



# Allergy & Ear Disease

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Peter S Roland MD  
UT Southwestern Medical  
Center  
Dallas, Texas

## Disclosures

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■ NONE

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# The Middle Ear

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## Objectives

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- Recognize that some cases of COME have characteristics of allergic inflammation
  - Understand that these characteristics can offer an opportunity for therapeutic intervention
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# COME

- Joint Clinical Practice Guideline for Otitis Media with Effusion (2004)
  - Pay for Performance

## Otitis Media with effusion

- Statistical
- Histopathological
- Animal
- Clinical investigation
- Therapeutic efficacy

# COME

- Politzer 1869
- Proetz 1931 Koch 1947
- Extent of association---UNKNOWN
  - 14% - 89% ?
  - 15% - 25% ?
- Rigor Lacking
  - Definitions
  - Study design and controls

Miceli Arch Dis Child 2004, Bernstein Oto-HNS 1996, Cafferelli Clin Exp Allergy 1998, Alles Pediatr Allergy Immunol 2001

YEAR	AUTHOR	# PTS	% of Positive Tests	% Improved with allergy therapy
'42	Dohlman[38]	178	56%	
'42	Mao[99]	252	29%	of pathologically deaf children
			2%	of normal children
'49	Jordan[79]	123	74%	98%
'58	Solow[148]	50	72%	
'61	Lecks[93]	82	88%	
'65	Fernandez[49]	113	55%	95%
'65	Whitcomb[174]	38	100%	87%
'67	Draper[44]	340	53%	91%
'80	Hall[60]	92	100%	82%
'81	McMahan[101]*	119	93%	86%
'86	Sanz[140]*	20	30%	
'88	Tomonaga[164]	259	72%	of OME cases
		605	89%	of Nasal allergy cases
		104	29%	of Controls
'90	Hurst[66]++	20	100%	100%
'91	Becker[11]	35	34%	prick +
'94	Nsouli[110]*	104	78 %	86%
'94	Corey[32]*	89	61%	
'96	Hurst[68]	73	87%	
'96	Shubich[144]	40	100%	70% treatment group 45% controls
'98	Psfidis[127]	148	59%	78% prospective treatment
'98	Caffarelli[27]	172 Patients (26.7% SPT +) and 200 controls (30.5% SPT+) 37% OME Patients had other allergic symptoms 21% Controls had other allergic symptoms (p<0.001)		

Hurst Dissertation 2000

# COME

- Obstruction of ET
  - ET tube itself
  - Nose
- ME “shock” organ?
  - Does sensitization → effect ME?
- Aspiration of bacteria laden allergic secretions
- The allergic condition itself

Bluestone Pediatrics 1978, Tewfik Curr Opin Oto-HNS 2006, Doyle  
Curr Opin Oto-HNS 2002, Fireman Asthma & Allergy Proc 1997

# ETD

- Intranasal challenge
  - Cold dry air, histamine, D. Farinae, house dust
  - Lower doses in AR
  - Effect mitigated by pre-treatment
  - Not sustained

Skoner *et al* J allergy Clin Immunol 1987, Skoner *et al* Arch Oto-HNS  
1986, Stillwagon *et al* Ann /allergy 1987, Skoner *et al* Arch Oto-HNS 1986,  
Doyle *et al* Arch Otolaryngol 1849

By definition,  
atopy involves a type I, IgE mediated hypersensitivity reaction  
in which activated mast cells and eosinophils  
participate in a Th2 driven inflammatory reaction

