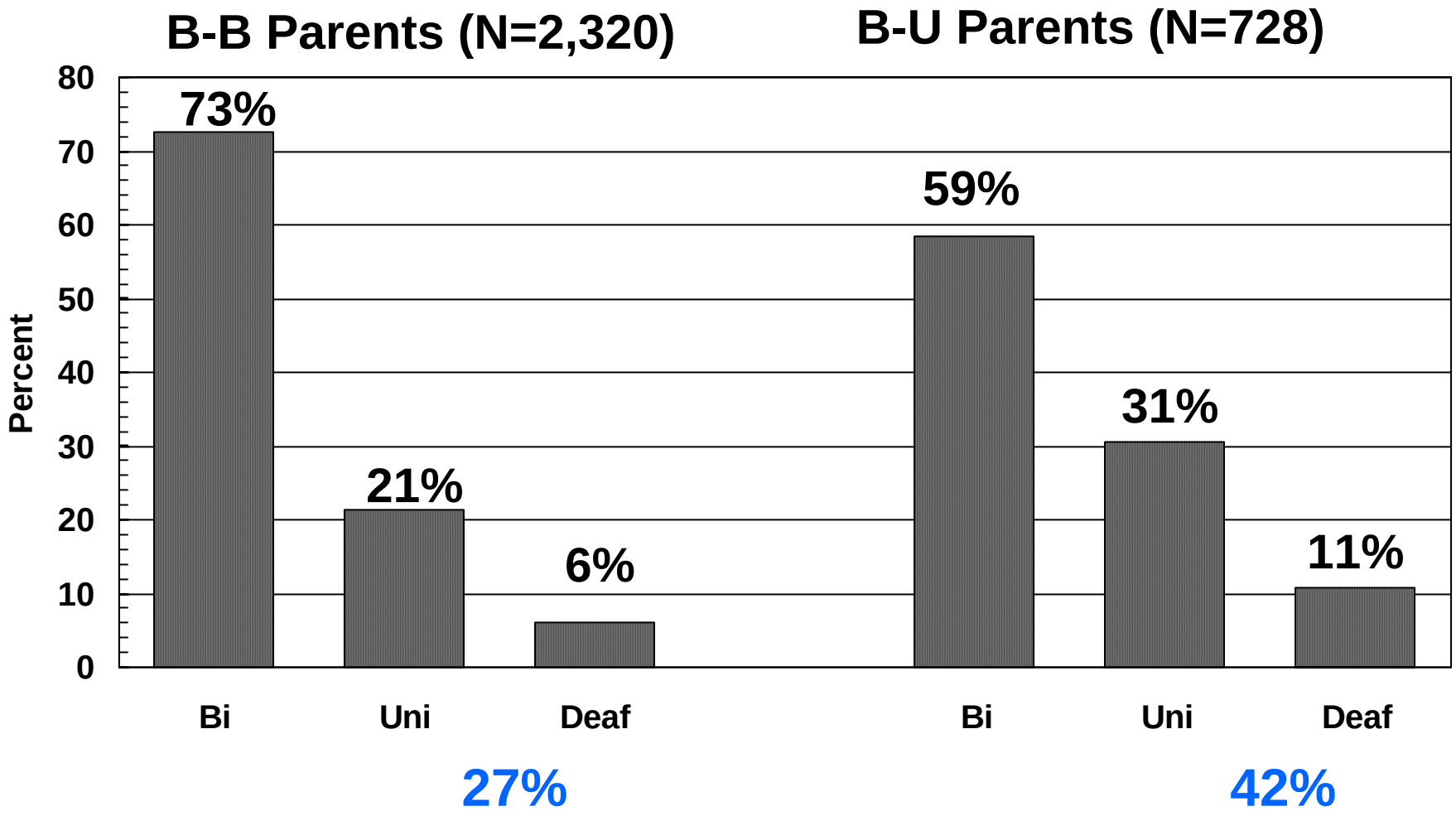


Observations on Pigment-Associated Congenital Hereditary Sensorineural Deafness in the Dalmatian

