Congenital Deafness in Dogs

Mechanisms and Current Research

Australian Cattle Dog Club of America
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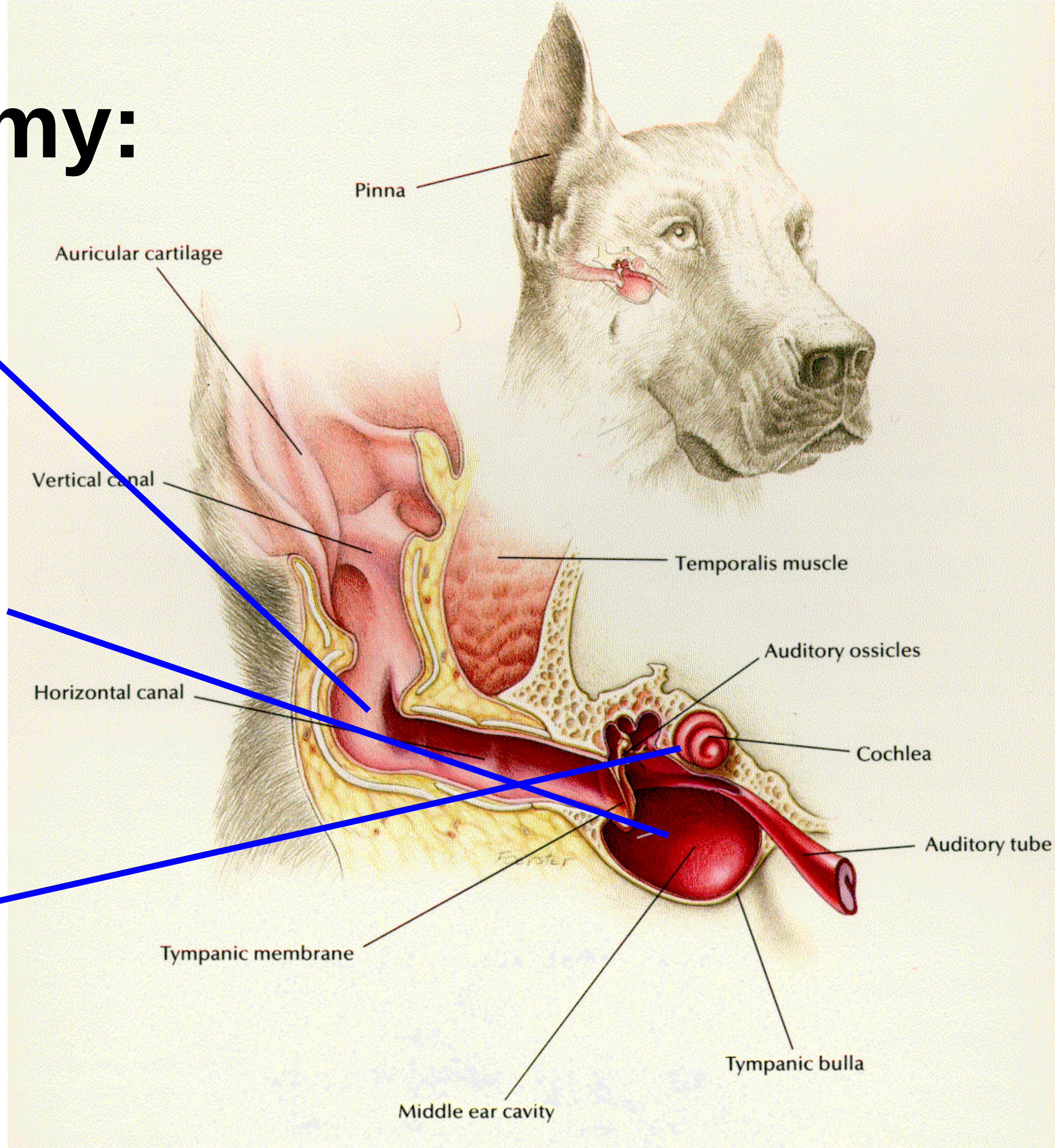
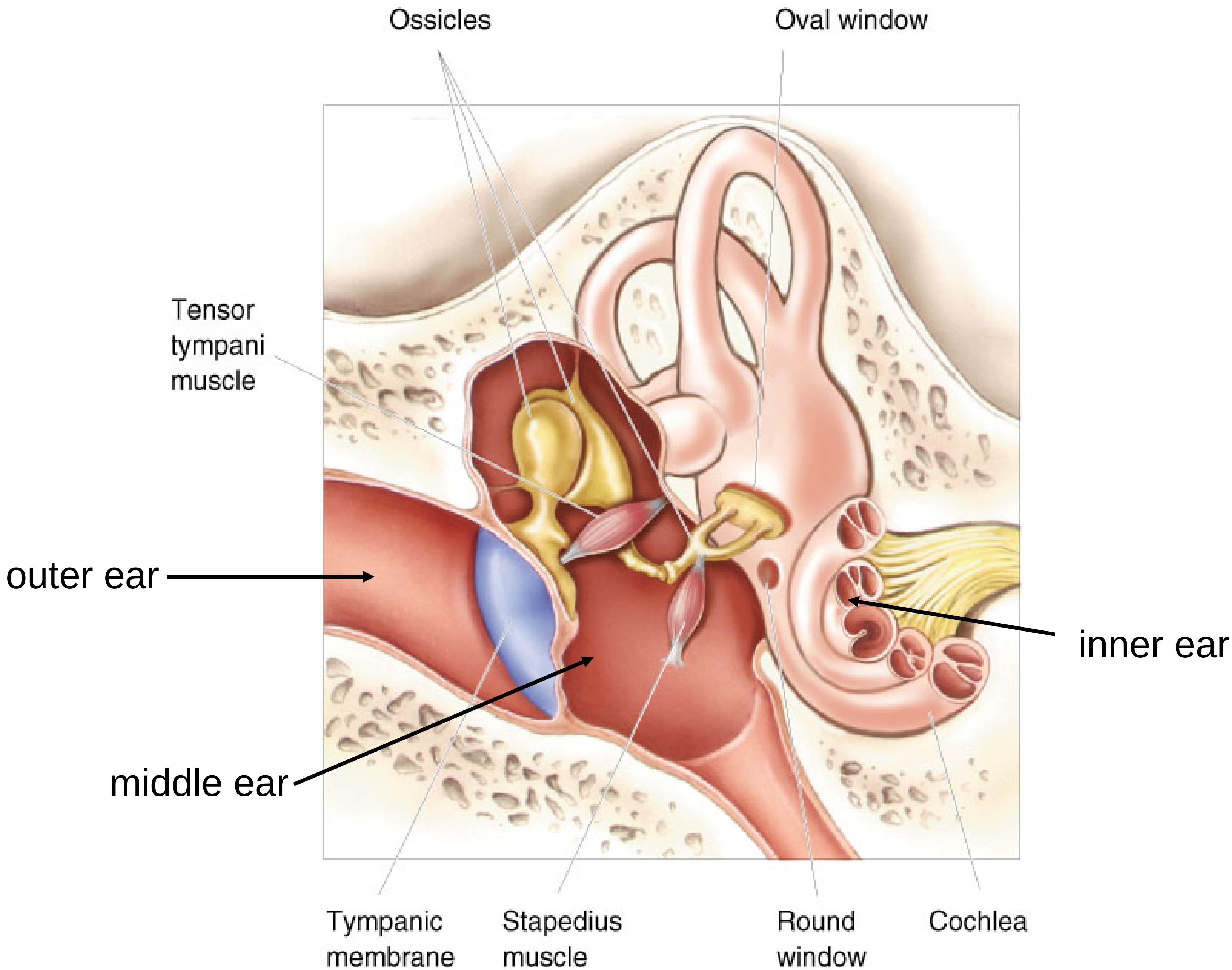
Outline