David Hurst 2000

# Inflammation

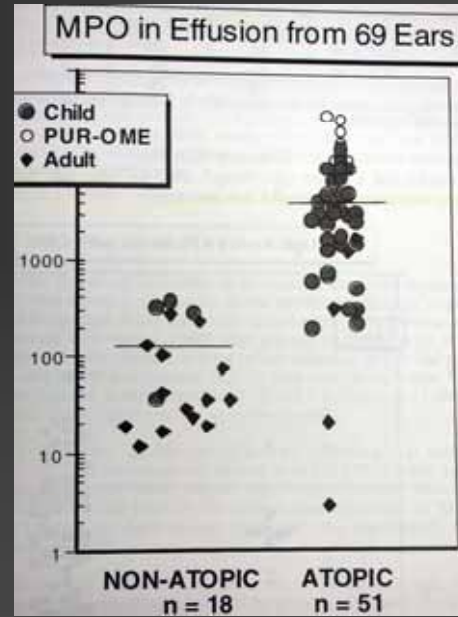
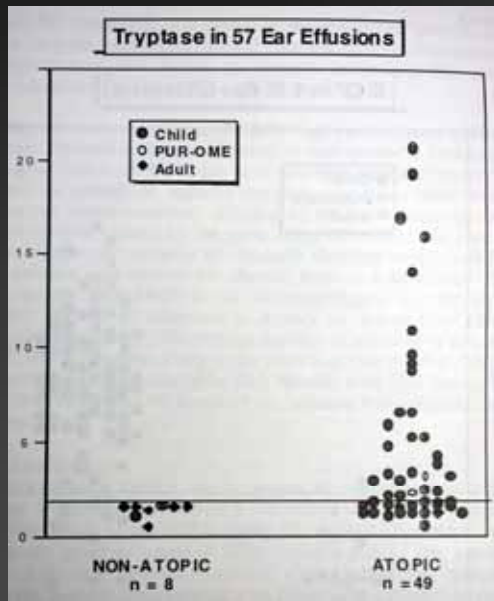
## Th2 Cytokines atopic

IL-4, IL-5, IL-9, IL-13,  
IgE production  
Eosinophil cationic protein  
Th2 cells  
Mucus production  
Myeloperoxidase  
Tryptase

## Th1 Cytokines infectious

IL-2  
IFN  $\gamma$   
Tumor necrosis factor  $\beta$   
Granulocyte-macrophage  
colony stimulating factor  
Neutrophils

# Hurst



Hurst & Venge Allergy 2000

# IL-5

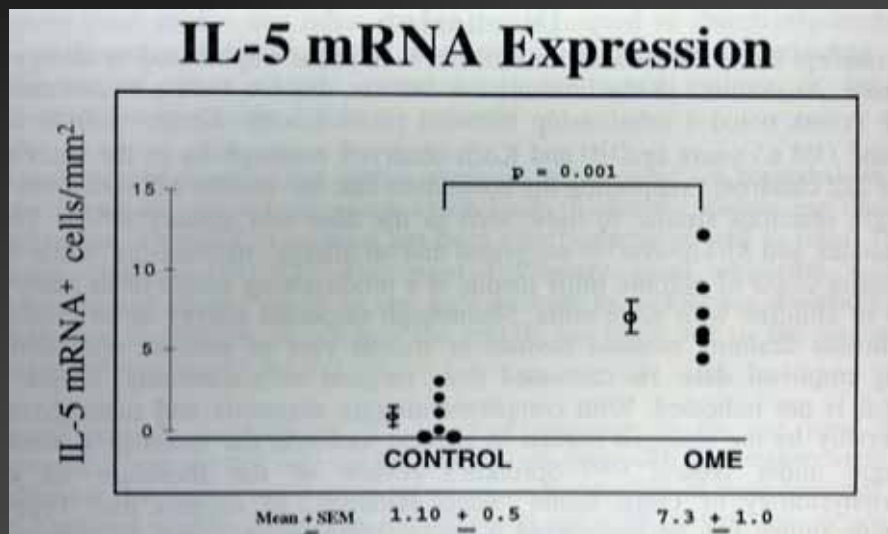
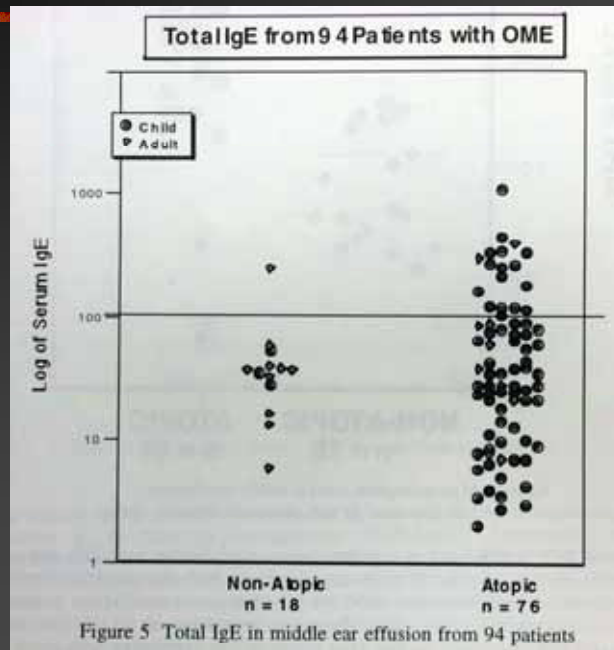


