# FROM YOUR MOUTH TO YOUR GUTS

*What They Don't Tell You About Oral-Systemic Healing*

Under One Roof RDH Conference | 2-Hour CE Course

*Where science meets the sulcus — bridging microbiology, diagnostics, and modern hygiene care for systemic healing*

### LEARNING OBJECTIVES

1. Describe the components of adjuvants and the oral microbiome that drive immune system education
2. Define SLIT (sublingual immunotherapy) and compare delivery routes relevant to oral-systemic care
3. Distinguish healthy versus dysbiotic oral microbiomes and connect periodontal disease to systemic health outcomes
4. Interpret the murine periodontal disease model timeline and translate findings to human clinical relevance
5. Articulate how targeted oral care products can serve as platforms for immune priming and microbiome support

## Course Roadmap (2 Hours)

| Module | Topic | Time |
|---|---|---|
| 1 | The Mouth as an Immune Organ — Foundations | 20 min |
| 2 | What Makes a Person Sick? Adjuvants & the Oral Microbiome | 25 min |
| 3 | SLIT Therapy & Delivery System Science | 20 min |
| 4 | The Periodontal–Gut–Systemic Axis | 25 min |
| 5 | Mouse Models to Human Translation | 15 min |
| 6 | The Oral Hygiene Product as a Clinical Tool | 10 min |
| — | Q&A / CE Credit Wrap-Up | 5 min |

# 1 The Mouth as an Immune Organ

*Foundations of oral immune architecture*

## 1.1 Why the Oral Cavity Is Immunologically Unique

The oral mucosa is one of the most immunologically active surfaces in the human body. It is simultaneously a site of constant antigen exposure, a barrier epithelium, and a training ground for both local and systemic immunity. Understanding this dual role reframes every clinical encounter.

| Parameter | Detail |
|---|---|
| Oral mucosa surface area | ~200 cm² (deceptively small, immunologically enormous) |
| Daily microbial exposures | 700+ species encountered routinely |
| MALT component present | Waldeyer's ring — tonsils, adenoids, lingual tonsil |
| Key immune cell residents | Langerhans cells, dendritic cells, IgA-secreting plasma cells, T-regulatory cells |
| Primary secretory antibody | Secretory IgA (sIgA) — first-line oral mucosal defense |
| Link to gut immunity | Common mucosal immune system (CMIS) — shared B-cell homing |

## 1.2 Oral-Associated Lymphoid Tissue (OALT) & the Common Mucosal Immune System

The common mucosal immune system (CMIS) links mucosal sites — oral cavity, gut, respiratory tract, and urogenital tract — through shared lymphocyte homing pathways. Antigen priming at one mucosal surface can elicit protective immunity at a distant site.

- IgA-committed B cells primed in oral-associated lymphoid tissue home to distant mucosal effector sites via the thoracic duct and systemic circulation
- This is the immunological rationale for oral vaccine development and sublingual immunotherapy
- Periodontal pathogens exploiting this system help explain remote-site inflammatory seeding

**KEY CONCEPT — The CMIS**

Antigen encountered sublingually or within the gingival sulcus does not stay local. Through the CMIS, oral immune events ripple outward — to the gut lamina propria, the lung, the cardiovascular endothelium, and beyond. This is not metaphor. It is lymphocyte trafficking.

## 1.3 What Makes an Oral Vaccine Work? — Principles of Mucosal Vaccine Design

The same principles that govern oral vaccine success inform how we think about immunologically active oral care. Three elements are non-negotiable:

### A. Antigen

- Must be stable in the harsh oral/GI environment (enzymatic, pH challenge)
- Must be presented in a form recognizable by mucosal dendritic cells
- Protein, peptide, or polysaccharide conjugates — each has distinct APC presentation pathways

### B. Adjuvant (the immunological 'alarm signal')

- Without adjuvant co-stimulation, mucosal antigen exposure defaults to tolerance, not immunity
- Classical mucosal adjuvants: cholera toxin B subunit (CTB), CpG oligonucleotides, MPL, flagellin
- Oral microbiome-derived PAMPs function as natural adjuvants — the microbiome IS an adjuvant reservoir
- Dysbiosis disrupts the quality and quantity of adjuvant signaling

### C. Delivery System

- Contact time at mucosal surface is critical — sublingual > buccal > gingival crevicular
- Sustained-release formulations (bioadhesive tablets, micro-encapsulated emulsions) outperform simple rinses
- Nanoparticle and liposomal carriers protect antigen and target M-cells and dendritic cell processes

**CLINICAL BRIDGE**

An immune-tailored toothpaste or oral rinse is, mechanistically, a delivery vehicle. Its capacity to influence mucosal immunity depends on dwell time, formulation stability, and the biological activity of its active components — the same parameters that define mucosal vaccine success.