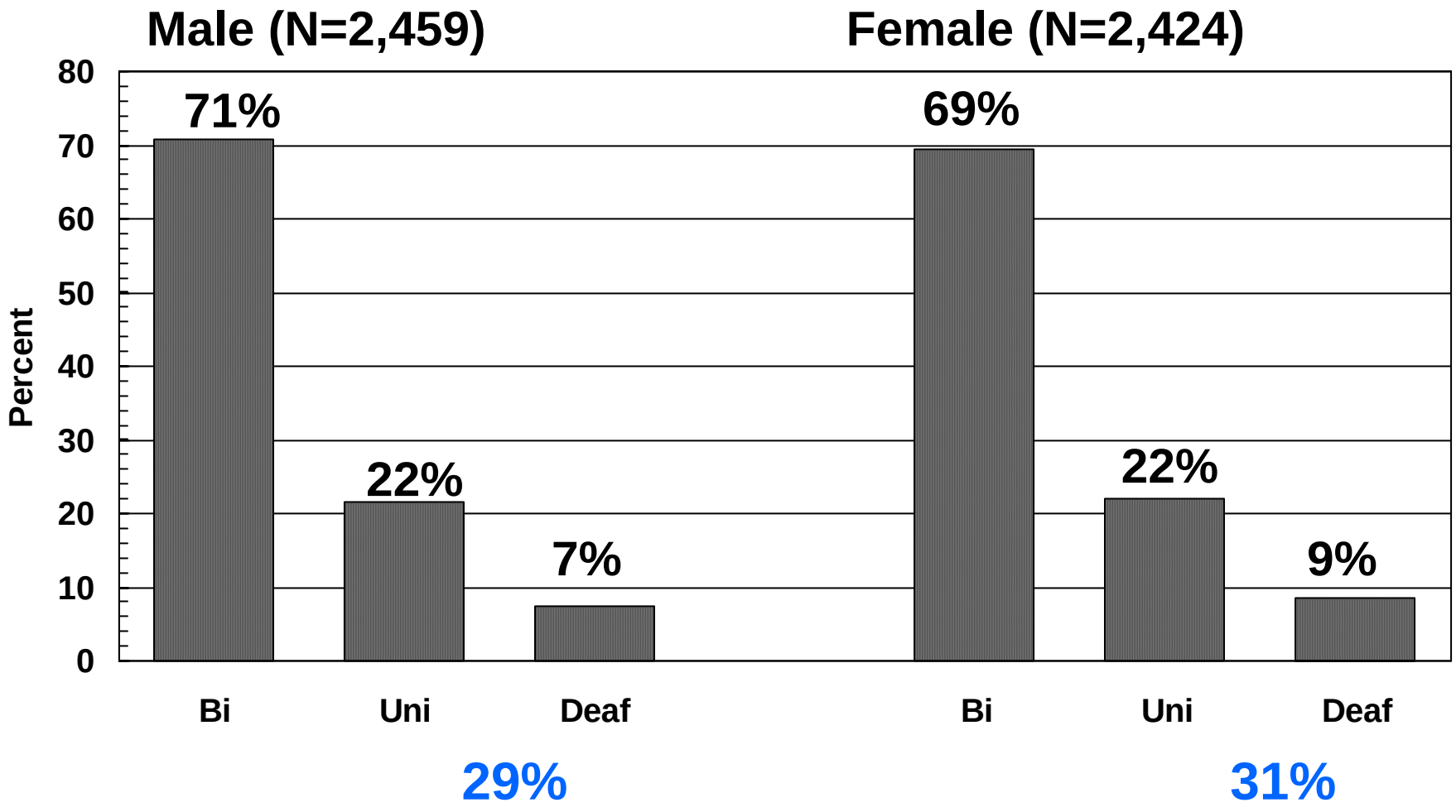
Dalmatian Deafness Prevalence in the US



Effect of Parent Hearing Status On Deafness Prevalence



Effect of Sex On Deafness Prevalence



Coat Pigmentation Genes In Dalmatians

- base coat - underlying coat color
  - B - black (dominant)
  - b - liver (recessive)
- extreme-white piebald gene - s^w - white covering; recessive but homozygous in all Dalmatians [hair is white if it contains no pigment granules (melanin) or other substances which absorb light.]
- ticking gene - T - dominant, produces holes in white to show underlying coat color