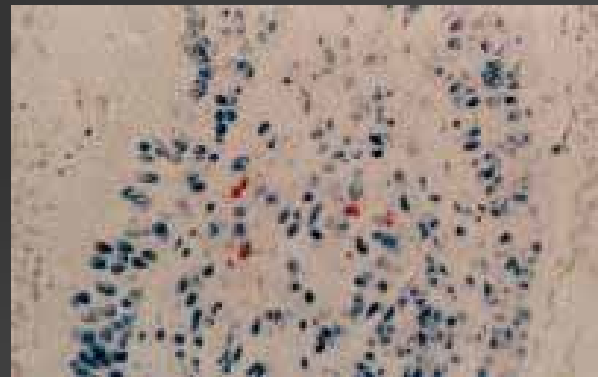
Figure 8. Immunohistostaining of IL-5 mRNA in 8 OME and 7 Controls

Wright et al Oto-HNS 2000

# IgE



Hurst & Venge Allergy 2000



Hurst & Venge Allergy 2000

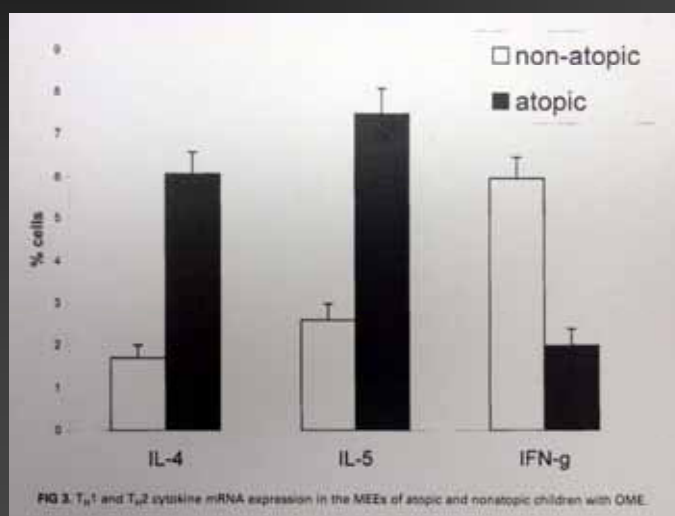


# McGill

- MEE @ time of M&G n=75
- Allergic (+ SPT) vs Non-allergic  
**30%** **70%**
- Adenoids and torus tubaris
- Newcastle-on-Tyne

Sobol J Allergy Clin Immunol 2002, Nguyen J Otolaryngol 2004, Nguyen J Allergy Clin Immunol 2004, Smimova Acta Otolaryngol 2005

# McGill



Sobol et al J allergy Clin Immunol 2002, Tewfik & Mazer Curr Opin Oto-HNS 2000, Nguyen et al J Otolaryngol 2004, Nguyen et al J Allergy Clin Immunol 2004

# Importance of IL 4 & IL 5

- Rats pre-sensitized to OVA
- 2 TT inj of OVA w &w/o IL4 & IL5 antagonists
  - Unprotected: 100% MEE
  - IL4 antagonist: 7/7 no MEE
  - IL5 antagonist: 4/7 no MEE

Pollock HW *et al*: Otolaryngol Head Neck Surg 2002;127:169–76

# UNIFIED AIRWAY

- Shared physiology and pathophysiology of upper and lower airway
  - Braunstahl:
    - grass pollen challenge
    - Segmental bronchoprovocation

Braunstahl GJ *et al*: The Journal of Allergy and Clinical Immunology 2001;107:469–76.