# 2 What Makes a Person Sick?

*Adjuvants, the oral microbiome, and systemic disease*

## 2.1 Reframing 'Sick': From Pathogen to Immune Failure

The presence of a pathogen is necessary but rarely sufficient to produce disease. The decisive variable is the immune response — specifically, whether that response is well-trained, well-calibrated, and capable of resolving inflammation without chronic activation.

**THE CORE QUESTION**

What makes a person sick? More precisely: why does the same pathogen devastate one patient and cause mild symptoms in another? Answer: the immunological context — shaped in large part by the microbiome, prior antigen exposure, and the quality of mucosal immune training.

## 2.2 Adjuvant Biology — The Danger Signal Requirement

The innate immune system requires a 'danger signal' alongside antigen to mount a productive adaptive response. This is the conceptual foundation of adjuvant science.

| Concept | Explanation |
|---|---|
| Pattern Recognition | Toll-like receptors (TLRs), NOD-like receptors, C-type lectins on APCs recognize PAMPs and DAMPs |
| PAMPs | Pathogen-associated molecular patterns (LPS, flagellin, CpG DNA, peptidoglycan) |
| DAMPs | Danger-associated molecular patterns released by damaged host cells (HMGB1, uric acid crystals, heat shock proteins) |
| Adjuvant Effect | PRR engagement triggers APC maturation, cytokine production, and co-stimulatory molecule upregulation — enabling T-cell priming |
| Oral Dysbiosis as Adjuvant Source | Polymicrobial biofilm provides chronic, low-grade PRR stimulation — training the immune system toward tolerance OR chronic inflammation, depending on microbial composition |

## 2.3 The Oral Microbiome: Health State vs. Periodontal Disease State

| Feature | Healthy Oral Microbiome |
|---|---|
| Dominant species | Streptococcus sanguinis, S. gordonii, Rothia spp., Veillonella spp. |
| Oxygen environment | Aerobic/microaerophilic — favors commensals |
| pH | Near-neutral — maintained by commensal metabolism |

| | |
|---|---|
| Immune tone | Tolerogenic — Treg-dominant, low-grade sIgA surveillance |
| Inflammatory markers | Low GCF IL-1β, IL-6, TNF-α, PGE2 |
| Systemic correlates | Cardioprotective nitrate-nitrite-NO axis; intact gut barrier; normal HPA tone |

| Feature | Periodontal Disease Microbiome |
|---|---|
| Dominant species | Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola (Red Complex) + Fusobacterium nucleatum |
| Oxygen environment | Anaerobic — sulcular depth favors obligate anaerobes |
| pH | Alkaline shift — proteolytic metabolism raises sulcular pH |
| Immune tone | Inflammatory — Th1/Th17 dominance, IL-17, IL-23 axis activated |
| Inflammatory markers | Elevated GCF IL-1β, TNF-α, MMP-8, PGE2, IL-6 |
| Systemic correlates | Endotoxemia (LPS translocation), elevated CRP, insulin resistance, gut dysbiosis |

## 2.4 Health Outcomes: COVID-19, Influenza, and the Oral Connection

Emerging data from the COVID-19 pandemic provided a natural experiment linking oral-systemic immune health to infectious disease severity.

