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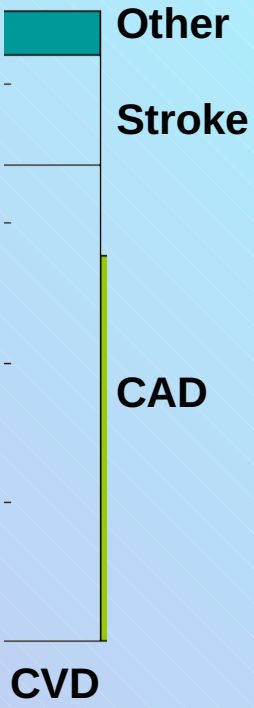
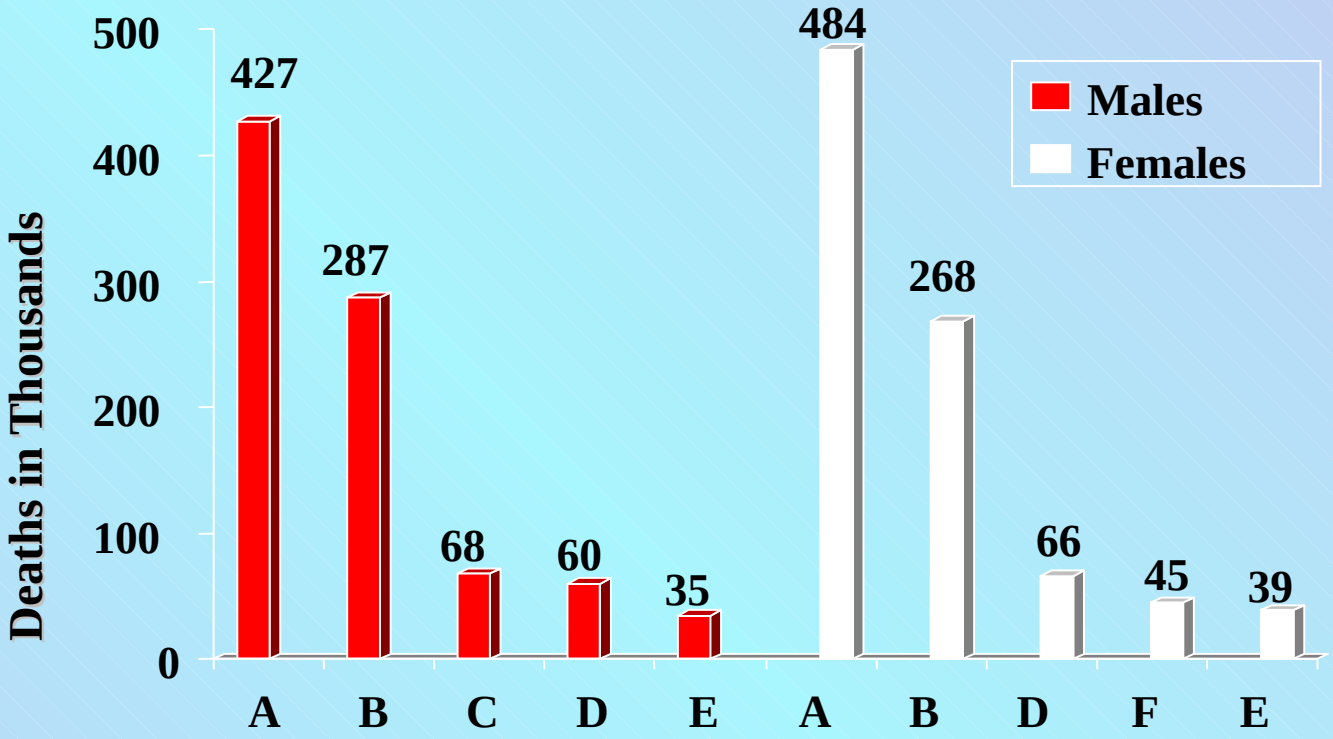
Leading Causes of Death in the US





A Total CVD
B Cancer
C Accidents
D Chronic Lower Respiratory Diseases
E Diabetes Mellitus
F Alzheimer's Disease