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

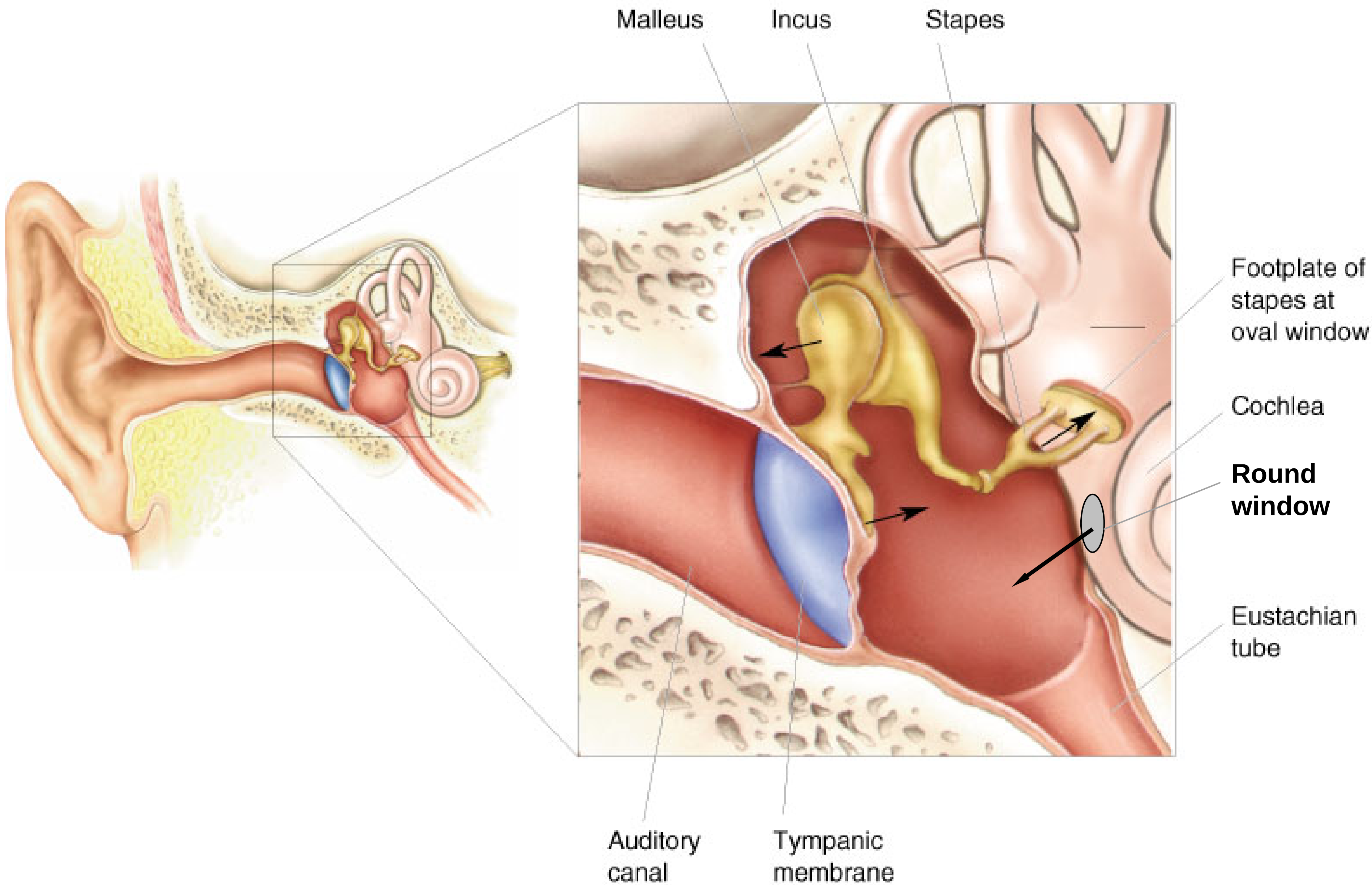
Ear Anatomy:

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

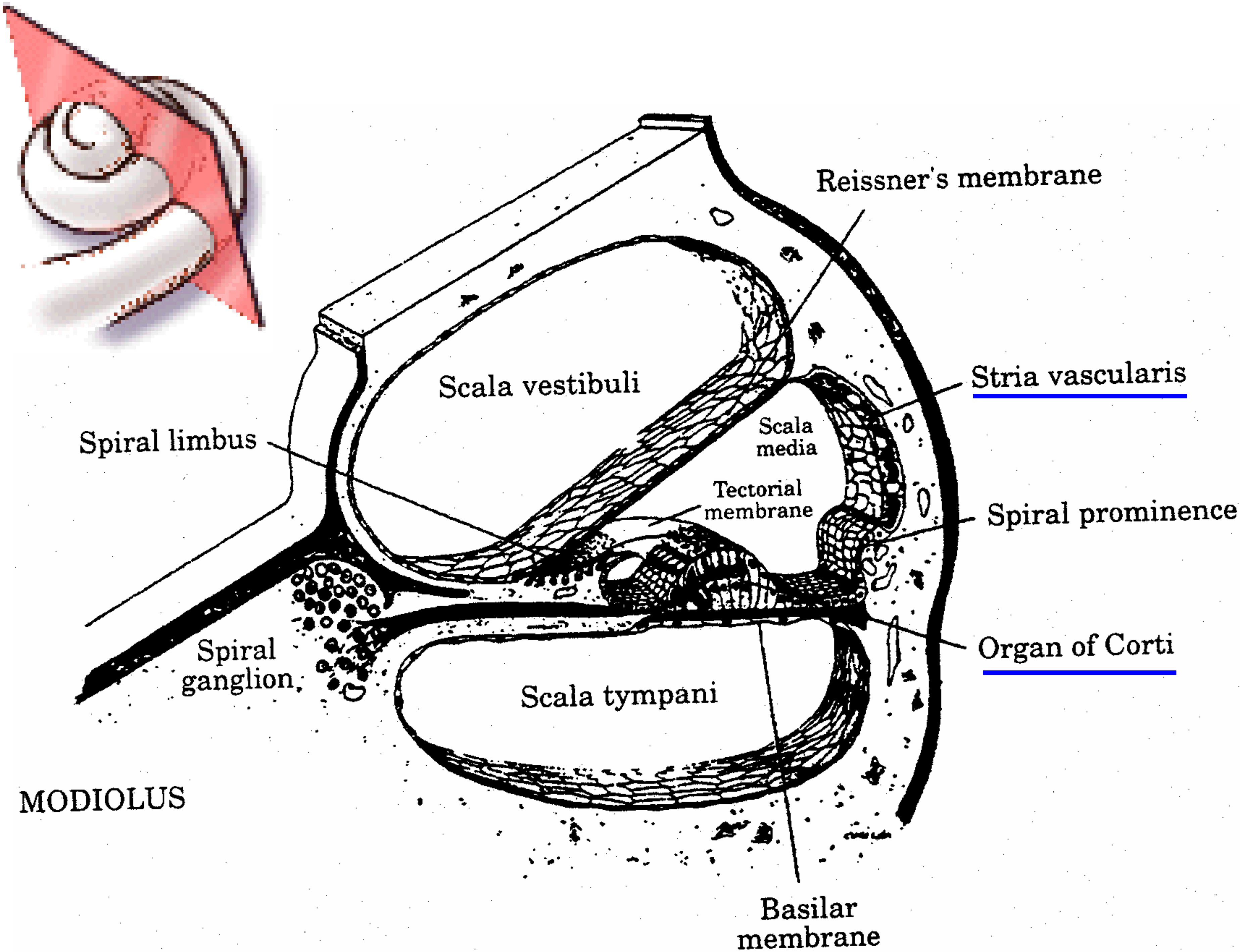


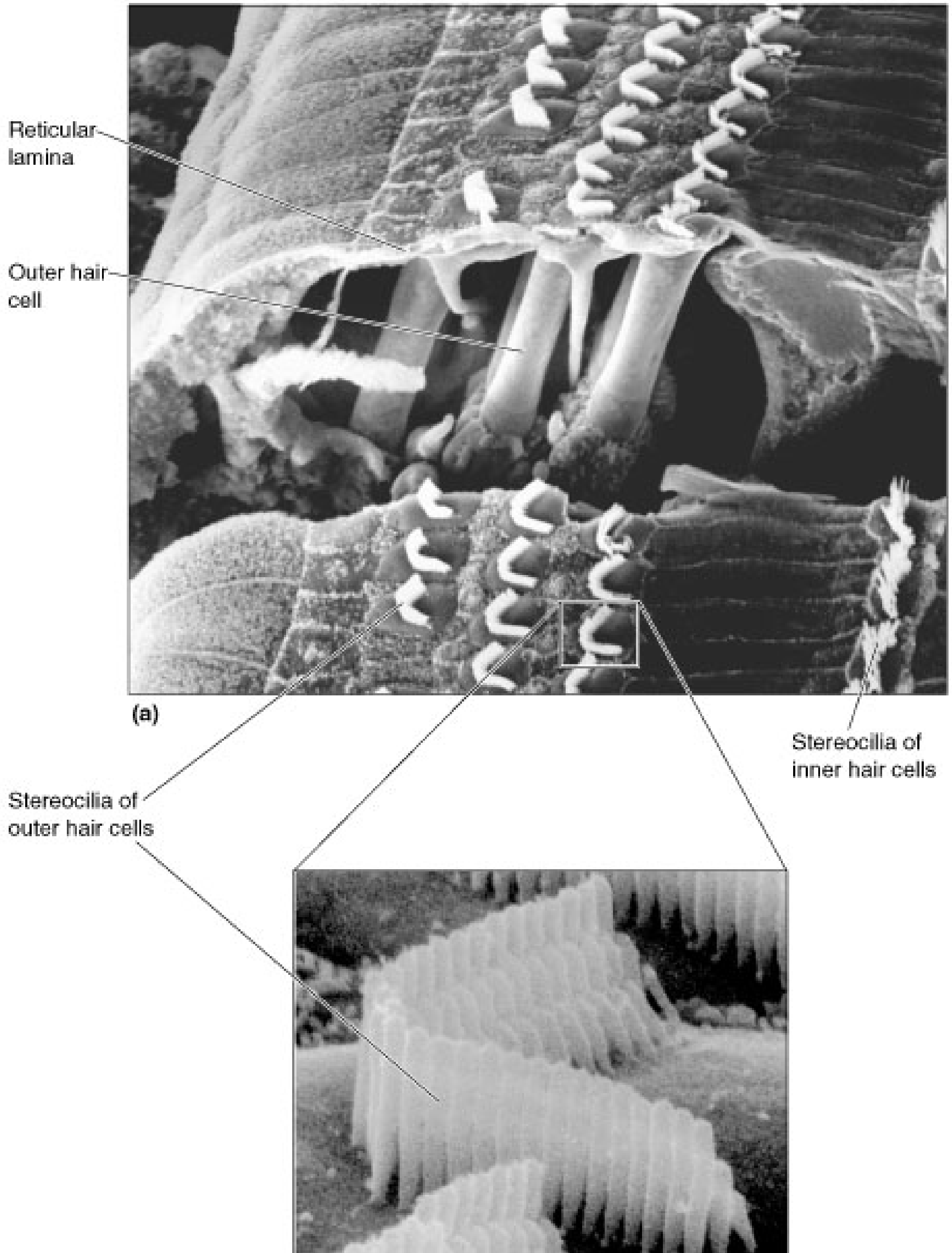


Ossicles
Oval window
Tensor tympani muscle
outer ear
inner ear
middle ear
Tympanic membrane
Stapedius muscle
Round window
Cochlea



