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Where Does Sinusitis Come From?

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SOUTHERN STATES RHINOLOGY FOUNDATION

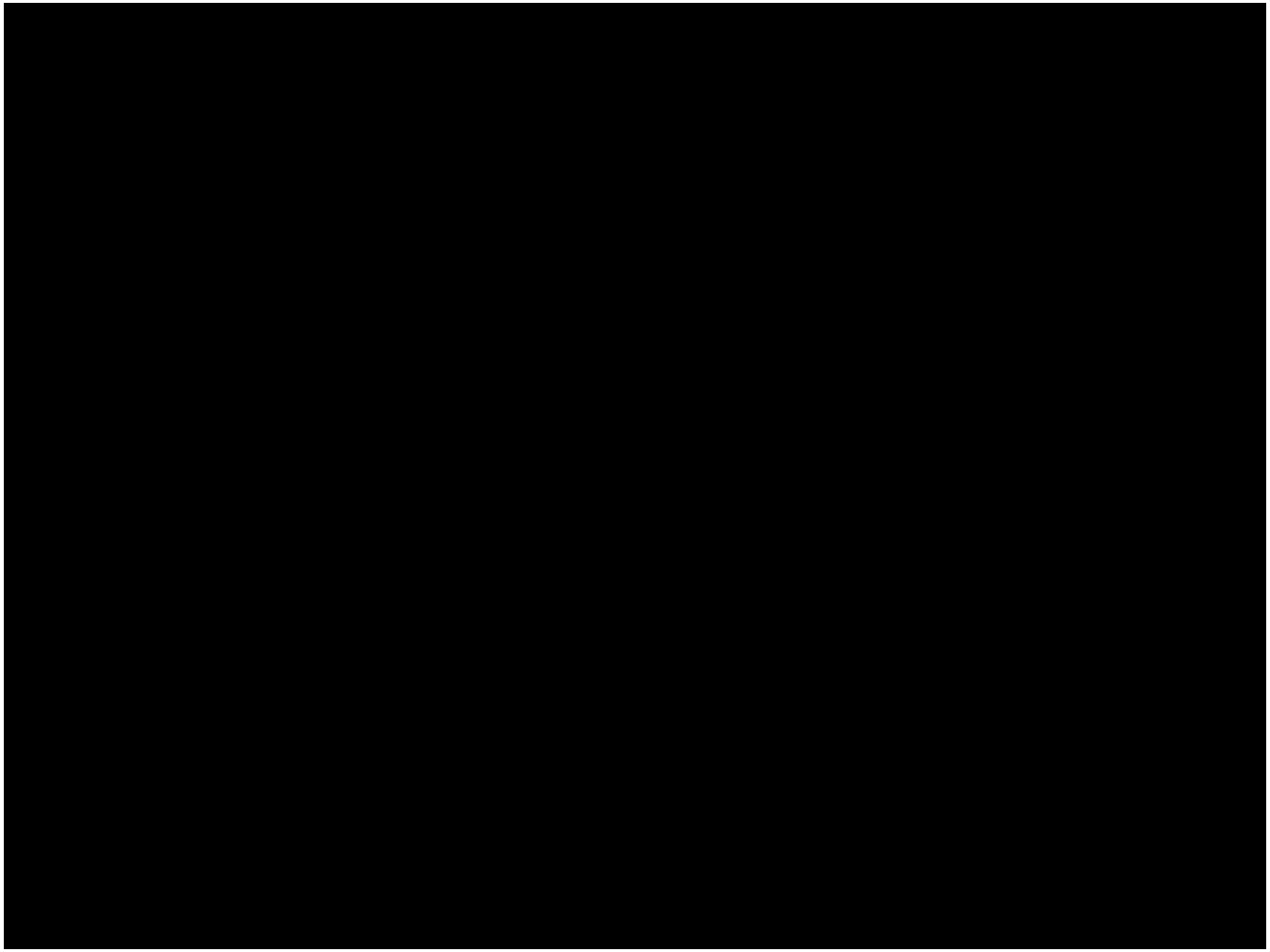
Disclosures

- Consultant
  - Sinuwave
  - Laurimed
  - Entrigue
  - Nasoform
  - Olympus Gyrus
- Speaker
  - Stryker
  - Genentech
- Stockholder
  - Entrigue
  - Remedease
  - Nasoform

Objectives

- To define rhinosinusitis
- To discuss several proposed extrinsic mechanisms of the disease
  - Mucosal infection
  - Fungal infection
  - Staph Superantigen
  - Biofilms
  - Bone inflammation
- To review intrinsic mechanical and immunological defects in the disease

We Think We Know Everything…



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Factors Associated in Diagnosis of Rhinosinusitis

MAJOR

- **Nasal obstruction/blockage**
- **Hyposmia/anosmia**
- **Purulence in nasal cavity on examination**
- **Fever*** **(in children)**
- **Facial pain/pressure*** **(used in conjunction with other factors)**

MINOR

- **Headache**
- **Fever (all nonacute)**
- **Halitosis**
- **Fatigue**
- **Dental pain**
- **Cough**
- **Ear Pain /pressure/fullness**

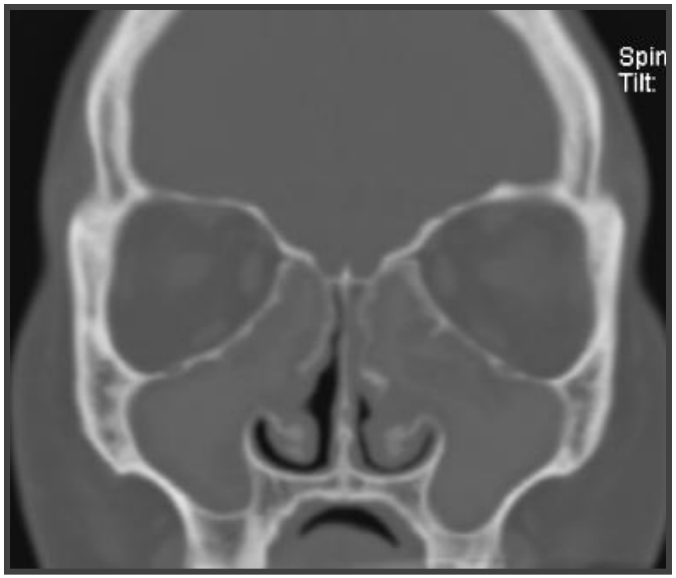
Lanza, DC, Kennedy, DW, Adult Rhinosinusitis Defined Otolaryng Head Neck Surg 117; S1-7, 1997