### COVID-19 & Periodontal Disease

- Multiple cohort studies demonstrated that patients with moderate-severe periodontitis faced significantly higher odds of ICU admission, mechanical ventilation, and mortality from COVID-19
- Proposed mechanisms: (1) elevated baseline IL-6 lowering the threshold for cytokine storm; (2) ACE2 receptor expression in gingival epithelium enabling direct viral entry and translocation; (3) impaired IFN-I response secondary to chronic TLR desensitization
- P. gingivalis produces a gingipain protease that has been shown to cleave and activate viral spike protein — raising the possibility of oral cavity as a priming site for SARS-CoV-2

### Influenza & Oral Hygiene

- Mechanically reducing oral biofilm (toothbrushing) has been associated with reduced influenza incidence in institutionalized elderly populations in prospective Japanese cohort data
- Proposed pathway: reduced aspiration of periodontal pathogens that upregulate viral receptors and impair ciliary clearance

**TEACHING POINT**

The oral cavity is not a bystander in systemic infection. It is an entry point, an immune calibration site, and — in the setting of dysbiosis — a reservoir for pro-inflammatory mediators that prime patients for worse infectious outcomes. Oral hygiene is infection control.

# 3 SLIT Therapy & Delivery System Science

*Sublingual immunotherapy and its oral care parallels*

## 3.1 Defining SLIT — Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) involves administering allergen extracts under the tongue to induce allergen-specific immune tolerance. It is a WHO-endorsed treatment for allergic rhinitis and asthma and represents one of the best-characterized mucosal immune modulation strategies available.

| Parameter | Detail |
|---|---|
| Route | Sublingual (under tongue) — held 1–2 minutes before swallowing |
| Mechanism | Tolerogenic DCs in floor-of-mouth mucosa capture allergen → Treg induction → IL-10, TGF-β production → suppression of Th2 response |
| Key cell type | CD103+ tolerogenic dendritic cells in sublingual mucosa |
| Systemic effect | Reduced IgE, increased blocking IgG4, blunted mast cell and basophil activation |
| FDA status (US) | Approved grass pollen and house dust mite SLIT tablets (Grastek, Odactra, Ragwitek) |
| Timeline to effect | Clinical benefit typically at 3–6 months; disease modification persists post-treatment |

## 3.2 SLIT vs. Alternative Mucosal Delivery Routes — Recent Comparative Data

A critical area of active research concerns which oral mucosal route most efficiently induces therapeutic immune responses. The following comparison is based on recent preclinical and clinical literature comparing sublingual, lingual, buccal, and gingival delivery.

| Route | DC Density | Contact Time (Practical) | Systemic Spread | Clinical Utility |
|---|---|---|---|---|
| Sublingual | High (floor of mouth) | Excellent — 1–2 min hold | Via thoracic duct & portal | Best established; gold standard for SLIT |
| Buccal | Moderate | Good — buccal mucosa | Via superior vena cava | Buprenorphine, fentanyl — explored for immunotherapy |
| Lingual (dorsal tongue) | Low (keratinized) | Poor — saliva clears rapidly | Limited | Least effective; mechanical barrier |
| Gingival Crevicular | Moderate-high | Intermediate — fluid flush limits dwell | Via GCF into systemic circulation | Novel; relevant to oral care product design |

**HIGHLIGHTED FINDING — Sublingual vs. Gingival Application**

Recent animal and early human studies examining mucosal vaccine and allergen delivery have found that sublingual administration consistently outperforms gingival application in magnitude of tolerogenic DC engagement, but gingival delivery offers unique advantages in the context of treating local periodontal immune dysregulation. For systemic immune priming, sublingual remains preferred. For modifying the local sulcular immune environment, gingival-targeted formulations show distinct promise.

## 3.3 The Oral Care Product as a Delivery System

Understanding SLIT mechanics immediately contextualizes why oral care product formulation matters immunologically. The mouth is not just a cavity to be cleaned — it is a mucosal surface with defined DC populations, IgA secretion machinery, and direct lymphatic access.

### What Immune-Tailored Oral Care Must Achieve

- Sufficient dwell time at the mucosa — particularly the sublingual and gingival regions
- Delivery of biologically active components that engage PRRs or support commensal microbiome
- Avoidance of formulation components that disrupt mucosal barrier integrity (e.g., SLS)
- pH compatibility with healthy oral environment (~6.5–7.5)
- Prebiotic or postbiotic components that selectively support health-associated commensals

### Emerging Ingredient Categories of Interest

- Postbiotics (heat-killed commensal bacteria, bacterial cell wall fragments): provide controlled PRR stimulation without live organism risk
- Nitrate-rich substrates (e.g., derived from beets, leafy greens): support nitrate-reducing commensals that produce cardioprotective nitric oxide
- Lactoferrin, lysozyme: innate immune support peptides that modulate biofilm and have immunoregulatory properties
- Xylitol: selectively disrupts Streptococcus mutans without harming health-associated commensals
- Hydroxyapatite: enamel remineralization with emerging evidence of biofilm modulation

**FOR YOUR PRACTICE**

The next time a patient asks 'what toothpaste should I use?' — that is an immunological question. Formulation components shape the microbial and immune environment of the oral mucosa. Directing patients to evidence-informed oral care is as immunologically meaningful as recommending a dietary change.