Braunstahl G *et al*: Am J Respiratory and Critical Care Medicine 2001;164:858–65

# ME & unified airway

- ME mucosa is lined with the same pseudostratified, ciliated columnar epithelium as the upper and lower airways.
- With inflammation, similar histologic changes are noted in ME and bronchials.
  - Mucosa thickened with increases in goblet and columnar cells
  - ME mucosa becomes infiltrated with eosinophils and T-helper lymphocytes. ME cleft has shown active degranulation of mast cells w elevated tryptase
  - COME in atopic patients shows ↑ IL-4, IL-5, IL-10, and IL-13d as seen in asthma and AR.

Takahashi H *et al.*: Archives of Oto– HNS 1990;Palva T, *et al.* Amsterdam/Berkeley: Kugler Publications, 1987; Hurst DS, Venge P.Allergy; Sobol SE *et al.*: J of Allergy and Clin Immun 2002

# Treatment

- AAO-HNS guidelines and Cochrane review reject antihistamines & steroids

VS

- Evidence suggests strategies directed against allergy should be useful & perhaps necessary for some patients

# Antihistamines

- COME inflammation characterized by eosinophils, IL4 & IL5. These are late-phase reactants
- Therefore, anti-histamines not likely to help

Hansen I *et al*: Mediators of inflammation in the early and the late phase of allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2004.

# Corticosteroids

- Meta-analysis of 9 studies shows efficacy until DCed
- Mandel
  - @2 wks twice as many MEE free (33.7 vs 16.7)
  - @ 4 wks & 4 months no difference

Thomas CL *et al*: *Cochrane Database Syst Rev* 2006; Mandel EM *et al*: *Pediatrics* 2002;110:1071–

# Intra-nasal steroids

- Shapiro--dexamthasone
  - Stat sign more kids TXed w INS had normal ME pressures after 2 wks
  - No diff @ 3 wks
- Tracy—beclamethasone
  - More rapid resolution of MEE but no diff @ 3 months

Shapiro GG *et al.*: Ann Allergy 1982;49:81–5.

racy JM *et al.*: Ann Allergy Asthma Immunol 1998;80:198–206

# Nagamine

- Eosinophilic Otitis Media
  - Adults with asthma & bronchitis
  - Viscous MEE with eosinophils
  - Elevated serum IgE
  - Elevated levels of ECP
  - Resistant to conventional RX

Nagamine H *et al.*: Auris Nasus Larynx 2002;29:19–28.;

Iino Y *et al.*: Clinical & Experimental Allergy 2001;31:1135–43.

# EOM

## ■ lino

- 43 ears with EOM with TT triamcinolone acetonide.
- Controls: tube placement with daily beclamethasone drops
- @ 3 weeks 81% RXed with triamcinolone had resolution of the MEE vs 26% controls.

lino Y *et al.*: Annals of Allergy. Asthma and Immunology 2006.

# Immune modulation

- Synthetic CpG oligodeoxynucleotides (CpG ODN) treats murine asthma by driving a shift toward the Th1 cytokine response, counteracting the Th2 inflammation
- Human trials of CpG ODN in AR and atopic asthma have had promising results
  - a decrease in nasal eosinophilia and improved clinical nasal symptoms and rhinitis.
  - Inhalation therapy with CpG ODN for atopic asthma resulted in increases in Th1 cytokines, but airway hyperresponsiveness to allergen challenge did not change
- Blanks
  - CpG ODN showed normalized Eustachian tube function and improved mucociliary clearance in rats sensitized to OVA.

Wang LC *et al.*: Current Medicinal Chemistry 2007; Jain VV *et al.*: J of All and Clin Immunol 2002; Jain VV *et al.*: Am J Physiology– Lung Cellular and Molecular Physiology 2003; Marshall JD *et al.*: J All Clin Immunol 2001; Creticos PS *et al.*: N Engl J Med 2006; Blanks DA *et al.*: OTO-HNS

# Summary

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- Atopy is more common in OME
  - Atopy increases likelihood of ETD.
  - A subgroup of COME has Th2 mediated inflammation
    - Unified airway concept
    - Likely will respond to long term allergy management
    - Lack method of identification
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## The Inner Ear

