Oral Dermatology

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Getting paid for Oral Medicine Services:

1. ICD / CPT v. CDT coding and payors
2. Getting paid for knowledge and time v procedure

ICD

MUCOSA		**MASS**		**NEURO/VASCULAR**	
682.9	Abscess	210.4	Fibroma NOS	781.1	Altered Taste
528.2	Aphthous	228.09	Hemangioma NOS	350.2	Atypical Facial Pain
112.0	Candidiasis	214.0	Lipoma	337.0	Autonomic Neuropathy
909.2	Complication Radiation Tx	350.8	Neuroma	351.0	Bell's Palsy
909.3	Complication Med or Surg. Tx	528.9	Pyogenic Granuloma	355.9	Causalgia
695.1	Erythema Multiforme	078.10	Papilloma Wart	787.2	Dysphagia
528.79	Erythroplakia	229.8	Benign Neoplasm	350.9	Trigeminal Deafferentation Pain
054.2	Herpes Simplex	**MALIGNANCY**		529.6	Glossodynia
053.19	Herpes Zoster	140.0	Upper Lip	352.1	Glossopharyngeal Neuralgia
523.1	Hyperplasia, Gingivae	140.1	Lower Lip	053.12	Post Herpetic Neuralgia
528.6	Leukoplakia	141.1	Dorsal Tongue	951.2	Trigeminal Injury
697.0	Lichen Planus	141.3	Ventral Tongue	350.1	Trigeminal Neuralgia
694.4	Pemphigus, Vulgaris	144.9	Floor of Mouth	346.00	Migraine with Aura
694.5	Pemphigoid, Cicatricial	176.8	Kaposi Sarcoma	346.10	Migraine without Aura
523.3	Periodontitis, Acute	**MUSCULOSKELETAL**		307.81	Tension Type Headache
523.4	Periodontitis, Chronic	726.90	Capsulitis	346.20	Cluster Headache
OTHER		715.98	Degenerative Arthritis	**PIGMENTED LESIONS**	
995.3	Allergy	830.1	Dislocation, Open	709.09	Melanosis
995.1	Angioedema	830.0	Dislocation, Closed	709.00	Exogenous Pigmentation
529.1	Migratory Glossitis	729.1	Fibromyalgia	216.9	Nevus
SALIVARY GLANDS		524.69	Internal Derangement	172.9	Melanoma
527.2	Sialoadenitis	728.85	Myofascial, Trigger Points	228.01	Hemangioma
527.5	Sialolith	729.1	Myofascitis, Myalgia	**OTHER**	
710.2	Sjogren's Syndrome	332.82	Orofacial Dystonia/dyskinesia		
527.6	Mucocele	718.38	Recurrent Dislocation		
		716.98	Rheumatoid Arthritis		
		716.18	Traumatic Arthropathy		

CPT

OFFICE VISIT		
New Patient Visit		
99202 (20)	Limited	$149
99203 (30)	Intermediate	$
99204 (45)	Extended	$
99205 (60)	Comprehensive	$
Established Patient Office Visit		
99213 (15)	Limited	$
99214 (25)	Intermediate	$
99215 (40)	Extended	$
Office Consult		
99241 (15)	Limited	$
99242 (25)	Intermediate	$
99243 (40)	Extended	$
99244 (60)	Comprehensive	$
RADIOLOGY		
70300	Intraoral single	$
70310	Partial Exam	$
70320	Complete Exam	$
70330	TMJ Bilateral	$
70355	Panoramic	$
ADJUVANT		
97703	Appliance Check / Adj.	$ min.

INJECTIONS		
20605	Intra-articular Injection	$180
11900	Intralesional, <7	$182
11901	Intralesional, >7	$
20550	Trigger Point	$
64400	Trigeminal Anesthesia	$
64402	Facial Nerve Anesthesia	$
90780	IV Pharm Blockade	$
96408	Intralesional Chemotherapy	$
90782	IM injection _____	$
64612	Neurolytic Injection	$
64505	SPG / Anesthesia	$
OTHER		
21480	Simple Dislocation	$
21485	Complex Dislocation	$
42330	Sialolithotomy	$
42409	Salivary Marsupialization	$
PROSTHESIS / DEVICES		
21079	Interim Obturator	$
21080	Definitive Obturator	$
21085	Surgical Splint	$
99002	Orthotic	$
99070	Drug Delivery Device	$

SURGICAL		
Biopsy		
40808	Vestibule of Mouth	$358
41100	Ant 2/3 Tongue	$
41105	Post 1/3 Tongue	$
42100	Palate	$
42405	Salivary Gland	$
20240	Bone	$
41108	Floor of Mouth	$
Excision (benign, mucosa, face, lips)		
11440	<0.5 cm	$
11441	0.6-1.0 cm	$
11442	1.1-2.0 cm	$
11443	>2.0 cm	$
40820	Destroy any Method	$
40810	Vestibule, w/o Repair	$
40812	Vestibule, w/ Repair	$
Incision and Drainage		
41800	Intraoral, Simple	$
41018	Extraoral, Simple	$
Other		

You won't see it if you're not looking for it……

- Estimated point prevalence of oral mucosal lesions in the U.S.: 10-25% (based on community screenings >40,000)
  - *Shulman JD. Beach MM. Rivera-Hidalgo F.. J Amer Dental Assoc. 2004;135(9): 1279-86*
  - *Bouquot JE, Gorlin RJ. Oral Surg Oral Med Oral Pathol 1986;61(4):373-381.*
  - *Bouquot JE. J Amer Dental Assoc. 1986; 112(1):50-7*
- **That's 1:10 to 1:4 patients.**
- **How many patients did you see last week?**
- **How many oral lesions did you observe?**
- **Have to look for them to find them!**

American Academy of Oral Medicine:
http://www.aaom.com

The process

- **History (CC, HPI, MHx...)**
- **Examination**
- **Differential Diagnosis**
- **Diagnostic / Assessment tests**
  - **Definitive Diagnosis**
  - **Presumptive Diagnosis**

History: 90% of the story!!!

- Prior occurrence
- Frequency
- Number
- Texture and border features
- Location (intra / extra oral)
- Size
- Associated events
- Changes in size or behavior
- Duration
- Pain
- Other (constitutional) symptoms

Examination

- Location
- Homo / heterogenous
- Size
- Appearance
- Texture
- Depth / induration
- Borders
- Fixation
- Adenopathy

Skin and Mucosal Disorders

- **Traumatic / reactive**
- **Immunologic**
- **Infectious**
- **Malignant**

By disease process…..
Very helpful for choosing therapy

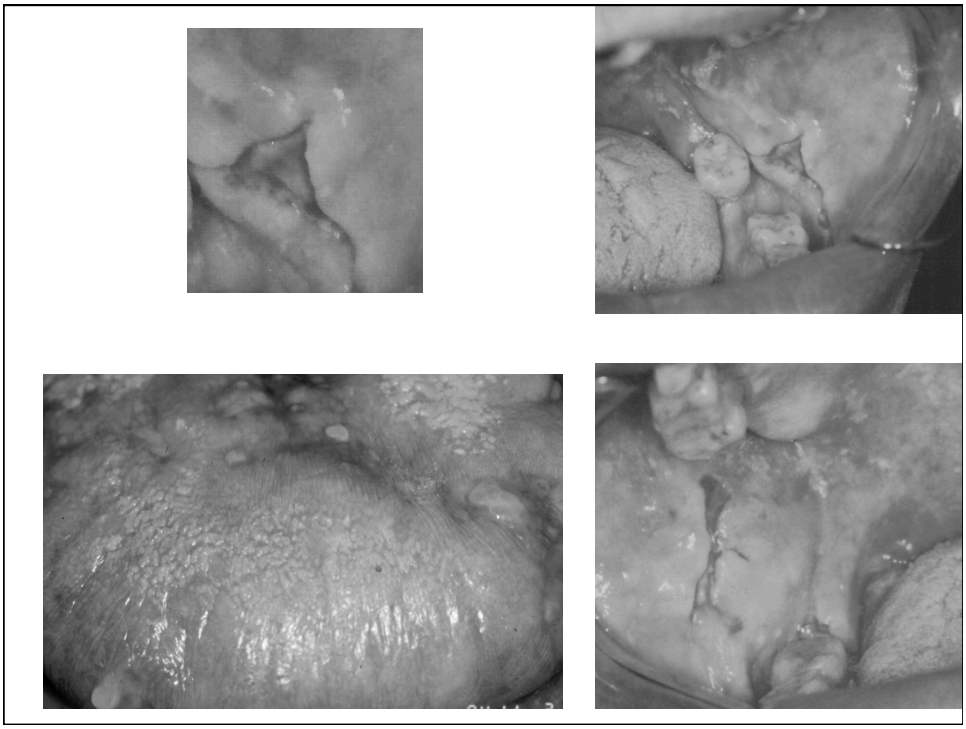
Not very helpful for establishing a clinical differential diagnosis…. For this, the history and appearance are KEY!

For Any Lesion……

- How Many? Single v. multiple.
- How Long? Acute v. Chronic.
- Had it before? Primary v. recurrent.
- Anywhere else? Local v. general.

ORAL ULCERATIONS

Finding	Immunologic	Infectious	Hematologic	Other
Chronic Solitary	Major Aphthous	Fungal, bacterial, viral	Leukopenia	Trauma Malignancy
Chronic Multiple	Pemphigus Pemphigoid Erosive lichen planus	Chronic HSV	Anemia Dietary: folate, B12, iron	Trauma
Acute Solitary	Aphthous	Herpes Simplex	Unlikely	Trauma
Acute Multiple	Erythema multiforme Aphthous Ulcer Allergy - contact v systemic	Herpes Simplex Herpes Zoster Coxsackie	Severe or frequent aphthous may be due to anemia, malabsorption	



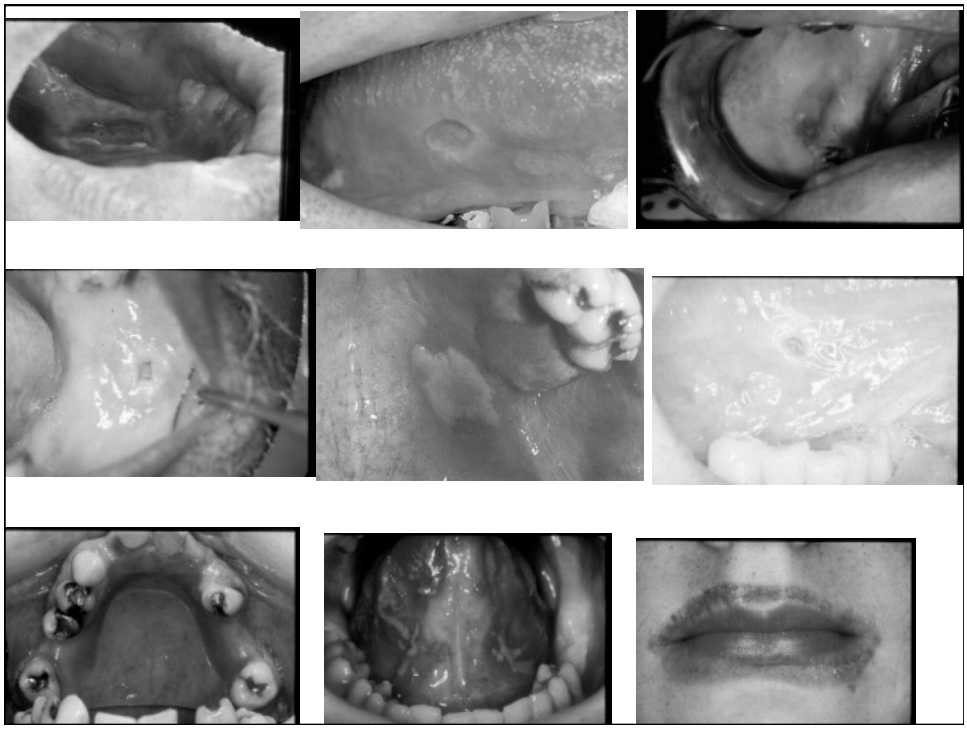
- Acute, Single
  - trauma
  - aphthous
  - recurrent HSV
- Acute, Multiple, Primary
  - primary HSV
  - aphthous, EM
  - trauma
- Acute, Single, Recurrent
  - HSV, RAS, VZ
  - erythema multiforme

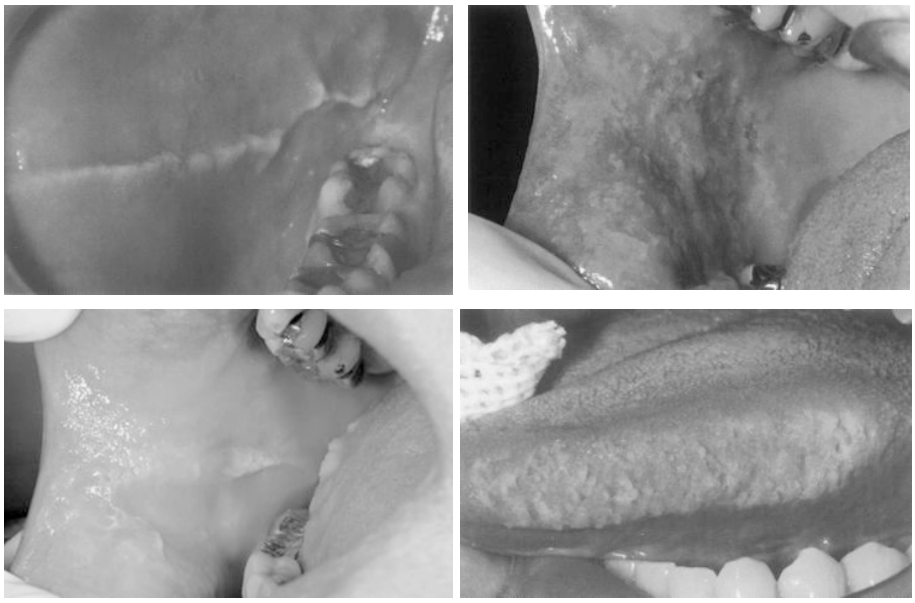
- **Chronic**, solitary
  - trauma
  - infection
  - malignancy
- **Chronic**, multiple
  - erosive lichen planus
  - pemphigus
  - pemphigoid
  - EBA, SLE, Behcet's

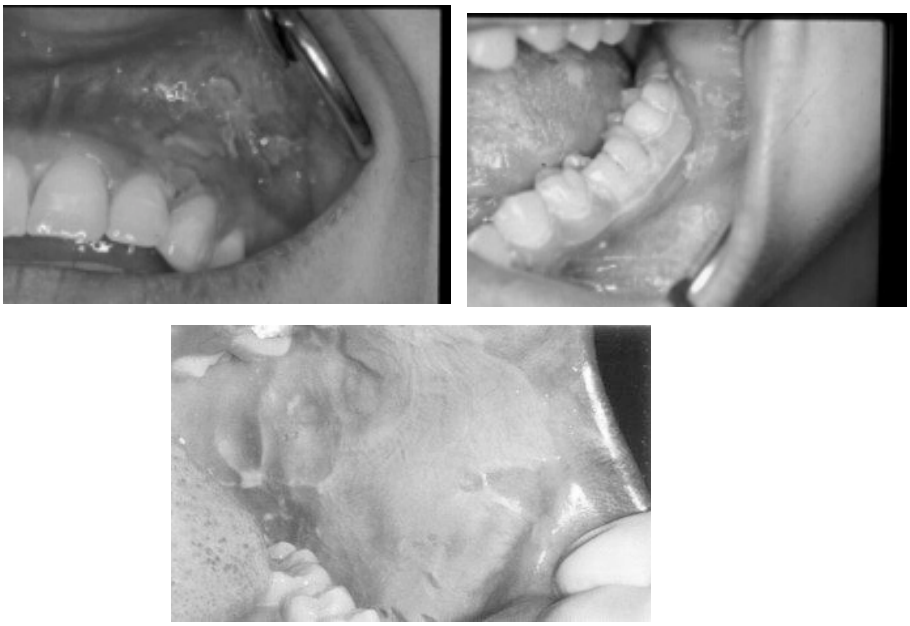
Traumatic Ulcerations

- mechanical
- thermal
- chemical

- associated local and historical findings
- elimination and re-evaluation
- palliation







- **Chronic, single**
  - trauma
  - infection
  - malignancy

- **Chronic, multiple**
  - lichen planus
  - pemphigus
  - pemphigoid
  - EBA

Immunologic – Lichenoid Lesions

- **Idiopathic oral lichen planus,** oral lichenoid lesions not readily attributable to any defined cause.
- **Oral Lichenoid Contact Lesions**, direct topographic relationship to dental restorative materials, most commonly amalgam.
- **Oral Lichenoid Drug Reactions**, oral or cutaneous lesions occur, temporally associated with the use of certain medications (such as oral hypoglycaemic drugs, angiotensin converting enzyme (ACE) inhibitors, and non-steroidal anti-inflammatory agents (NSAIDS)).
- **Oral Lichenoid Lesions of Graft versus Host Disease** in the setting of patients with acute, but predominantly chronic graft versus host disease (GVHD).

VS

Lichenoid Dysplasia

Immunologic – i-Lichen Planus

- non-ulcerative vs. ulcerative forms
- chronic, multiple lesions

- Non erosive LP:
  - White papules or plaques with linear striae (Wickham's striae)
  - Usually bilateral
  - Skin lesions are flat-topped, papule with a red to violet color
  - May develop in a linear distribution in areas of trauma (Koebner phenomenon)

- Patients with primarily skin lesions: ~ 70% also show oral lesions.
- Patients with initially oral lesions: ~ 20 to 40% show skin lesions.

"Typical" Patient Profile of OLP

Characteristic(s)	Data
Age:	Mean = ~ 40-60 years of age
Female to Male Ratio:	2:1
Ethnic Predisposition/ Geographic Distribution:	not known
Sites of Intra-Oral Involvement:	buccal mucosa > tongue > gingiva >> palate
Extra-Oral Involvement:	15% current or history of cutaneous involvement 20% of women have genital involvement
Risk of Malignant Transformation:	Yes, but low = ~ < **0.1- 0.2% per annum** in contrast to the incidence of oral squamous cell carcinoma (OSCC) of 0.005% per annum for the general population

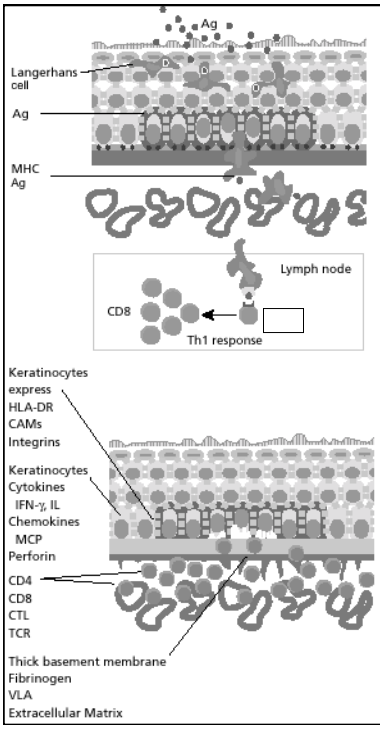
Eisen D, Carrozzo M, Bagan Sebastian JV, Thongprasom K. Number V. Oral lichen planus clinical features and management. Oral Dis 2005; 11:338-49

Al-Hashimi et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Mar;103 Suppl:S25.e1-12.

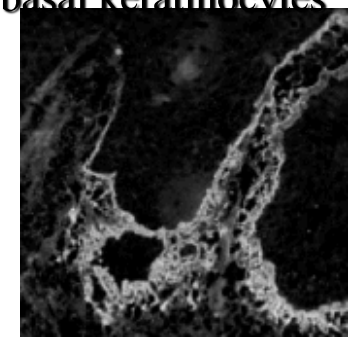
Chan ES, Thornhill M, Zakrzewska J. Interventions for treating oral lichen planus: review. The Cochrane Library 2005; 4: 1-21.