# 4 The Periodontal–Gut–Systemic Axis

*How the sulcus talks to the gut and beyond*

## 4.1 Pathways of Communication: Mouth to Gut

The oral-gut axis is bidirectional and operates through at least four distinct pathways, each with clinical implications for your patient panel.

| Pathway | Mechanism |
|---|---|
| 1. Microbial translocation | Daily swallowing deposits ~1.5 billion oral bacteria into the GI tract; dysbiotic oral bacteria seed the gut and alter gut microbiome composition |
| 2. Systemic bacteremia | Gingival manipulation (toothbrushing, scaling) causes transient bacteremia; in inflamed periodontium this is chronic and repetitive |
| 3. Inflammatory mediator trafficking | GCF-derived IL-1β, TNF-α, and PGE2 enter systemic circulation → hepatic acute phase response (elevated CRP, fibrinogen, SAA) |
| 4. Immune cell trafficking | Activated oral neutrophils, monocytes, and T-cells re-circulate systemically — carrying an oral inflammatory 'set point' |

## 4.2 Gut Dysbiosis as a Downstream Consequence of Oral Dysbiosis

Emerging metagenomic data from multiple cohorts demonstrate enrichment of oral-origin bacteria (P. gingivalis, F. nucleatum, Prevotella copri) in the fecal microbiome of patients with periodontitis, inflammatory bowel disease, and colorectal cancer.

- F. nucleatum in colorectal cancer: one of the most replicated oral-gut cancer associations; fusobacterial abundance in tumor tissue correlates with worse prognosis and resistance to chemotherapy
- P. gingivalis in rheumatoid arthritis: capable of inducing citrullination of host proteins via peptidylarginine deiminase (PAD), generating neo-antigens that drive anti-CCP antibody production — a hallmark of RA
- Prevotella copri enrichment: found in both periodontitis and new-onset RA, suggesting the oral cavity as a potential site of RA immune priming

**SYSTEMS THINKING**

Periodontal disease is not a local oral condition with occasional systemic complications. It is a systemic inflammatory condition with a local oral manifestation. Treating the sulcus IS treating systemic inflammation.

## 4.3 Associated Systemic Conditions — Summary Evidence Table

| Condition | Strength of Evidence | Proposed Primary Mechanism |
|---|---|---|
| Cardiovascular disease / atherosclerosis | Strong (multiple meta-analyses) | LPS-driven endothelial activation; P. gingivalis in atheromatous plaques |
| Type 2 diabetes (bidirectional) | Strong | Chronic inflammation → insulin resistance; hyperglycemia → altered GCF → dysbiosis |
| Adverse pregnancy outcomes | Moderate-Strong | Systemic prostaglandins; fetal membrane colonization by oral bacteria |
| Alzheimer's disease | Emerging | Gingipains detected in brain tissue; neuroinflammation via systemic LPS |
| Rheumatoid arthritis | Moderate-Strong | PAD-mediated citrullination; Prevotella/P. gingivalis immune priming |
| Colorectal cancer | Moderate | F. nucleatum oncogenic promotion; modulation of tumor microenvironment |
| COVID-19 severity | Moderate (pandemic cohorts) | Baseline IL-6 elevation; ACE2 expression; gingipain viral activation |
| IBD / gut dysbiosis | Moderate | Oral bacterial gut seeding; shared microbiome disruption |

# 5 Mouse Models to Human Translation

*Reading the science — what animal data actually tells us*

## 5.1 The Murine Periodontal Disease Model — Standard Protocol

The ligature-induced or P. gingivalis oral gavage murine model is the workhorse of periodontal immunology research. Understanding its timeline and limitations is essential to critically evaluating the literature you will encounter.