Rhinosinusitis Task Force, AAO/HNS, 1995

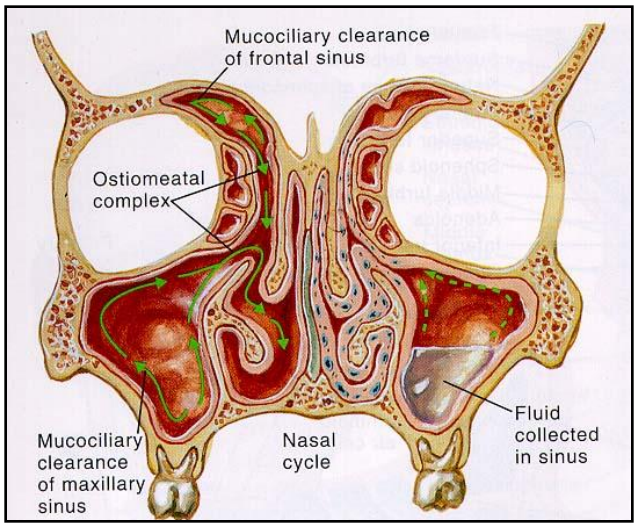
- Diagnosis: 2 Major or 1 Major and 2 Minor

Is This Really Right???

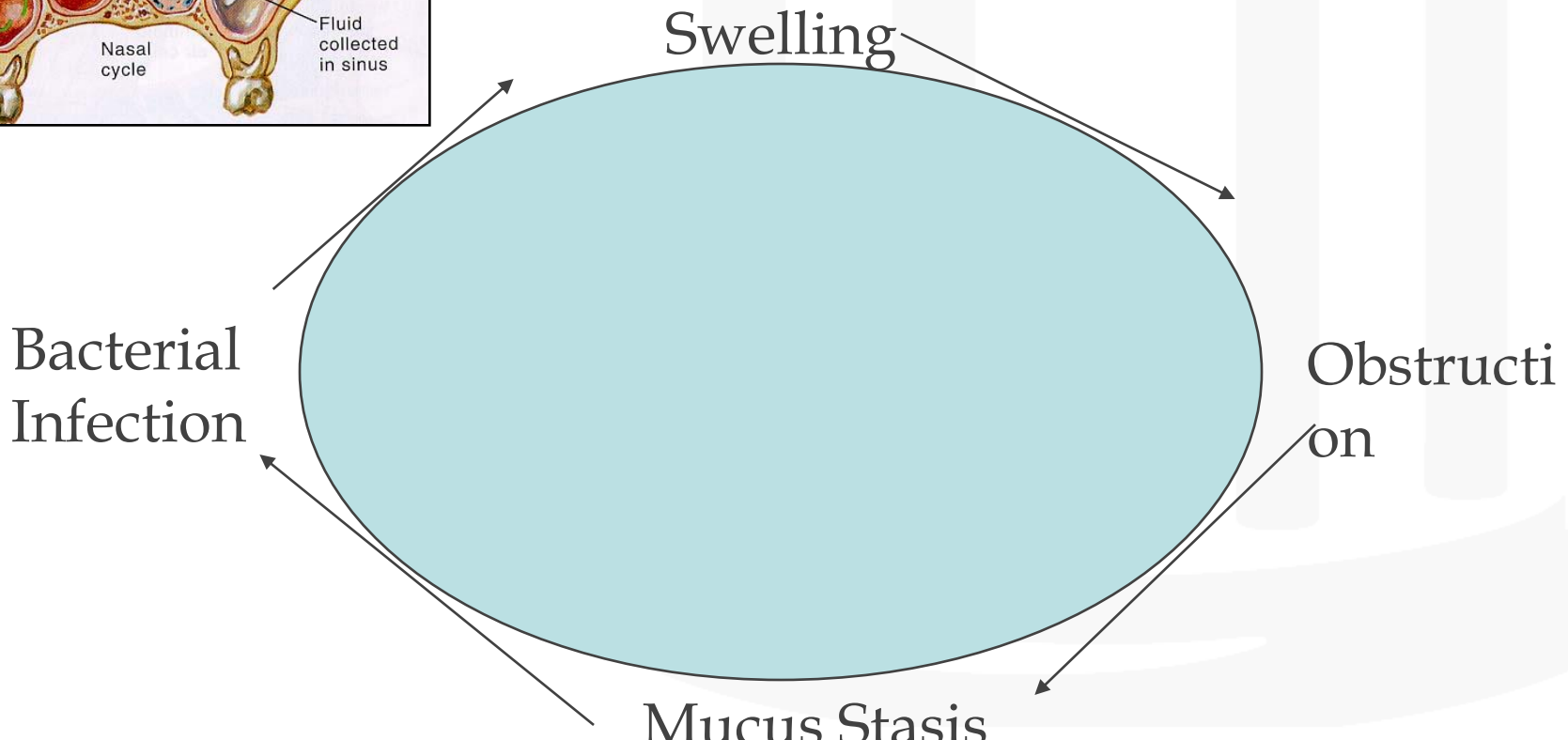
- "A Diagnostic Dilemma for Chronic Rhinosinusitis: Definition Accuracy and Validity"
  - *Stankiewicz and Chow, AJR 16(4): 199-202, Jul-Aug 2002*
    - 78 patients prospectively evaluated and meeting criteria
    - Only 37/78 with positive CT-No correlation between CT and severity of symptoms