LP Histologic Features

1. areas of hyperkeratosis, often with a thickening of the granular cell layer and a saw-toothed appearance to the rete pegs
2. necrosis of the basal cell layer, which is often replaced by an eosinophilic band: ATROPHY
3. a dense subepithelial band of lymphocytes



CD8 T cells induce apoptosis of basal keratinocytes



Fibrinogen reactivity

Lichen Planus and dysplasia, cancer

Area of confusion:

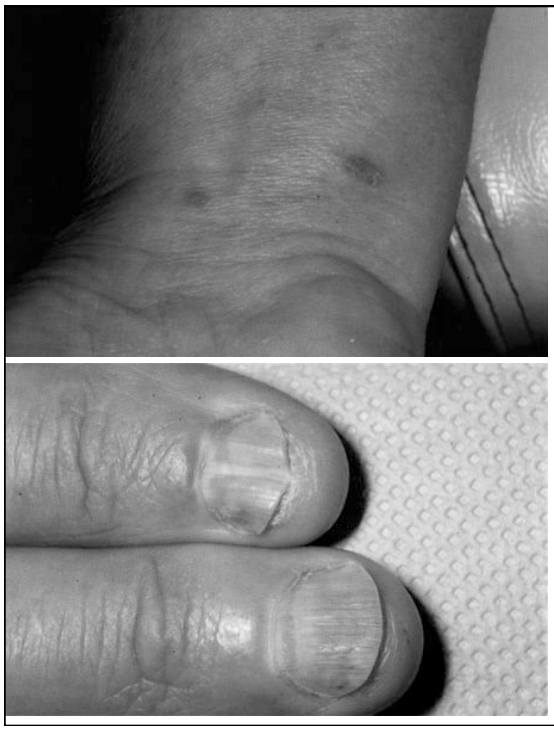
- Discussion:
  - Idiopathic Ulcerative / Erosive LP
    - Look for Wickham's striae; bilateral; +/- skin lesions
  - Lichenoid Reaction (drug or contact)
    - Bilateral (drug) or unilateral (contact – amalgam, metals)
  - Lichenoid Dysplasia
    - Unilateral, mixed erythroleukoplakia

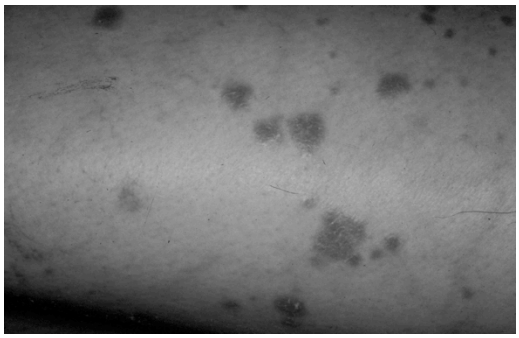
Lichen Planus & OSSC

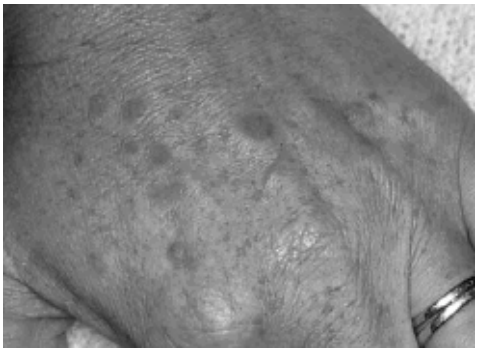
- **mixed literature on the malignant potential of lichen planus**
- **<1% (0.25-2.5%) Ca in ULCERATIVE LP**
- **Question of correct initial diagnosis**
  - **Lichenoid dysplasia**
    - **Higher likelihood when only one area / unilateral, and when the characteristic white striae are NOT present**

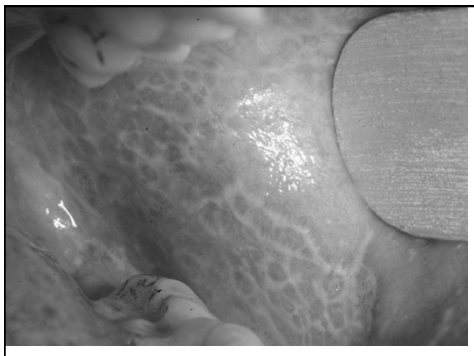
Lichenoid Reactions: Medications

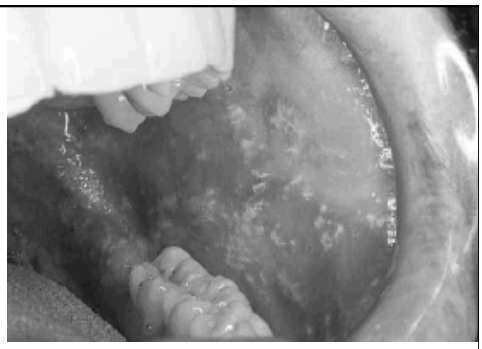
- Antimicrobials
  - Dapsone
  - Ketoconazole
  - Tetracycline
  - Sulfamethocazole
- Antihypertensives
  - ACE inhibitors
  - HCTZ
  - Beta blockers
- NSAIDs
  - Ibuprofen, naproxen
- Oral Hypoglycemics
- Anxiolytics
  - Lorazepam
- Misc:
  - Penicillamine

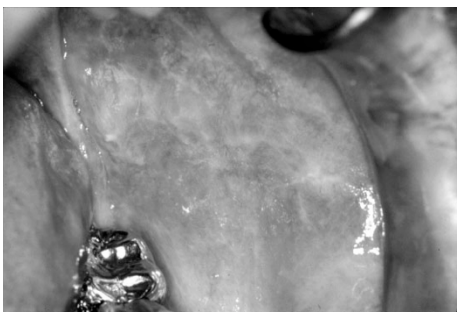












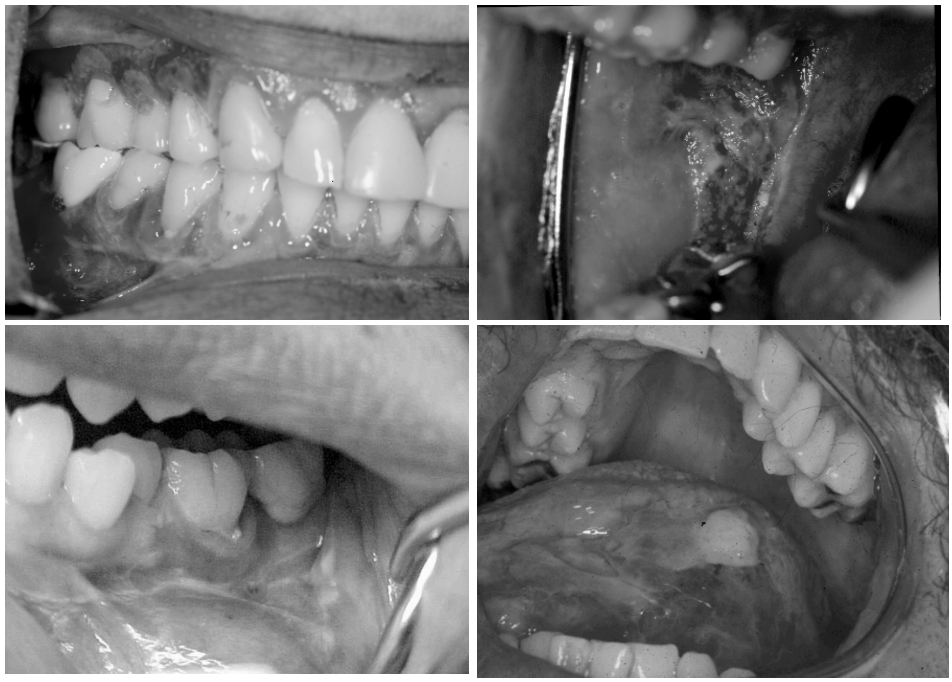
Diagnosis: Lichen Planus

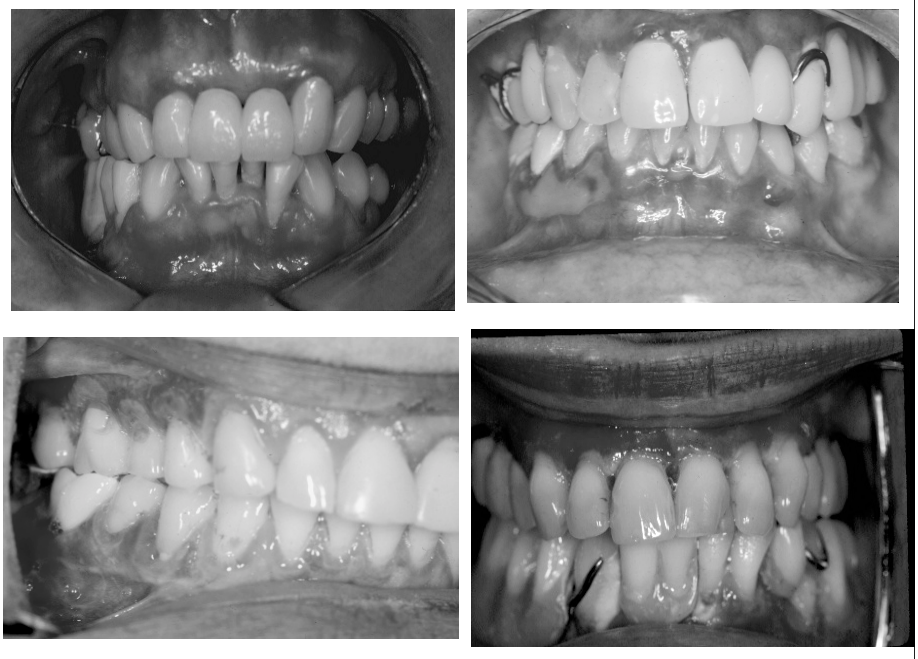
- History and examination with:
- non-ulcerative vs. ulcerative forms
- chronic, multiple ulcerations still with areas of characteristic white striae
- Any mucosal surface (BM and tongue most common)
- Desquamative gingivitis

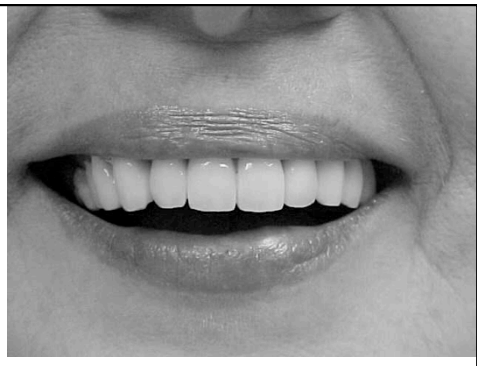
- DDx: pemphigus, pemphigoid, SLE, GVHD; trauma, lichenoid rxn

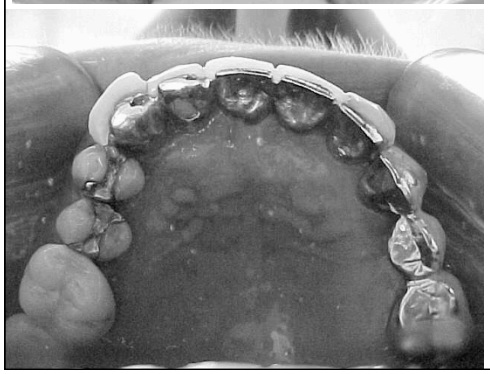
- Dx:
  - biopsy (H&E)
  - DIF may be necessary if higher likelihood of AI disease

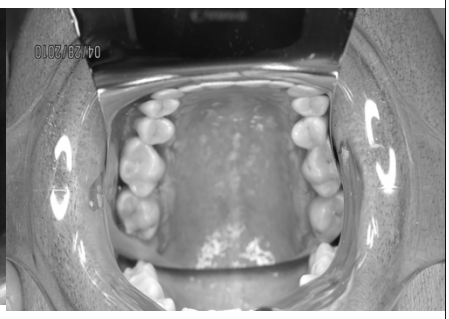








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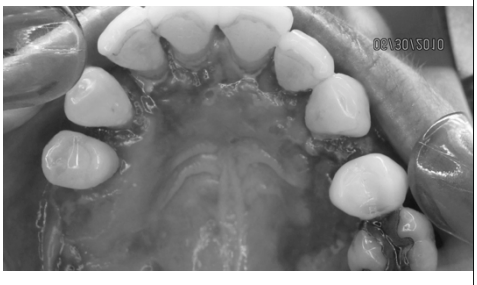


EVIDENCE BASED GUIDELINES FOR OLP TREATMENT (WWOM IV):

Corticosteroids:

Topical high(er)-potency corticosteroids (+/- topical anti-mycotics) are the first-line treatment for symptomatic iOLP.

Systemic corticosteroids (+/- topical anti-mycotics are the first-line treatment for:
- severe, wide-spread, symptomatic iOLP
- symptomatic oral erosive/atrophic lichen planus recalcitrant /resistant to topical therapies
- symptomatic LP involving other muco-cutaneous sites recalcitrant /resistant to topical therapies

Topical calcineurin-inhibitors (cyclosporin, tacrolimus, pimecrolimus) for symptomatic iOLP.
On first-principles, topical tacrolimus and pimecrolimus are likely to perform better than topical cyclosporine, but the evidence-base for the use of these two agents in OLP remains weak

FDA's "Black Box" Warning: possibility of increased risk of malignancy (squamous cell carcinoma and lymphoma) in patients using topical tacrolimus/pimecrolimus for cutaneous psoriasis these agents should be used in limited circumstances, and patients made aware of these concerns).

Other Disease Modifying Drugs and Steroid Sparing Agents

Hydroxychloroquine and azathioprine as "steroid-sparing" agents in systemic corticosteroid responsive iOLP, or widespread LP with oral involvement.

Caution is indicated with these agents because of risk of retinal damage and marrow aplasia

Mycophenolate Mofetil (CellCept): studies lacking, but promising and safer than alternatives (azathioprine, cyclosporin, long-term prednisone)

Systemic retinoids are *NOT* recommended

- ***Al-Hashimi et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Mar;103 Suppl:S25.e1-12.***
- ***Chan ES, Thornhill M, Zakrzewska J. Interventions for treating oral lichen planus: review. The Cochrane Library 2005; 4: 1-21.***

Immunologic - Erosive Lichen Planus

- Management:
  - topical: steroid ointments and creams, rinses (dexamethasone elixir 0.5mg/5cc)
  - systemic: prednisone, cyclosporin, imuran, *cellcept, tacrolimus*
  - injection: steroid (triamcinolone, dexamethasone)

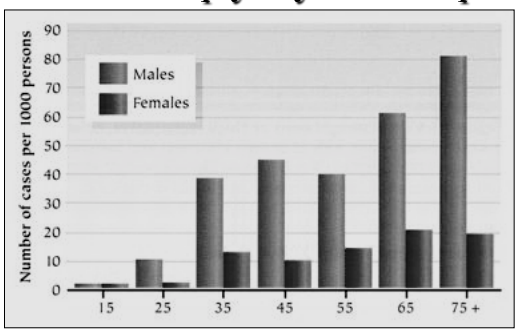
  - Surveillance / monitoring…….. Is there risk for malignant transformation?
    - Periodic topical steroid
    - Brush biopsy prn

Topical Steroid Relative Potency

Most Potent:	*clobetesol 0.05%* *halbetesol 0.05%*	*temovate* *ultravate*
High Potency:	*flucinonide 0.05%* *halcinonide 0.01%*	*lidex* *halog*
Moderate:	*triamcinolone 0.5%* *betameth diprop 0.05%*	*aristocort* *diprosone*
Low Potency	*triamcinolone 0.1%* *betameth valerate*	*kenalog* *valisone*
Weak	*hydrocortisone 1%*	

Leukoplakia

- A white patch that cannot be categorized clinically or pathologically as any other disease
- Strictly a clinical term
- Does not imply any microscopic tissue alteration



Perspective

- If 10-25% of population has an oral mucosal lesion
- And it is estimated that 3% of adult population has a lesion c/w leukoplakia
- Then roughly 1/3 – 1/8 of all oral lesions are leukoplakia

Leukoplakia: Microscopic Diagnoses at First Diagnosis.

Hyperkeratosis—80%
Dysplasia—12%
In situ carcinoma—3%
Squamous cell carcinoma—5%

- Epithelial dysplasia or invasive carcinoma found in 5% - 20% of leukoplakias studied
  - *90% of dysplastic leukoplakias occur on tongue, lip vermillion, and floor of mouth*

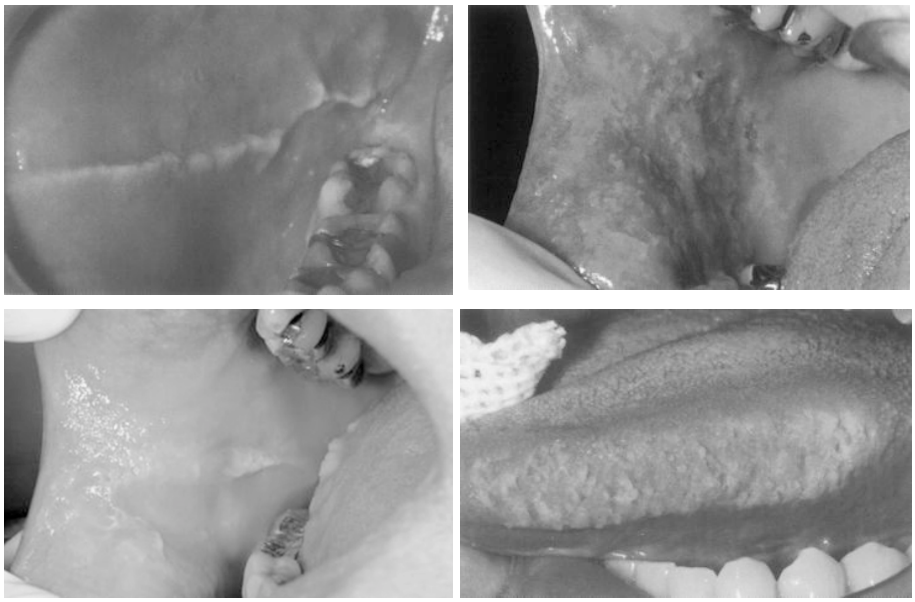
Etiology of Leukoplakia

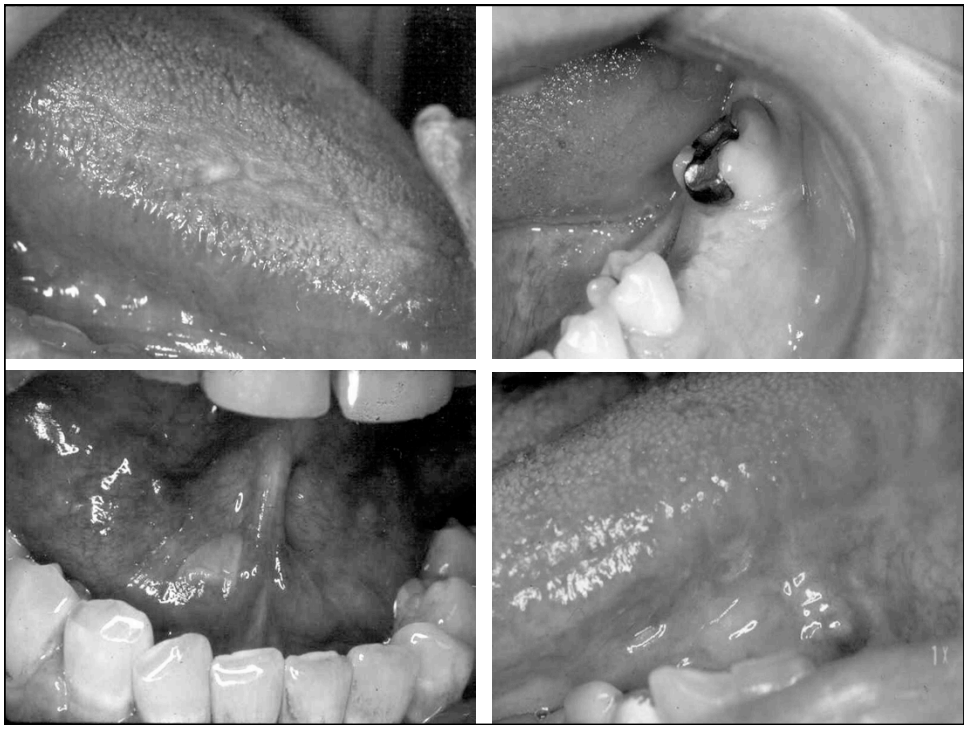
- Tobacco
- Sanguinaria
- UV Radiation (lips)
- Micro-organisms
- Trauma (frictional hyperkeratosis)

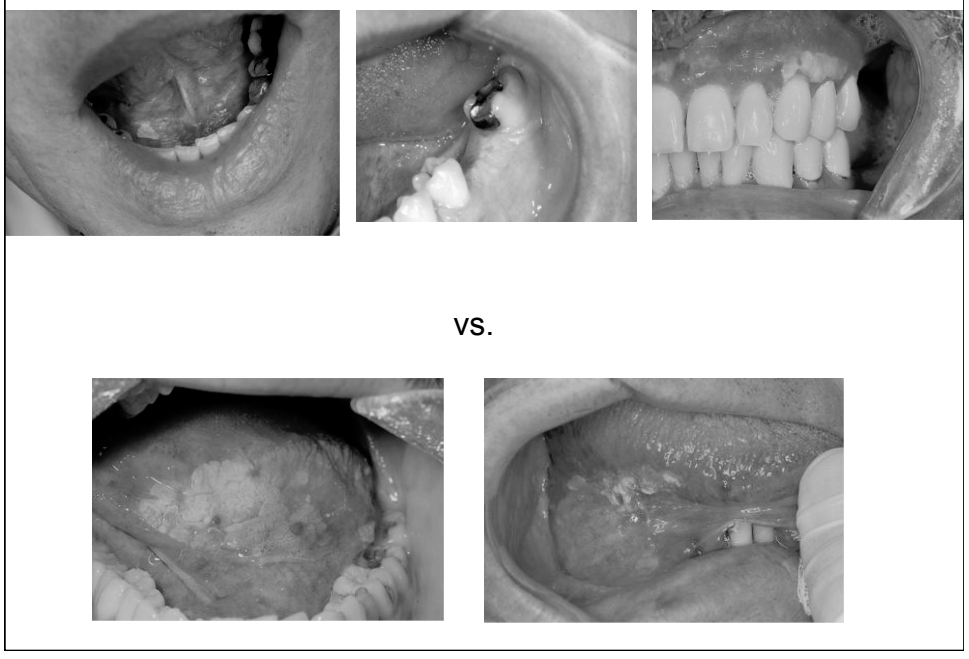
Leukoplakia: Microscopic Diagnoses at First Diagnosis.