### Ligature-Induced Model (Most Common)

| Timepoint | Procedure / Observation | Human Correlate |
|---|---|---|
| Day 0 | Silk or nylon ligature placed around maxillary second molar; P. gingivalis gavage (×3/week) may be added | Equivalent to plaque-retentive restoration or orthodontic appliance |
| Day 3–5 | Initial neutrophil influx into sulcular tissue; elevated GCF volume; IL-1β detectable in gingival tissue | Early gingivitis — reversible stage |
| Day 7–10 | Osteoclast activation; early alveolar bone resorption detectable by micro-CT; Th17 cells accumulate | Accelerated Stage I–II periodontitis onset |
| Day 14–21 | Peak alveolar bone loss (~30–40% CEJ-to-crest distance); RANKL:OPG ratio maximally skewed; systemic IL-6 elevation | Established periodontitis; systemic inflammatory burden begins |
| Day 28+ | Systemic effects detectable — gut dysbiosis, metabolic changes, arterial stiffness in susceptible strains | Chronic periodontitis with early systemic complications |
| Day 28–42 (removal) | Ligature removal; spontaneous partial healing; bone NOT fully restored — permanent structural loss | Post-treatment maintenance phase; residual bone defects persist |

## 5.2 Oral Gavage / P. gingivalis Mono-Infection Model

| Parameter | Detail |
|---|---|
| Protocol | Oral gavage 3×/week × 6 weeks (standard Hajishengallis protocol); antibiotics pre-treatment to reduce competing flora |
| Colonization rate | Transient; P. gingivalis does not stably colonize the mouse oral cavity — requires repeated re-introduction |
| Immune response | Complement dysregulation (C5a–C5aR axis); neutrophil paralysis; Th1/Th17 activation |
| Systemic readouts | Aortic plaque in ApoE−/− mice; gut microbiome shifts; cognitive decline assays in aged mice |
| Key limitation | No spontaneous periodontitis in wild-type mice — disease must be induced; human disease is polymicrobial over decades |

## 5.3 Mouse Model vs. Human Disease — Translational Gaps

| Variable | Translational Consideration |
|---|---|
| Disease timeline | Mouse: Days–weeks \| Human: Months–decades — chronic inflammatory conditioning is fundamentally different |
| Microbiome composition | Mouse oral microbiome lacks most human Red Complex species natively; gavage creates artificial mono-infection |
| Bone anatomy | Mouse alveolar bone lacks true cortical plate; cancellous structure makes micro-CT volumetrics not directly comparable to human CBCT |
| Immune system | Mouse Th17 response dominates in periodontitis models; human disease shows more complex Th1/Th17/Treg balance |
| Gut-oral axis | Mouse coprophagy means bidirectional oral-gut contamination is confounded; humans do not exhibit this |
| Sex hormones | Mouse estrous cycle ≠ human menstrual cycle; pregnancy/hormonal periodontitis models need species-specific interpretation |
| Genetic background | C57BL/6 mice ≠ human genetic diversity; susceptibility genes differ substantially |
| Strength of model | Excellent for mechanistic pathway elucidation; poor for direct clinical extrapolation of magnitude or timing |

**CRITICAL APPRAISAL PRINCIPLE**

When evaluating animal model data: ask (1) which model was used — ligature vs. gavage vs. germ-free reconstitution? (2) What was the endpoint — micro-CT bone loss, histology, or systemic readout? (3) Does a human longitudinal cohort replicate this finding? Mouse models generate hypotheses. Human cohort data tests them. Both are necessary; neither is sufficient alone.

## 5.4 Connecting to Gut Health — Translational Evidence

- Rodent studies: ligature-induced periodontitis consistently produces gut microbiome shifts (reduced Bacteroidetes:Firmicutes ratio, increased Proteobacteria) within 2–3 weeks
- Human cross-sectional data: patients with Stage III–IV periodontitis demonstrate fecal microbiome differences vs. periodontally healthy controls, including enrichment of oral-origin taxa
- Mechanistic bridge: oral LPS (primarily from P. gingivalis lipid A — structurally distinct, TLR4-antagonistic in some contexts, agonistic in others) enters portal circulation and modulates hepatic immune tone
- Intervention data: non-surgical periodontal therapy (SRP) is associated with improvements in fecal microbiome diversity in small RCTs — suggesting the oral-gut axis is therapeutically modifiable

# 6 The Oral Hygiene Product as a Clinical Tool

*Translating immune science to chairside guidance*

## 6.1 Rethinking the Toothbrush Appointment

The dental hygiene appointment is — in immunological terms — a mucosal immune intervention. Mechanical debridement reduces PAMP load. Fluoride and antimicrobials modify the microbial community. Homecare recommendations shape the daily immunological environment at the oral mucosal interface.