Source: CDC/NCHS and NHLBI. 2003

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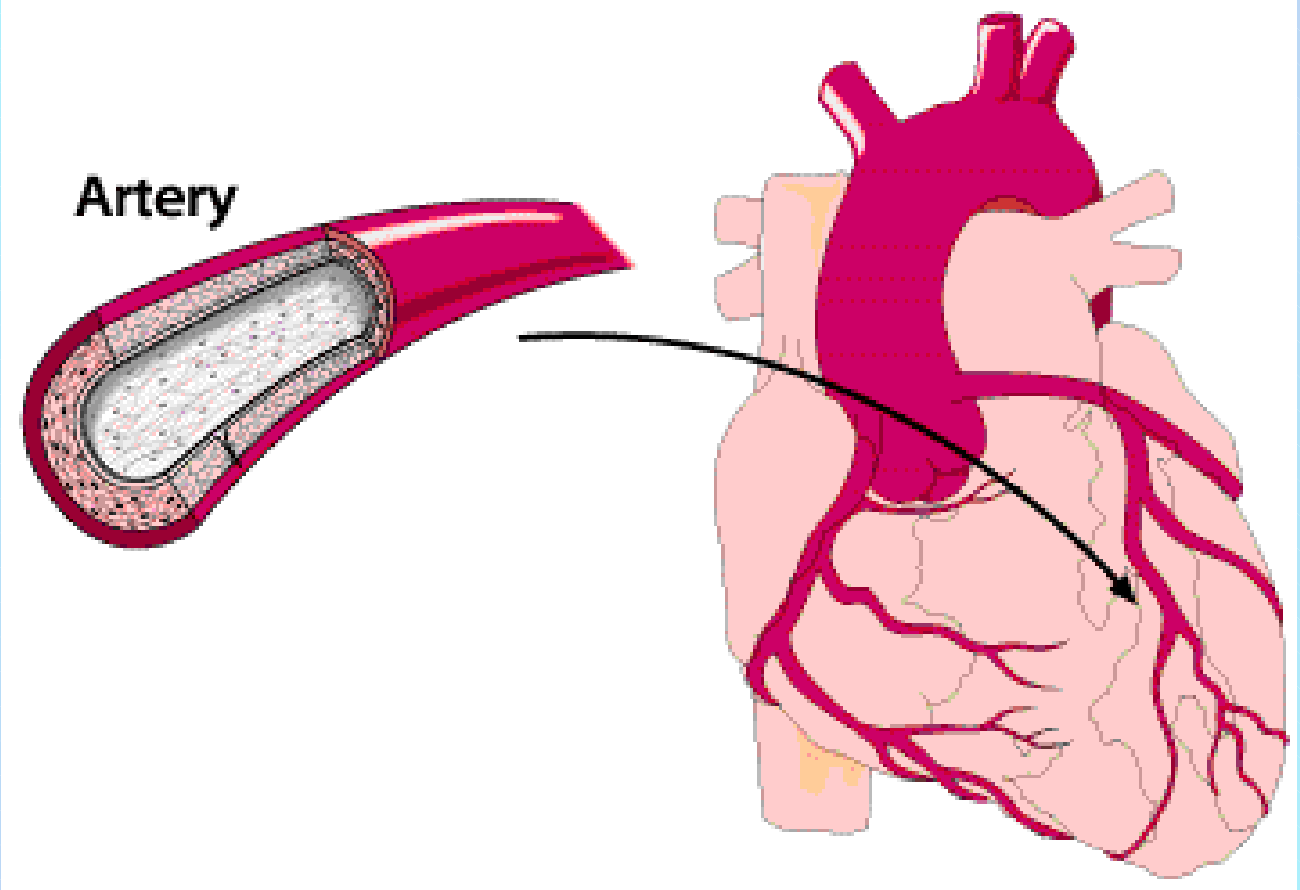
Myocardial Infarction