Hyperkeratosis—80%
Dysplasia—12%
In situ carcinoma—3%
Squamous cell carcinoma—5%

- Epithelial dysplasia or invasive carcinoma found in 5% - 20% of leukoplakias studied
- 85% of oral mucosal lesions considered to be precancer present as leukoplakia



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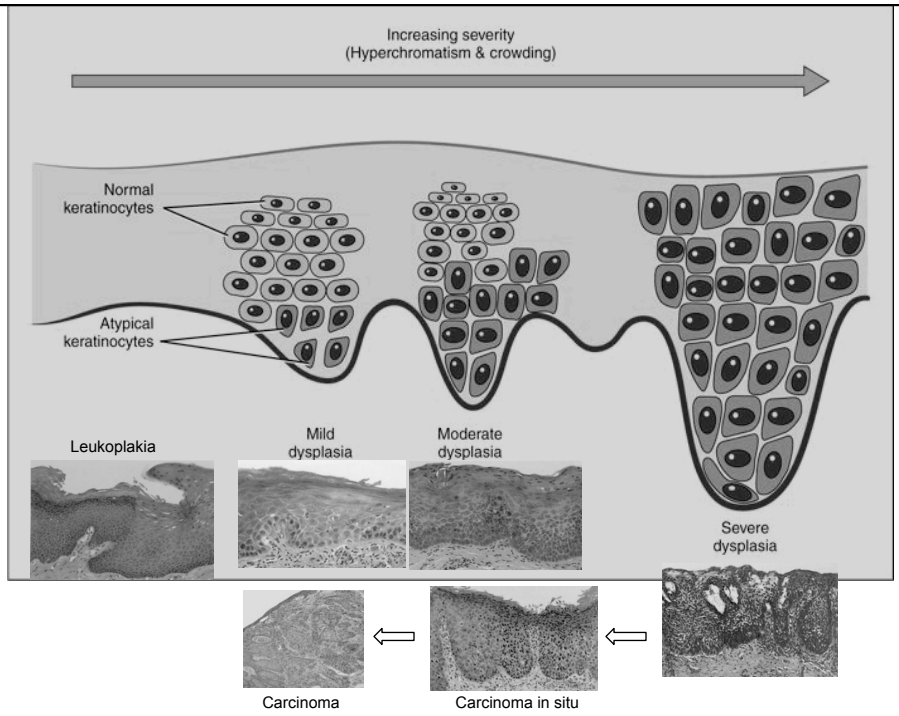
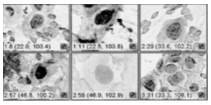
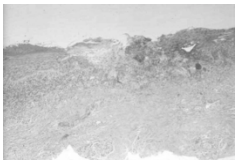
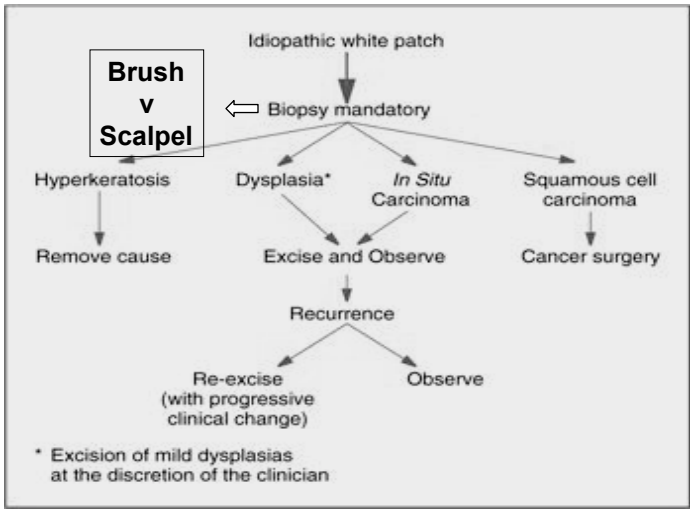


Leukoplakia: Diagnosis and Management

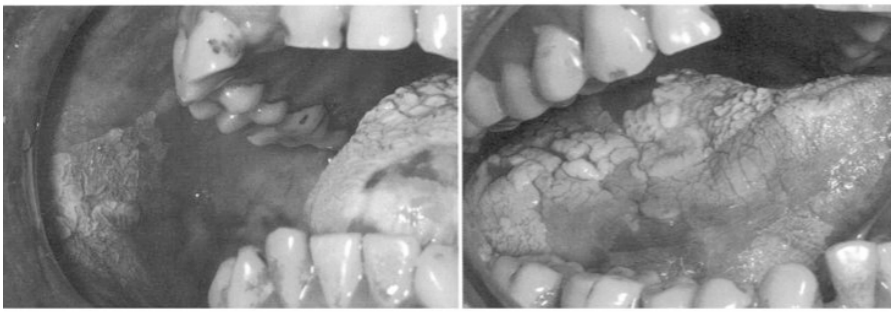




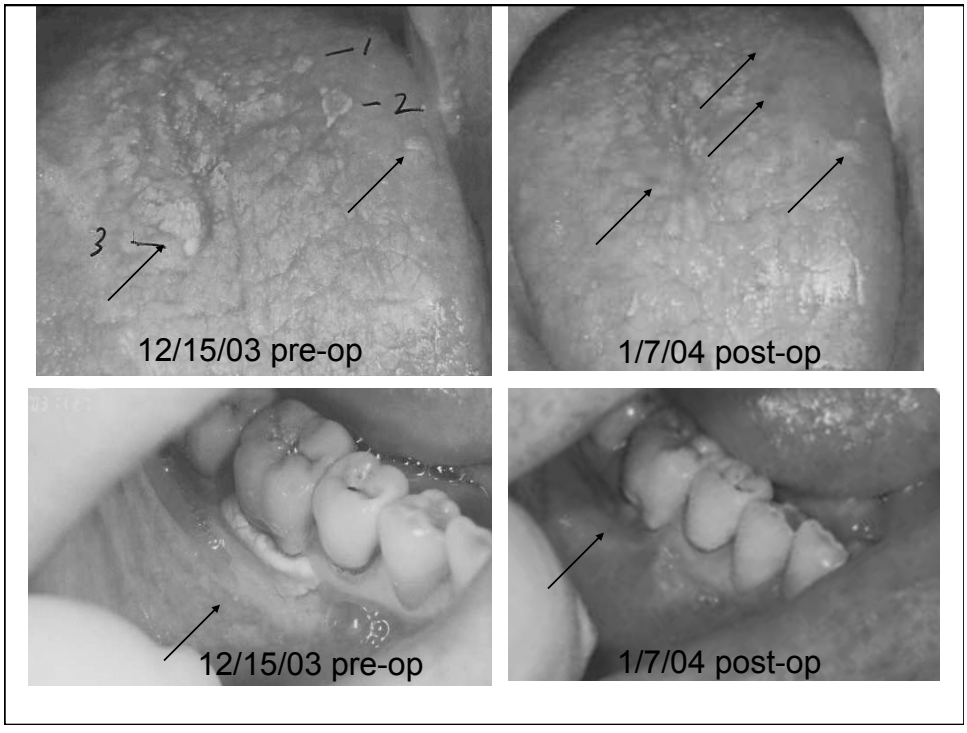


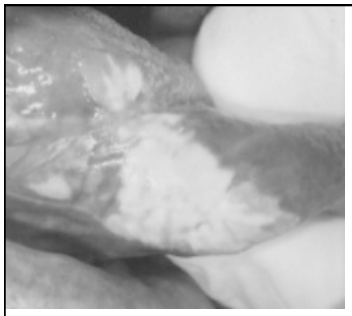
Proliferative Verrucous Leukoplakia (PVL)… wolf in sheep's clothing?

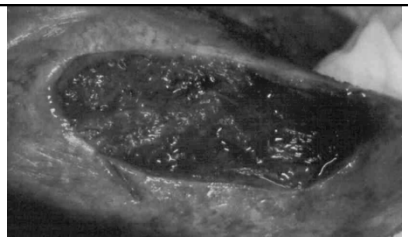
- A special high-risk form of leukoplakia
- Multiple keratotic plaques with roughened surface projections
- Plaques tend to slowly spread and involve additional oral mucosal sites
- Variable microscopic appearance
  - Hyperkeratosis to dysplasia
- Women > men, > age 50

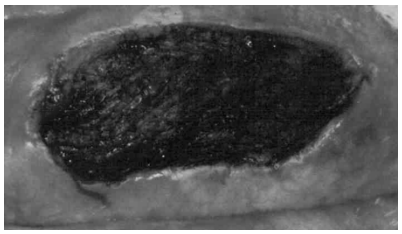


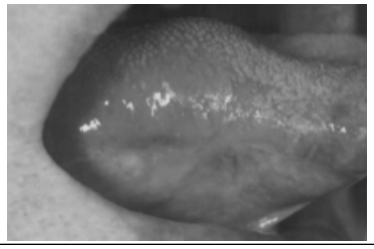

1
2
3

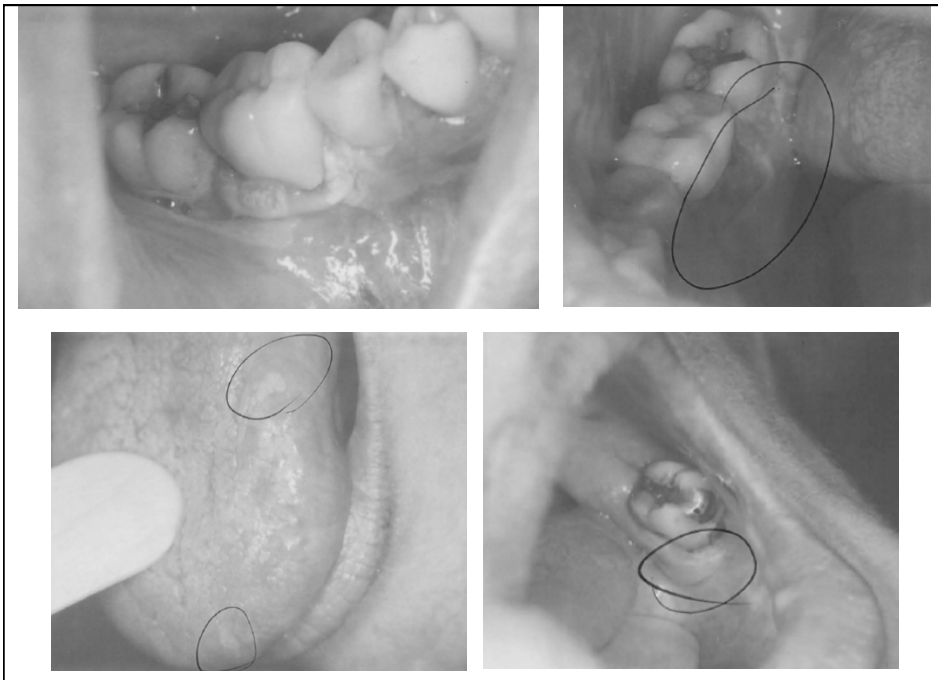

1
2
3
12/15/03 pre-op
1/7/04 post-op
12/15/03 pre-op
1/7/04 post-op









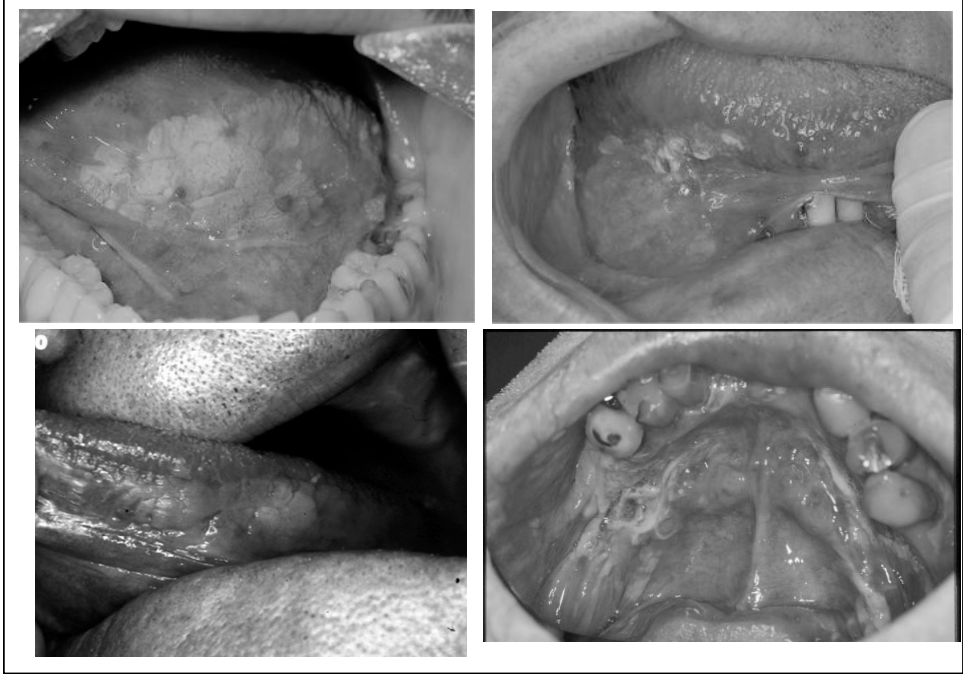


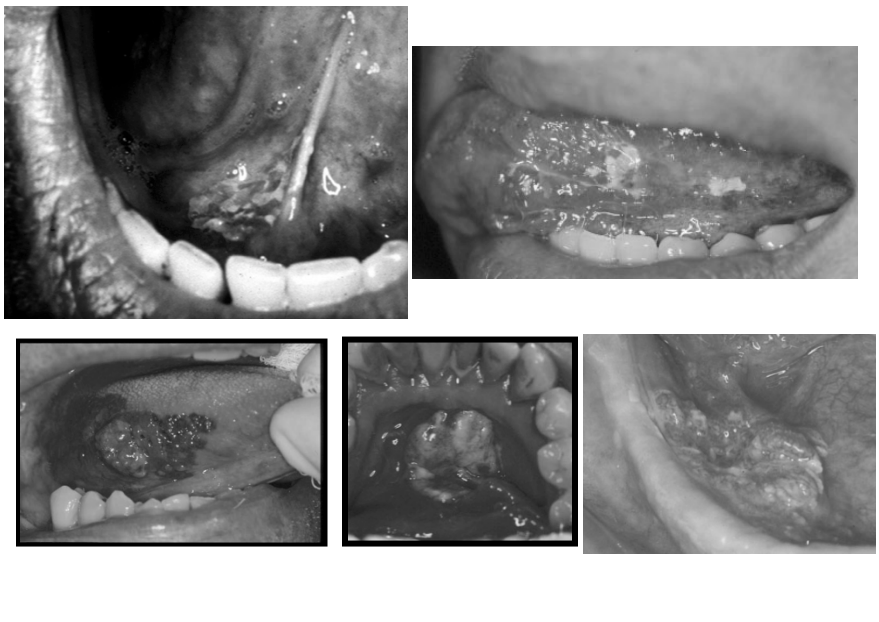
Erythro-leukoplakia (Speckled Leukoplakia)

- Some leukoplakic lesions develop scattered patches of redness
- These areas usually represent sites in which epithelial cells are so immature or atrophic that they can no longer produce keratin
- Higher dysplasia risk

Erythroplakia

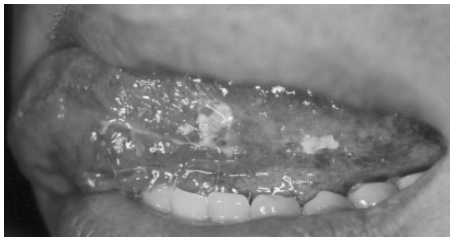
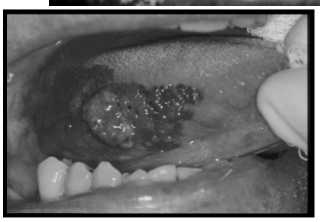
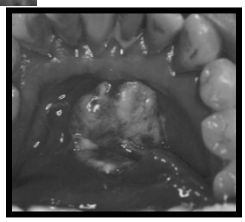
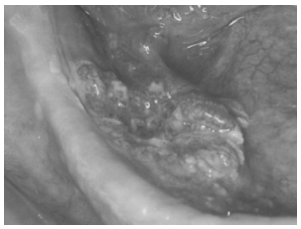
- A red patch that cannot be clinically or pathologically diagnosed as any other condition
- Almost all true erythroplakias demonstrate significant epithelial dysplasia, carcinoma *in situ,* or invasive squamous cell carcinoma





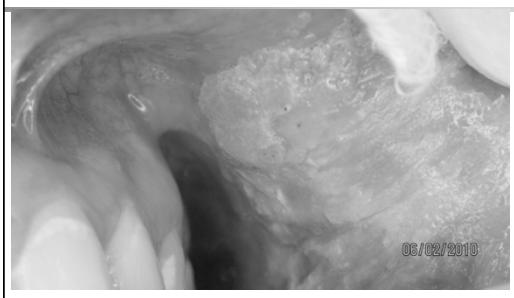
Dysplasia

A mucosal lesion appearing as a white and/or red patch or as a soft ulcer…. Risk factors include tobacco and/or alcohol use – but not required!

HPV…oral warts.