**A NEW FRAMING**

We are not just removing calculus. We are resetting the microbial adjuvant environment. We are reducing the chronic PRR stimulation that drives systemic inflammation. We are giving the mucosal immune system a chance to recalibrate toward tolerance rather than chronic activation.

## 6.2 Product Selection Criteria — An Evidence-Informed Framework

| Product Property | Immunological Relevance | What to Look For |
|---|---|---|
| No SLS (sodium lauryl sulfate) | SLS disrupts mucosal barrier; increases permeability and allows antigen translocation | SLS-free formulations |
| Prebiotic/postbiotic content | Feeds health-associated commensals; provides controlled PRR stimulation | Inulin, FOS, heat-killed Lactobacillus |
| Nitrate substrates | Supports nitrate-reducing oral bacteria → systemic NO production | Beet-derived nitrates; potassium nitrate |
| Hydroxyapatite (HAp) — form and dose matter | Biomimetic remineralization; biofilm modulation; dentinal tubule occlusion. Particle shape and concentration are clinically significant | Rod-shaped HAp at 10% (toothpaste); avoid needle-shaped nanoparticles; micro-HAp is a lower-controversy alternative |
| Niacinamide / Nicotinamide (Vit. B3) | NAD+ precursor → supports gingival epithelial cell energy, DNA repair, and oxidative stress management; anti-inflammatory via cytokine suppression; in vitro data show inhibition of S. mutans biofilm, acid production, and EPS synthesis. Asian oral care market leader in formulation innovation. No oral-specific RCTs published yet | 0.5%–5% typical in skincare; no oral-specific concentration standard yet published |
| Lactoferrin / lysozyme | Natural innate immune peptides; anti-biofilm, immunomodulatory | Present in some therapeutic rinses |
| Xylitol | Selectively impairs S. mutans without harming commensals | 1–20% concentration range studied |
| pH-buffered formulation | Maintains the neutral pH that favors health-associated commensals | pH 6.5–7.5 target |

## 6.3 Patient Conversation Framework

Patients are more motivated by systemic relevance than by oral aesthetics alone. Connecting oral care to their existing health concerns unlocks adherence.

| Patient Type | Suggested Language |
|---|---|
| Patient with diabetes | "Your oral microbiome directly influences your insulin sensitivity. Reducing gingival inflammation is part of blood sugar management." |
| Patient with cardiovascular risk | "The bacteria in periodontal pockets have been found in arterial plaque. Oral hygiene is cardiovascular risk management." |
| Pregnant patient | "Periodontal disease is an independent risk factor for preterm birth and low birth weight. This is one of the most important things you can do during pregnancy." |
| Post-COVID patient | "Emerging evidence suggests chronic oral inflammation may amplify post-COVID inflammatory burden. Supporting your oral immune environment matters." |
| Autoimmune patient | "Several autoimmune conditions — including rheumatoid arthritis — have documented links to oral bacteria. Your dental hygiene appointment is part of your rheumatology management." |

**ON OSSA AND LIKE-MINDED INNOVATIONS**

A growing category of oral care products is being developed with explicit attention to the oral microbiome, mucosal immune architecture, and systemic health connections. When evaluating any product in this space — ask for the science. What is the active mechanism? What clinical or microbiome data support it? Is dwell time and delivery route optimized? These are the questions that separate immune-informed oral care from marketing language.

# REF Key References & Further Reading

*Evidence supporting today's course content*

## Foundational Papers


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## SLIT & Mucosal Immunotherapy


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- Recent comparative route study: [Consult current literature — 2023–2025 SLIT vs. gingival delivery comparisons in preclinical models]


## Oral-Systemic Connections


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## Animal Models


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# MY NOTES

*Use this space during the lecture*

*Thank you for attending. Your practice of integrating oral and systemic health makes a profound difference in your patients' lives.*