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## Duke: case 1

1. 35 y/o woman
2. Rotational vertigo w N/V. Q 1-2 days
3. IFT ⊕ for fruits, vegetables, esp. peas & beans. Provoked SxS
4. IC Epi & elimination diet → no SxS

Duke JAMA 1923

## Duke: case 2

1. 43 y/o man
2. L roaring tinnitus followed by vertigo w N/V
3. IFT ⊕ for vegetables, fruits nuts, esp. spinach. Provoked SxS
4. SQ Epi & elimination diet → no SxS

Duke JAMA 1923



## Common Elements:

1. Classic SxS of Meniere's linked to food allergens
2. IFT was  $\oplus$  for these food allergens
3. A diet eliminating these foods eliminated attack of Meniere's
4. Oral challenge feeding tests were  $\oplus$
5. Treatment directed at the allergic response could avert an attack

## Immune Privilege

Blood Brain Barrier

Blood Labyrinthine Barrier

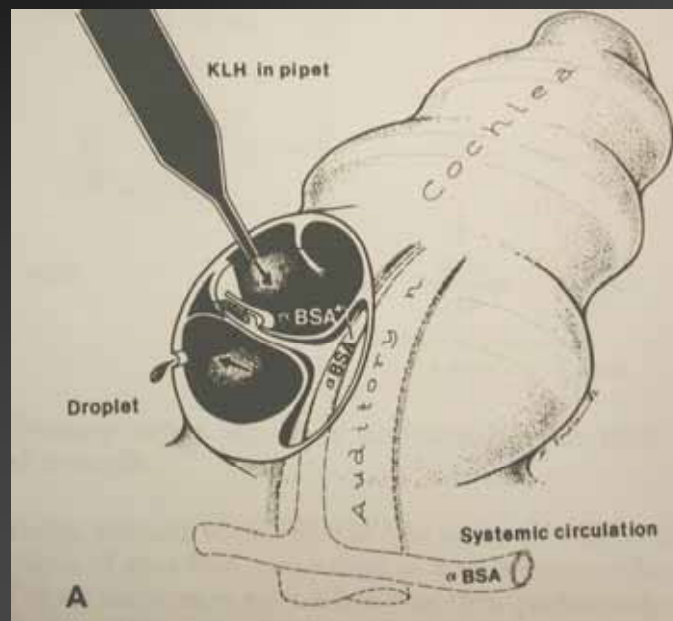
No lymphatic system but immunological events do occur in both systems

# Harris

- Antigens introduced into intracochlear fluids pass into systemic circulation
- Antigens into IE of sensitized animals:
  - Cochlear inflammation
  - Cellular infiltration
  - Local tissue injury
  - Local production of antibody

Harris Oto-HNS June 1995

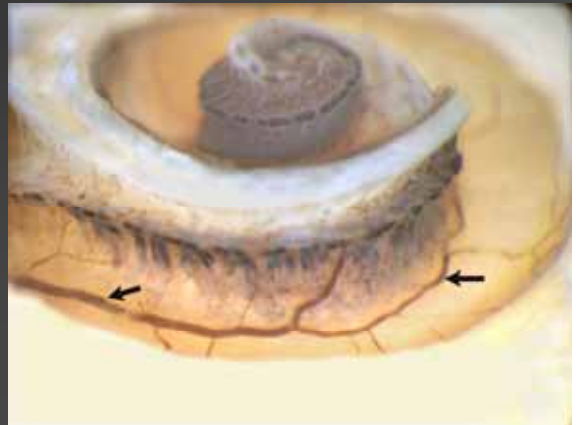
## Harris: local antibody



Harris Oto-HNS June 1995

# Harris

- Spiral Modiolar Vein
- Endothelial cells → adhesion molecules
- Response eliminated if ELS removed !!