Challenging management and cancer risks



- 24yo healthy while male
- heterosexual oral sex
- morsicatio buccarum
- cigar use

- Independent of wart presence significant increased risk for SCCa (HPV 16)
- Oro-genital warts as STD in healthy individuals
- Oral warts in immuno-suppressed individuals

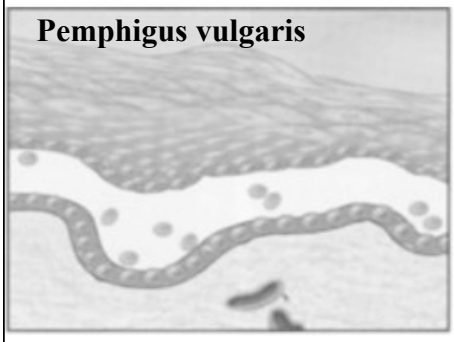
Pemphigus Vulgaris

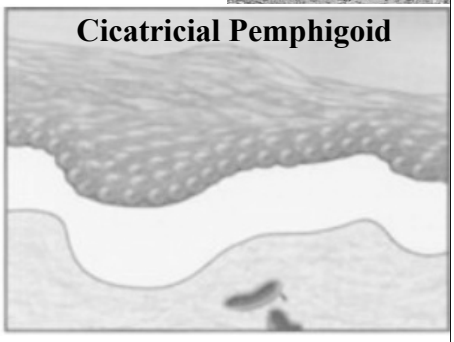
- Multiple, chronic mucocutaneous ulcers
- mucocutaneous autoimmune disease characterized by intra-epithelial blisters (bullae) which ruptures to form large, non-healing ulcerations
- onset usually in fifth and sixth decades

International Pemphigus Foundation
A common hope, an uncommon bond
www.pemphigus.org

Pemphigus and Pemphigoid

- Both are autoimmune disorders that destroy proteins important in holding together the skin and mucous membranes
- The result is multiple, chronic ulcerations and erosions of the skin an/or mucosa



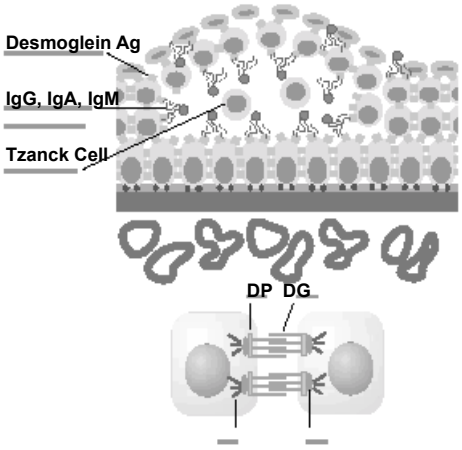


Intraepithelial:
Between the bricks

Subasilar:
At the foundation

Pemphigus Vulgaris

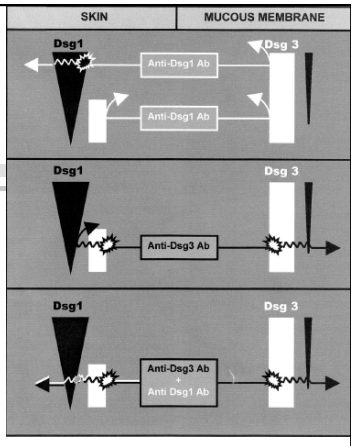
- circulating IgG, C3 directed against desmoglian 1 and or 3 on keratinocyte surface
- loss of desmosomal attachment
- epithelial separation / detachment



Pemphigus Vulgaris

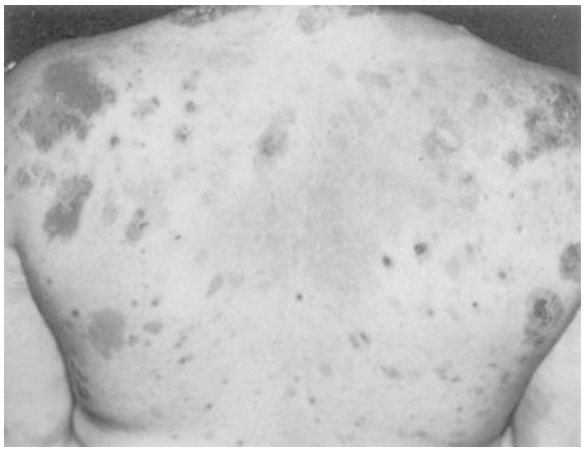
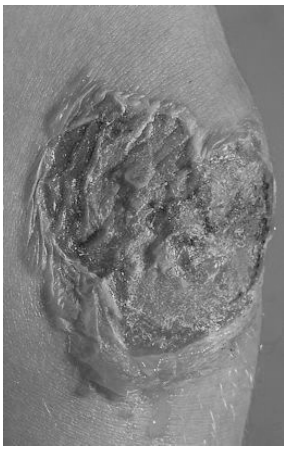
- Pemphigus Vulgaris
  - Most common form, any mucosal or skin surface
- Pemphigus foliaceous
  - Superficial, skin only (face, neck, chest, back)
- Paraneoplastic pemphigus
  - Associated with cancer
- Drug-induced

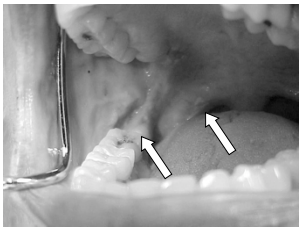
Pemphigus Vulgaris

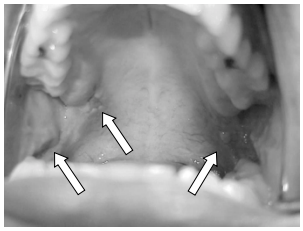


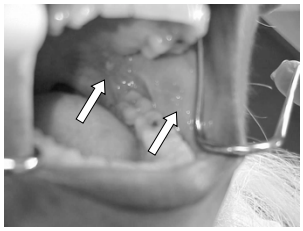
- circulating IgG, C3 directed against desmoglian on keratinocyte surface
- loss of desmosomal attachments
- epithelial acantholysis and Tzank cells

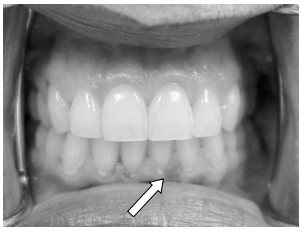
ELISA		Diagnosis
Anti-Dsg1 IgG	Anti Dsg3 IgG	
+	-	Pemphigus foliaceus (skin dominant)
-	+	Mucosal dominant PV
+	+	Mucocutaneous type PV

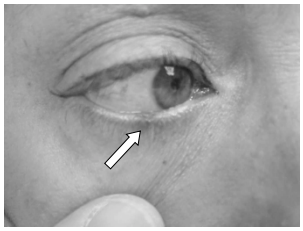



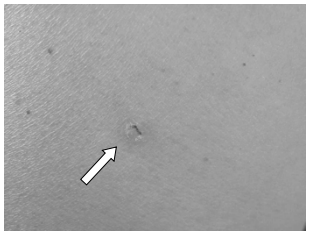


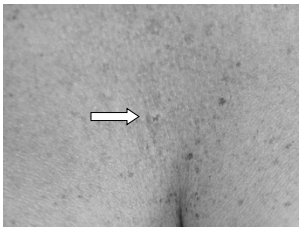


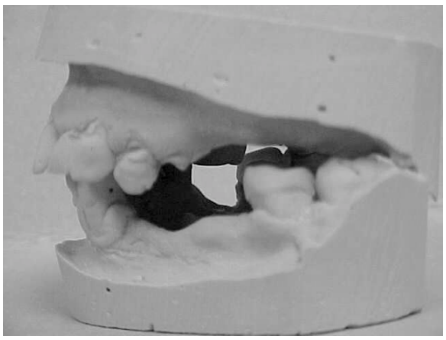


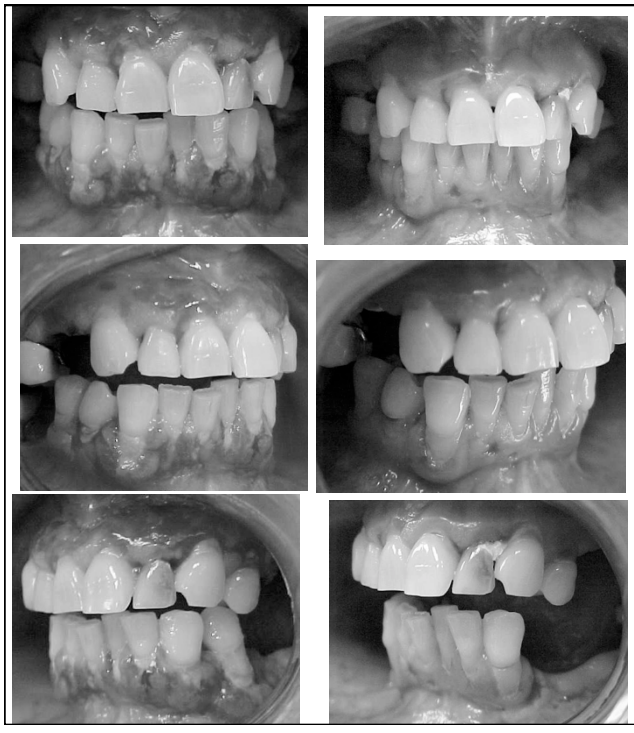












Pemphigus Vulgaris

- The significant majority of patients develop oral lesions before cutaneous
- multiple shallow, burn-like ulcerations which begin as a bulla
- (+) Nikolsky sign
- chronic, multiple, generalized

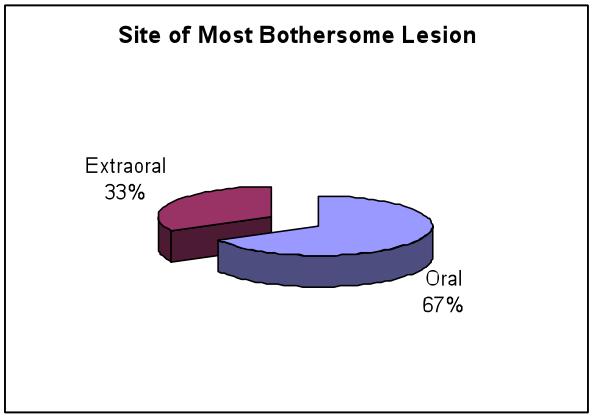
Diagnostic Patterns and Delays in Pemphigus Vulgaris Sirois D and Fatahzadeh M, Arch Derm 136:1569, 2000

99 patients studied to determine patterns of disease onset and diagnosis

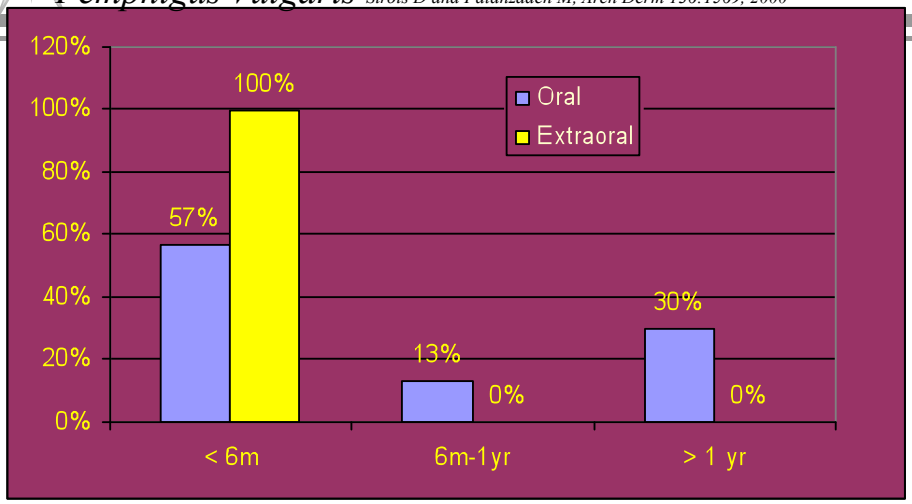
Sex	(%)	Present age	Age @ Dx	Duration	Interval between skin-mucosa
M	29%	52.3± 11.2	48± 10.8	5± 4.1 yrs	8.8± 8.1 months
F	71%	56.1± 11	50 ± 11.2	6.6± 6.1 yrs	7.6± 7.9 months

Characteristic	Oral Mucosa	Skin	Skin and Mucosa
Site of 1st lesion	79 (80%)	20 (20%)	---
Exclusive site of lesion	24 (24%)	7 (7%)	69 (69%)
# Clinicians to achieve dx	4.3 ± 3.5	2.1 ± 1.3	---

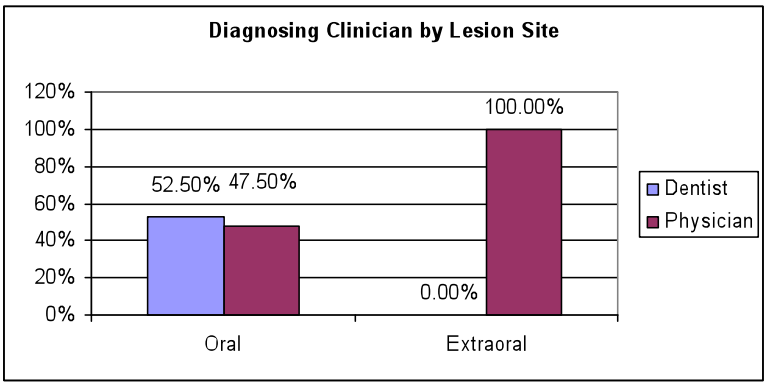
Diagnostic Patterns and Delays in Pemphigus Vulgaris Sirois D and Fatahzadeh M, Arch Derm 136:1569, 2000



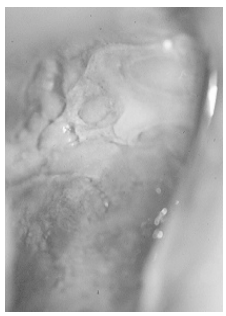
Diagnostic Patterns and Delays in Pemphigus Vulgaris *Sirois D and Fatahzadeh M, Arch Derm 136:1569, 2000*

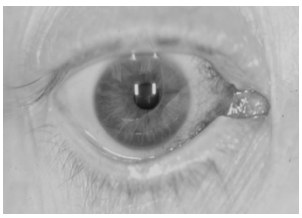


Diagnostic Patterns and Delays in Pemphigus Vulgaris *Sirois D and Fatahzadeh M, Arch Derm 136:1569, 2000*



Oral PV: 1.3 dentists compared to 3.1 MDs to achieve diagnosis






04/21/2010


03/24/2010

Pemphigus Vulgaris

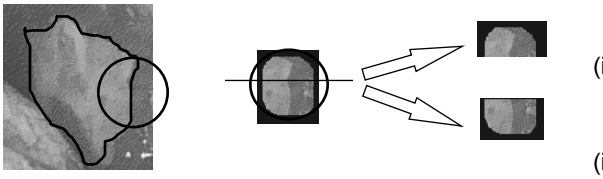
- Differential Diagnosis
  - pemphigus
  - pemphigoid
  - erosive lichen planus
  - epidermolysis bullosa

Pemphigus Vulgaris

- Diagnosis:
  - history, physical examination
    - multiple, chronic mucocutaneous ulcerations, bullae
  - BIOPSY:
  - H&E: acantholysis and Tzank cells
  - Direct immunofluorescence from perilesional tissue reveals suprabasilar, intraepithelial reaction product
  - +/- circulating antibodies (IIF)

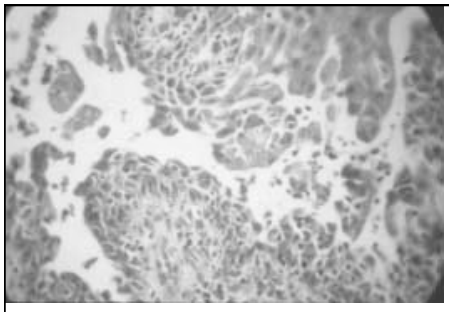
Pemphigus Vulgaris

BIOPSY TECHNIQUE FOR VB Disease



H&E
(in formalin)

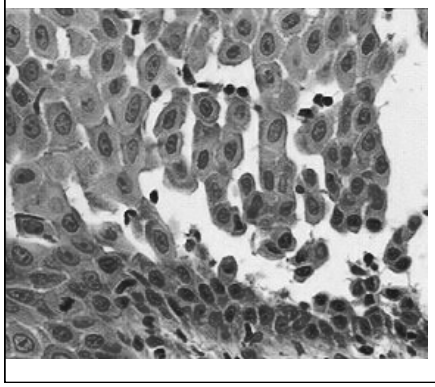
DIF
(in Michels solution)

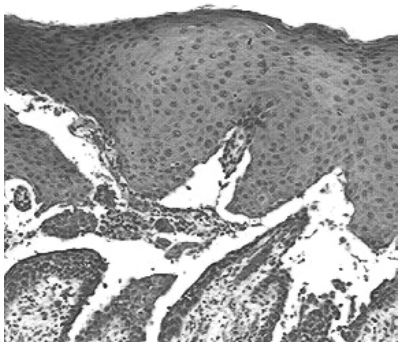


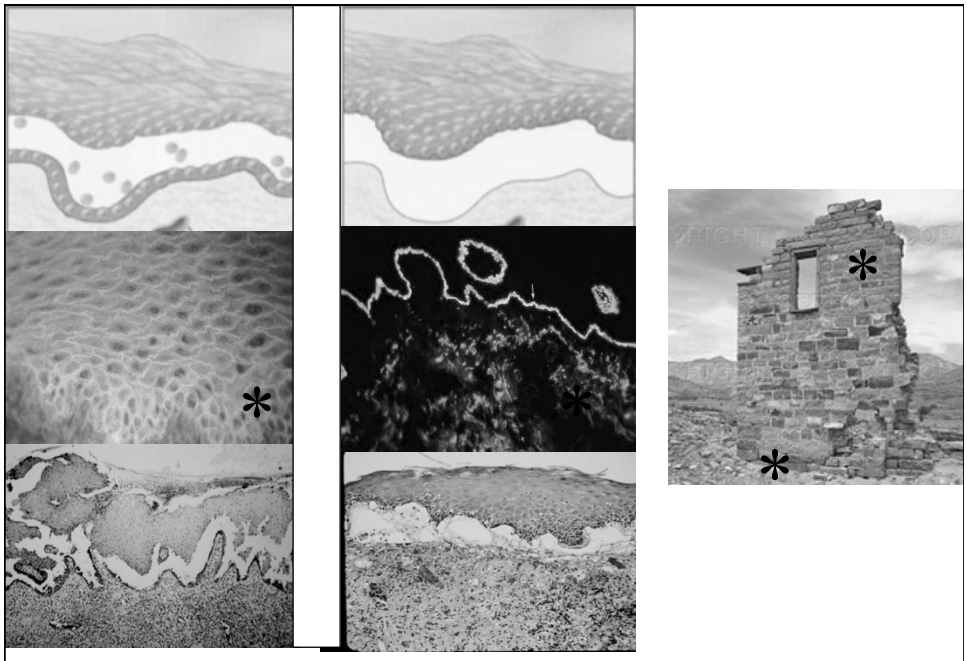
Separation of spinous epithelial layer from basal epithelial layer

Spinous layer falls apart: acantholysis

Rounded single cells- Tzanck cells







pemphigus pemphigoid

Pemphigus Vulgaris: Treatment

SYSTEMIC TREATMENT

- Prednisone (oral, pulse)
- Mycophenolate
- Azathioprine
- Methotrexate
- Cyclophosphamide
- **IVIg**
- **Rituxmab**
- Cyclosporin
- Plasmaphoresis
- Monoclonal Ab

Pre-tx bloodwork and continued monitoring

Local Treatment:

- Topical
- Injection treatment (celestone, dexamethasone, triamcinalone) for refractory lesions

Trials:

- Biologics: IVIg, Rituxmab
- TNF: Enbrel, Remicade, etanercept infliximab

Pemphigus vulgaris - Treatment Approaches

- **Initial Therapy:**
- **Prednisone - 1 mg / kg / day**
- **Prednisone & mycophenolate 35 - 45 mg / kg, or azathioprine 3 - 4 mg / kg / day**
  - ⇨ **(IvIG or biologic agents such as rituximab)**
- **Prednisone & cyclophosphamide 2.5 mg/ kg / day.**
- **Prednisone & cyclophosphamide & plasmapheresis, 5 - 6 exchanges.**

Prednisone side effects

- Sodium and water retention, edema, HTN
- hyperglycemia
- calcium mobilization and osteoporosis
- agitation, psychosis
- fat redistribution
- muscle atrophy, weakness
- *alternate day dosing, steroid sparing meds*

F 59 — DR SEROIS 1000, 345 E 24 ST, NEW YORK, NY 10010 — WILD1 1

Ordering Physician / Patient I.D./Soc. Sec Number: 109345279

C.L.I.A. # 31D0696246 — Specimen Number: 49904402 — Time Collected: 0821 — FASTING

PAGE 2

TEST NAME	RESULT ABNORMAL	RESULT NORMAL	UNITS	REFERENCE RANGE
CBC W/ DIFF & PLT				
WBC		8.0	Thous/cu.mm	3.9-11.2
RBC		4.49	Mil/cu.mm	3.80-5.20
HEMOGLOBIN		12.9	g/dL	11.6-15.5
HEMATOCRIT		38.4	Percent	34.0-46.0
MCV		86	fl	80-98
MCH		28.8	pg	27.0-34.0
MCHC		33.7	Percent	32.0-36.0
RDW		14.7	Percent	11.0-15.5
PLATELET COUNT		360	Thous/cu.mm	150-400
MPV		8.5	fl	7.5-11.5
TOTAL NEUTROPHILS,%		55.1	Percent	38.0-80.0
TOTAL LYMPHOCYTES,%		30.2	Percent	15.0-49.0
MONOCYTES,%		11.0	Percent	0.0-13.0
EOSINOPHILS,%		2.7	Percent	0.0-8.0
BASOPHILS,%		1.0	Percent	0.0-2.0
NEUTROPHILS,ABSOLUTE		4408	Cells/cu.mm	1700-8500
LYMPHOCYTES,ABSOLUTE		2416	Cells/cu.mm	1000-3500
MONOCYTES,ABSOLUTE		880	Cells/cu.mm	40-900
EOSINOPHILS,ABSOLUTE		216	Cells/cu.mm	30-550
BASOPHILS,ABSOLUTE		80	Cells/cu.mm	0-125
DIFFERENTIAL				

An instrument differential was performed.