Effect of Varying the Expression of the Extreme-White Piebald Gene

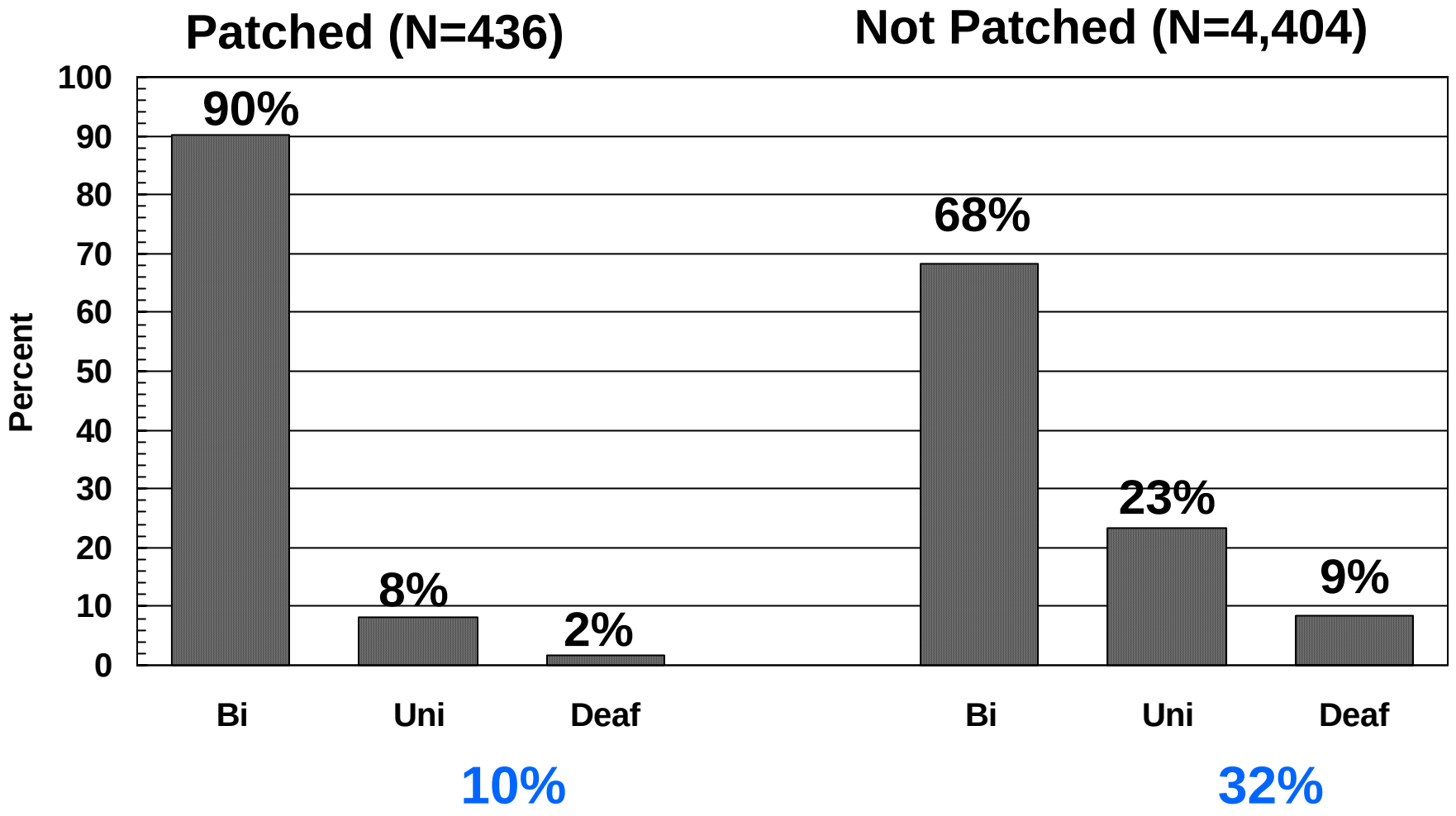
- weak gene expression: failure of the piebald gene to completely suppress the underlying coat color (black or liver) results in a patch; animals are less likely to be deaf

- strong gene expression suppresses pigmentation in the iris (blue eyes) and tapetum (red eye shine), and in the stria vascularis (deafness)