Malleus
Incus
Stapes
Footplate of stapes at oval window
Cochlea
Round window
Eustachian tube
Auditory canal
Tympanic membrane


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



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

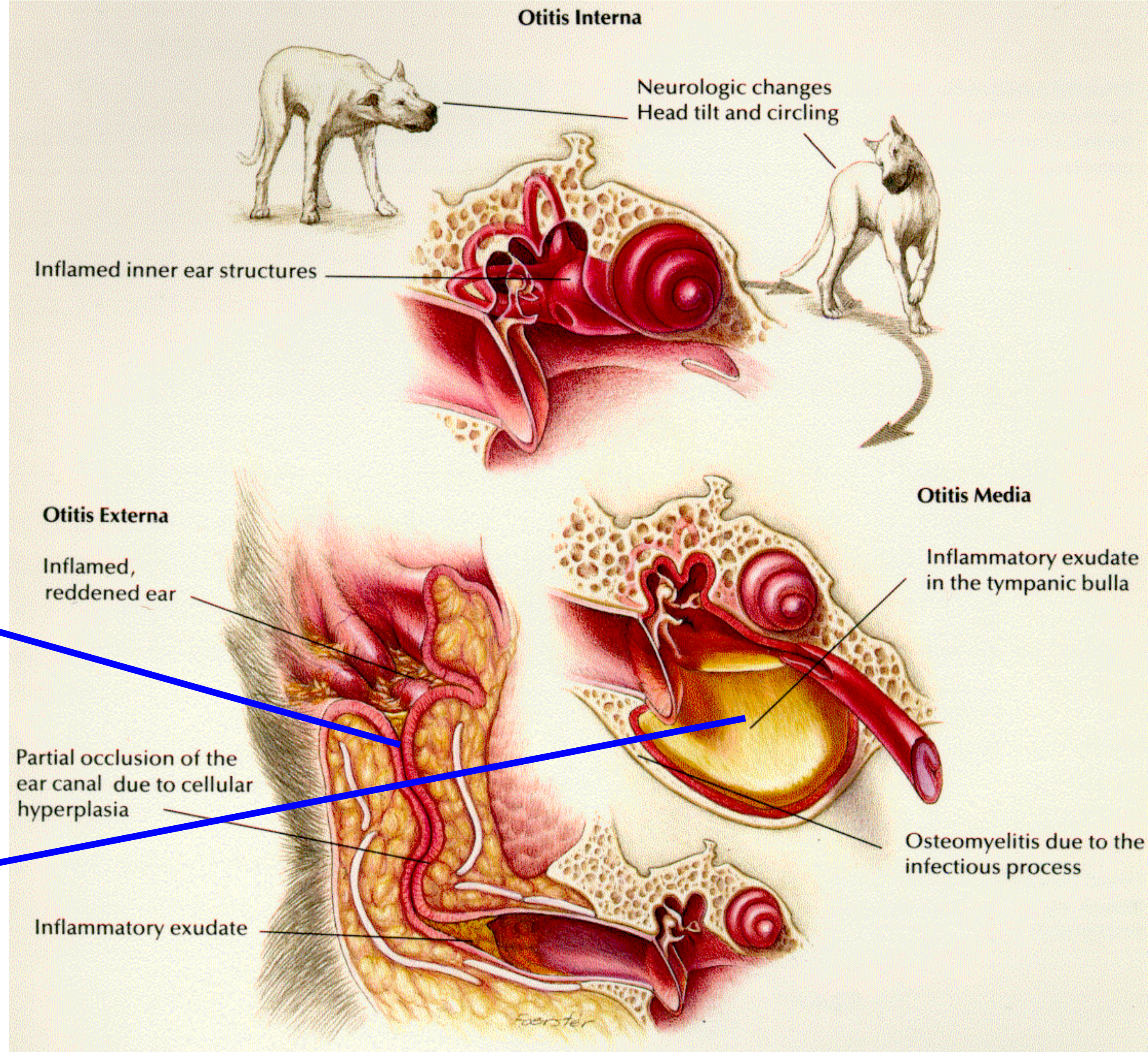
- **hereditary congenital sensorineural**
- **acquired later-onset sensorineural**
- **acquired later-onset conductive**

(with human deafness, the terms syndromic and nonsyndromic deafness are also used to distinguish deafness accompanied by other health problems, such as Alport syndrome)

Infectious causes of conductive deafness:

otitis externa

otitis media

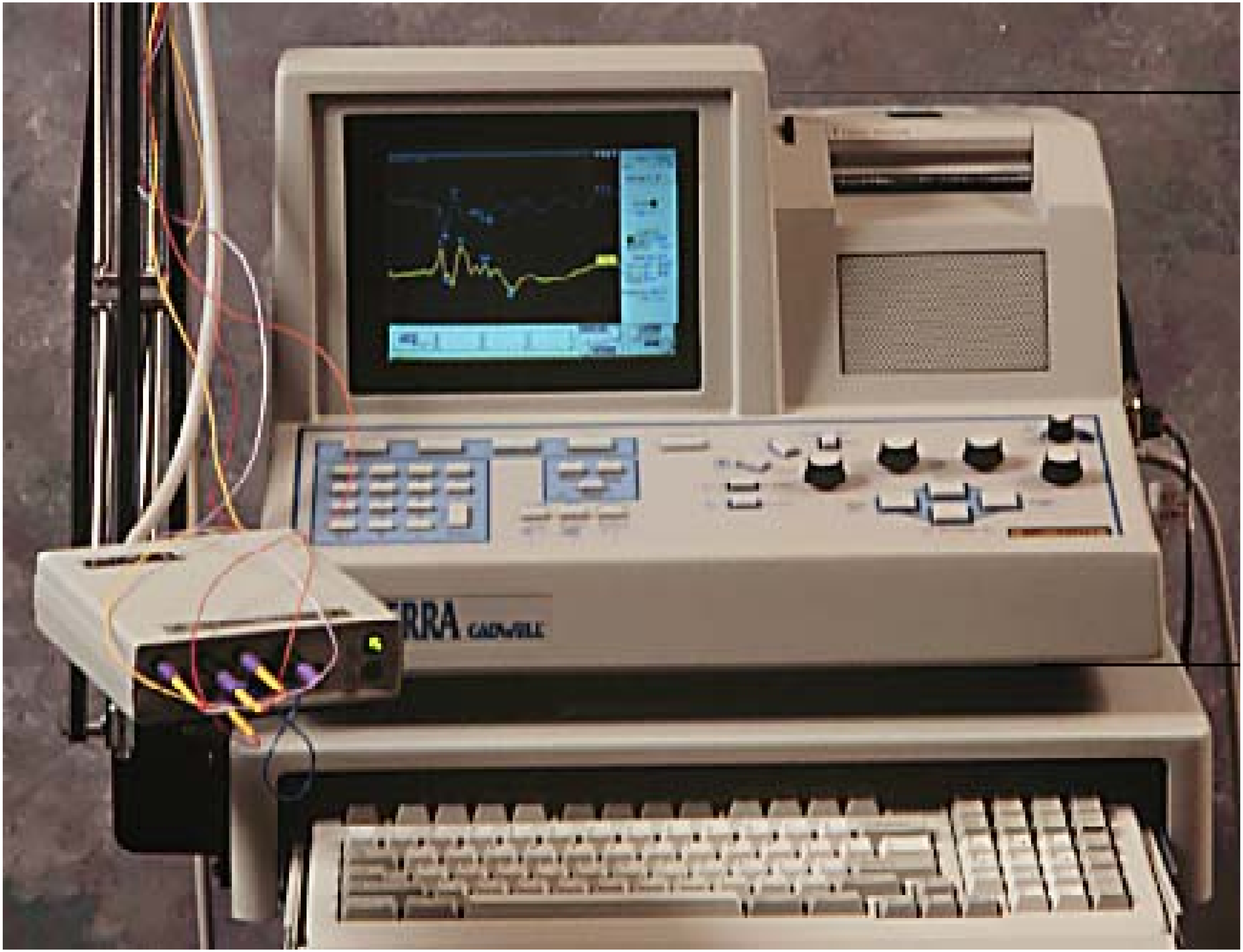


Otitis Externa, Media, Interna

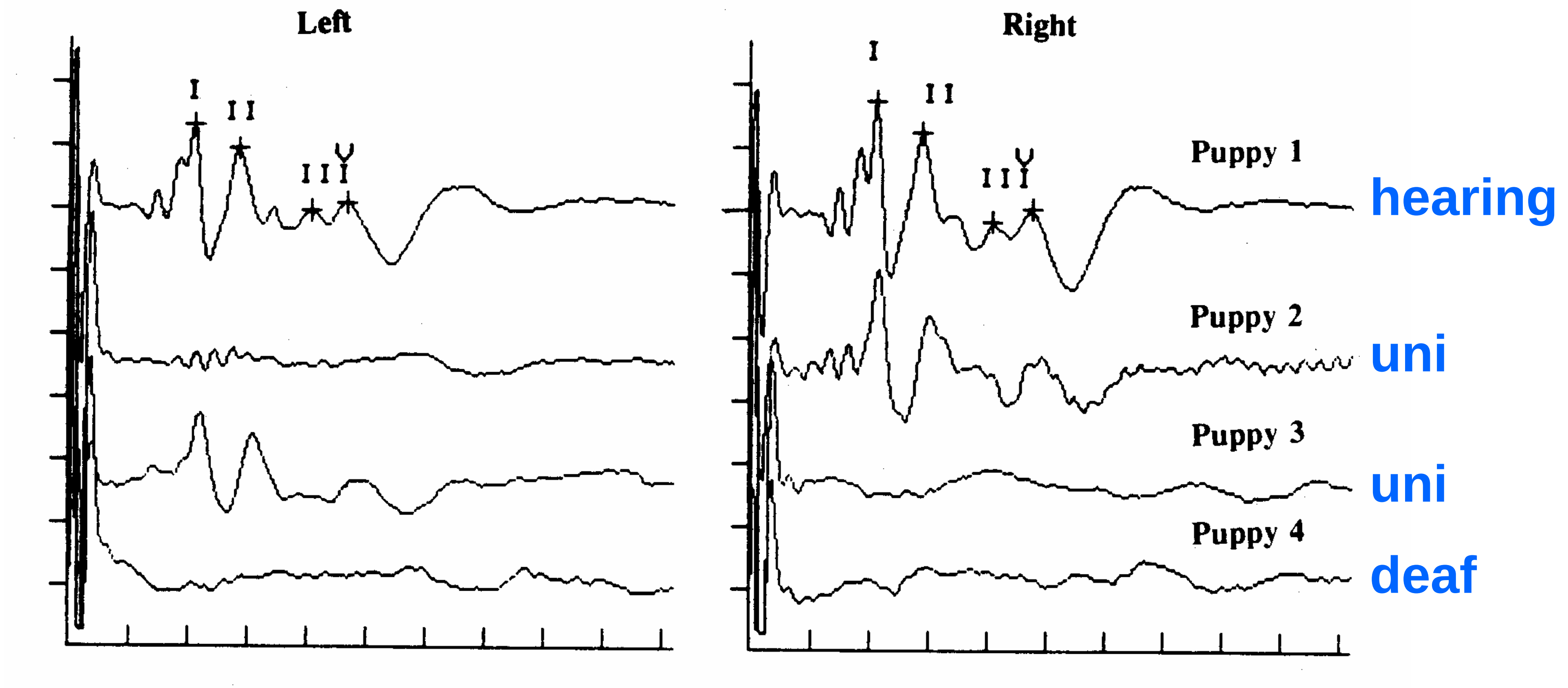
Hearing Testing

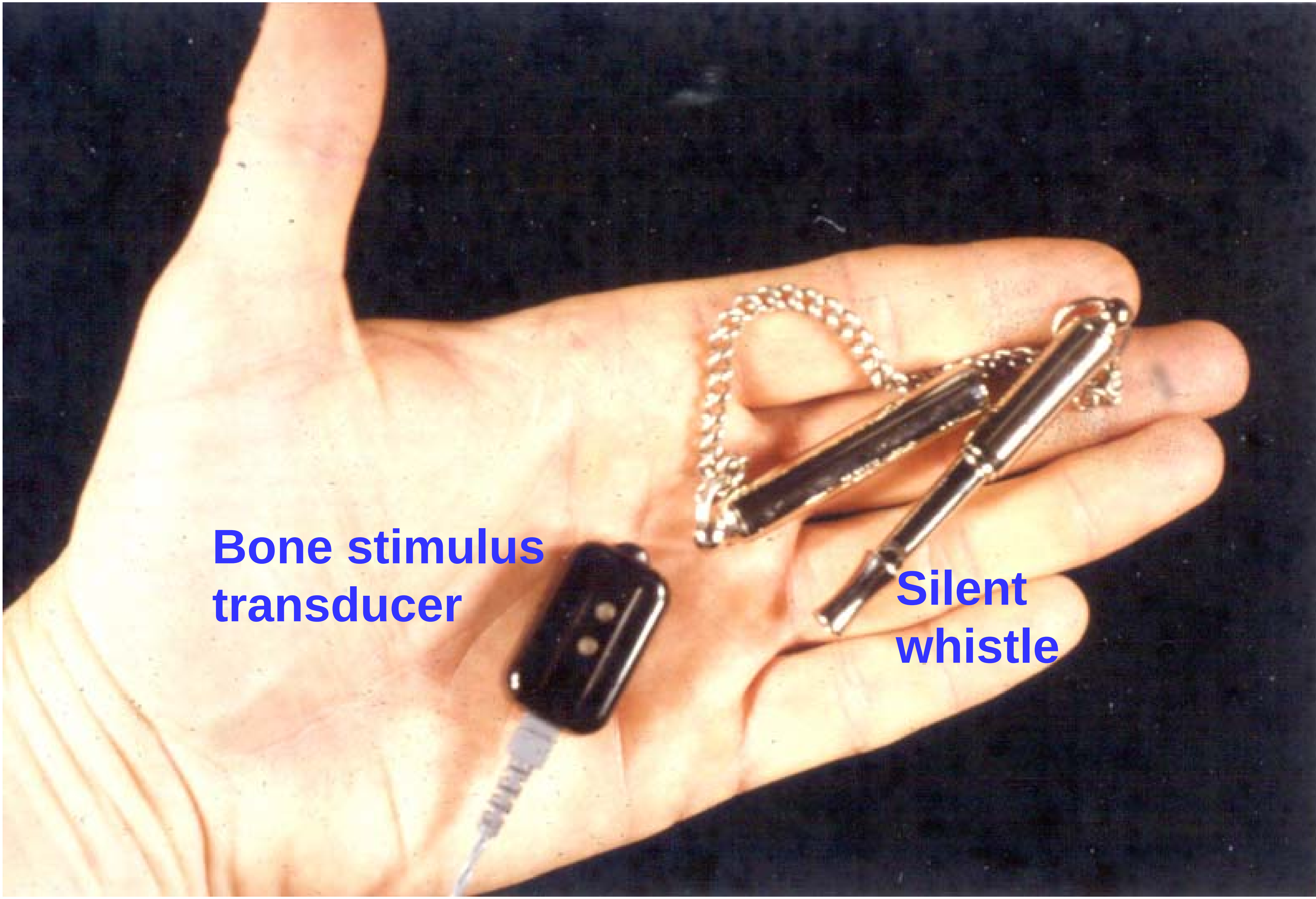
- <u>**behavioral testing**</u> **- sound stimuli produced outside of the animal's visual field**
  - ➔ **cannot detect unilateral deafness**
  - ➔ **animals quickly adapt to testing**
  - ➔ **stimuli detected through other sensory modalities**

- <u>**electrodiagnostic testing**</u> **- 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

- <u>usually</u> linked to the genes responsible for white
  - ➔Recessive alleles of the piebald gene: Irish spotting (s^i), piebald (s^p), extreme-white piebald (s^w)
  - ➔Merle (M) 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