7/19/01

F 59 — DR SIROIS 1000, 530 FIRST AVE #9QQ, NY, NY 10016 — WILD1 1

Ordering Physician / Patient I.D./Soc. Sec Number: 109345279

Specimen Number: 68560322 — Time Collected: 0730 — FASTING

PAGE 2

TEST NAME	RESULT ABNORMAL		RESULT NORMAL	UNITS	REFERENCE RANGE
CBC W/ DIFF & PLT					
WBC	12.1	H		Thous/cu.mm	3.9-11.2
RBC			4.42	Mil/cu.mm	3.80-5.20
HEMOGLOBIN			12.6	g/dL	11.6-15.5
HEMATOCRIT			38.1	Percent	34.0-46.0
MCV			86	fl	80-98
MCH			28.4	pg	27.0-34.0
MCHC			33.0	Percent	32.0-36.0
RDW	16.8	H		Percent	11.0-15.5
PLATELET COUNT			375	Thous/cu.mm	150-400
MPV			7.8	fl	7.5-11.5
TOTAL NEUTROPHILS,%			67.6	Percent	38.0-80.0
TOTAL LYMPHOCYTES,%			23.0	Percent	15.0-49.0
MONOCYTES,%			7.9	Percent	0.0-13.0
EOSINOPHILS,%			1.2	Percent	0.0-8.0
BASOPHILS,%			0.3	Percent	0.0-2.0
NEUTROPHILS,ABSOLUTE			8180	Cells/cu.mm	1700-8500
LYMPHOCYTES,ABSOLUTE			2783	Cells/cu.mm	1000-3500
MONOCYTES,ABSOLUTE	956	H		Cells/cu.mm	40-900
EOSINOPHILS,ABSOLUTE			145	Cells/cu.mm	30-550
BASOPHILS,ABSOLUTE			36	Cells/cu.mm	0-125
DIFFERENTIAL					

An instrument differential was performed.

*** ORIGINAL REPORT SENT TO:
LONG ISLAND PSC'S
575 UNDERHILL BLVD STE 90
SYOSSET , NY 11791

>> END OF REPORT - SUSA,ANN 68560322 <<

9/25/01

F 59 — DR SEROIS 1000, 345 E 24 ST, NEW YORK, NY 10010 — WILD1 1

Ordering Physician / Patient I.D./Soc. Sec Number: 109345279

C.L.I.A. # 31D0696246 — Specimen Number: 49904402 — Time Collected: 0821 — FASTING

Comments: FAX 212-995-4243

TEST NAME	RESULT ABNORMAL		RESULT NORMAL	UNITS	REFERENCE RANGE
CHEM SCREEN PANEL					
GLUCOSE,FASTING			85	mg/dL	65-109
SODIUM			145	mmol/L	135-146
POTASSIUM			4.4	mmol/L	3.5-5.3
CHLORIDE			110	mmol/L	98-110
CARBON DIOXIDE			23	mmol/L	21-33
UREA NITROGEN			13	mg/dL	7-25
CREATININE			0.8	mg/dL	0.5-1.2
BUN/CREATININE RATIO			16.3		6.0-25.0
URIC ACID			3.9	mg/dL	1.7-7.5
PHOSPHORUS			3.3	mg/dL	2.5-4.5
CALCIUM			9.1	mg/dL	8.5-10.4
CHOLESTEROL,TOTAL	237	H		mg/dL	<200
See note 1					
TRIGLYCERIDES			111	mg/dL	<150
PROTEIN,TOTAL			6.3	g/dL	6.0-8.3
ALBUMIN			3.8	g/dL	3.5-4.9
GLOBULIN,CALCULATED			2.5	g/dL	2.2-4.2
A/G RATIO			1.5		0.8-2.0
BILIRUBIN,TOTAL			0.32	mg/dL	0.20-1.30
BILIRUBIN,DIRECT			0.05	mg/dL	0.00-0.30
ALKALINE PHOSPHATASE			55	U/L	20-125
GGT			29	U/L	2-60
AST			13	U/L	2-35
ALT			18	U/L	2-40
LD			165	U/L	100-250
IRON			59	ug/dL	35-175

7/19/01

F 59 — DR SIROIS 1000, 530 FIRST AVE #9QQ, NY, NY 10016 — WILD1 1

Ordering Physician / Patient I.D./Soc. Sec Number: 109345279

Specimen Number: 68560322 — Time Collected: 0730 — FASTING

Comments: FAX 212 995 4243 PH.212 26[illegible]

TEST NAME	RESULT ABNORMAL	RESULT NORMAL	UNITS	REFERENCE RANGE
COMP METABOLIC PANEL				
GLUCOSE,FASTING		78	mg/dL	65-109
SODIUM		145	mmol/L	135-146
POTASSIUM		4.0	mmol/L	3.5-5.3
CHLORIDE		108	mmol/L	98-110
CARBON DIOXIDE		22	mmol/L	21-33
UREA NITROGEN		16	mg/dL	7-25
CREATININE		1.0	mg/dL	0.5-1.2
BUN/CREATININE RATIO		16.0		6.0-25.0
CALCIUM		8.6	mg/dL	8.5-10.4
PROTEIN,TOTAL		6.1	g/dL	6.0-8.3
ALBUMIN		3.6	g/dL	3.5-4.9
GLOBULIN,CALCULATED		2.5	g/dL	2.2-4.2
A/G RATIO		1.4		0.8-2.0
BILIRUBIN,TOTAL		0.26	mg/dL	0.20-1.30
ALKALINE PHOSPHATASE		50	U/L	20-125
AST		13	U/L	2-35
ALT		17	U/L	2-40

9/25/01

Pemphigus vulgaris - Therapy trends

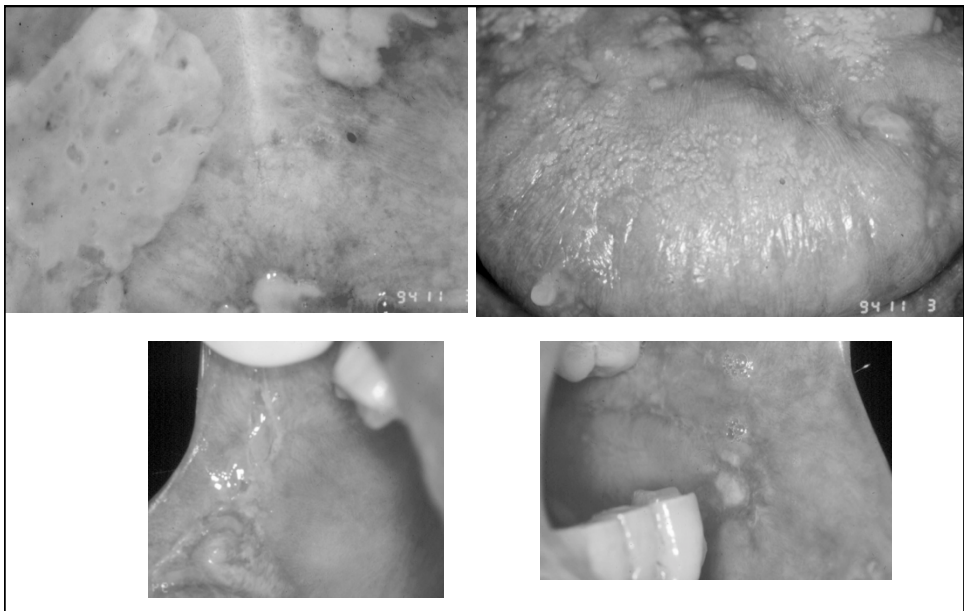
- Problem – lack of hard data to know which treatment protocol is most effective
- Definitions: remission?
- Increasing interest in biologic agents: IvIg and rituximab
- Awaiting data from trials on TNF blockers (Enbrel, Remicade)

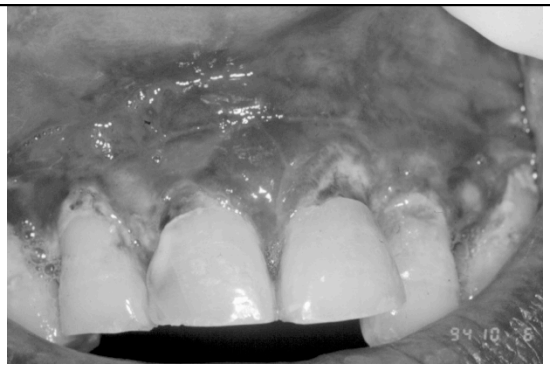
Pemphigus - Oral Complications

- **Drug effects:**
  - **Immunosuppression, mucositis, systemic SE**
- **pain, decreased food intake**
- **caries and periodontal disease if gingivae are involved and hygiene is painful**
- **Candidiasis**
- **removable prosthesis intolerance**

Considerations in Oral VB-Ulc Disease:

- medication side effects
  - prednisone, dapsone, imuran, cyclosporin
- gingival ulceration, pain, and oral hygiene
- removable prosthesis vs. fixed
- prevention: periodontal dz and caries

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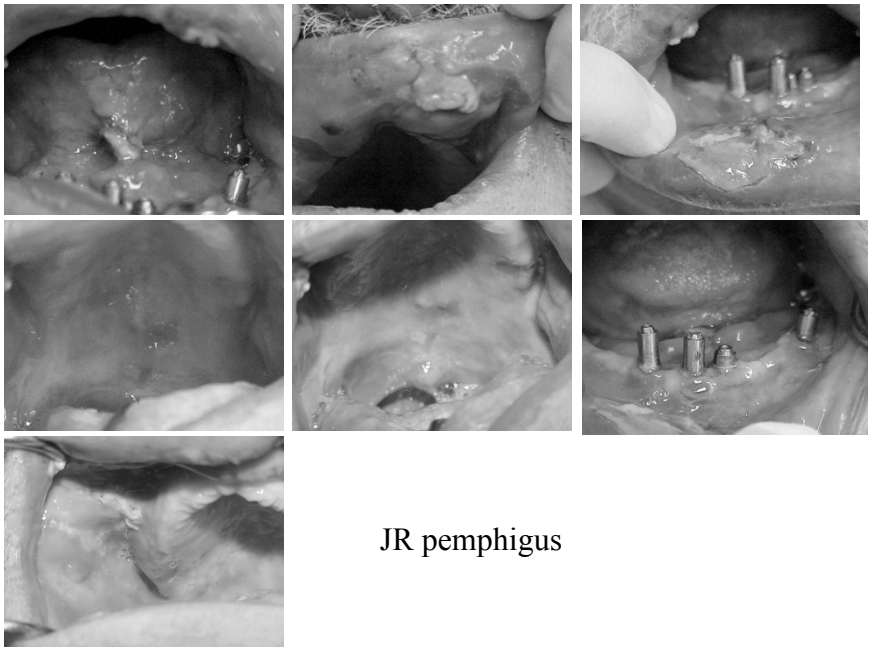
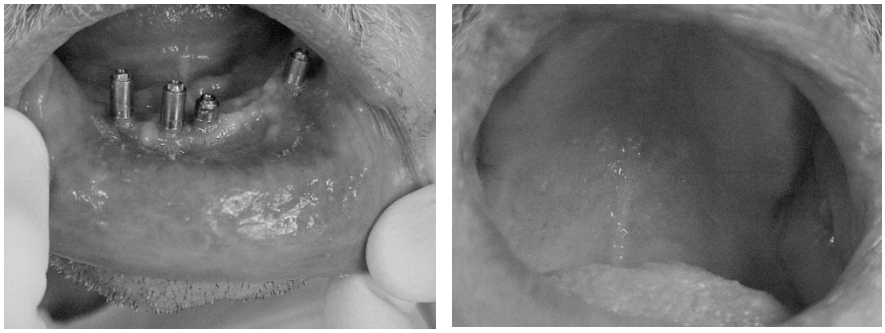
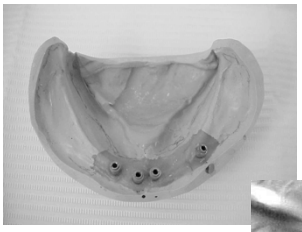
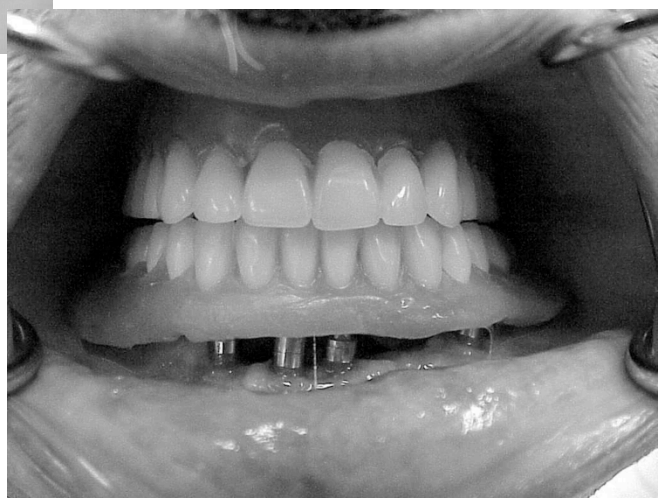


JR pemphigus



JR, pemphigus
s/p 1 week 70 mg pred/day



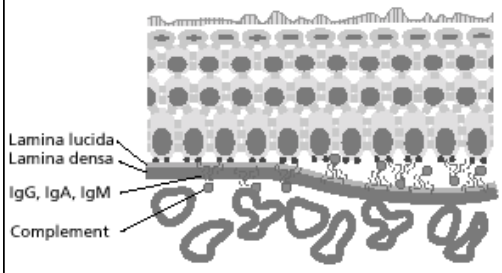


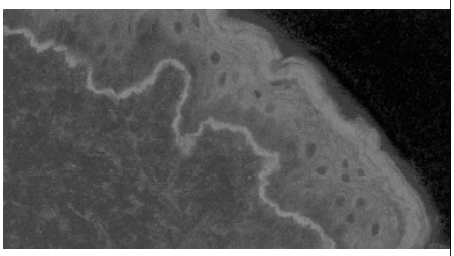
Pemphigoid

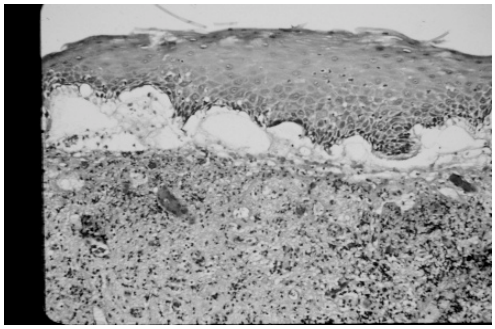
- mucocutaneous autoimmune disease characterized by sub-epithelial blisters (bullae) which ruptures to form large, non-healing ulcerations
- onset usually in individuals over age 45
- VARIANTS:
- Cicatricial (benign mucous membrane)
- Bullous (skin>mucosa)

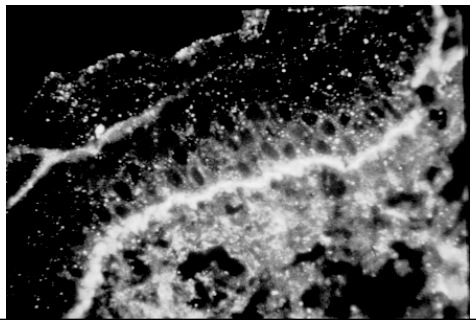
Pemphigoid

- tissue IgG, C3 directed against BPA2 in basement membrane zone
- separation of epithelium at junction









Pemphigoid

- more than 70% of patients develop oral lesions before cutaneous
- multiple shallow, ulcerations which begin as a bulla; bleeding more common
- (+/-) Nikolsky sign
- chronic, multiple, generalized

Pemphigoid

- Clinical Subtypes:
  - Mucous Membrane Pemphigoid
    - Oral
    - Ocular
  - Bullous
  - Cicatricial

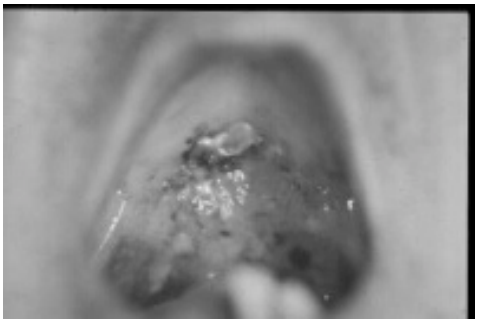
Site	Clinical subgroup	Isotype	Main target antigens
Skin	BP*	IgG ++	180,230 kDa
	Uncommon	IgA ++	180 kDa
Ocular only	MMP†	IgA ++	45 kDa
	Uncommon	IgG +	Beta 4 integrin
Oral	MMP	IgG ++	168,180,230 kDa
	Common	IgA +	180 kDa
Skin and oral	MMP	IgG ++	180,230 kDa
	Common	IgA ++	180 kDa

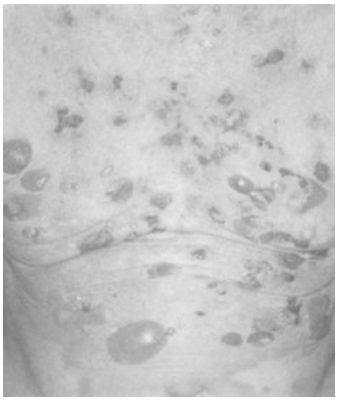
* BP = bullous pemphigoid.
† MMP = mucous membrane pemphigoid.

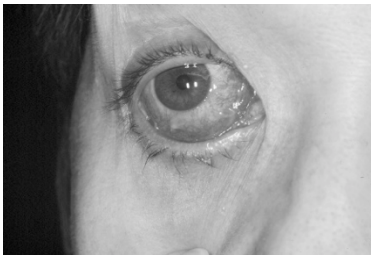
From: Thorne J, Anhalt G, Jabs D.
Ophthalmology *Volume 111, Number 1, January 2004*

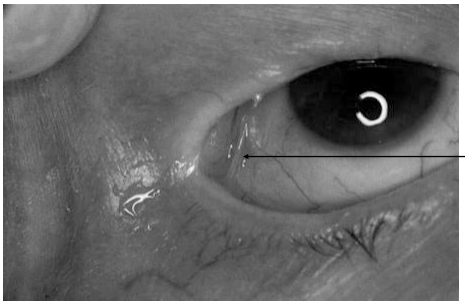
Pemphigoid

- Differential Diagnosis
  - pemphigus
  - pemphigoid
  - erosive lichen planus
  - epidermolysis bullosa