- Image courtesy of Heartpoint.com

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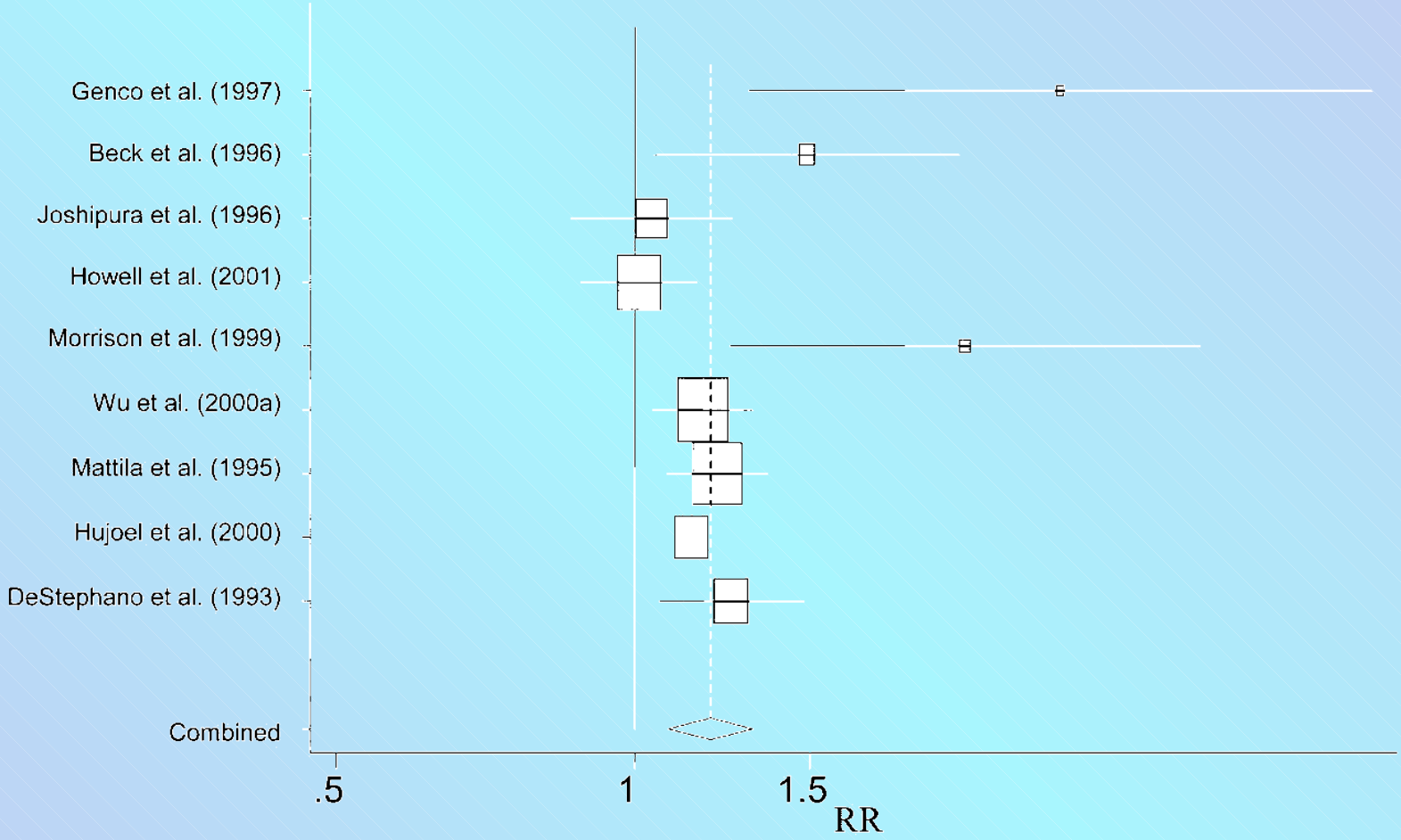
Epidemiologic Association of Periodontal Disease and CHD



Janket S, Baird A, Chuang S, Jones JA (2003), *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 95:559–569

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Dental Health and Acute Myocardial Infarction

- Used index based on caries, periodontal disease, periapical lesions, pericoronitis.
- Patients admitted for acute myocardial infarction had higher scores than matched controls.
- Patients above the upper quartile had twice the risk of acute myocardial infarction than did those with a score of zero.
- This was comparable to the risk of cigarette smoking, hypercholesterolemia and hypertension.

Mattila KJ et al. Brit. Med. J. 1989 298: 774

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Periodontal Disease in the United States

- 54% of U.S. population 13 years and older has gingival bleeding on probing
- In adults an average 19.6% of teeth have periodontal attachment loss of 3mm or more
- Based on data from NHANES III survey 1988-19994

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Healthy Gums

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Periodontitis

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Periodontal Disease Spectrum

- Healthy gums (may be colonized with some pathogens)
- Gingivitis (gum bleeding, no bone loss)
- Mild-moderate periodontitis (mild bone loss)
- Severe periodontitis (loose or missing teeth)