Dog Breeds With Congenital Deafness

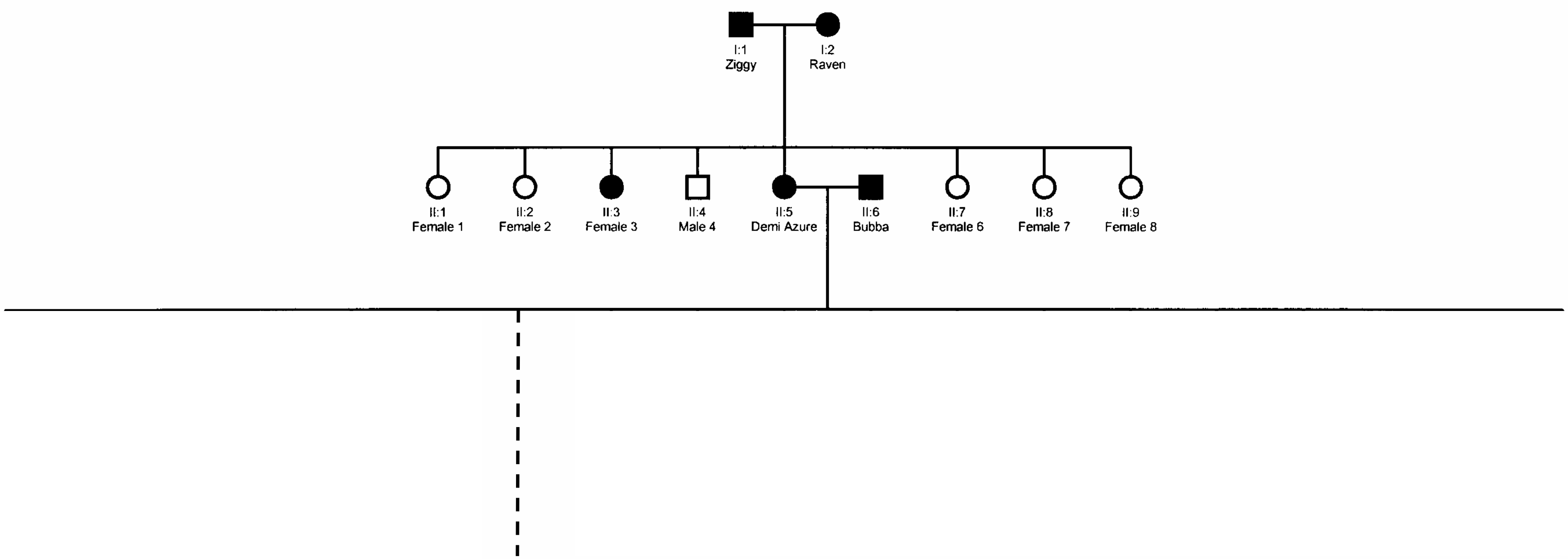
- reported in over 80 dog breeds
- prevalence (unilateral & bilateral) highest in:
  - Dalmatian (n=5,333) 30%
  - white bull terrier (n=346) 20%
  - English setter (n=3,656) 8%
  - English cocker spaniel (n=1,136) 7%
  - Australian cattle dog (n=296) 15%
  - Jack Russell terrier (n=56) 16%*
  - Catahoula leopard dog (n=78) 63%*

(prevalence unknown for most breeds)

Genetics of Congenital Deafness

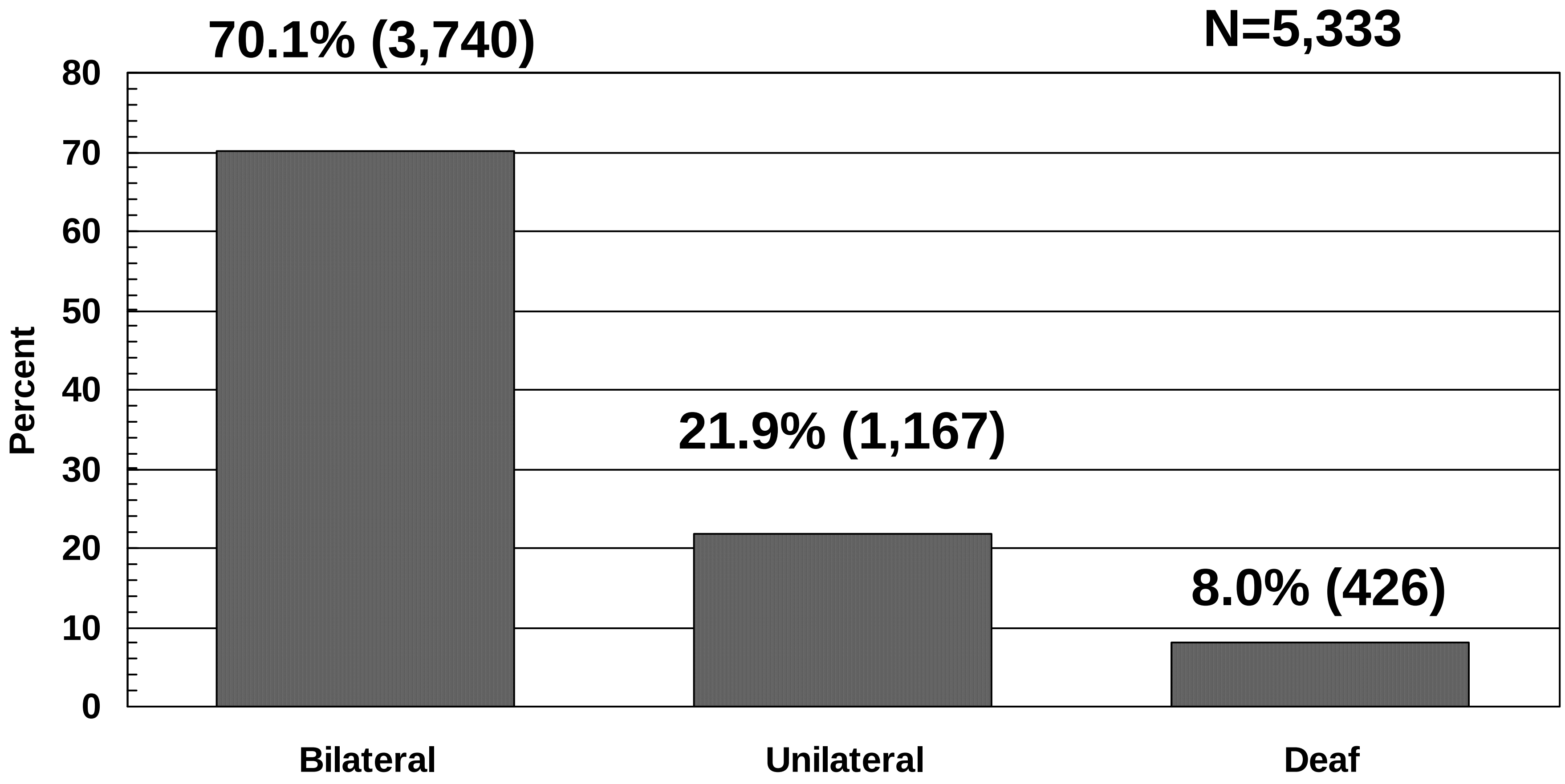
- Doberman – simple autosomal recessive, plus vestibular dysfunction, not pigment-associated
- “nervous” pointer deafness – simple autosomal recessive (bred for anxiety research studies)
- pigment-associated deafness in dogs - ?
  - merle gene (M) - dominant; homozygous dogs may have additional health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

Demi Azure Pedigree

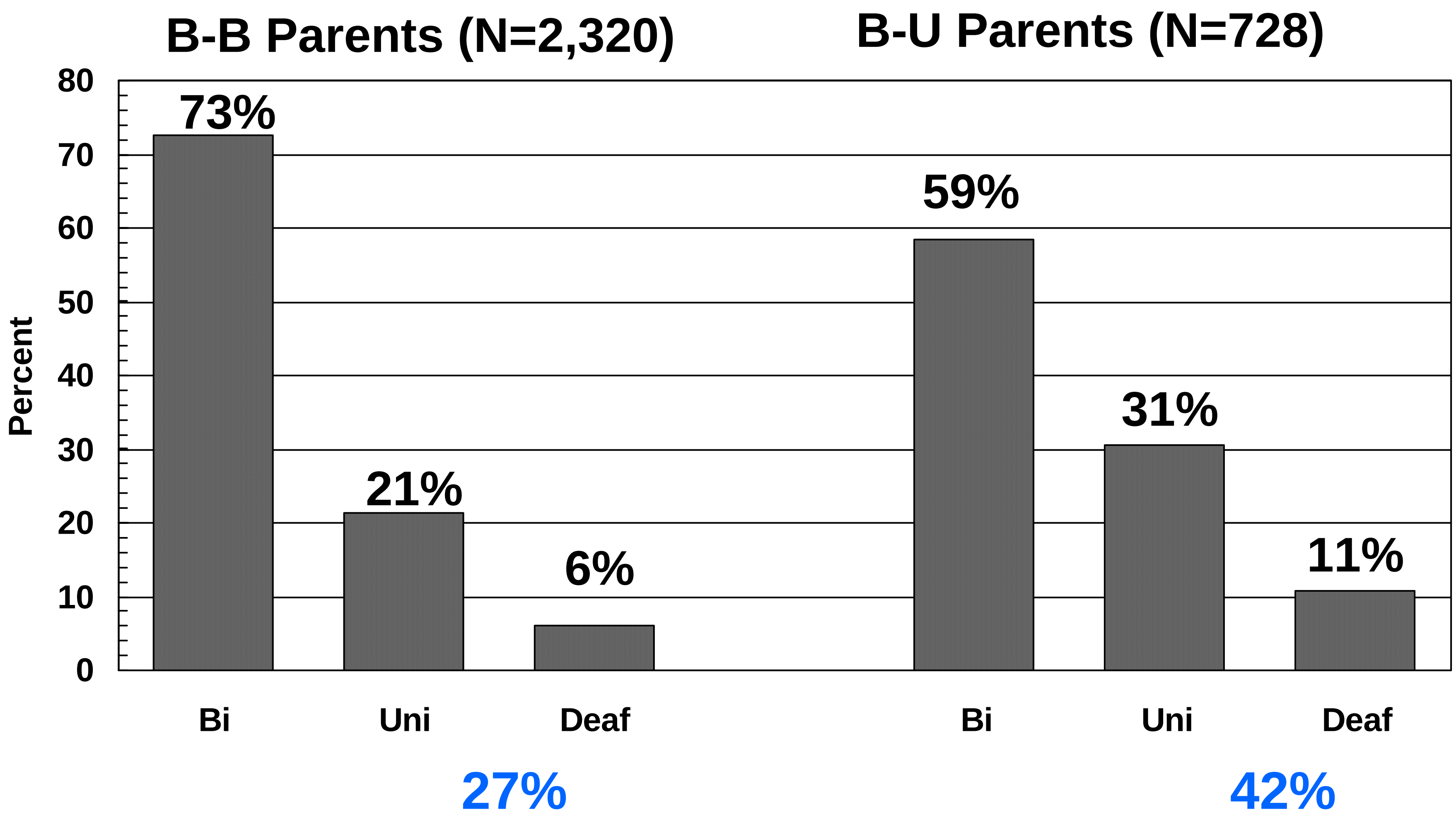


Observations on Features of Pigment-Associated Congenital Hereditary Sensorineural Deafness Based on Studies in the Dalmatian