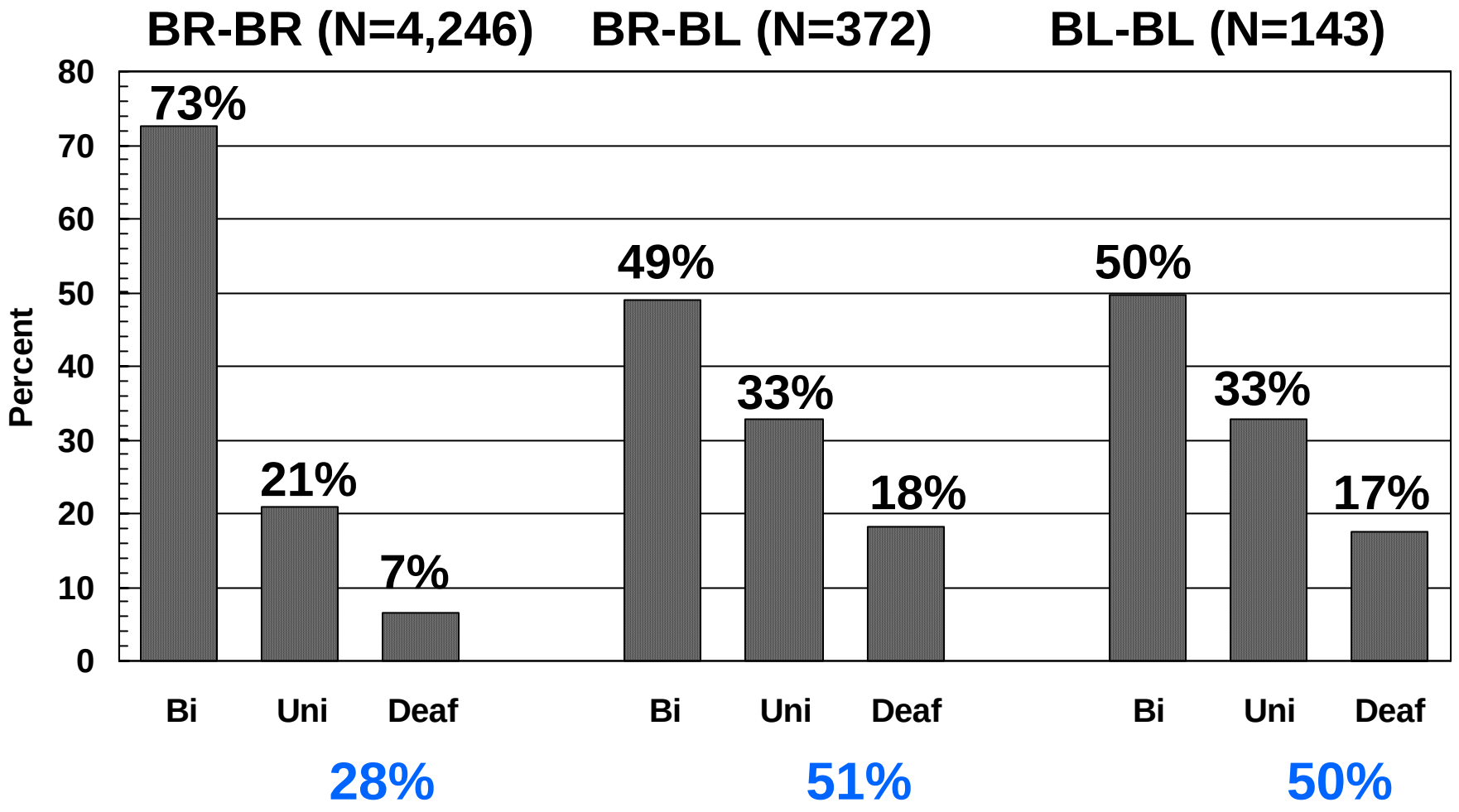
Patches

Present at birth when spots have not yet appeared

Effect of Patch On Deafness Prevalence



Effect of Eye Color (Brown or Blue) On Deafness Prevalence



Prevalence of Deafness In Dalmatians By Country

- **United States** **30%** **(G Strain, N=5,333)**

- **UK** **21%** **(M Greening, N=2,282)**
- **Holland** **18%** **(B Schaareman, N=1,208)**
- **Belgium** **19%** **(L Poncelet, N=122)**

Impact Of Breed Standards

- United States: allows blue eyes
- Europe & Canada: do not allow blue eyes
- efforts through breeding to reduce blue eyes in Norwegian Dalmatians also reduced deafness prevalence.

Breeding Recommendations

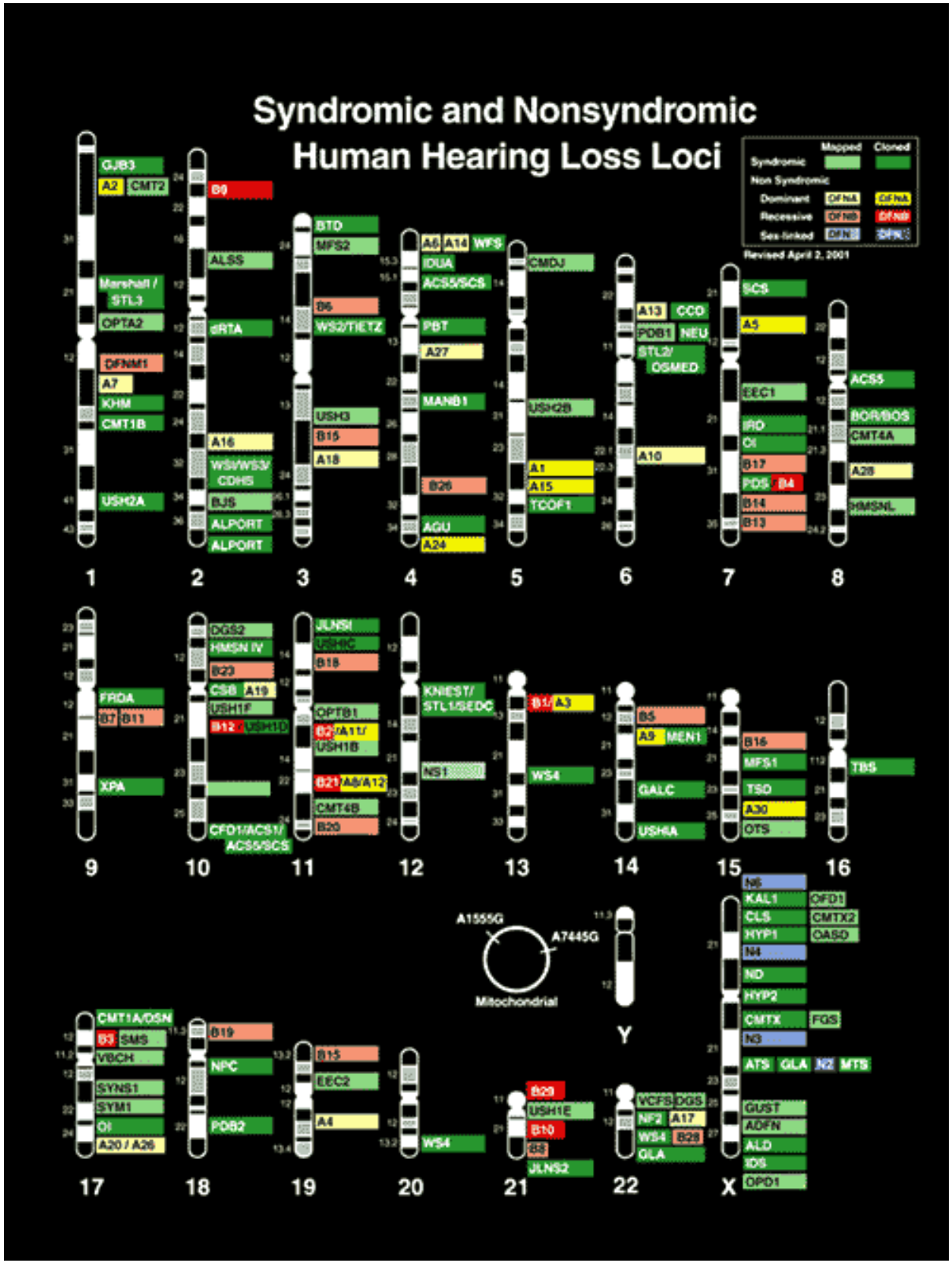
- **BEST ADVICE: don't breed affected animals**