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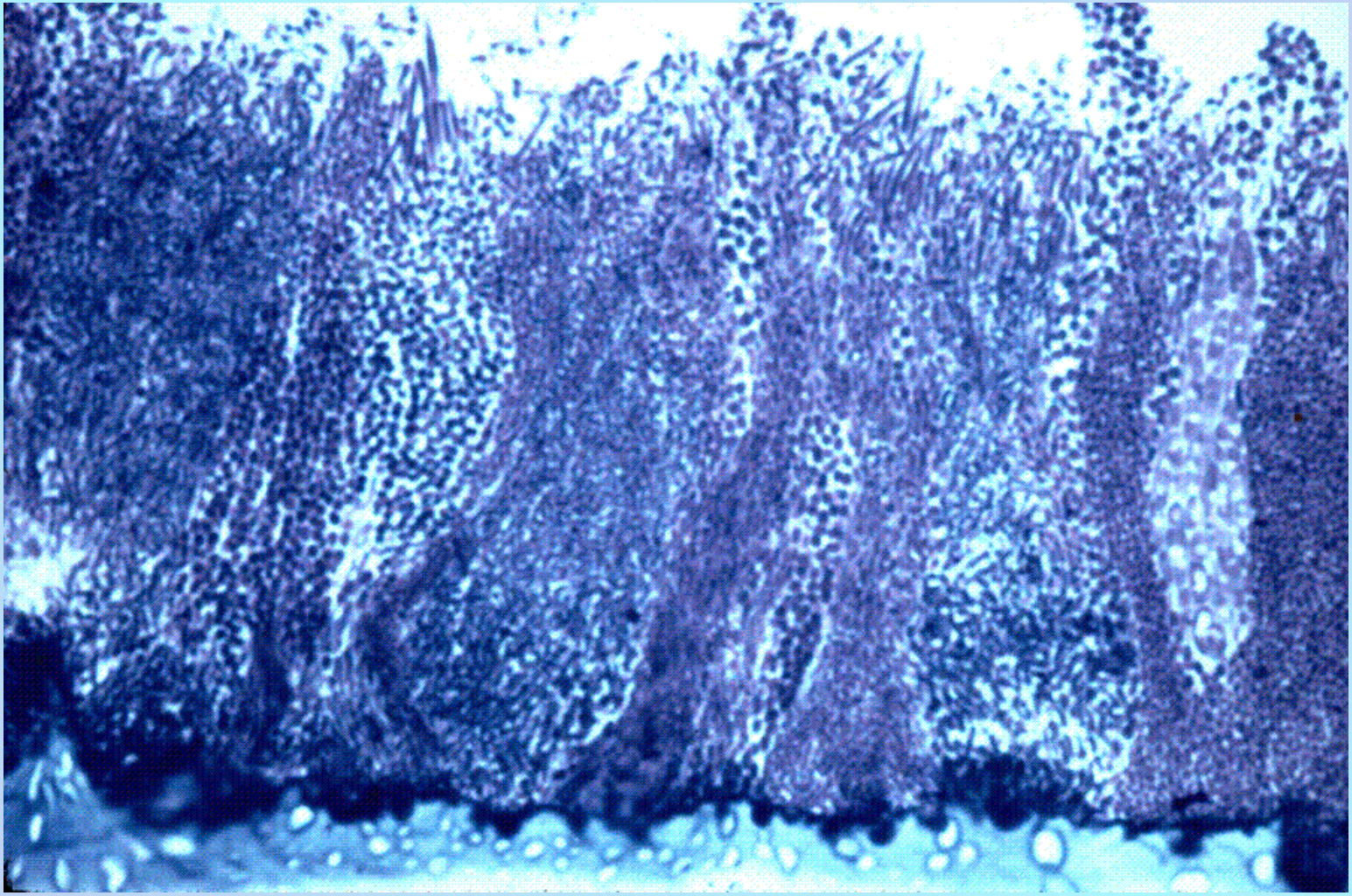
Human Supragingival Plaque



TOOTH SURFACE

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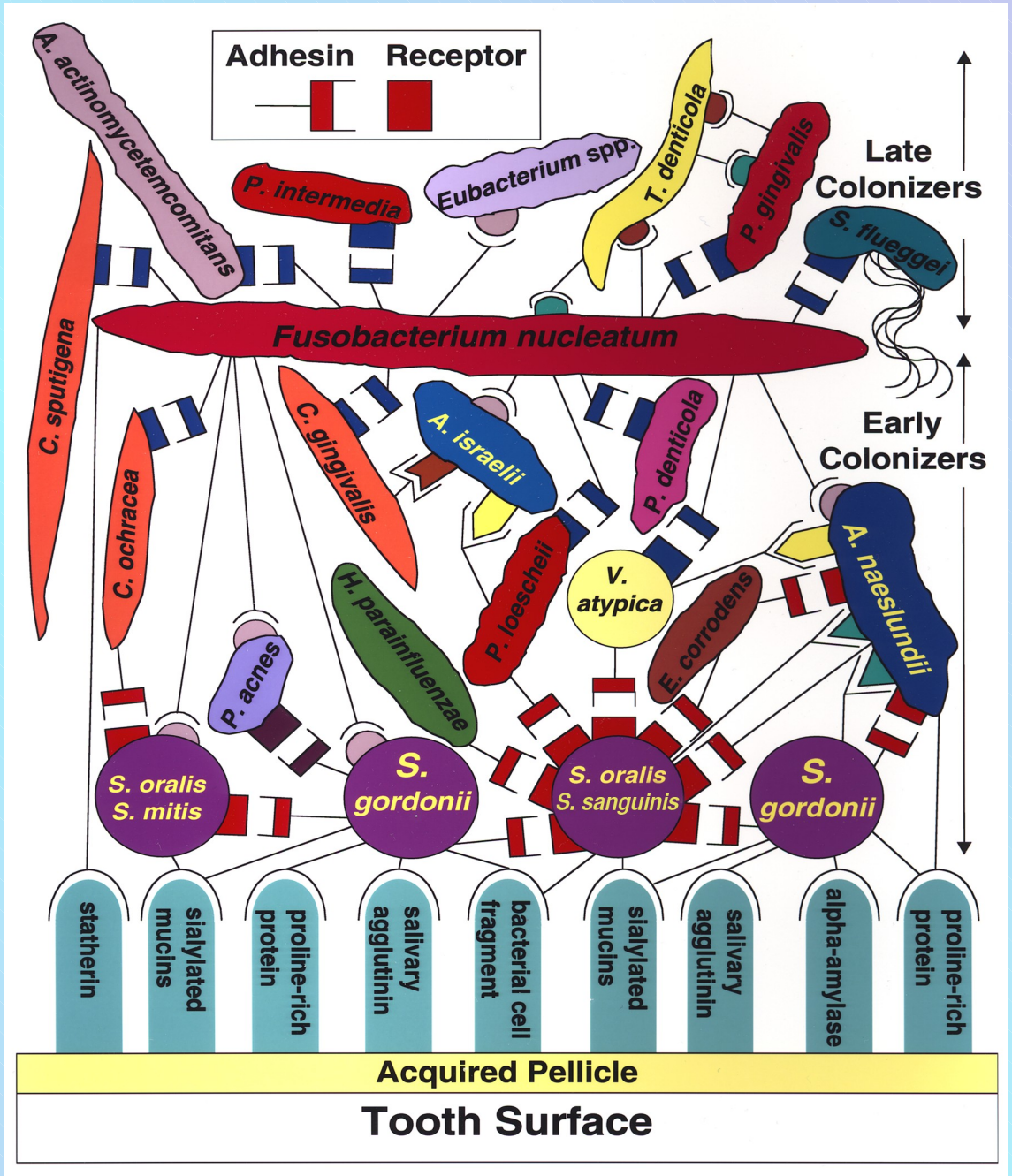
Spatio-temporal model of oral bacterial colonization