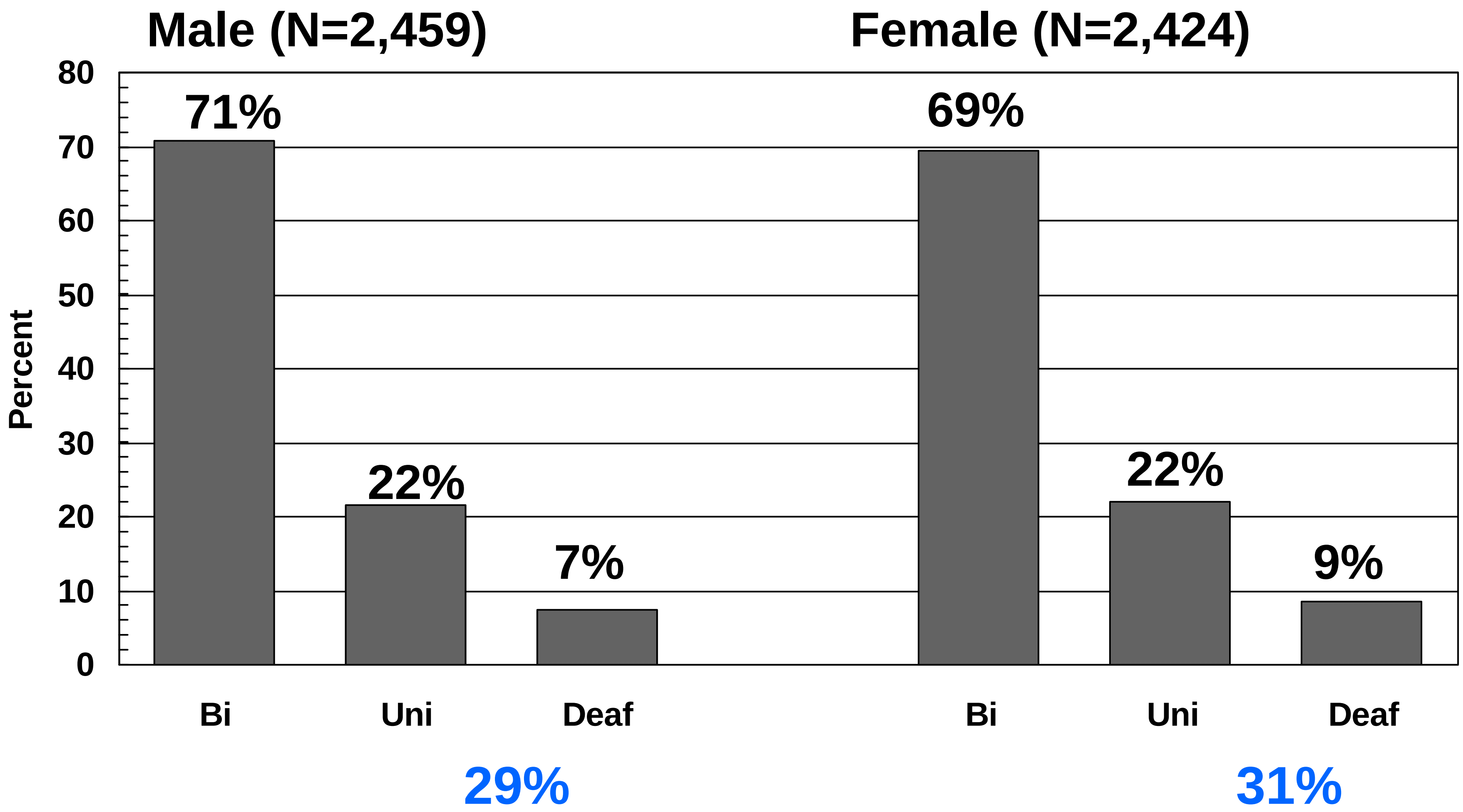
Dalmatian Deafness Prevalence in the US



Effect of Parent Hearing Status On Deafness Prevalence



Effect of <u>Sex</u> On Deafness Prevalence



Coat Pigmentation Genes In Dalmatians

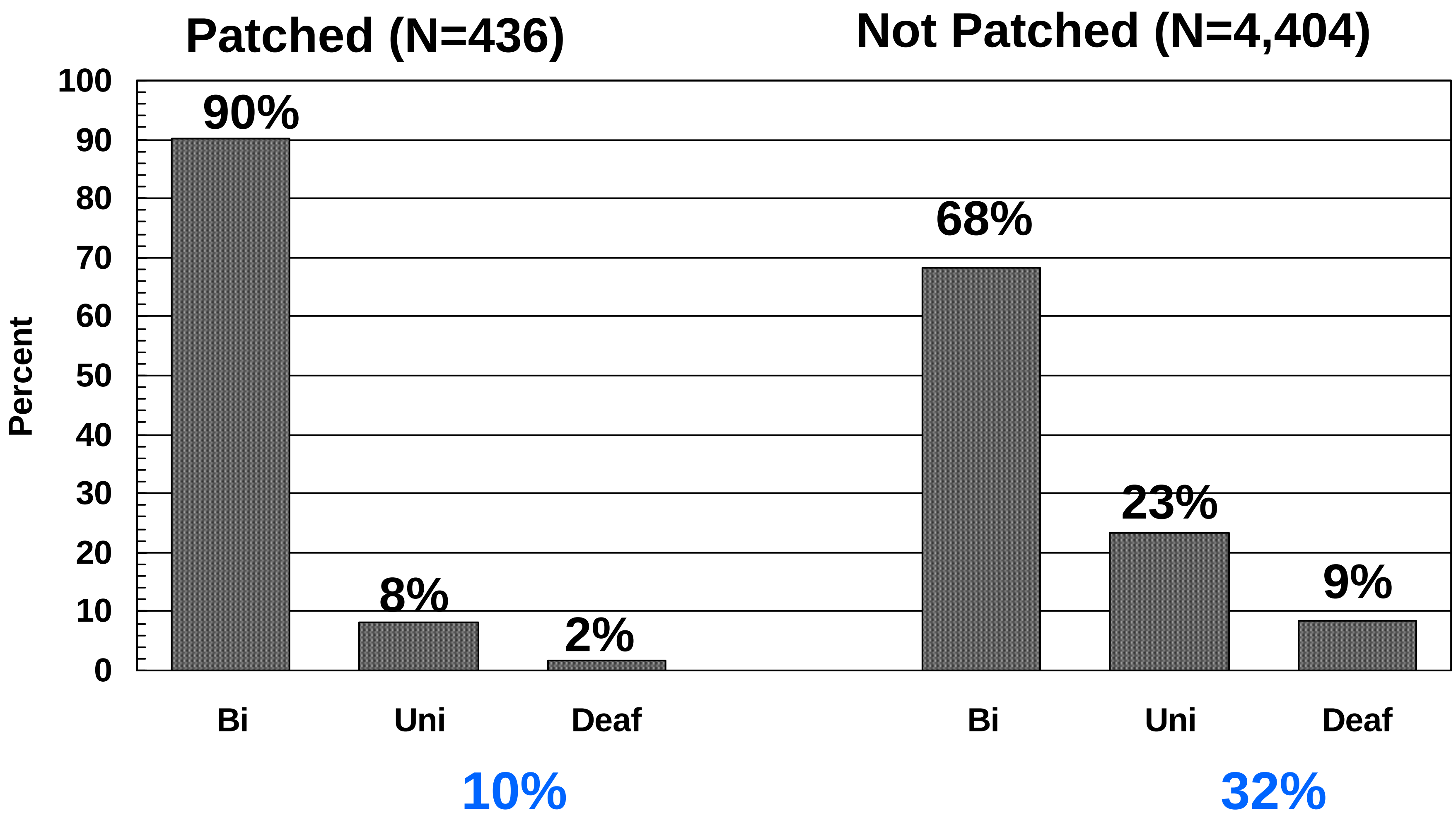
- base coat - underlying coat color
  - B - black (dominant)
  - b - liver (recessive)
- extreme-white piebald gene - s^w - white covering; recessive but homozygous in all Dalmatians [hair is white if it contains no pigment granules (melanin) or other substances which absorb light]
- ticking gene - T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