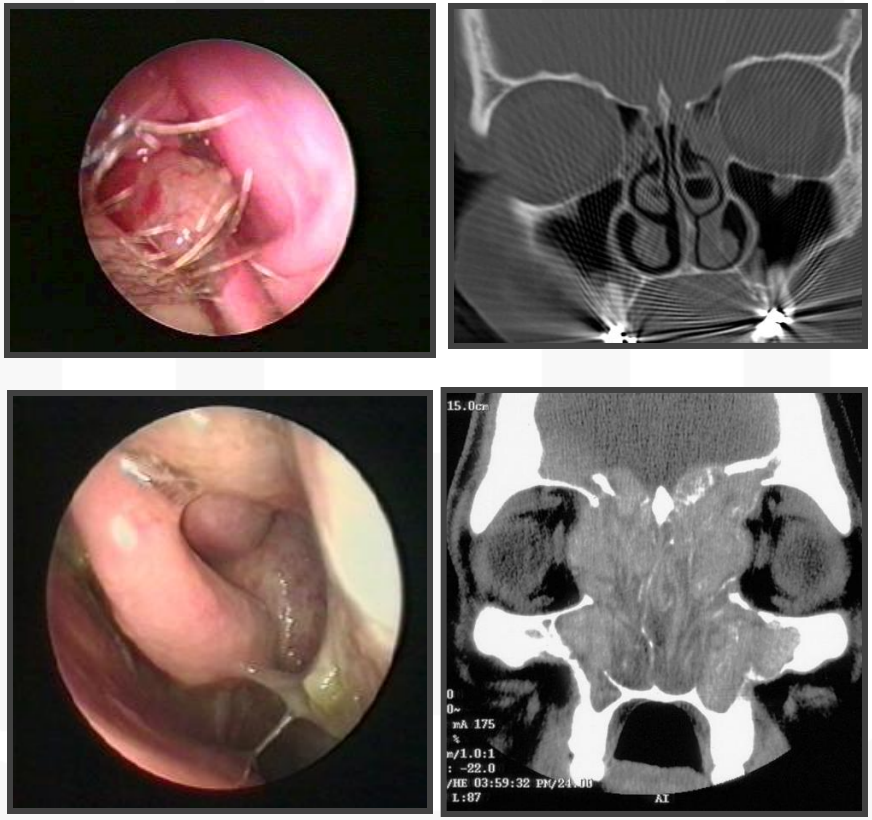
What is Chronic Rhinosinusitis?



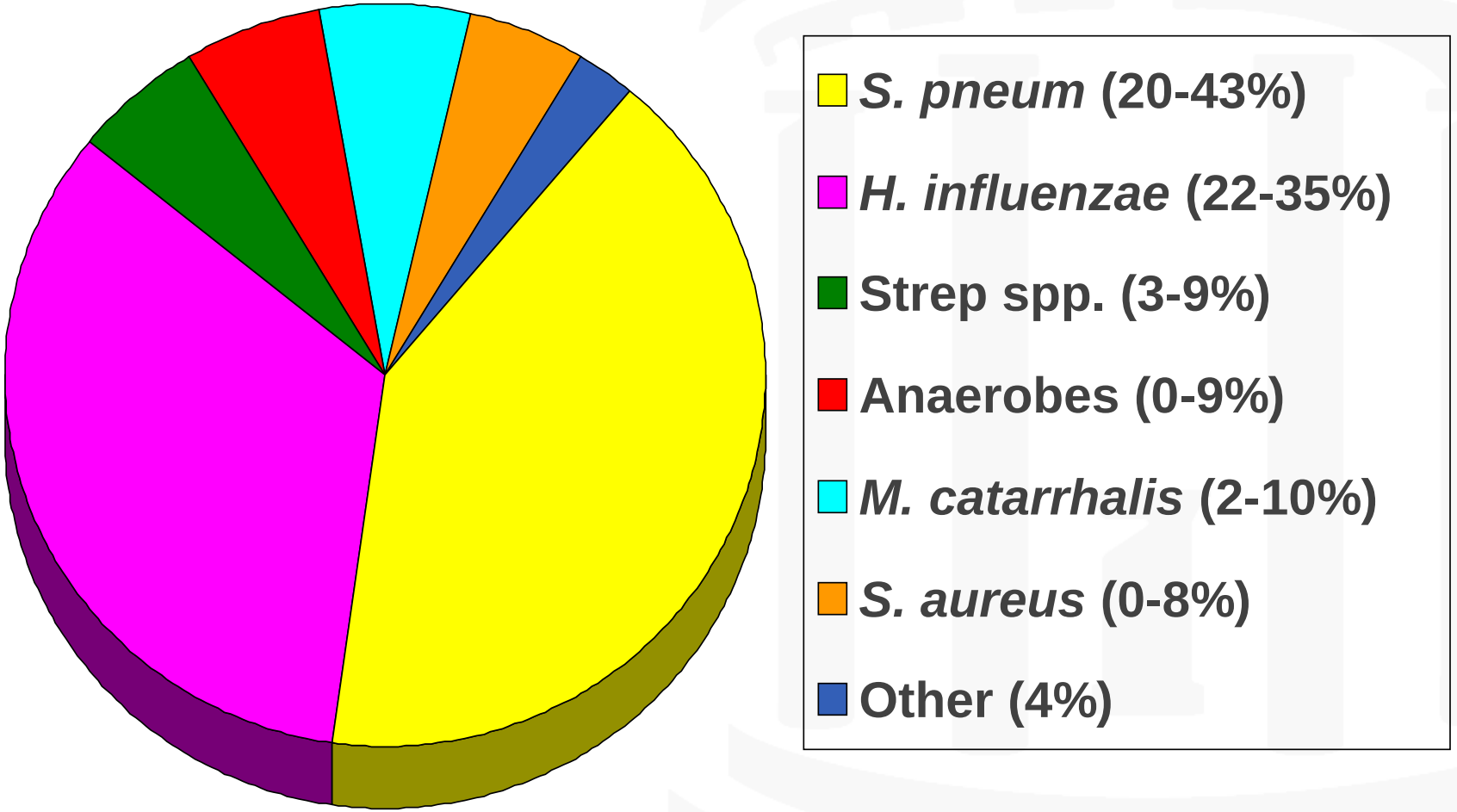
- Old Paradigm
  - » Chronic Rhinosinusitis is a mucosal infectious disease
  - » A “plumbing problem”