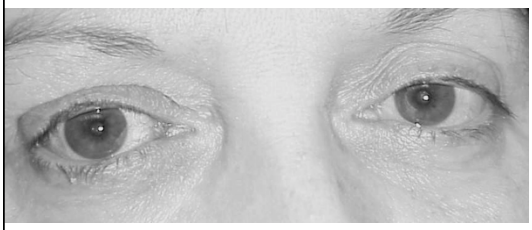


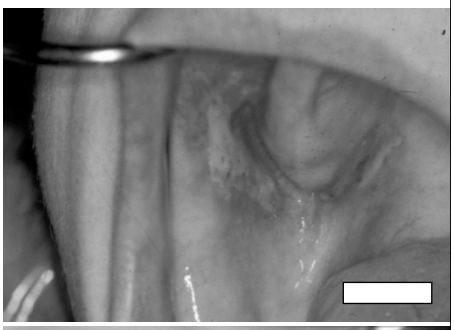


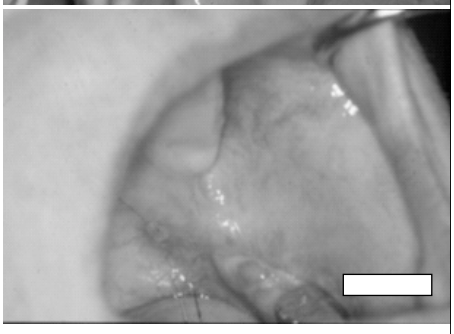




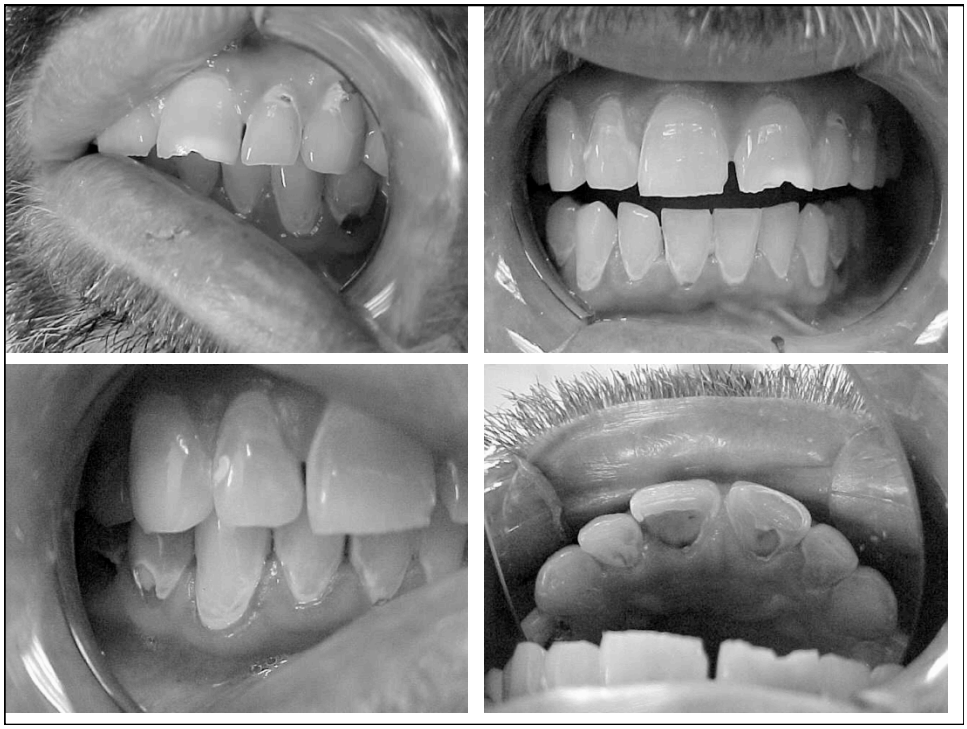
Symblephron

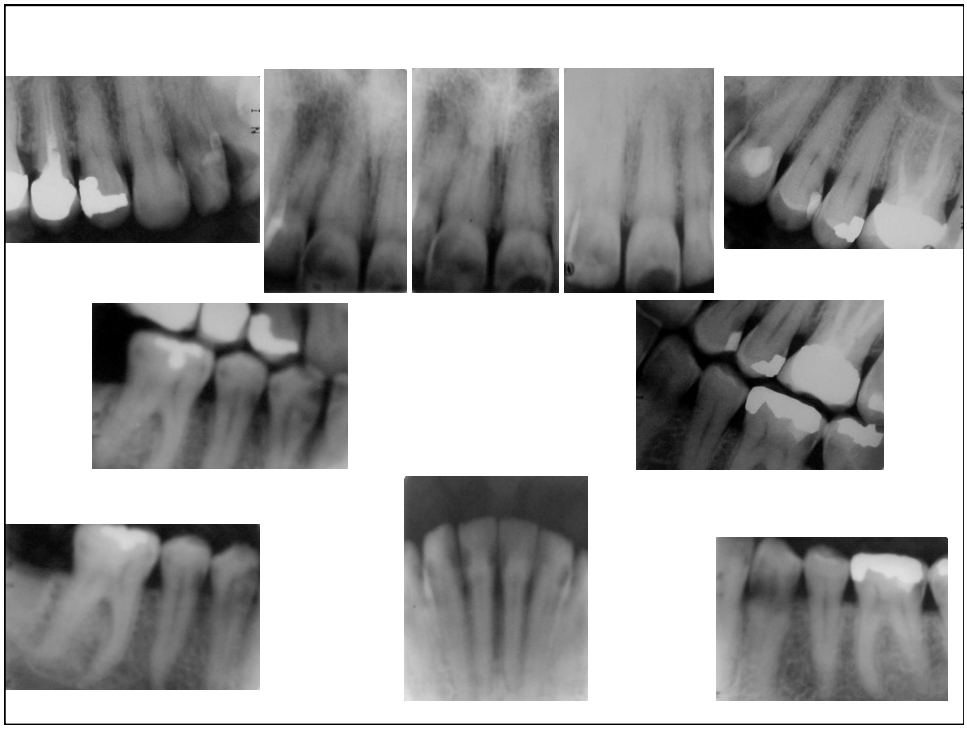






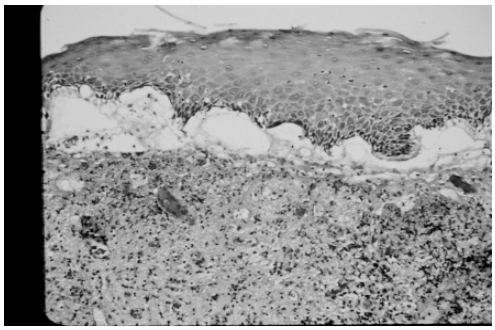
Controlling other inflammatory processes helps!!!!

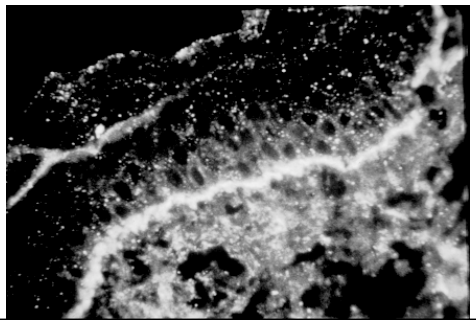




Pemphigoid

- Diagnosis:
  - history, physical examination
  - <u>BIOPSY:</u>
  - H&E: sub-basilar clefting, lymphocytic infiltration
  - Direct immunofluorescence from perilesional tissue reveals linear sub-basilar deposition
  - less commonly have circulating antibodies





Pemphigoid

- Treatment:
- oral medicine, ophthalmology and dermatology consultation
- limited disease: POTENT topical steroid (clobetseol)
- systemic treatment:
  - prednisone (1 mg/kg bw)
  - **DAPSONE** (must check G6PD to eval hemolysis risk)
  - DMD's: imuran, cyclophosphamide
  - Injection treatment (celestone, dexamethasone, triamcinalone) for refractory lesions

Topical Steroid Relative Potency

Most Potent:	*clobetesol 0.05%* *halbetesol 0.05%*	*temovate* *ultravate*
High Potency:	*flucinonide 0.05% lidex* *halcinonide 0.01% halog*	
Moderate:	*triamcinolone 0.5%* *betameth diprop 0.05%*	*aristocort* *diprosone*
Low Potency	*triamcinolone 0.1%* *betameth valerate*	*kenalog* *valisone*
Weak	*hydrocortisone 1%*	

Human Herpes Viruses

- ***Herpses Simplex 1,2*** ***(HHV 1,2)***
- ***Varicella Zoster*** ***(HHV3)***
- ***Epstein Barr*** ***(HHV4)***
- ***Cytomegalovirus*** ***(HHV5)***
- ***HHV6***
- ***HHV7***
- ***HHV8*** ***(Kaposi Sarcoma)***

Herpes Simplex Virus 1,2

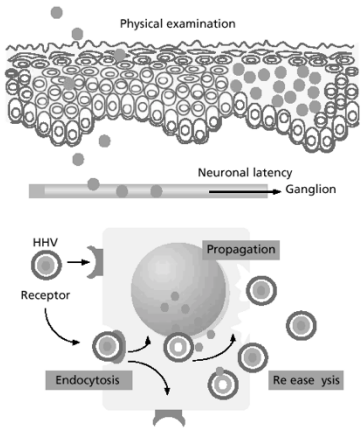
- ***50% of population age 1-7 are HSV1+***
- ***75% of population by age 35 are HSV1+***
- ***16% of population age 15-75 are HSV2+***

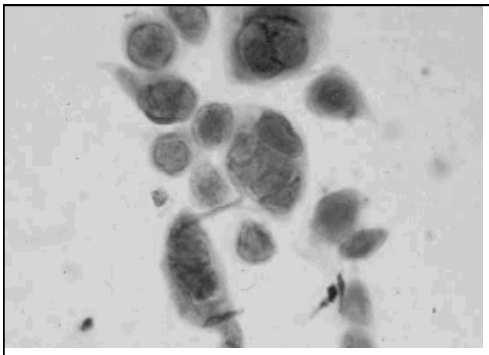
- ***~40% HSV+ patients get recurrent lesions***
- ***many HSV+ patients are "silent" secretors***

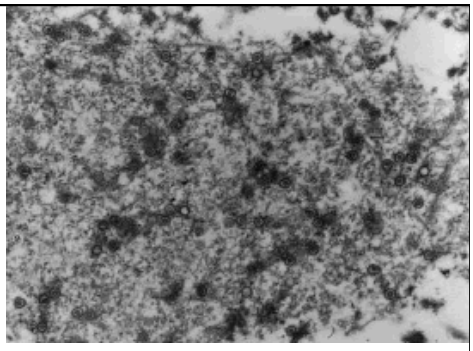
Herpes Simplex 1

- ***DNA virus spread by direct contact***
  - ***open lesion***
  - ***silent secretor***

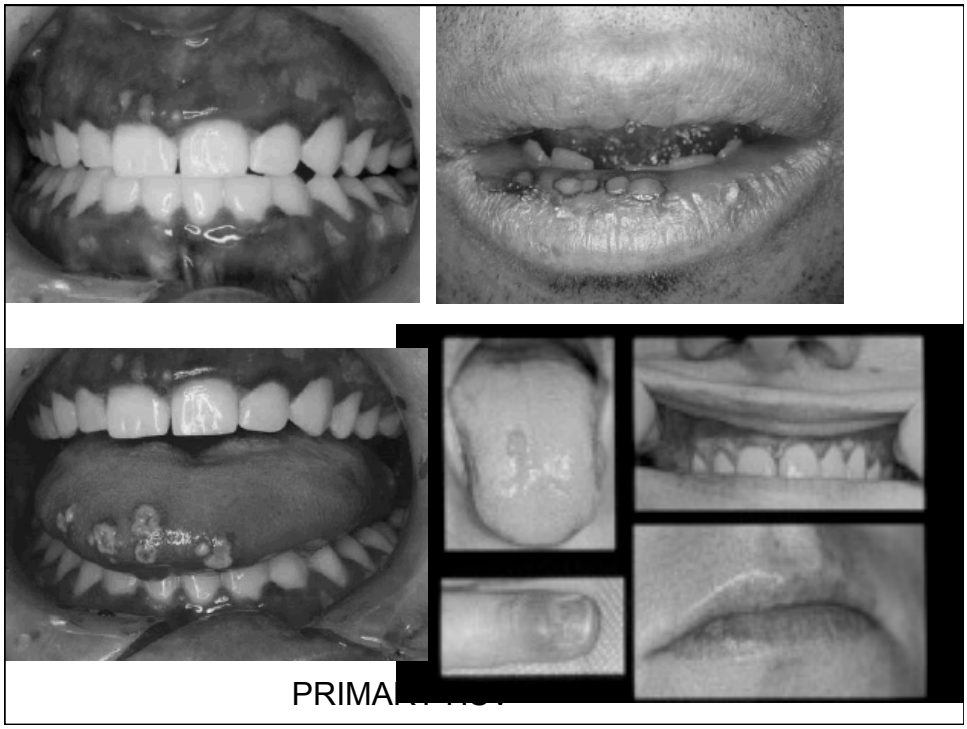
- ***<u>Primary infection:</u>*** ***gingivostomatitis***
- ***(acute, multiple, systemic, constitutional signs)***
- ***Latency (neurotropic)***
- ***<u>Secondary disease:</u>***
  - ***recurrent herpes labialis***
  - ***recurrent intraoral herpes (keratinized tissue,***







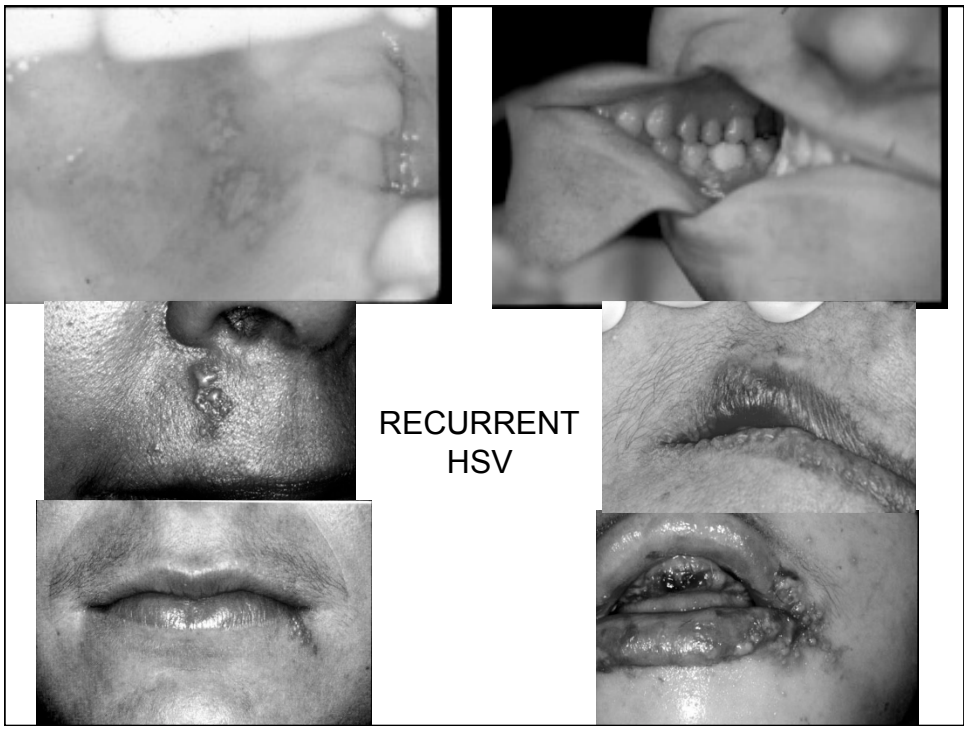
ballooning degeneration, margination of chromatin, and multinucleation.



PRIMARY HSV

PRIMARY HSV

RECURRENT HSV



RECURRENT HSV

Re-emergence from Latency

Neuron activation
- UV irradiation
- Trauma
- Heat

Virus multiplies

Virus spreads down axons to tissue

Virus infects tissues

Recurrent Herpes Simplex 1

- ***Differential Diagnosis: aphthae, EM***
- ***clinical appearance:***
  - ***vesicular stage***
  - ***keratinized mucosa***
  - ***raised white irregular border***
- ***history of recurrent lesions; prodrome***
- ***laboratory diagnosis:***
  - ***exfoliative cytology***
  - ***culture***
  - ***ELISA***

Herpes Simplex 1

- ***Prevention:***
  - ***barrier techniques, medical prophylaxis***
- ***Treatment:***
  - ***palliative:***
    - ***emoillent, diphenhydramine + kaopectate, dyclonine***
  - ***abortive: oral acycolvir; famciclovir; valcyclovir***
  - ***preventive:***
    - ***sun protection >15 SPF for RHL***
    - ***oral acyclovir (400mg bid or tid)***
    - ***topical acyclovir or pencyclovir (FDA topical for HSV1)***

Herpes Simplex 1

SYSTEMIC:

- ***Acyclovir 400 mg tid x 4d***
- ***Famciclovir 125 mg tid x 5d***
  - ***for severe or frequent lesions***
  - ***for immunocompromised hosts***
- ***Valacyclovir 500mg bid x 5d***

TOPICAL: (q2-3 hrs)

- ***Penciclovir (1%)***
- ***Acyclovir (5%)***
- ***Docosanol cream (10%)***

Analgesic
Anti-inflammatory
(medrol dosepak)

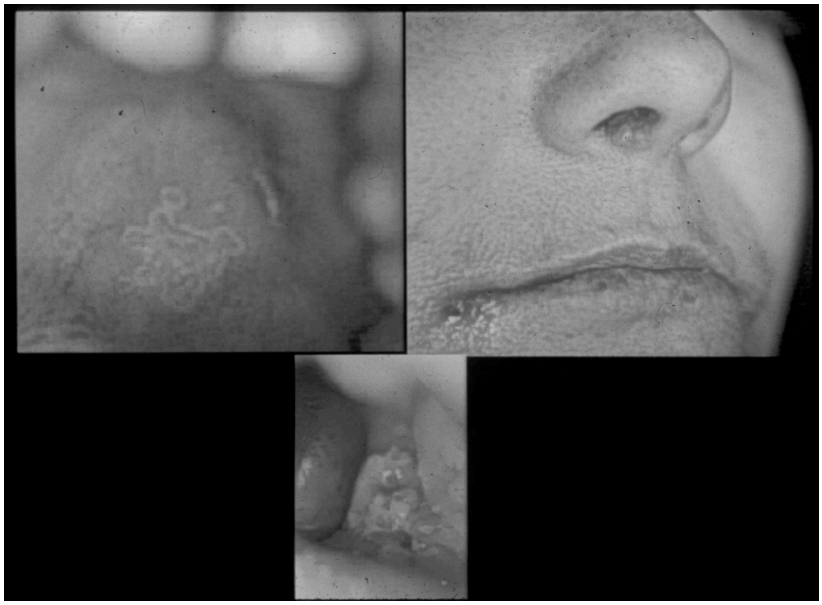
Herpes Simplex 1

Complications:

- ***immunosuppressed (therapeutic, pathologic)***
  - ***chronic and more severe oral HSV***
  - ***hematologic dissemination more common***
- ***erythema multiforme***
- ***frequent recurrence***

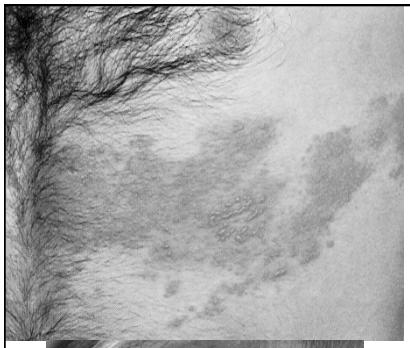
  - *alternate treatments:*

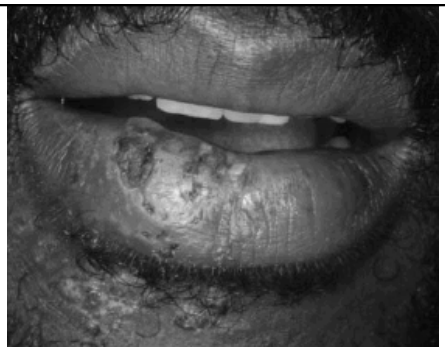
    •famciclovir, foscarnet, valacyclovir, vidarabine

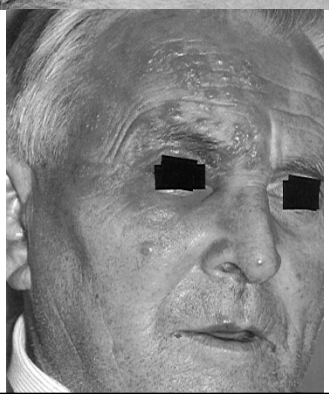


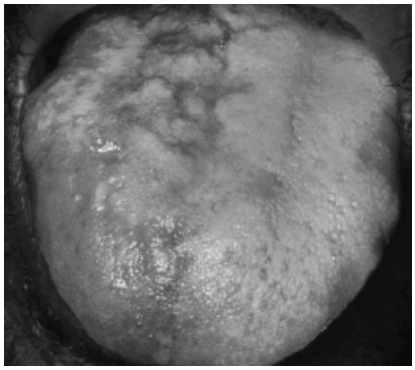
Herpes Zoster (HHV-3)

- ***DNA virus spread by direct contact and airborne***
- ***<u>Primary infection:</u> varicella , chicken pox***
- ***Latency (neurotropic)***
- ***<u>Recurrent infection:</u> h. zoster, shingles***
  - ***3-5/1,000 VZV+ patients***
  - ***80% affect spinal nerves C3, T5, L1, L2***
  - ***19% affect trigeminal nerve; 1st division most common***







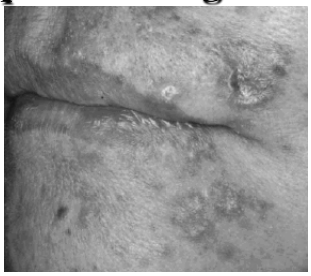


Herpes Zoster

- ***Diagnosis:***
  - ***unilateral dermatomal distribution with sensory prodrome***
  - ***cytology***
  - ***culture***

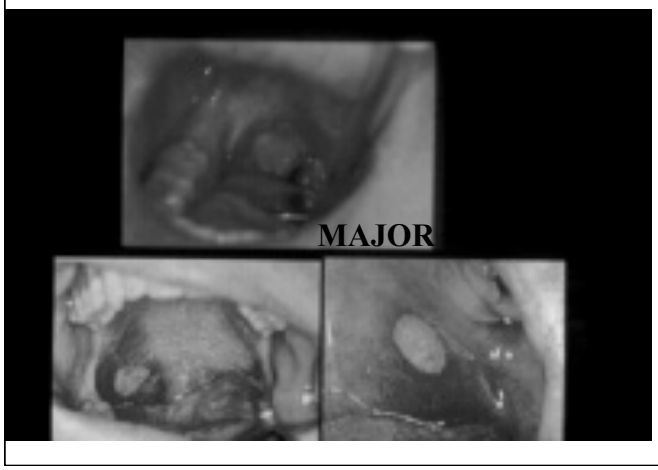
Herpes Zoster: *Post Herpetic Neuralgia*

- ***Neuropathic pain persisting for months to years***
- ***Increased risk over age 55***
- ***Early famcyclovir, steroid, tri-cyclic antidepressant (amitriptyline, nortriptyline)***
- ***Adjuvant neuropathic analgesics for established pain***



Immunologic - APHTHOUS

- MINOR - one or several small, shallow ulcers (<1cm) with brisk erythema; mucosa (v. gingiva)
  - ± prodrome; heal < 2weeks; adolescent onset with variable frequency
  - DDx: HSV, trauma
- MAJOR (Sutton's Dz)- single; posterior more common, >1cm
  - DDx: trauma, infection, carcinoma
  - Maj Aphthae in HIV infection
- HERPETIFORME ……no clinical significance, may be related to, or appear similar to, HSV.