Courtesy of Paul Kolenbrander

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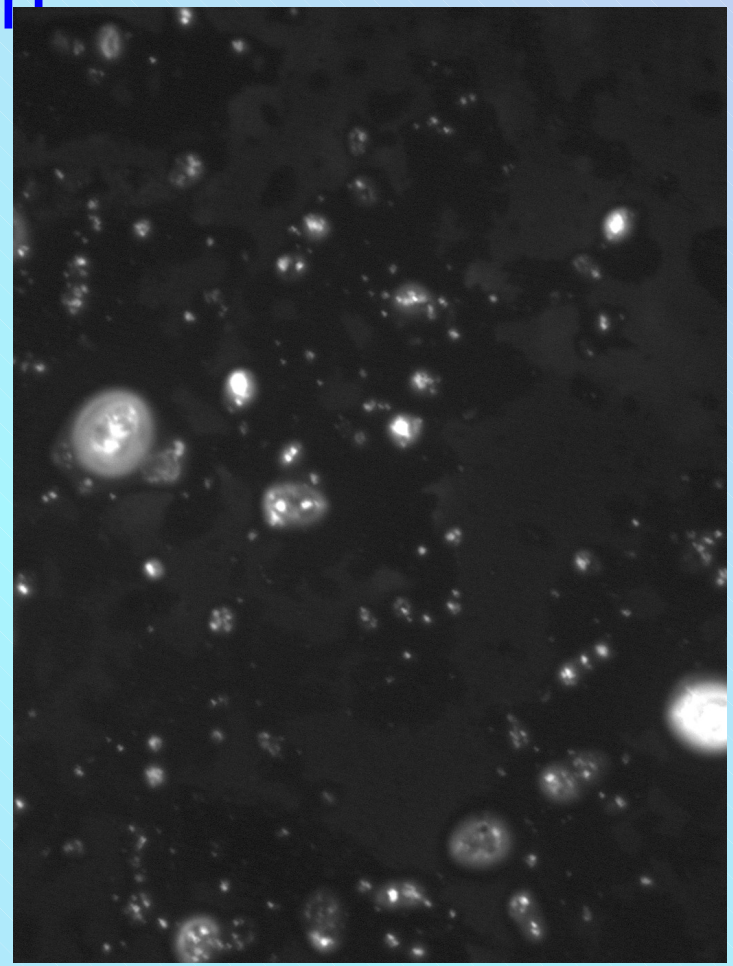
The Mouth Is a Universe

Complex Ecosystem

- Bacteria
- Viruses
- Fungi
- Protozoa



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Metagenomics

The study of genetic material recovered directly from environmental samples. Traditional microbiology and microbial genome sequencing rely upon cultivated clonal cultures. This relatively new field of genetic research enables studies of organisms that are not easily cultured in a laboratory as well as studies of organisms in their natural environment.

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Oral Microbiome

- The mouth is a complex ecosystem
- Oral health is a reflection of balanced, complex microbial communities
- Periodontal disease is a reflection of overgrowth of certain pathogens
- Archaea, bacteria, fungi, and viruses comprise the oral microbiome
- To date, little is known about the bacteria and almost nothing about the viruses, fungi, or Archaea that inhabit the mouth

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Oral Microbiome

- Expect at least 1000 different species of organisms in each mouth
- Will enroll 200 patients
- Collect samples before and 3 months after periodontal treatment
- Identify organisms based on 16S rRNA sequencing
- Novel species categorized based on sequence similarity to known organisms