- New Paradigm
  - Rhinosinusitis is mucosal ***inflammation***
  - CRS Defined By
    - 12 or more weeks in duration
    - Physical findings on endoscopy or anterior rhinoscopy
    - CT helpful, but not necessary
      - » Otolaryngol HNS, 120(3), Sept 2003
  - » *Where does the inflammation arise from?*



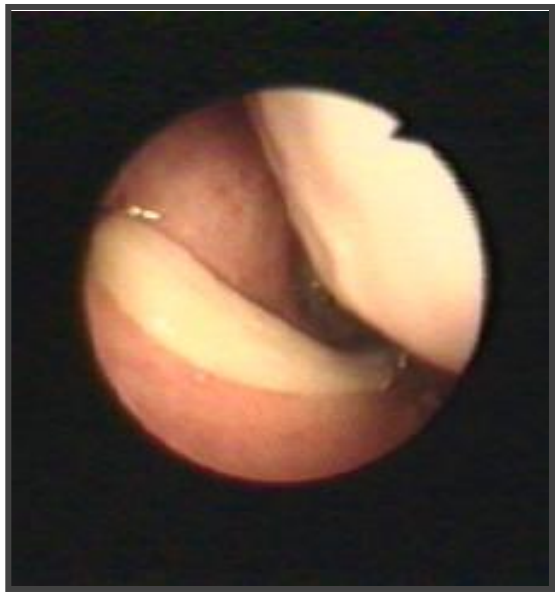
Microbiology of Acute Bacterial Rhinosinusitis (Adults)



Sinus & Allergy Health Partnership Guidelines for Treatment of Acute Bacterial Sinusitis Otolaryngol Head & Neck Surg July 2000

Microbiology of Chronic Sinusitis

- Prospective evaluation of 174 adults with CRS requiring surgery had cultures of maxillary sinus.
- Most common isolates:
  - Coag-neg staph 36%
  - S aureus 25%
  - Strep viridans 8.3%
  - Corynebacterium 4.6%
  - Anaerobes 1.4%



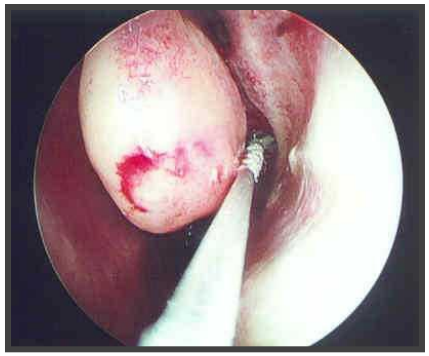
Biel MA, et al

Ann Otol Rhinol Laryngol 1998;107:942-5

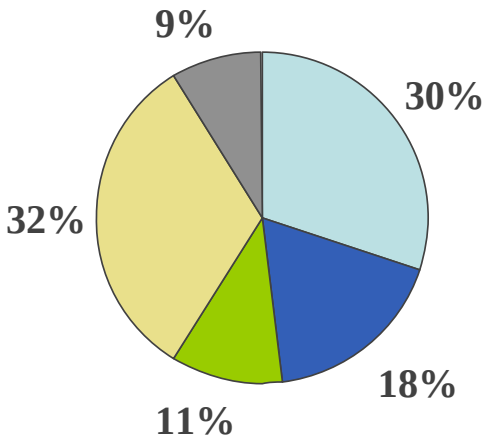
Theory 1: Mucosal Infectious Disease

Microbiology of Chronic Sinusitis- Post-op

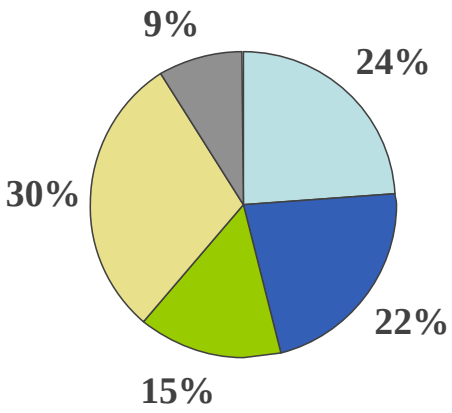
Am J Rhinol. 2006 Jan-Feb;20(1):72-6

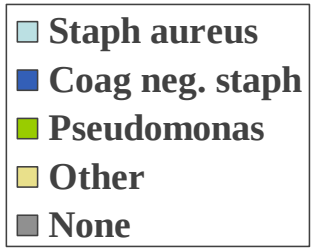


Single Culture Performed N = 48



> 3 Cultures Performed N = 17





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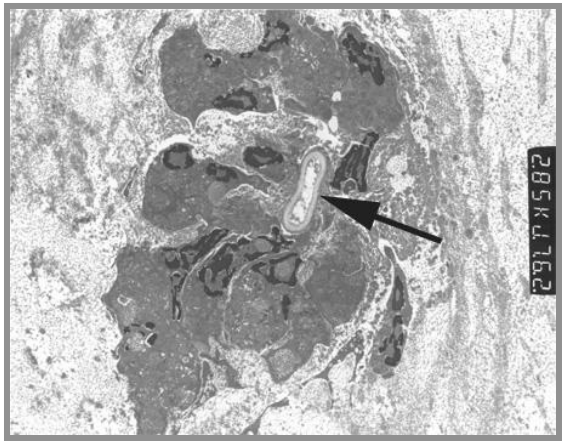
Theory 2:

Fungal Involvement in Chronic Rhinosinusitis

- Fungal cultures were positive in 202/210 consecutive CRS patients
- Allergic mucin was found in 97/101 consecutive surgical cases
- Therefore “all CRS is fungal sinusitis”
  - Ponikau, et al. Mayo Clin Proc 1999; 74: 877-884
    - ☞ But, 14/14 controls were also fungus positive with the identical fungal organisms seen in the CRS group.