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

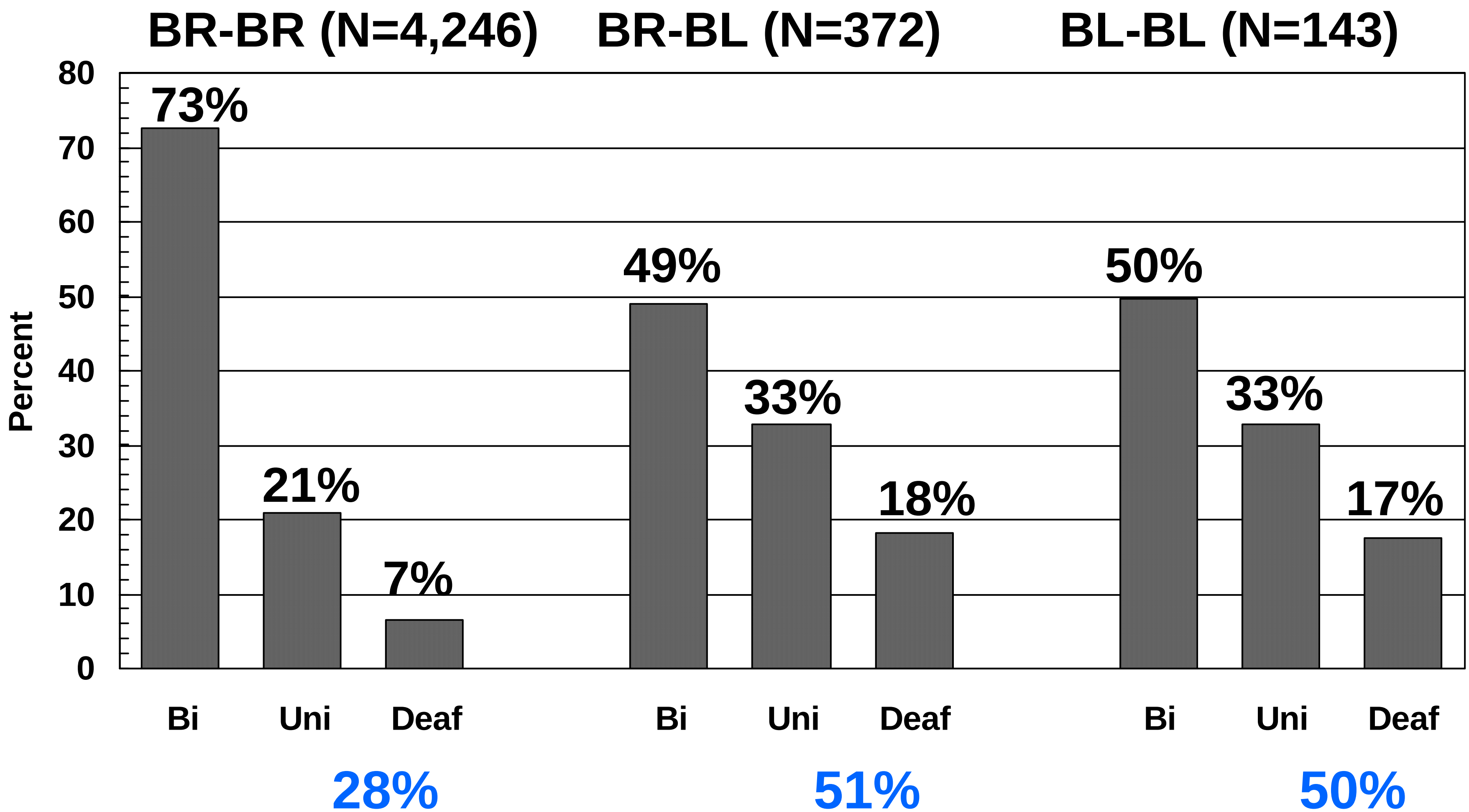
- weak gene expression: failure of the piebald gene to completely suppress the underlying coat color (black or liver) results in a patch, animals are less likely to be deaf

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

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

Current Research

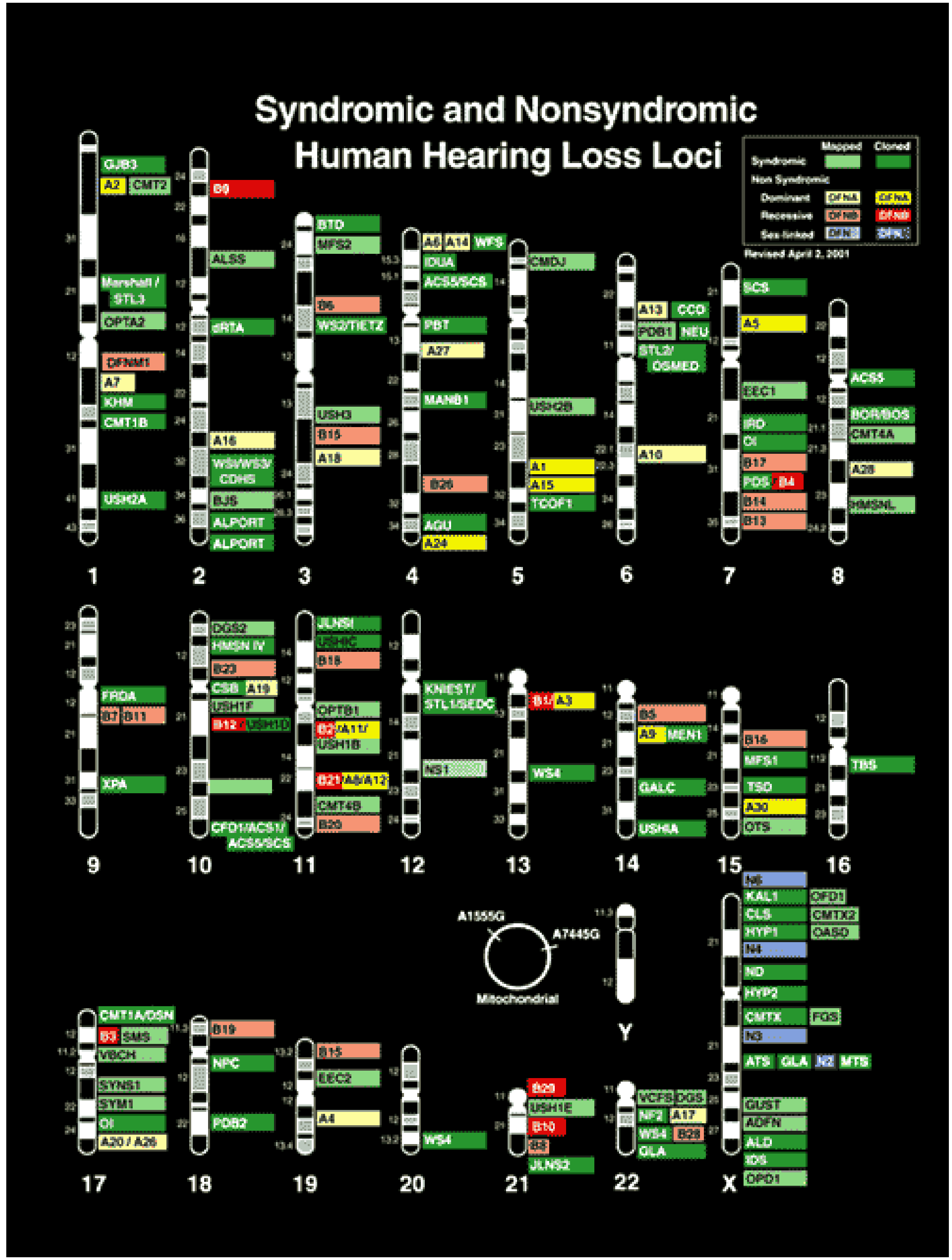
Canine Genome Project

- sequencing of canine genome was designated a priority project of the National Human Genome Research Institute (NIH) and sequencing of the boxer (7X) has been completed (a 1.5X sequence of a poodle was also published earlier)
- expected cost - about $50M
- microsatellite marker sets now available for whole genome screen studies (MSS1=178, MSS2=327)
- 3,270-marker canine radiation hybrid linkage map now available

Molecular Genetic Approaches to Identifying Defects Responsible for Deafness

- **candidate gene approach: sequence dog genes equivalent to ones identified in the mouse or in man that have been shown to be causative for deafness (i.e. *mitf, c-kit*)**
- **whole genome screen approach: use a set of microsatellite markers that cover all dog chromosomes with minimal spacing to identify markers that co-segregate with deafness, then narrow down to specific gene**