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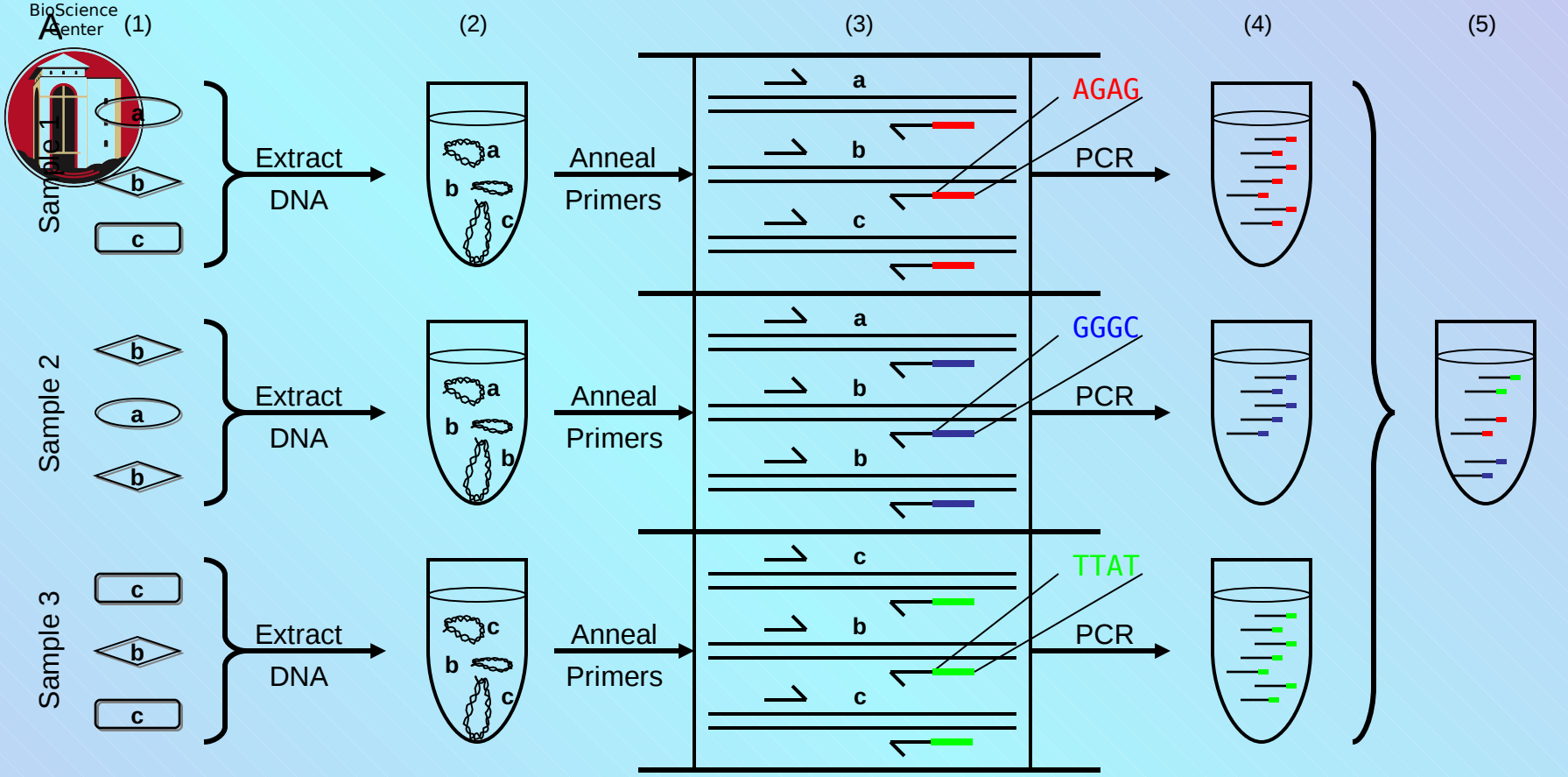
A



B

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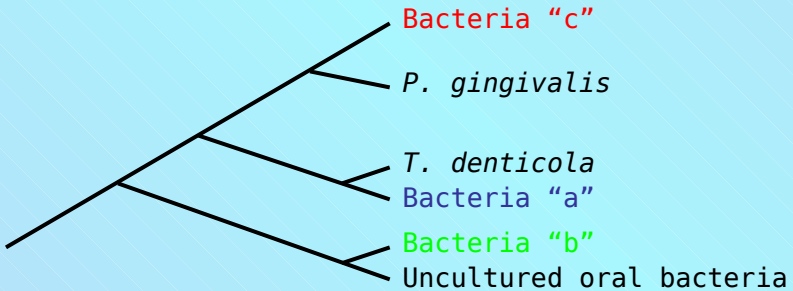
C



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Unique Features of Periodontal Infections

- Etiologic agents reside within a *biofilm* that is located *outside the body* (double protection)
  - Protected from host defense mechanisms
  - Protected from antibiotics
- Endogenous infection
  - Pathogens are part of the indigenous microbio
  - Pathogens found in health for long periods pri to disease initiation
- Multiple reservoirs for pathogens beyond the periodontal pocket

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Transition to Periodontal Disease

- Pre-existing bacteria acquire new behavior
- Invasiveness, overgrowth, other factors
- Possibly aided by viruses?
- IgA antibodies in saliva correlate with periodontitis
  - Diagnostic test on saliva, from GeneEx
  - Potential vaccine development
- Risk of CVD proportional to degree of