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Theory 2:

Fungal Involvement in Chronic Rhinosinusitis

- Similar findings reported in Austria
  - Positive fungal cultures in 84/92 patients
  - Controls positive in 21/23
    - Braun H, et al. Laryngoscope 113(2): 254-9, 2/2003
- Nasal mucosa of neonates
  - 5 days-40%; 4 months-94%
- Conventional fungal isolation not as successful
  - 45 random CRS specimens: 56% positive
    - Lebowitz R, et al. Laryngo112: 2189-91, 2002

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Effect of Antifungal Treatment on Inflammation in CRS

- Ampho B BID in the nose for 13 weeks and levels of proinflammatory cytokines, chemokines, and growth factors
  - IL-1beta, IL-1RA, IL-2, IL-2R, IL-3, IL-4, IL-5, etc. TNF-alpha, IFN-gamma, RANTES, eotaxin, etc.
  - No effect on any marker of inflammation
    - ☞Laryngoscope 2009 Feb;119(2):401-8

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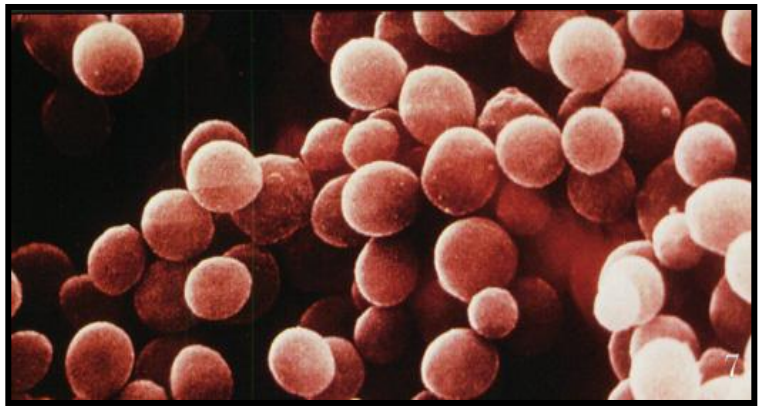
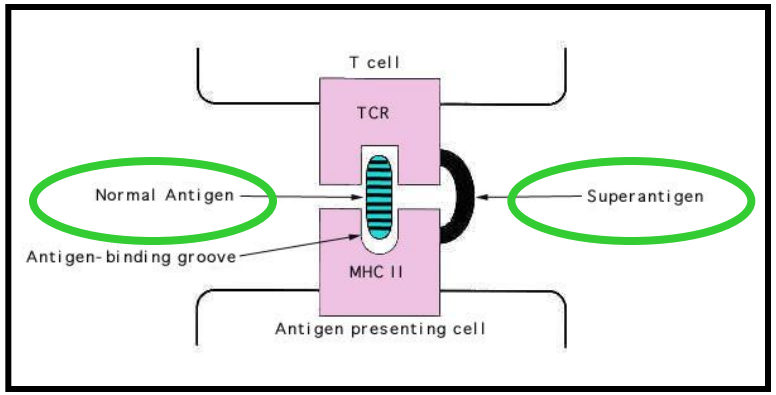
Theory 3:

Staphylococcus Aureus Superantigen

- Staph Super-antigen
  - 25% of the population are carriers of staphylococcus aureus
  - Enterotoxin and TSS toxin both exhibit super-antigen activity
    - Less specific Cross-linking T cell receptor with the MHCII on APC
    - May cause 20-25% of all T Cells to be activated
      - normal stimulation will result in 1/10,000
    - Has a role in atopic dermatitis, Kawasaki's disease, TSS, and rheumatoid arthritis
  - Bachert, et al. Curr Allergy Asthma Rep. 2002; May;2(3):252-8

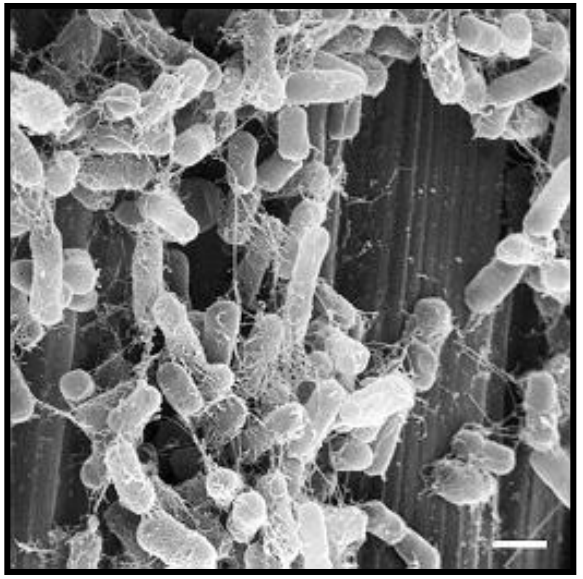


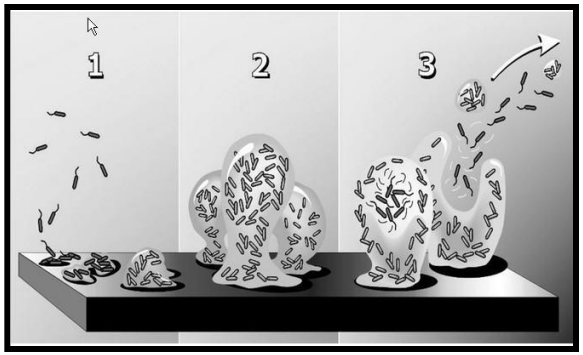


Theory 4:

Biofilms

- "an assemblage of microbial cells enclosed in a self-produced polymeric matrix that is irreversibly associated (not removed by gentle rinsing) with an inert or living surface"
  - Reduced oxygen and nutrient state
  - Increased antibiotic resistance
  - 99% of all bacteria are believed to exist in biofilms and only 1% in planktonic state
  - CDC: 65% of all human bacterial infectious processes involve biofilms
  - First noted by Van Leeuwenhoek
  - Reemerged in 1970s