- **a unilaterally deaf animal is genetically the same as a bilaterally deaf animal, and should not be bred!**
- **it is unwise to repeat a breeding that produced large numbers of deaf animals**
- **avoid breeding to animals with a history of producing many deaf offspring**

Breeding Recommendations (cont.)

- do not totally breed away from patches (Dal)
- avoid breeding blue eyed animals
- if deafness is a problem in your breed, ALWAYS know the hearing status of animals you breed to!
- breeding decisions should always take into consideration the overall good of the breed

Syndromic and nonsyndromic human hearing loss loci



Identification Of the Piebald Gene

- **in the Dalmatian the mode of inheritance is NOT simple autosomal recessive**
- **best modeled statistically as being inherited as a single “locus” but one that does not follow Mendelian genetics**
- **human/mouse genes excluded to date:**

  mitf ***c-kit*** ***endrb*** ***pax3***
- **work on isolation continues**

Merle Gene

Merle (M)

- homozygous recessive dogs (mm) – uniform pigmentation
- heterozygous dogs (mM) – dappling or alternate body areas of fully pigmented coat and pale or white coat; may be deaf
- homozygous dominant dogs (MM) – usually nearly solid white, may be deaf, blind with microphthalmic eyes, and sterile

Merle Pattern in Various Breeds

Retrotransposon insertion in *SILV* is responsible for merle patterning of the domestic dog

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Edited by Susan R. Wessler, University of Georgia, Athens, GA, and approved November 26, 2005 (received for review August 11, 2005)

Merle is a pattern of coloring observed in the coat of the domestic dog and is characterized by patches of diluted pigment. This trait is inherited in an autosomal, incompletely dominant fashion. Dogs heterozygous or homozygous for the merle locus exhibit a wide range of auditory and ophthalmologic abnormalities, which are similar to those observed for the human auditory–pigmentation disorder Waardenburg syndrome. Mutations in at least five genes have been identified as causative for Waardenburg syndrome; however, the genetic bases for all cases have not been determined. Linkage disequilibrium was identified for a microsatellite marker with the merle phenotype in the Shetland Sheepdog. The marker is located in a region of CFA10 that exhibits conservation of synteny with HSA12q13. This region of the human genome contains *SILV*, a gene important in mammalian pigmentation. Therefore, this gene was evaluated as a candidate for merle patterning. A short interspersed element insertion at the boundary of intron 10/exon 11 was found, and this insertion segregates with the merle phenotype in multiple breeds. Another finding was deletions within the oligo(dA)-rich tail of the short interspersed element. Such deletions permit normal pigmentation. These data show that *SILV* is responsible for merle patterning and is associated with impaired function of the auditory and ophthalmologic systems. Although the mutant phenotype of *SILV* in the human is unknown, these results make it an intriguing candidate gene for human auditory–pigmentation disorders.

short interspersed element | pigmentation | linkage disequilibrium

of ocular abnormalities, including increased intraocular pressure and ametropic eyes. Microphthalmia and colobomas are well described in merle and double merle Dachshunds and Australian Shepherds (3, 7, 8). In all breeds, the double merle genotype can be sublethal and is associated with multiple abnormalities of the skeletal, cardiac, and reproductive systems (3, 9, 10). For these reasons, merle-to-merle breedings are strongly discouraged (9).