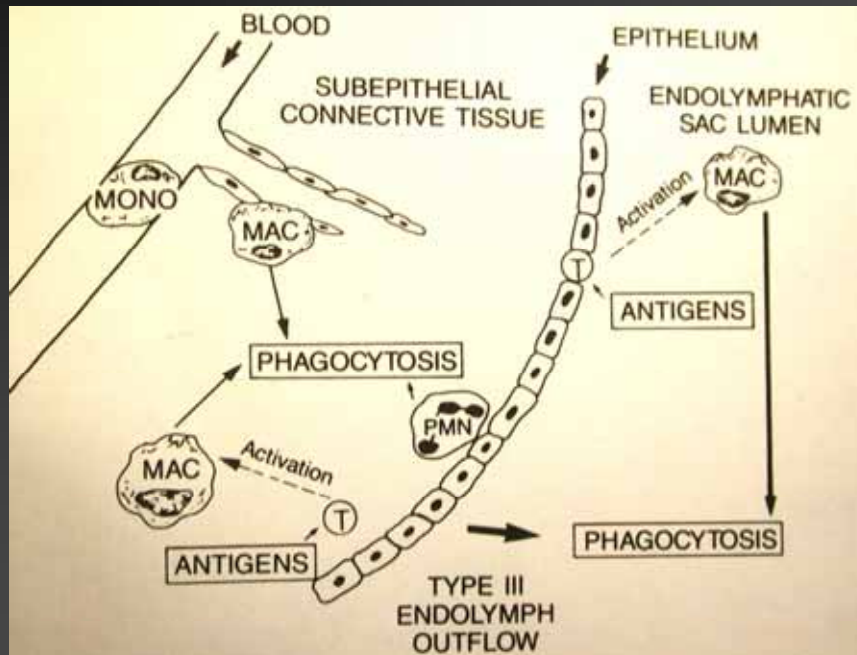
Harris Oto-HNS June 1995

# ELS

- Vasculature shows “fenestrated” capillaries
- IgA, IgM, IgG & secretory immunoglobulins
- Perisaccular tissues: plasma cells ,  
leukocytes & lymphocytes

Wackym Ann Otol Rhinol Laryngol 1987

# ELS: Immune function



Harris Oto-HNS June 1995

# Derebery

- ELS a direct “Target Organ”
- CICs produced elsewhere deposited in IE structures
- Shambaugh & Wiet: low grade chronic inflammation → degrades capacity of ELS

Derebery Oto-HNS March 1996

## Dereberry: CICs

- 30 Meniere's subjects vs 20 controls
- 27 of the Meniere's subjects had higher CICs than the highest controls
- 26 Meniere's had CIC levels that were 3 or more SD above the mean of the controls

Dereberry Oto-HNS Laryngoscope  
1991

## Dereberry: Clinical Response

- Clinical improvement documented after allergic &/or immunologic Rx based on pre- vs post treatment questionnaires
- Nearly 50% of 113 subjects had complete or considerable control of vertigo
- Hearing was stabilized or improved in 64%

Dereberry Oto-HNS Feb  
2000

# Cogan's Syndrome

- Meniere's SxS ass w interstitial keratitis
- Relentlessly progressive → deafness without Rx
- Pathology:
  - Endolymphatic hydrops
  - Plasma cell & lymphocyte infiltrate of SL
  - Saccular rupture

Wolff *et al* Ann Otol Rhinol Laryngol 1965

## Questions that remain

- How many patients with Meniere's have an allergic or immunologic origin?
- How can such patients be identified?
- How are they best treated?

# Direct Indicators of Allergic Response

- FEV<sub>1</sub>
- Patch test
- Decreased airflow on rhinometry
- Increased nasal inflammatory mediators