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Perio-Athero Project

- Collaboration with Price Charities in City Heights, Indian Health Council, SDSU Graduate School of Public Health, UCSD Cardiology, and the BioScience Center
- Enroll patients in dental clinic
- Measure vascular function
- Score periodontal disease and collect samples

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Periodontitis and Heart Disease

- **Hypothesis: treating periodontal disease in young adults will prevent atherosclerosis**

The complex mixture of organisms in the mouth is distinctively different in patients with PD

Specific organisms or groups of organisms may be associated with endothelial dysfunction *and* PD

Specific organisms or groups of organisms may be associated with oral and vascular health

Treatment will change the microbial population and will improve vascular function

Viruses represent an important and unknown

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Atherogenic Cytokines

- TNF-alpha
- Interleukin-1
- Interleukin-6
- Interleukin-8
- Monocyte chemoattractant protein-1
- C-reactive protein
- **ALL of these are induced by LPS**
- *We will measure TNFα, IL-1, IL-6, CRP*

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Inflammation & Atherosclerosis

- Gingival bacteria or their remnants enter the bloodstream
- Cytokines are released in response to LPS
- Cytokines increase adhesiveness of endothelium and trigger superoxide release
- Superoxide inactivates nitric oxide causing vasoconstriction = endothelial dysfunction

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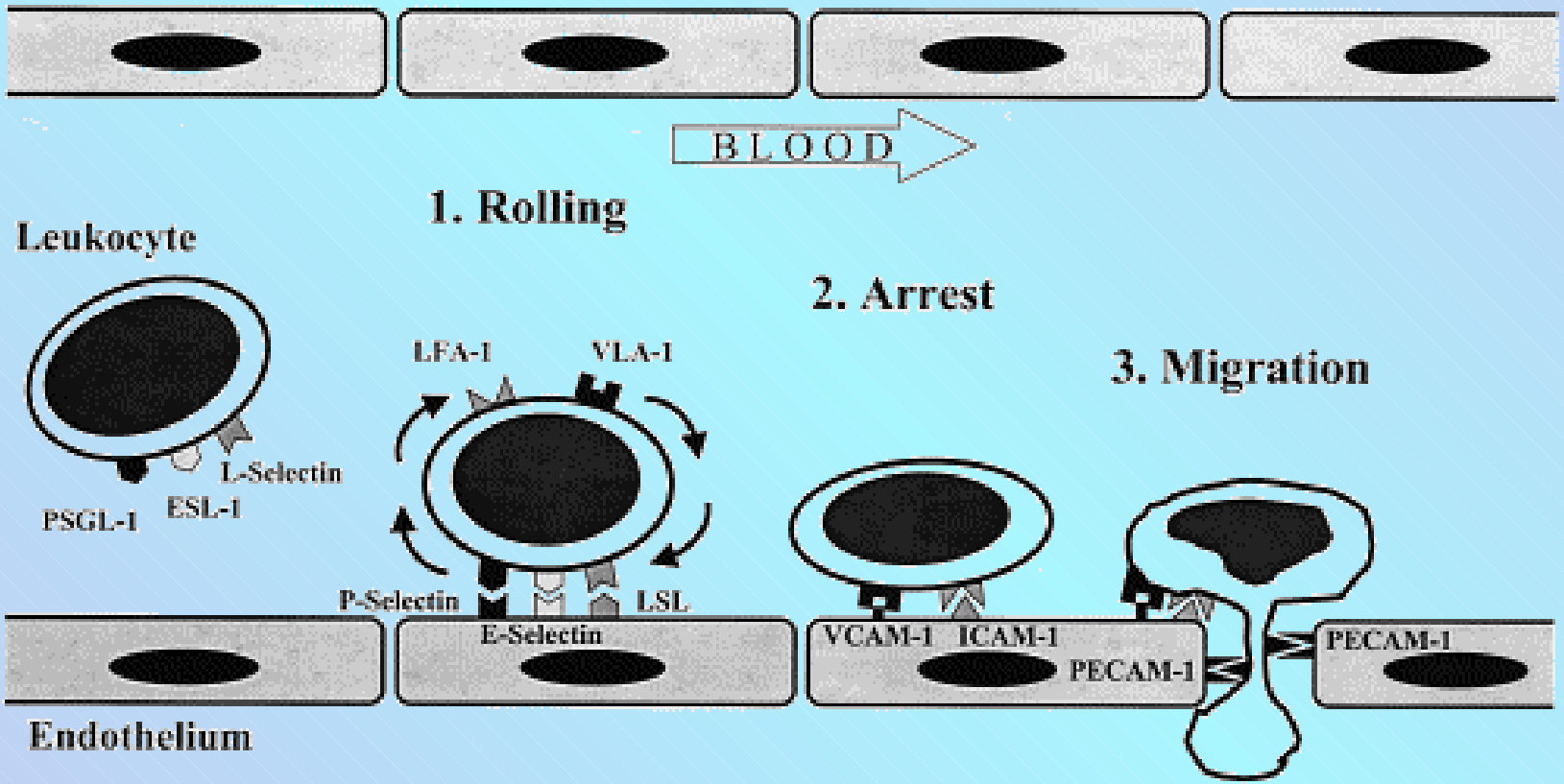
Endothelial Dysfunction and Atherogenesis