Interestingly, many of the abnormalities associated with merle dogs are remarkably similar to those observed in Waardenburg syndrome (WS) (11). WS is an autosomal dominant auditory–pigmentation disorder in humans (1 per 40,000 live births) that accounts for 2% of all cases of congenital deafness (12). Several genes have been implicated in the four clinical varieties of WS: Mutations in *PAX3* cause WS type 1 and type 3 (13, 14) and mutations in *SOX10*, *EDNRB*, or *EDNR3* cause WS type 4 (15–17). Mutations in *MITF* cause WS type 2; however, the genetic basis for 85% of type 2 cases remains unidentified (18, 19).

To identify a chromosomal region segregating with merle, we carried out a whole-genome scan for the Shetland Sheepdog by using the multiplexed Minimal Screening Set 2 (20, 21). Linkage disequilibrium (LD) for merle was identified with a microsatellite marker in a region of CFA10 that exhibits conservation of synteny with HSA12q13. This region of HSA12 harbors the *SILV* gene.

SILV (also known as *Pmel17*; gp100) is a pigment gene best known as the *Silver* locus responsible for a recessive trait in an inbred strain of black mice in which the hair color dilutes with

Proceedings of the National Academy of Sciences, 9 January 2006, 103(5):1376-81.

Merle Gene

- located on the centromeric tip of canine chromosome 10
- wild type gene known as *SILV* (*Silver* in mice)
  - plays a role in the biogenesis of premelanosomes
  - encodes a protein thought to be necessary for matrix fibrils where melanin is deposited
- *SILV* mutation responsible for merle consists of a short interspersed element (SINE) insertion at the intron 10/exon 11boundary
  - SINE size is approximately 253 base pairs
  - variable oligo(dA)-rich tail length

Canine *SILV* Gene

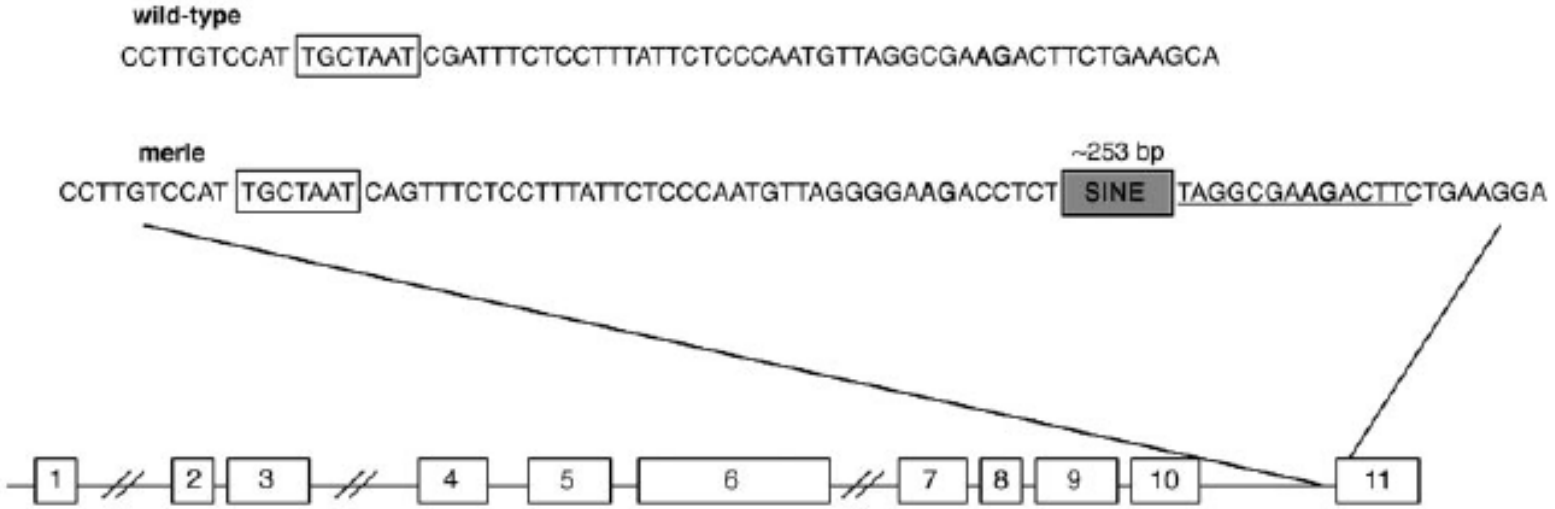


Fig. 2. Structure of wild-type canine *SILV* and sequence of the SINE insertion site in merle dogs. The putative lariat branch point sequence is boxed. Splicing acceptors are indicated by bold type. In merle dogs, the splicing acceptor is located in the 15-bp duplicated sequence (underlined) that flanks the SINE insertion. The average insertion size (not including the duplicated sequence) for the merle dogs analyzed herein is 253 bp.