# Indirect Indicators of Allergic Response

- Skin testing for inhalant nasal allergy

# Electrocochleography (ECoG)

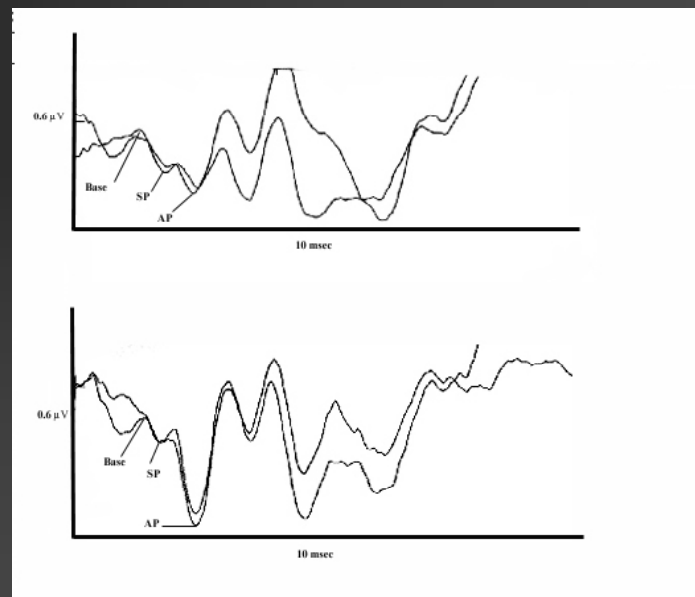
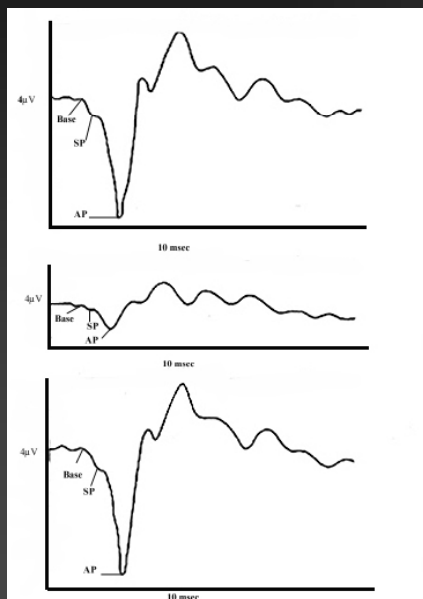
- Measures evoked intracochlear electrical potentials
- AP: compound action potential of the cochlear nerve
- SP: summing potential. Reflects micromechanics of the basilar membrane. Endolymphatic pressure increase “biases” the membrane and alter micromechanics

# Electrocochleography (ECoG)

- Since the absolute magnitude of the recorded SP varies among individuals, the SP/AP ratio is used clinically
- The SP/AP ratio is elevated in @ least 75% of patients w Meniere's disease



# ECoG



## Viscomi & Bojrab

1. 5 subjects w  $\oplus$  IC food tests evaluated
2. Tested to 27 antigens 6 showed real time increases in SP/AP ratio:

- No SP/AP  $\Delta$  in subjects w neg skin tests
- All  $\Delta$  in subjects w  $\oplus$  tests & 6/8 had SxS

*Direct link of provocative food challenge with a measurable alteration of physiology*

# Gibbs

- n 1. 7 subjects w Meniere's & AR ⊕RAST
- n 2. Extra-tympanic ECoG before and after direct intra-nasal challenge.
- n 3. # of RDST disc applied inversely proportional to RAST score

Gibbs et al Oto-HNS Sept 1999

# Gibbs: results

**Table 2.** Relationship of change in SP/AP ratios and subjective symptoms produced by intranasal antigen challenge

	N1	N2	N3	N4	N5	N6	N7
Aural/vestibular symptoms	+	+	-	+	-	+	-
Nasal symptoms	+	-	+	-	-	+	+
Change in SP/AP (%)							
Right	+29	+5	+14	-17	-27	-15	-9
Left	-8	+4	+45	+19	0	+25	-1

Gibbs et al Oto-HNS Sept 1999

## Gibbs: conclusion

- n Antigen provoked elevation of the SP/AP ratio might be a reasonable method of identifying patients with allergy mediated Meniere's disease

Gibbs et al Oto-HNS Sept 1999

## Noell

- 11 pt w Meniere's & AR
  - 6 subjects had had @ least 1 yr of immunotherapy
  - 5 had had less than 1 yr of immunotherapy
- 2 of 5 subjects < 1 yr Rx ↑ SP/AP
  - Both had Meniere's SxS after challenge

# Noell

- BUT:
- 4 of the 6 > 1 yr Rx still had ↑ SP/AP
  - 3 experienced nasal SxS
  - 2 experienced Meniere's SxS

# Summary

- The inner ear is capable of an immunologic response
- There is good evidence that in at least some patients with Meniere's disease the disease is due to an Allergic process.
- Antigen provoked increase in SP/AP ratio may be a direct indicator of an allergically mediated response



QUESTIONS