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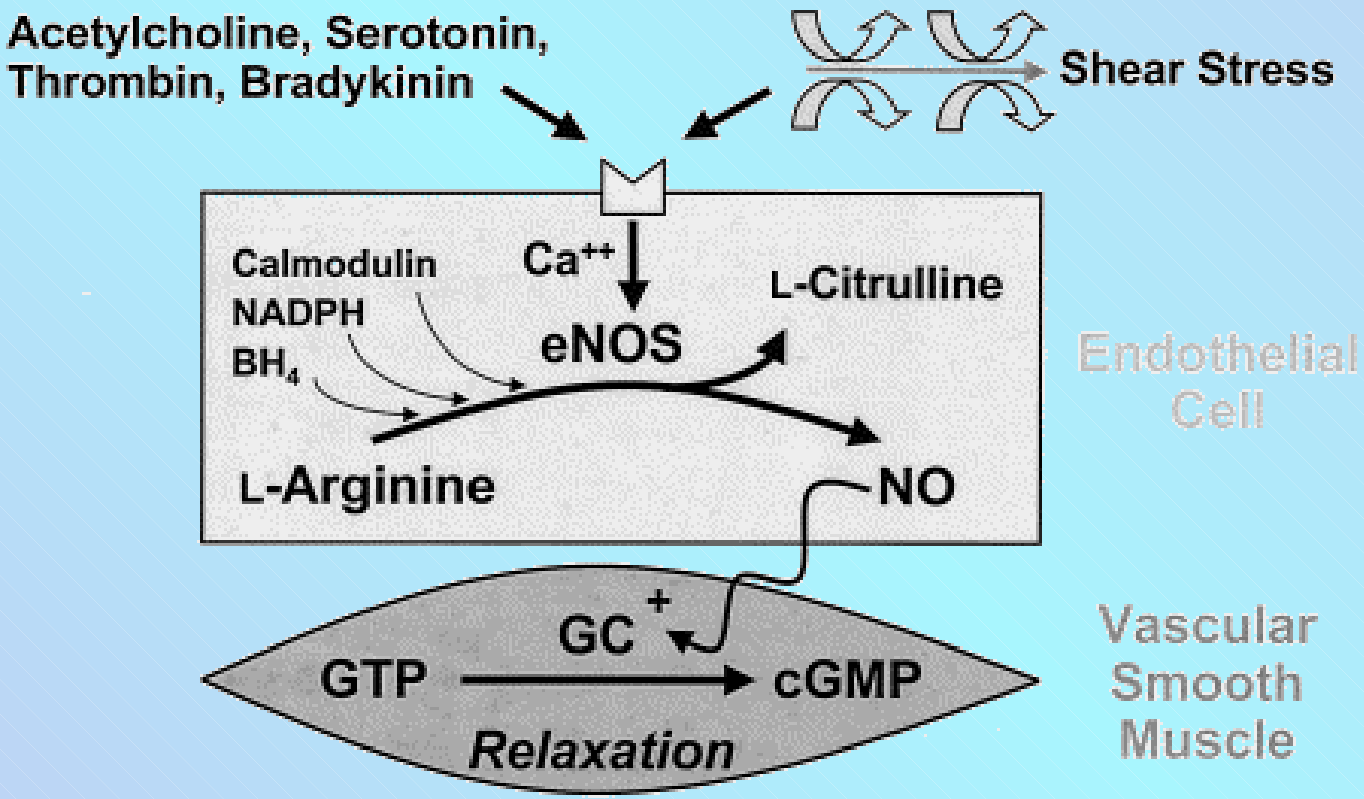
Endothelial Function



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Measures of Vascular Function

- CA-IMT
  - Ultrasound: detects thickening of large vessel
- BA-FMD
  - Ultrasound: detects endothelial function in mid-size artery
  - Based on hyperemic response after constriction
- LDF
  - Laser Doppler: detects changes in arteriolar flow due to endothelial function
  - Based on response to acetylcholine

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Research Plan

- Enroll 200 patients
- Collect samples, analyze blood and vascular function, metagenomics
- Treat and re-analyze
- Estimated cost: $1.5M over 5 years
- Applying for funding from NIH, NARCH, CDAF

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The Team

- Scott Kelley, John Mokili, Forest Rohwer
  - Sergey Gazarov, Lena van der Stap
- Sue Lindsay, Balambal Bharti
- Tony Demaria, Wendy Austin
- Jack Luomanen
- Clinic staff and medical directors at IHC and LMC
- **BioScience Center**