SINE – short interspersed element, at the inton 10 / exon 11 boundary

A commercial test for merle genotype is now available ($95/dog).

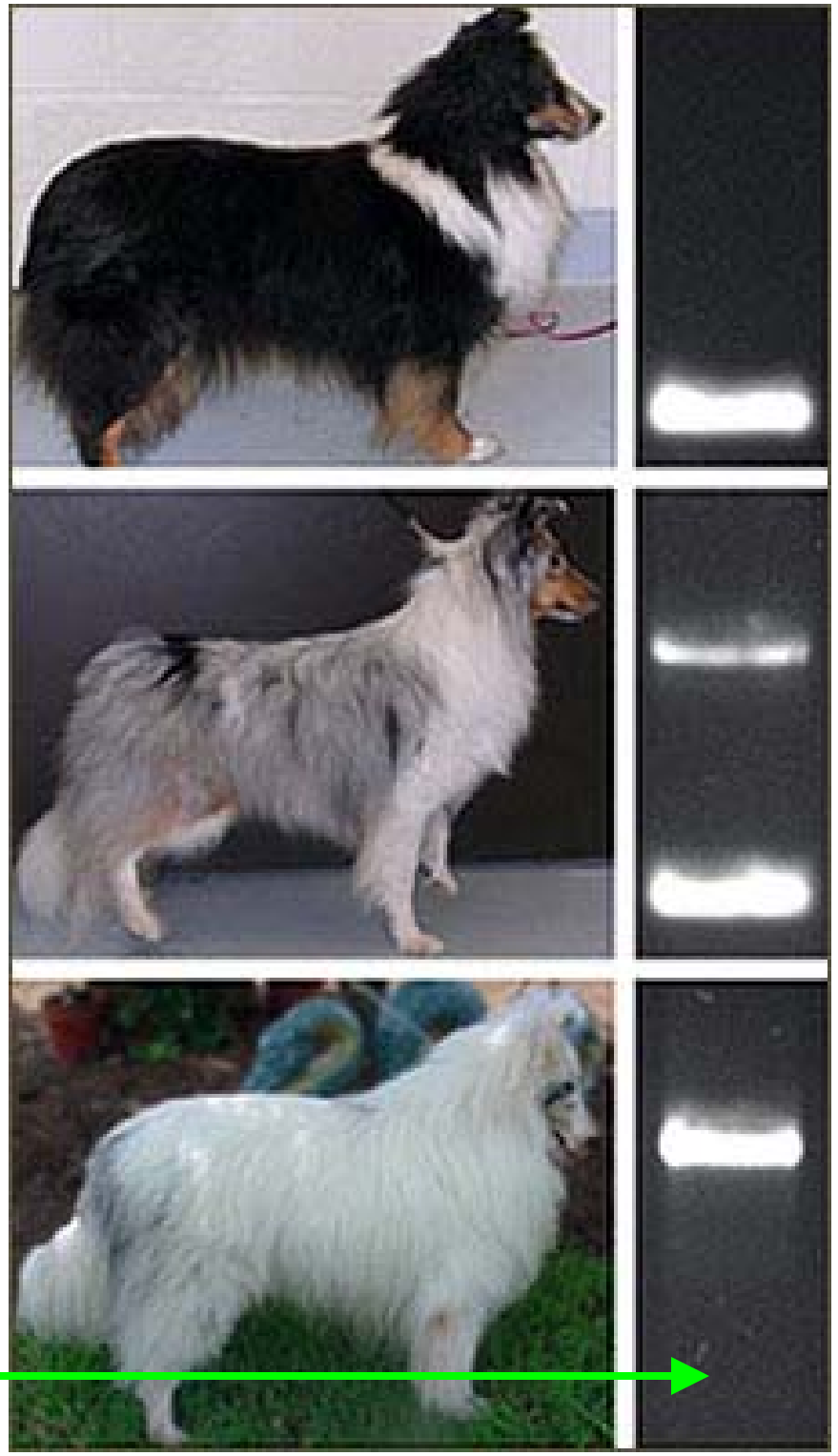
Shetland Sheepdogs

Tricolor (black, sable and white) non-merle (*mm*)

Blue merle (*Mm*)

Double merle (*MM*)