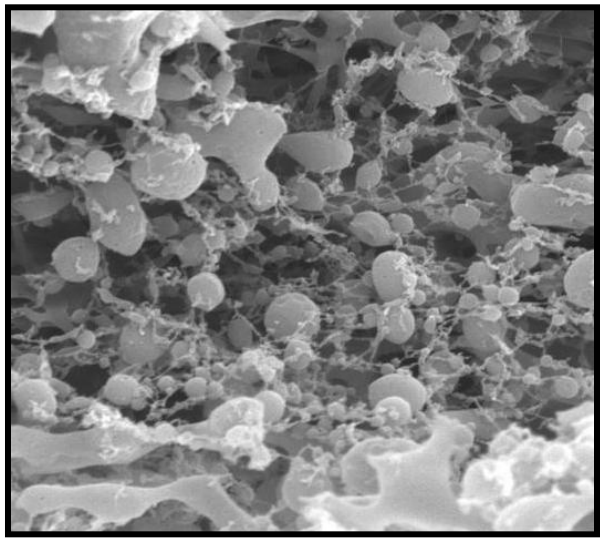


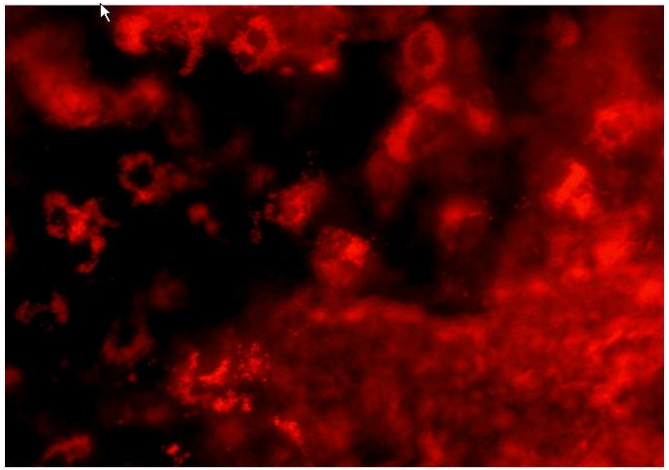


Theory 4:

Biofilms

- 24/30 (80%) of pts with CRS demonstrated biofilm by SEM.
- 4 controls were normal
- *Bacteria ided using TEM*
  - Sanclement, et al. Laryngoscope 2005;115:578-82
- Using fluorescent in situ hybridization (FISH), specific bacteria can be ided in the biofilm
  - 14/18 (78%) with biofilms. 2/5 controls were positive
  - H flu, S pneumo, SA all ided. *PA not identified*
  - *Intraop cultures did not correlate with biofilms ided*
  - Sanderson, et al. Laryngoscope 2006;116:1121-6





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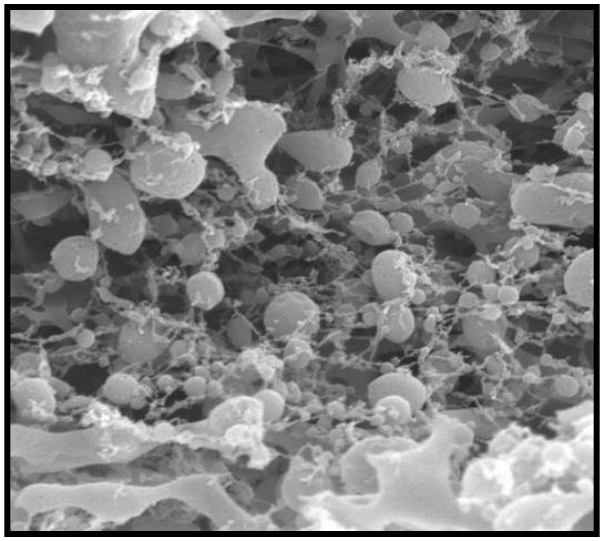
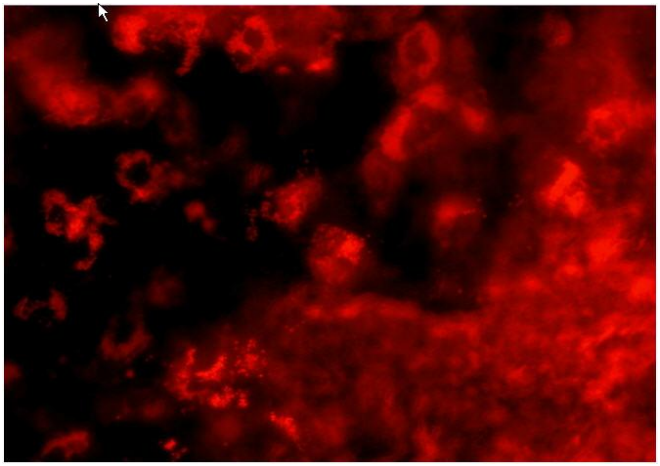
Theory 4:

Biofilms

- 40 patients retrospectively followed with CRS undergoing FESS
  - 50% with biofilms by confocal scanning laser microscopy
  - Patients with biofilms had significantly worse
    - Preoperative symptom scores
    - Preoperative radiologic scores
    - Postoperative symptom scores
    - Postop mucosal appearance
  - Presence of polyps, eosinophilic mucin, or pus did not result in poor outcomes
  - Psaltis et al. AJR 22, 1-6, 2008





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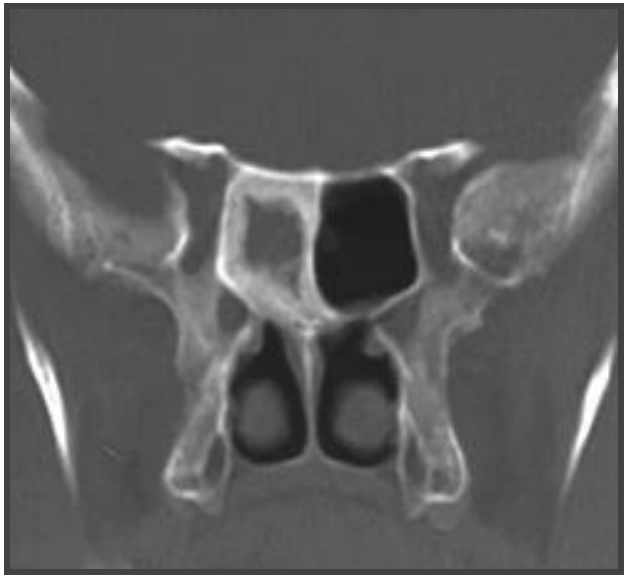
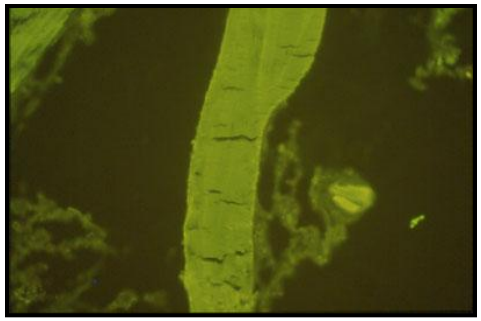
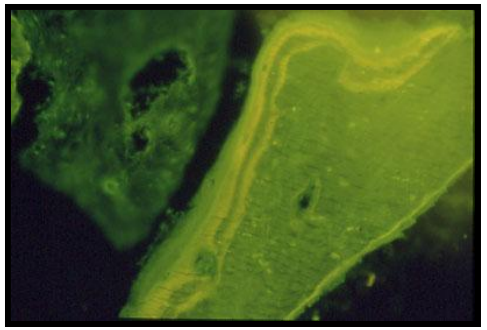
Theory 5:

Bone Inflammation

- Clinical Evidence
  - CT scan findings of thickened bone in paranasal sinuses
  - particularly in individuals with recalcitrant disease
- Quantitative Histomorphometry
  - Results: significant increase in bone activity seen in chronic rhinosinusitis
    - 70% of CRS showing moderate to marked activity
    - 70% of controls showed no activity
  - *Similar to chronic osteomyelitis*
  - Kennedy, Senior, et al. Laryngoscope 1998;108:502-7







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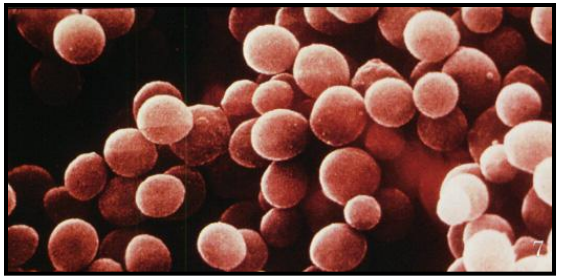
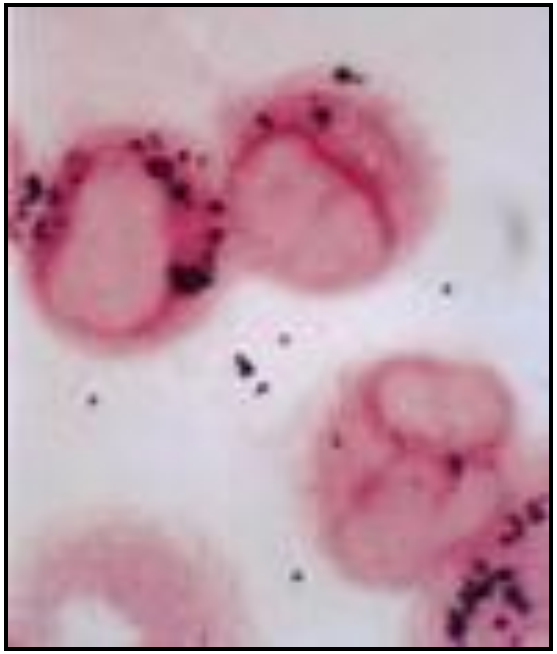
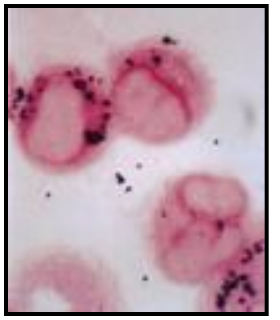
Etiology of Chronic Osteomyelitis in Long Bones

- 80% of Osteo is caused by staph aureus
  - Despite effective antibiotics for sa, infections tend to be persistent and recurrent
- One Theory: intracellular staph aureus
  - Other bacteria had long been known to invade “non-professional phagocyte” cells
    - Salmonella, tuberculosis, shigella, and listeria
  - Recently suggested as the etiology of endocarditis by SA invasion of endothelial cells
    - Thromb Hemostasis 2005;94:266-77
  - Also now implicated in prostatitis, cystic fibrosis, Darier’s disease





Yes, But Does This Have any Relation to the Nose?



- ICSA now ided in nasal epithelium, glandular, and myofibroblastic cells in patients with SA cultured from MM
  - Inverted confocal laser scan fluorescence and TEM from biopsies following abx treatment
    - Clement, et al. J Infect Dis 2005;192:1023-1028
- Follow-up study 27 pts who underwent surgery with one year follow-up
  - 17/27 (65%) had ICSA
    - 11/17 with ICSA relapsed over the ensuring year
    - 9/17 (>50%) had SA on MM cx
    - 2/12 (16%) without ICSA had SA on MM cx
    - "presence of ICSA in nasal epithelial cells is a significant risk factor for recurrent RS"
    - Plovin-Gaudon, et al. Rhinology 2006;44:249-54

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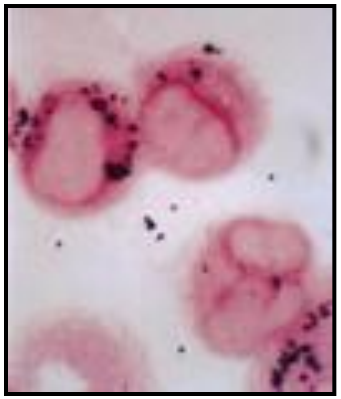
So A Relationship Exists, But…



- ICSA is probably pathogenic, but maybe a protective response by the cells?
- About 30% of cultures in CRS are SA (vs 80% in chronic osteo), what about the rest?
  - About 30% is coag neg staph—could this also go intracellular? Other bugs?
- What about the bone?

What about the Immune System?