Herpetiforme

Recurrent Aphthous Stomatitis

- 17% prevalence; most common non-traumatic oral ulcer
- multifactorial:
  - hereditary - HLA D77, B12, B51, Cw7; Behcet's
  - hematologic deficiency: Fe, B12, folate (5-7%)
  - immunologic: lymphocytotoxity, antigenic stimulus – microbial?; Antibody dependent cell mediated cytotoxicity (ADCC)
  - trauma, anxiety, allergy, endocrine: impaired barriers

Recurrent Aphthous Stomatitis

- **Diagnosis:**
  - **typically one of exclusion (HSV, trauma, infection, carcinoma for major aphthae)**
  - **History and examination (the 4 QUESTIONS)**
- **Onset after age 40 or frequent / severe ulcers:**
  - **CBC with differential, red cell indices**
  - **B12, folate, serum iron / TIBC => ANEMIAS**

Recurrent Aphthous Stomatitis

- ANEMIA: decreased oxygen carrying capacity
  - RBC destruction - hemolysis (infection, hypersplenism, autoimmune; G6PD deficiency, sickle cell and thalessemias)
  - Blood loss - iron deficiency
  - decreased RBC production: pernicious, B12 and folate anemia
- Signs and Symptoms:
  - skin v. mucosal pallor, fatigue, dyspnea
  - atrophic, erythematous tongue and mucosa

Anemia - Laboratory Evaluation

- Hgb < 11mg/dl
- MCV > 95-99: Macrocytic Anemia
  - B12, folate
  - Pernicious Anemia (anti IF, Shilling test)
- MCV < 80: Microcytic anemia
  - iron deficiency (blood loss v. dietary), thalassemia
- Serum B12, folate, iron

Treatment Recurrent Aphthous

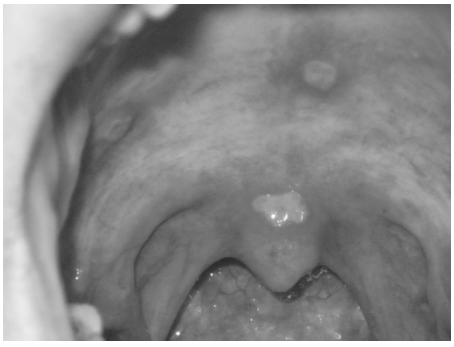
- MINOR:
  - topical moderate-weak steroid
  - aphthasol ointment, debacterol cautery
  - new OTCs on the way
- MAJOR:
  - topical potent steroid if accessible
  - steroid rinse (decadron elixir 0.5mg/5cc, tid)
  - injectable steroid (aristospan, dexamethasone)
  - medrol dosepak, 4mg x 21 tabs over 6 days

Topical Steroid Relative Potency

Most Potent:	*clobetesol 0.05%* *halbetesol 0.05%*	*temovate* *ultravate*
High Potency:	*flucinonide 0.05% lidex* *halcinonide 0.01% halog*	
Moderate:	*triamcinolone 0.5%* *betameth diprop 0.05%*	*aristosport* *diprosone*
Low Potency	*triamcinolone 0.1%* *betameth valerate*	*kenalog* *valisone*
Weak	*hydrocortisone 1%*	

Severe Recurrent Aphthous

- If underlying disease - treat
  - anemia, malabsorption, other systemic dz
- If no underlying disease
  - steroid rinse (decadron elixir 0.5mg/5cc, tid)
  - tetracycline rinse
  - judicious use of low dose prednisone
  - DMDs: dapsone, levamisol, cholchicine
  - ??: lysine, thalidomide, pentoxyphylline



Immunologic - Erythema Multiforme

- Acute, generalized, variable lesion with or without skin involvement (target / iris lesion); hands, feet, face most common
- hypersensitivity reaction (CMI, immune complexes)
- immunopathologic features nonspecific
- identified precipitating factors:
  - medications, infection, foods, oral hygiene products, HSV
  - sulfonamides, pcn, phenobarb, bactrim

Immunologic - Erythema Multiforme

- EM: acute onset with only mucosal involvement
- Stevens Johnson: skin, oral, ocular, genital
- Toxic Epidermal Necrolysis: > 25% skin surfaces; significant risk for infection, dehydration, electrolyte imbalance, visceral dz => death.


10 mm

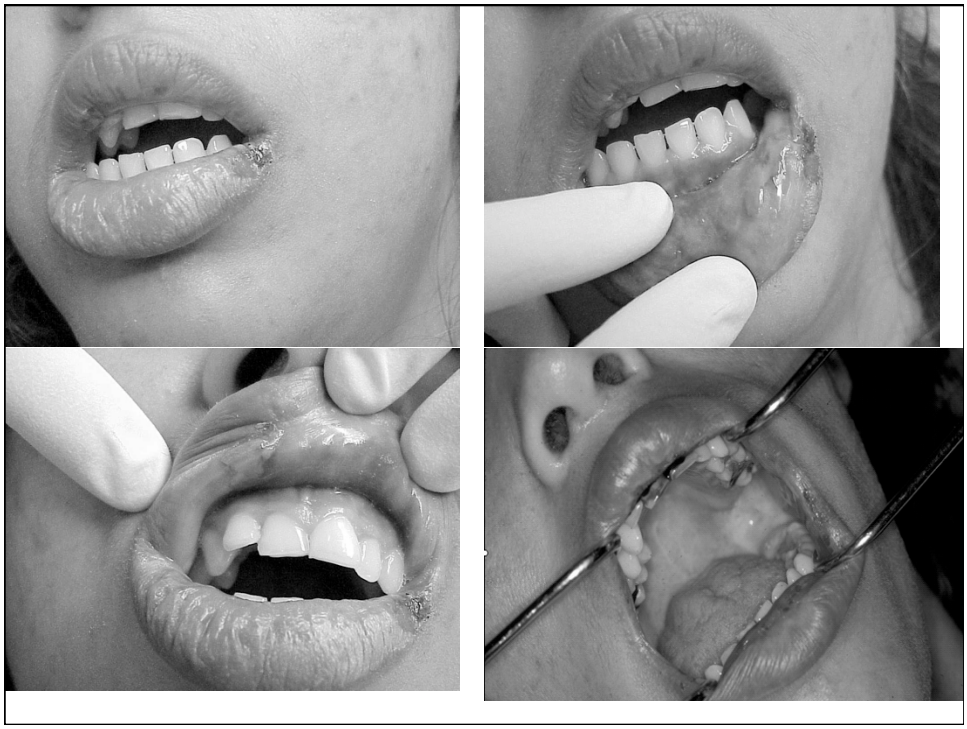
Immunologic - Erythema Multiforme

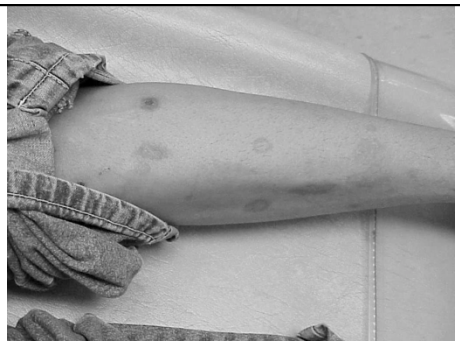
- **Treatment**

- palliative - OTC anti-inflammatory analgesic
- medrol dosepak 4mg x 21tabs over 6 days
- prednisone

Recurrent / Chronic Erythema Multiforme

- relationship to HSV
- 15% with h/o oral HSV
- increased serum HSV Ab titers





Recurrent / Chronic Erythema Multiforme

- empirical acyclovir prophylaxis and re-eval

Behcets Disease

- recurring aphthous-like oral ulcers,
- recurring genital ulcers
- eye lesions: uveitis or retinal vasculitis

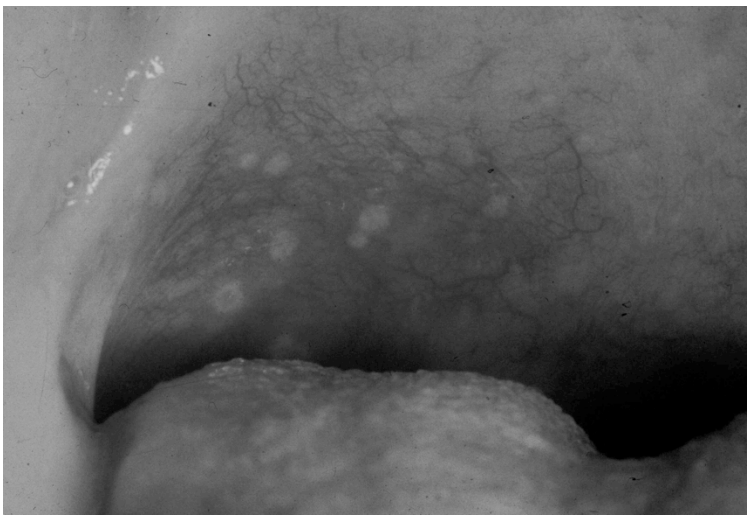
- Immunocomplexes, vasculitis of small and medium-sized blood vessels, immunocompetent T lymphocytes and plasma cell
- genetic component to the disease, with a strong association with HLA-B51

- TX: varies based on severity: azathioprine, pentoxyphylline, cyclosporin, colchicine; or palliative topical steroid

HAND-FOOT-AND-MOUTH DISEASE

- caused by infection with coxsackievirus A16

- low-grade fever
- RAS-like oral vesicles and ulcers
- Cutaneous nonpruritic macules, papules, and vesicles, particularly on the extensor surfaces of the hands and feet.
- TX: Palliative



Oropharyngeal Carcinoma

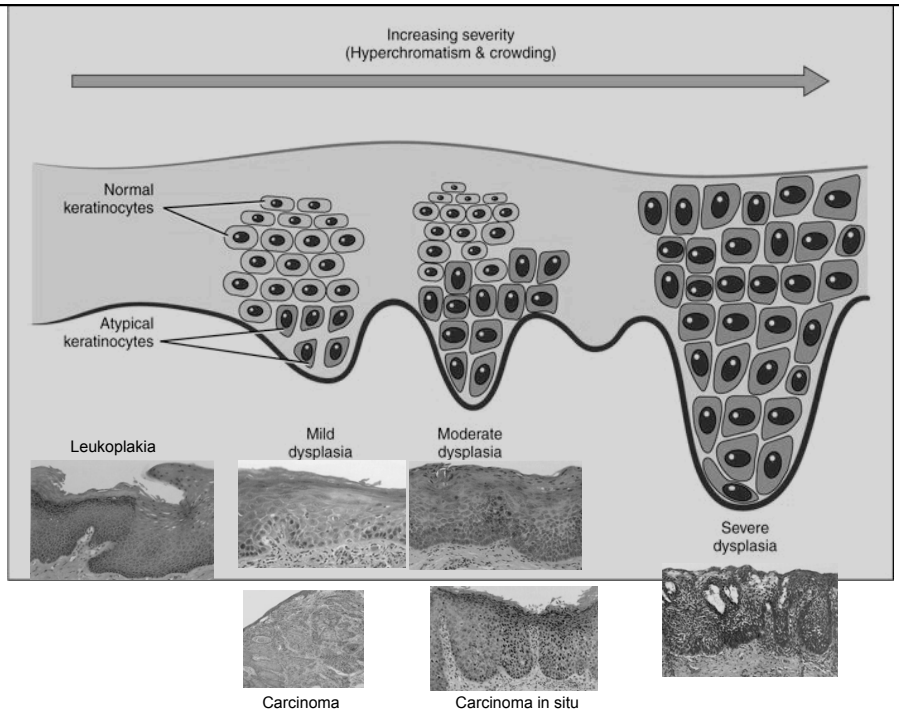
- 31,000 new cases yearly: 3.5 diagnoses each hour
- 9,000 deaths yearly: 1 death per hour
  - more deaths than from cervical cancer, malignant melanoma, Hodgkin's disease
- Oral cancer is more common than:

leukemia Hodgkin's Disease thyroid Ca

Ovarian Ca Cervical Ca

Cancer of the:

brain liver bone stomach

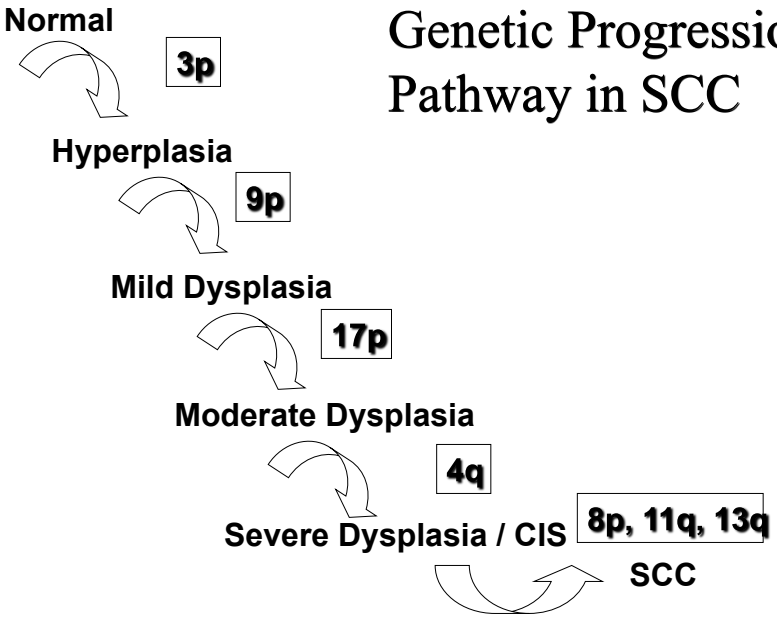


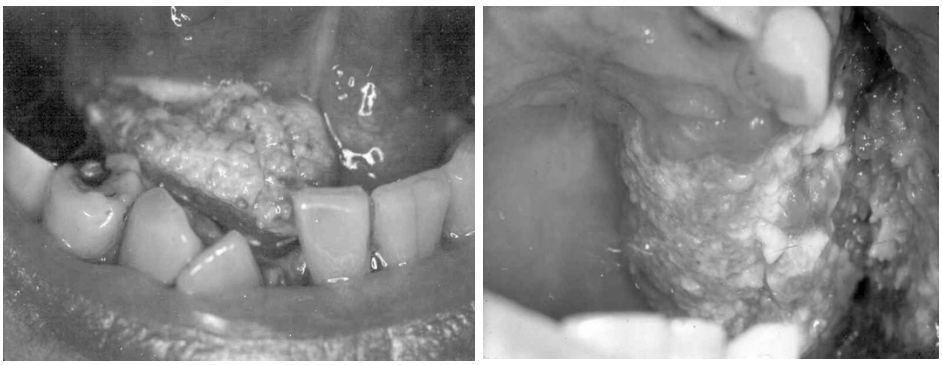
Molecular Events Culminating in Cancer

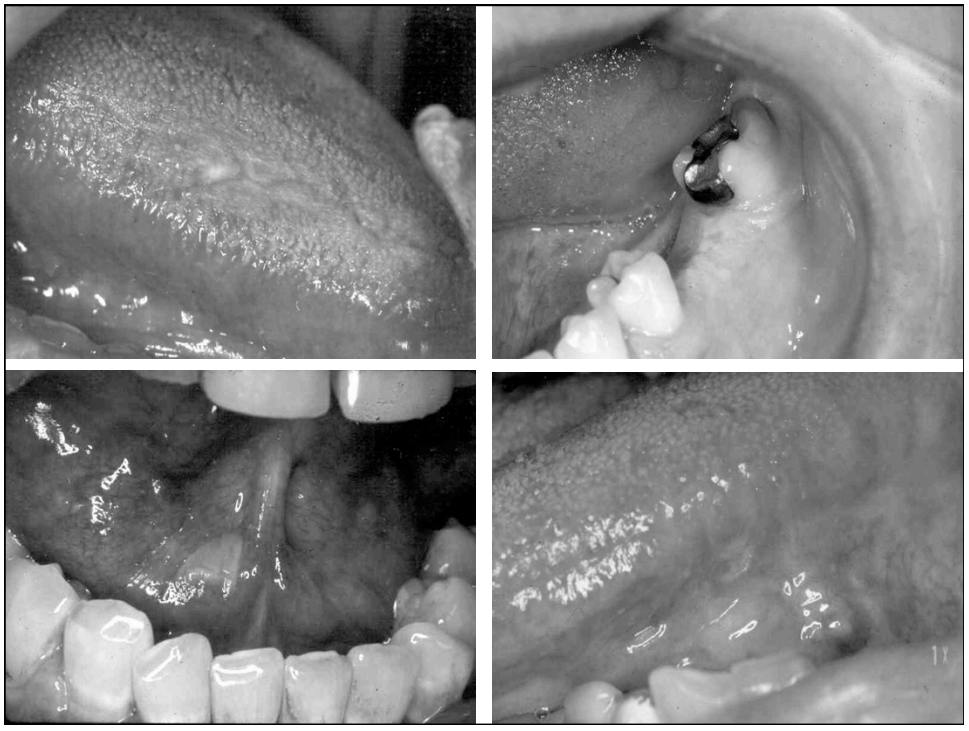
- Increased cell cycling
- Loss of tumor suppressor genes; expression of oncogenes
- Angiogenesis
- Cell motility
- Extracellular matrix invasion
- Vascular penetration
- Tumor cell adhesins bind to endothelium, penetration, invasion of connective tissue

- Responses associated with growth factors (eg: EGF, PDGF), growth factor receptors & altered tumor suppressor genes (eg: P53, Rb)

Genetic Progression Pathway in SCC





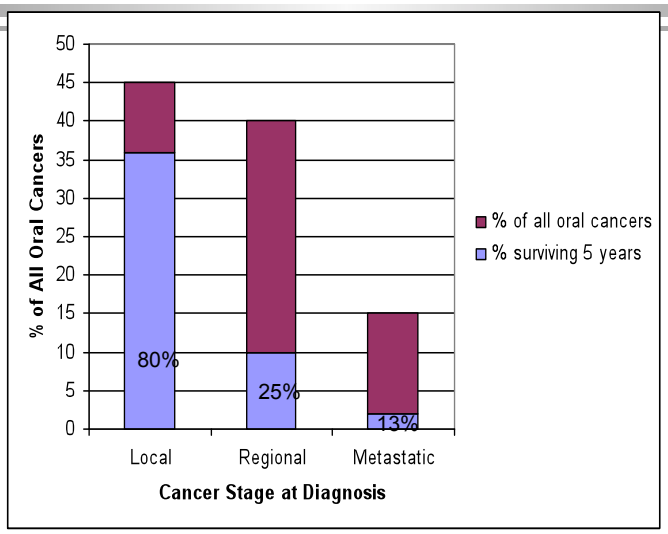


U.S. OROPHARYNGEAL CANCER STATISTICS

31,000 new cases yearly (3.5 every hour)

- Overall 5 year survival rate 50%
- 60% with advanced disease at diagnosis
- Mortality rate unchanged for 50 years
- Early detection = Improved survival

5 year survival rate for oral cancer by stage at diagnosis



Staging of Oral Squamous Cell Carcinoma

T=Tumor

- T1 – tumor less than 2 cm in diameter
- T2 – tumor 2-4 cm in diameter
- T3 – tumor greater than 4 cm in diameter
- T4 – tumor invades adjacent structures

N= Node

- N0 – No palpable nodes
- N1 – Ipsilateral (same side as primary tumor) palpable nodes
- N2 – Contralateral (opposite side from primary tumor) or bilateral nodes
- N3 – Fixed palpable node(s)

M= Metastasis

- M0 – No metastasis
- M – Clinical evidence of metastasis

TMN Staging System

Stage I	**T1**	**N0**	**M0**
Stage II	**T2**	**N0**	**M0**
Stage III	**T3**	**N0**	**M0**
	T1	**N1**	**M0**
	T2	**N1**	**M0**
	T3	**N1**	**M0**
Stage IV	**T1**	**N2**	**M0**
	T2	**N2**	**M0**
	T3	**N2**	**M0**
	T1	**N3**	**M0**
	T2	**N3**	**M0**
	T3	**N3**	**M0**
	T4	**N0**	**M0**
	Any patients with M1		

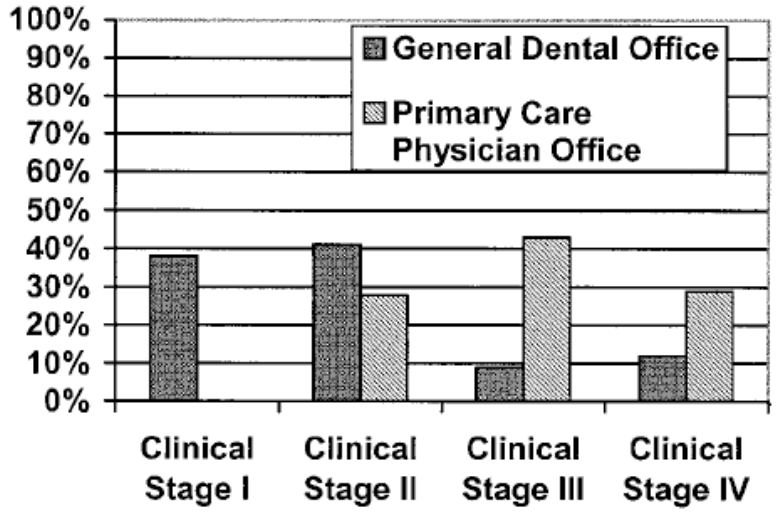


FIGURE 7. Percentage of patients in each clinical stage based on detection in a general dental office or a primary care physician office.