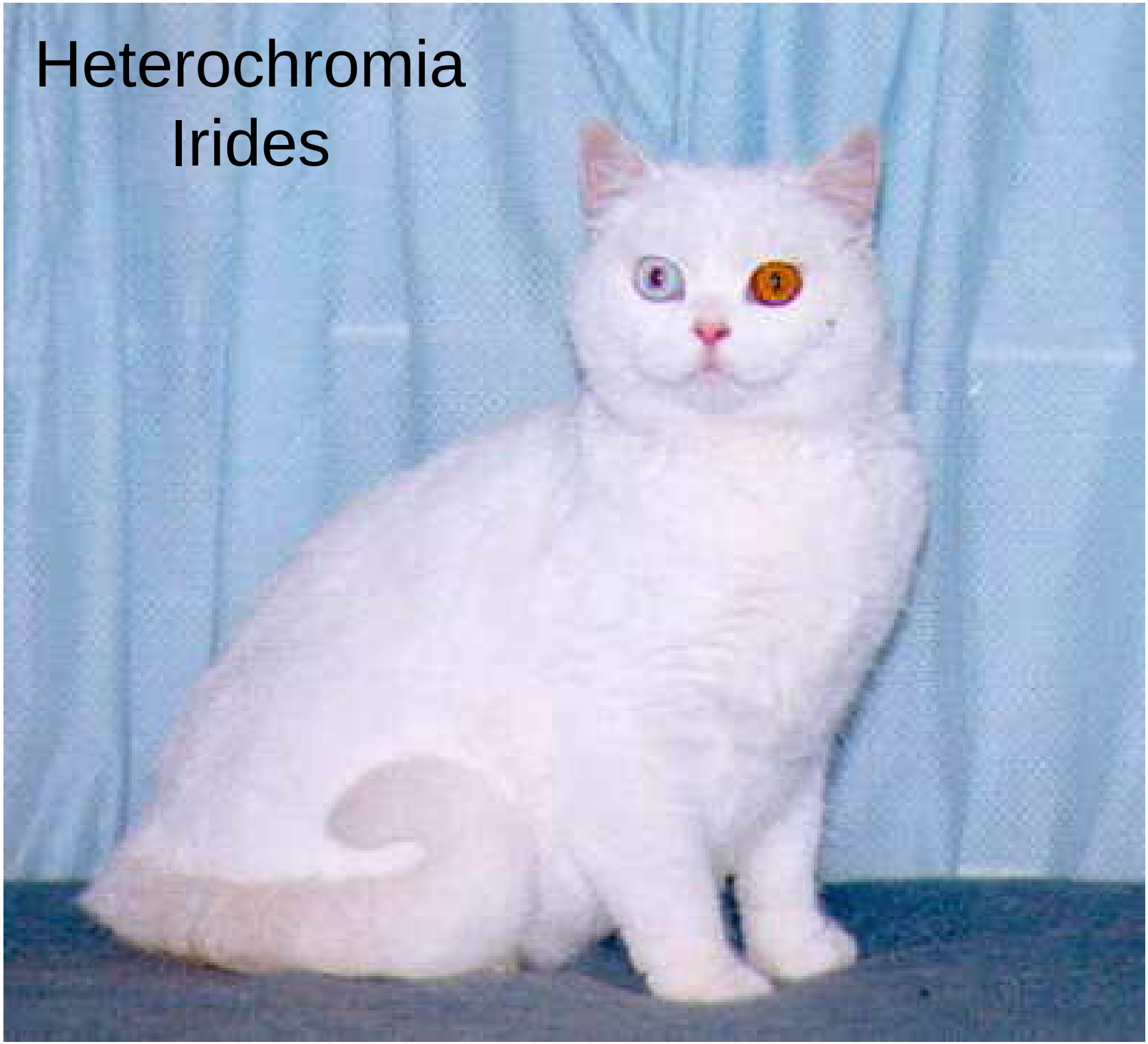
SILV gene Exon 11
PCR products



White Gene

White (W)

- autosomal dominant over color in cats
- cats are not always totally white – may have colored spots on the head that may disappear with age
- homozygous cats do not have visual or reproductive defects, but are more likely to have blue eyes and deafness
- likelihood of deafness increases with number of blue eyes – incomplete penetrance
- blue eyes may also result from the c^s Siamese dilution pigment gene – not associated with deafness
- no molecular genetic studies currently underway


Heterochromia
Irides

References:

- Strain GM. Deafness in Dogs & Cats web page: www.lsu.edu/deafness/deaf.htm
- Strain GM. 2004. Deafness prevalence and pigmentation and gender associations in dog breeds at risk. *The Veterinary Journal* 167:23-32.
- Cargill EJ, Famula TR, Strain GM, Murphy KE. 2004. Heritability and segregation analysis of deafness in U.S. Dalmatians. *Genetics* 166:1385-93.
- Clark LA, Wahl JM, Rees CA, Murphy KE. 2006. Retrotransposon insertion in SILV is responsible for merle patterning of the domestic dog. *Proc National Acad Sciences*, 103(5):1376-81.
- Strain GM. 1999. Congenital deafness and its recognition. *Vet Clinics of North America: Small Animal Practice* 29:895-907.
- Strain GM. 1996. Aetiology, prevalence and diagnosis of deafness in dogs and cats. *British Veterinary Journal* 152:17-36.
- Little CC. 1957. *The Inheritance Of Coat Color in Dogs*. Howell Book House: New York. 194 pp.