- CRS occurs at the interface of the nasal mucosa and the world
  - » Is the immune system hypo-, hyper-, or dysfunctional in CRS?
  - » Much of the pathology in CRS is collateral damage

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Normal Immune Function

- Innate Immunity
  - » Inborn resistance that is present *before the first pathogen exposure*
  - » Initiated by membrane-bound and cytoplasmic
    - pattern recognition receptors (PRRs) that recognize
      - » pathogen associated molecular patterns (PAMPs) in viruses, bacteria, mycobacteria, yeast, parasites= *danger signal*
      - » cellular damage through detection of debris from necrotic cells= *damage signal*

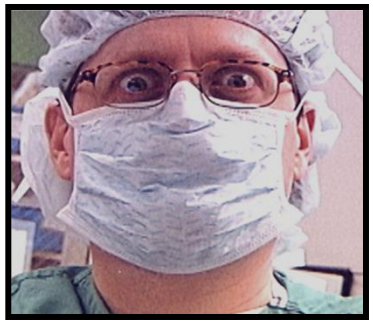
Cytoplasmic PRRs

- ***Toll-like Receptors (TLR)***
  - » Transmembrane receptor on many cell types including respiratory epithelial cells
  - » Subtypes respond to gram positive bacteria (including staph), fungal PAMPs, viral replication, etc.
- ***NOD-like Receptor Family***
  - » Recognize bacterial cell wall products including staphylococci
- *Recognition of PAMPs by Cytoplasmic PRRs results in secretion of cytokines and stimulation of APCs and chemokines that attract cellular components of the immune response*

Acquired Immune System

- Dendritic cells (APCs) become activated after stimulation by PRRs, migrate to LNs and present antigen to Th cells
  - » IL6 is the key cytokine mediating the transition from innate to acquired response
  - » TH1 response—IL12 and IFN gamma facilitate defense against intracellular pathogens (ie, bacteria)
  - » TH2 response– IL4, IL5, and IL13 facilitate defense against parasites and are assoc with allergy and asthma

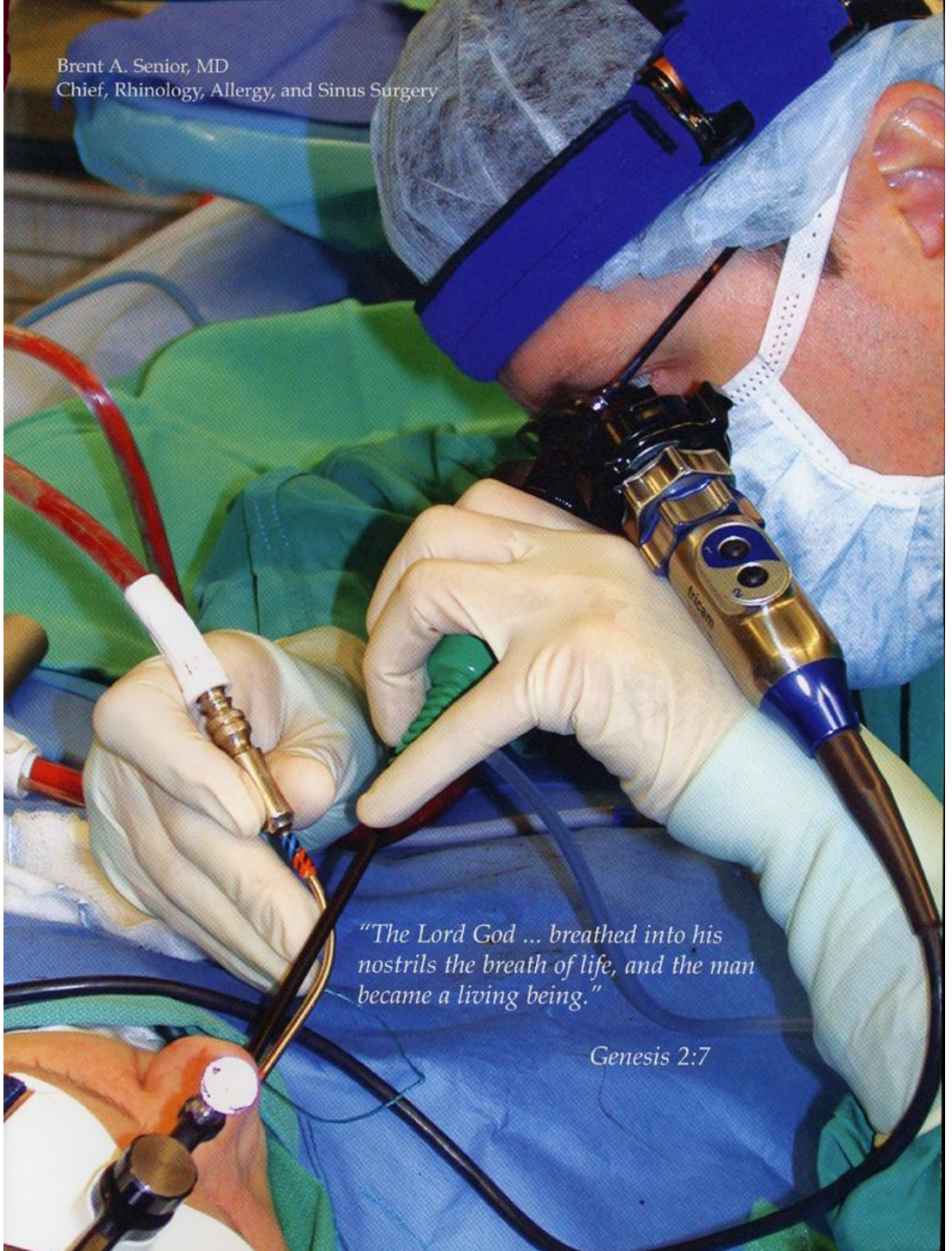
But wait, there's more!!



- TH 17 and T reg are 2 other Th subsets
  - » TH 17 is more akin to TH 2 with IL 17 in CRSwNP
- Modulation
  - » TH 1 and 2 inhibit one another
  - » TGF beta 1 promotes T reg, except in the presence of IL6
  - » T reg response is inactivated in situ by strong PRR stimulation, mostly TLR2

Summary

- Sinusitis is first and foremost medical disease and requires aggressive medical therapy
- Appropriate treatments must be aimed at presumed etiologies
- Multiple etiologies probably exist for rhinosinusitis
  - Extrinsic Contributers
  - Intrinsic Immune Barrier Problems
    - Innate
    - Acquired



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