Syndromic and nonsyndromic human hearing loss loci

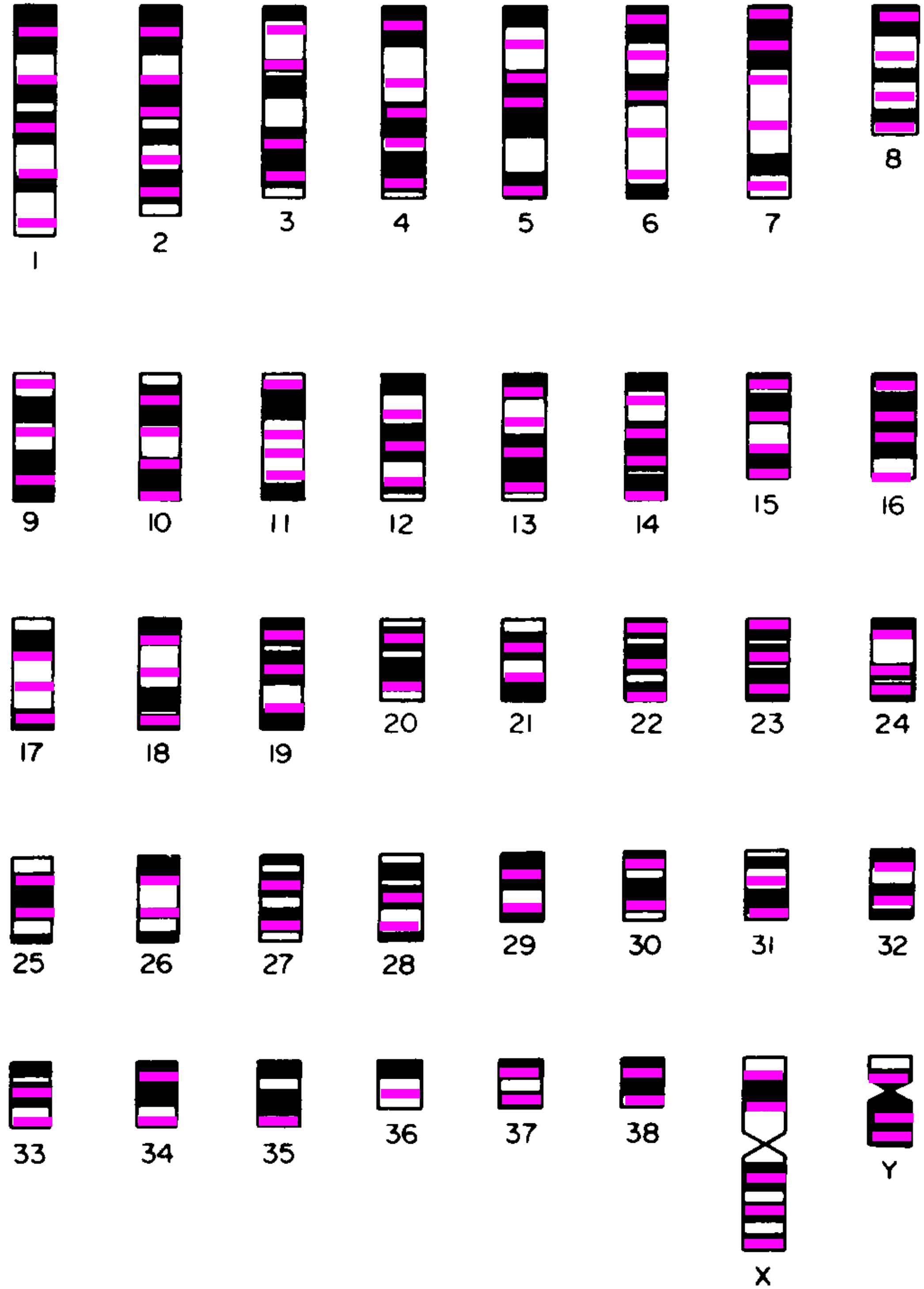


Dog Chromosomes (39 pairs - 38 autosomes and 1 sex chromosome)

Microsatellite Markers

Minimal Screening Set 1 (MSS1), n=178, 10 cM spacing

MSS2, n=327, 1 cM spacing, little overlap with MSS1



Study: Molecular Genetics of Deafness

AKC/CHF: Murphy, Strain "Genetics of Hereditary Deafness in the Domestic Dog“

1. examine candidate genes from mouse/human:
   - *mitf*
   - *c-kit*
2. DNA collection from affected pedigrees
   - Dalmatian
   - English setter
3. determination of mode of inheritance

Study: Molecular Genetics of Deafness

Results:

- ***mitf*** **– not causative for deafness in Dal**
- ***c-kit*** **– not causative for deafness in Dal**
- **mode of inheritance:**
  - **NOT simple autosomal recessive**
  - **best modeled as being inherited as a single “locus” but one that does <u>not</u> follow Mendelian genetics**

Other Ongoing Molecular Genetic Studies

- AKC/CHF - Murphy, Strain: "Whole genome screens using microsatellite markers in genetic analyses of hereditary deafness in the Dalmatian and English Setter”
  1. pedigree of >200 Dalmatians with DNA
  2. English setter DNA pedigree being assembled
  3. whole-genome screen
- JRT Research Foundation - Strain: “Assembly of a DNA pedigree for whole genome screens for hereditary congenital deafness in the Jack Russell Terrier”
- further funding being sought

Other Ongoing Molecular Genetic Studies

- **University of Pennsylvania:** genetics of deafness in “nervous” pointers (Steinberg)

- **Michigan State University:** candidate gene studies of deafness in various dog breeds (Yuzbasiyan-Gurkan)

- **Europe:** candidate gene studies and whole genome screen studies of canine deafness (Distl, Dolf)

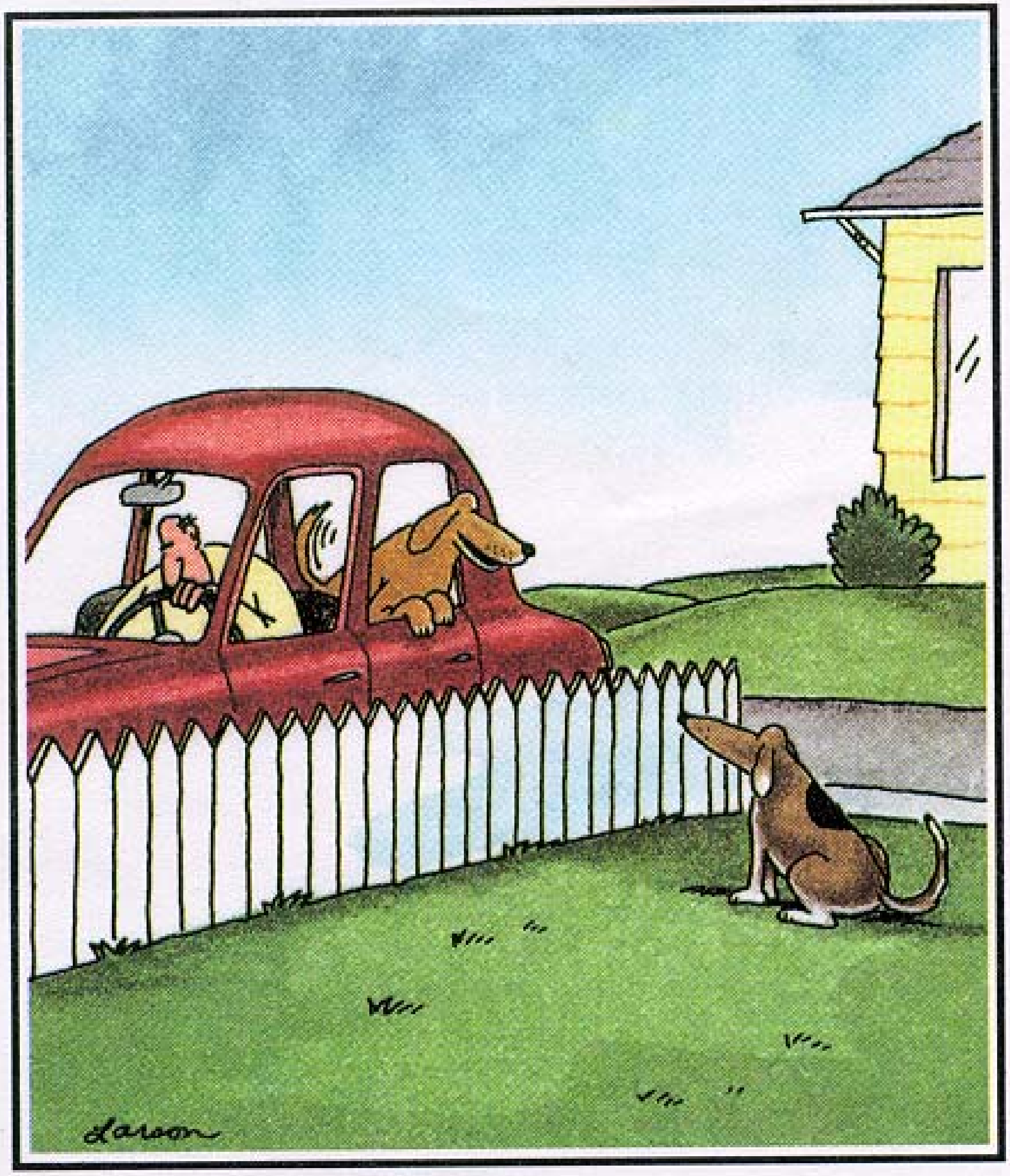
References:

- Strain GM. Deafness in Dogs & Cats web page: www.lsu.edu/deafness/deaf.htm
- Strain GM. 2003. Deafness prevalence and pigmentation and gender associations in dog breeds at risk. The Veterinary Journal (in press).
- Strain GM. 1999. Congenital deafness and its recognition. Vet Clin N Amer: Small Anim Pract 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.
- Searle AG. 1968. *Comparative Genetics of Coat Colour In Mammals*. Logos Press/ Academic Press: London. 310 pp.

The importance

of hearing:

(with thanks to Gary Larson's
Far Side)



"Ha ha ha, Biff. Guess what? After we go
to the drugstore and the post office,
I'm going to the vet's to get tutored."