Holmes et al J Oral Max Surg 2003

Detecting Early Oral Cancer

natural history of oral cancer is such that the asymptomatic, pre-malignant lesion can be identified long before malignant transformation if individuals are properly evaluated and adequate assessment technology exists to support the diagnostic process

The Difficulty With Oral Cancer Screening

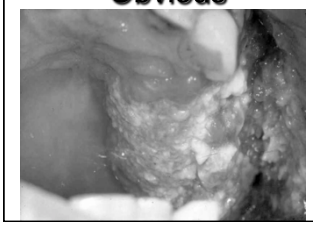
Classic features of oral cancer:

- Nodularity
- Chronic ulcer, red, white or mixed red/white lesion
- Fixation
- Large size are features of advanced lesions, not early ones

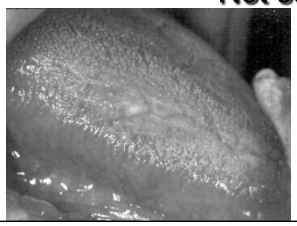
Precancerous and early cancerous lesions appear identical to common, benign-looking lesions- no distinctive features

Benign-looking but dangerous lesions are left to progress to advanced stages

Obvious

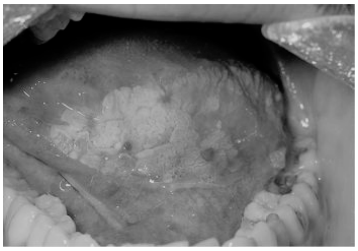


Not so obvious





vs.




What is the "state of the art"?

COVER STORY

Adjunctive techniques for oral cancer examination and lesion diagnosis

A systematic review of the literature

Lauren L. Patton, DDS, FDS RCSEd; Joel B. Epstein, DMD, MSD, FRCD(C), FDS RCSEd; A. Ross Kerr, DDS, MSD

Conclusions. There is evidence that TB is effective as a diagnostic adjunct for use in high-risk populations and suspicious mucosal lesions. OralCDx is useful in assessment of dysplastic changes in clinically suspicious lesions; however, there are insufficient data meeting the inclusion criteria to assess usefulness in innocuous mucosal lesions. Overall, there is insufficient evidence to support or refute the use of visually based examination adjuncts.

Practical Implications. Given the lack of data on the effectiveness of adjunctive cancer detection techniques in general dental practice settings, clinicians must rely on a thorough oral mucosal examination supported by specialty referral and/or tissue biopsy for OPML diagnosis.

JADA 2008;139(7):896-905

Systematic review of 23 papers meeting quality criteria

Toluidine Blue
Vizilite + TB
Vizilite
Microlux
Orascoptic
VELScope
Oral CDx Brush

What is the "state of the art"?

Critical evaluation of diagnostic aids for the detection of oral cancer ☆

Mark W. Lingen [a,*], John R. Kalmar [b,e], Theodore Karrison [c,f], Paul M. Speight [d,g]

Oral Oncology (2008) 44, 10–22

Summary Historically, the screening of patients for signs of oral cancer and precancerous lesions has relied upon the conventional oral examination. A variety of commercial diagnostic aids and adjunctive techniques are available to potentially assist in the screening of healthy patients for evidence of otherwise occult cancerous change or to assess the biologic potential of clinically abnormal mucosal lesions. This manuscript systematically and critically examines the literature associated with current oral cancer screening and case-finding aids or adjuncts such as toluidine blue, brush cytology, tissue reflectance and autofluorescence. The characteristics of an ideal screening test are outlined and the authors pose several questions for clinicians and scientists to consider in the evaluation of current and future studies of oral cancer detection and diagnosis. Although the increased public awareness of oral cancer made possible by the marketing of recently-introduced screening adjuncts is commendable, the tantalizing implication that such technologies may improve detection of oral cancers and precancers beyond conventional oral examination alone has yet to be rigorously confirmed.

C O V E R S T O R Y

JADA, Vol. 141. May 2010
http://jada.ada.org

Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas

Michael P. Rethman, DDS, MS; William Carpenter, DDS, MS; Ezra E.W. Cohen, MD; Joel Epstein, DMD, MSD, FRCD(C), FDS RCS(Ed); Caswell A. Evans, DDS, MPH; Catherine M. Flaitz, DDS, MS; Frank J. Graham, DMD; Philippe P. Hujoel, MSD, PhD; John R. Kalmar, DMD, PhD; Wayne M. Koch, MD; Paul M. Lambert, DDS; Mark W. Lingen, DDS, PhD; Bert W. Oettmeier Jr., DDS; Lauren L. Patton, DDS; David Perkins, DMD; Britt C. Reid, DDS, PhD; James J. Sciubba, DMD, PhD; Scott L. Tomar, DMD, DrPH; Alfred D. Wyatt Jr., DMD; Krishna Aravamudhan, BDS, MS; Julie Frantsve-Hawley, RDH, PhD; Jennifer L. Cleveland, DDS, MPH; Daniel M. Meyer, DDS; for the American Dental Association Council on Scientific Affairs Expert Panel on Screening for Oral Squamous Cell Carcinomas

Results. The panel concluded that screening by means of visual and tactile examination to detect potentially malignant and malignant lesions may result in detection of oral cancers at early stages of development, but that there is insufficient evidence to determine if screening alters disease-specific mortality in asymptomatic people seeking dental care.

Clinical Implications. The panel suggested that clinicians remain alert for signs of potentially malignant lesions or early-stage cancers while performing routine visual and tactile examinations in all patients, but particularly in those who use tobacco or who consume alcohol heavily. Additional research regarding oral cancer screening and the use of adjuncts is needed.

Optimal Detection of Oropharyngeal Carcinoma:
Current and Emerging Diagnostic Technologies

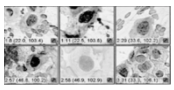
Investigators: David Sirois, DMD,PhD
Ross Kerr, DDS,MSc
Miriam Robbins, DDS,MPH
Silvia Spivakovsky, DMD
Francisco Bermudez, DMD,PhD (Puerto Rico)
Joseph Califano, MD (Johns Hopkins Univ)
Judy Goldberg Sc.D.

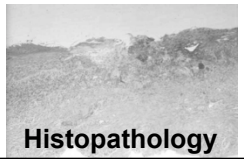
NIDCR/NIH Grant # U54-DE14257

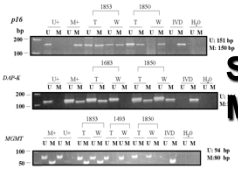
Visual Exam

Vizilite

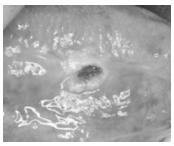
Brush Biopsy



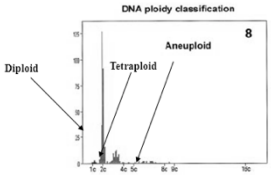




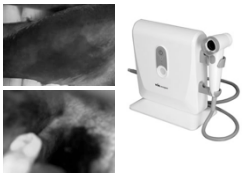
Saliva Markers



Toluidine Blue



Ploidy Analysis



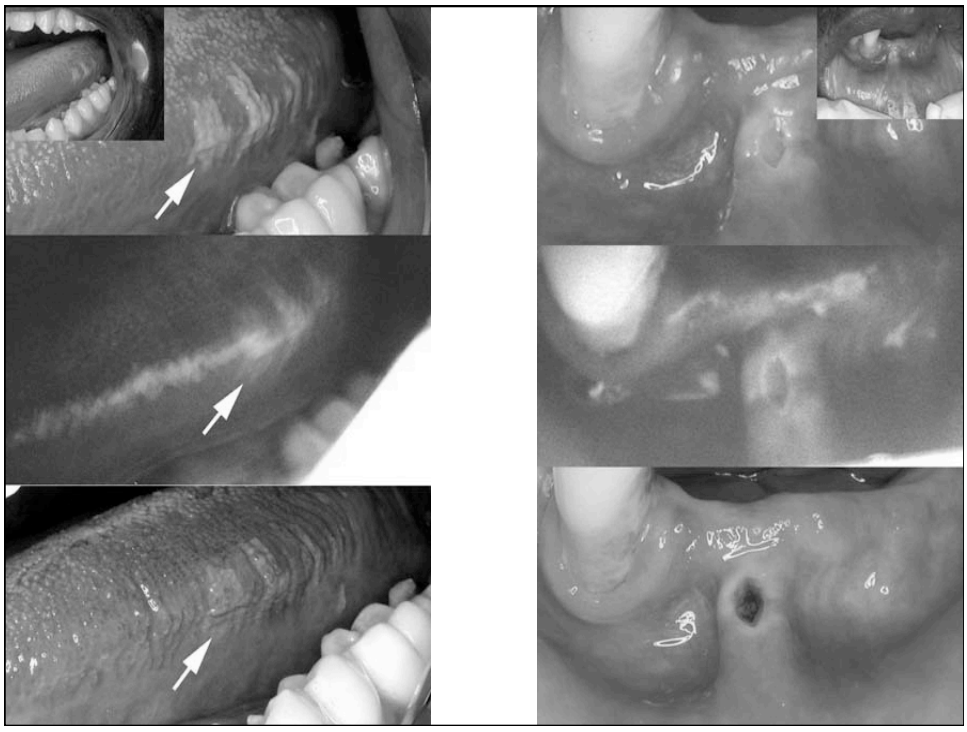
Velscope

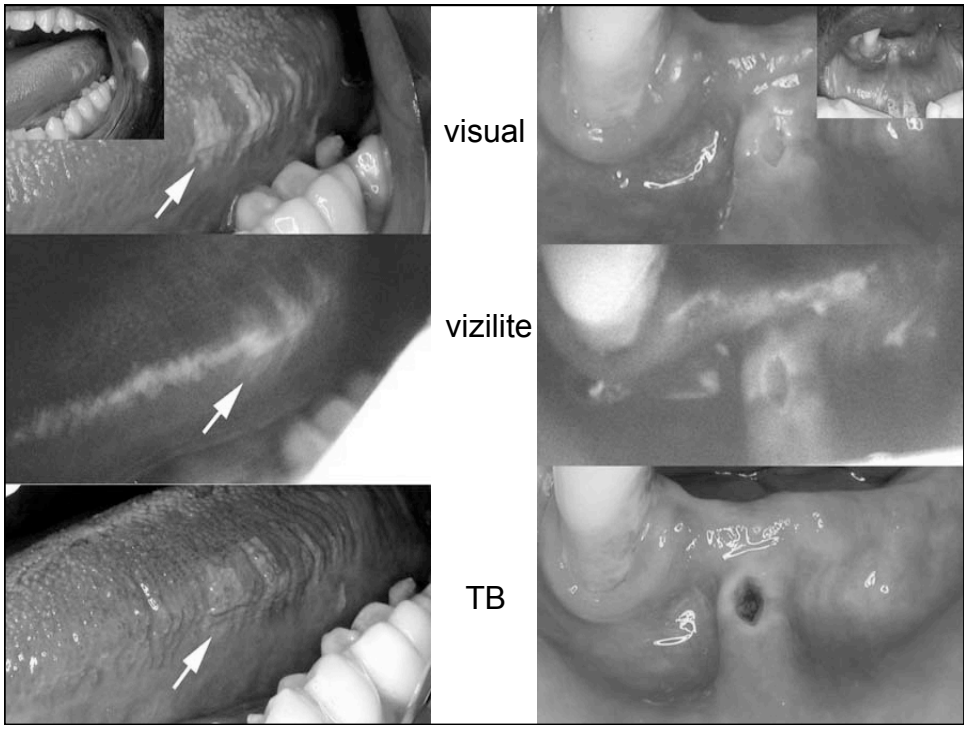
269 subjects with

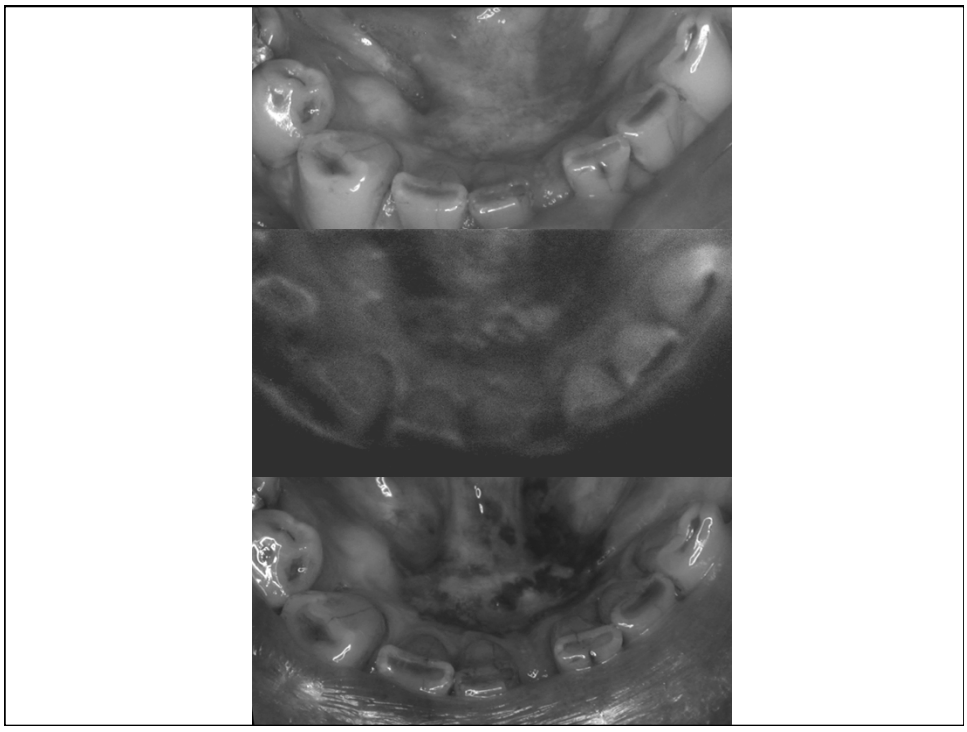
TABLE 3a. Demographic Characteristics by Enrollment Risk Group*

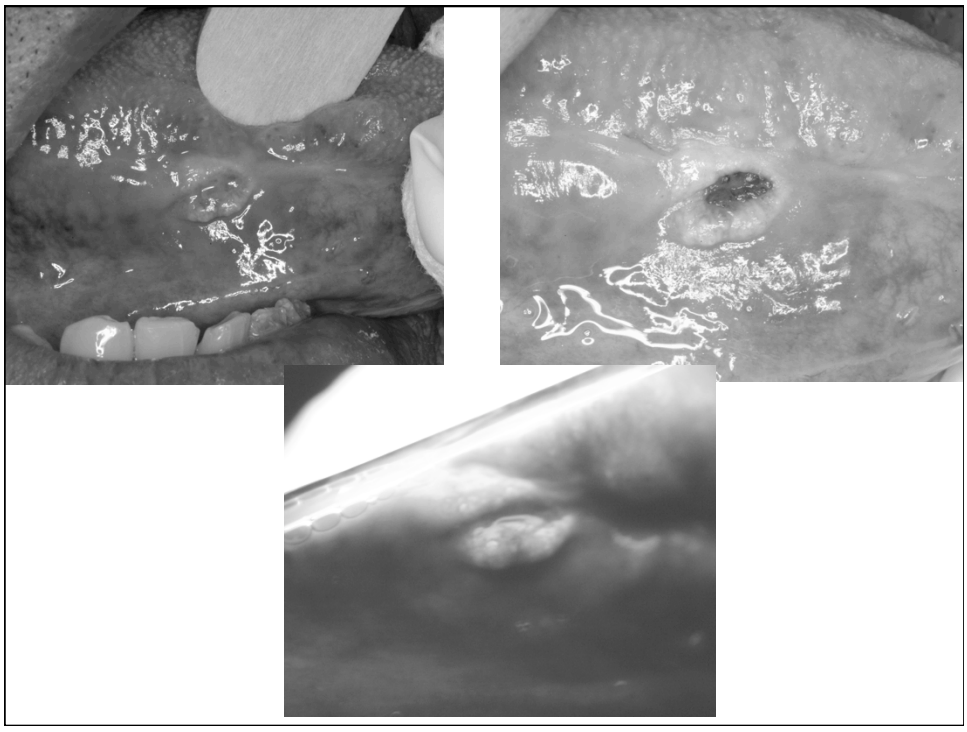
DEMOGRAPHIC CHARACTERISTICS	Low risk enrollment N=132 (100%)	High risk enrollment N=97 (100%)	Known cancer enrollment N=40 (100%)	Total N=269 (100%)	p-value**
Sex					0.29
Male	87 (65.9%)	62 (63.9%)	31 (77.5%)	180 (66.9%)	
Female	45 (34.1%)	35 (36.1%)	9 (22.5%)	89 (33.1%)	
Age (mean ± sd)	50.5±13.3	55.9±12.5	59.0±12.0	53.7±13.2	0.001
Age(25,50,75 percentile)	42,51.5,59	47,56,64	51,56,65	44,54,60	
Race					0.26
White	90 (68.2%)	70 (72.1%)	27 (67.5%)	187 (69.5%)	
African American	36 (27.3%)	19 (19.6%)	8 (20.0%)	63 (23.4%)	
Hawaii – Pac Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Asian	4 (3.0%)	8 (8.3%)	4 (10.0%)	16 (6.0%)	
American Indian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Mestiza	2 (1.5%)	0 (0.0%)	1 (2.5%)	3 (1.1%)	
Ethnicity					0.08
Hispanic – Latino	43 (32.6%)	45 (46.4%)	18 (45.0%)	106 (39.4%)	
Non Hispanic-Latino	89 (67.4%)	52 (53.6%)	22 (55.0%)	163 (60.6%)	
SOURCE INSTITUTION					
NYU Dental School	104 (78.8%)	67 (69.1%)	17 (42.5%)	188 (69.9%)	
Cancer Center Affiliates	5 (3.8%)	10 (10.3%)	11 (27.5%)	26 (9.7%)	
U of Puerto Rico	23 (17.4%)	20 (20.6%)	12 (30.0%)	55 (20.4%)	

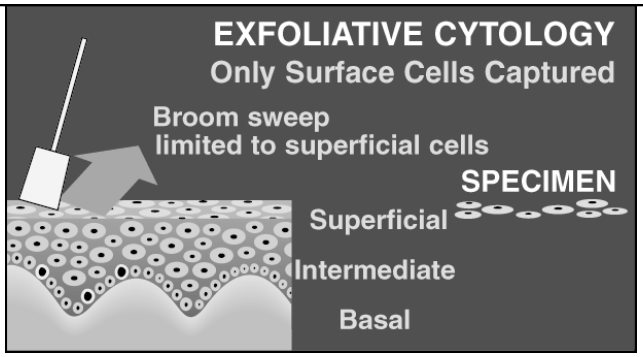
*A maximum of 3 subjects had missing data for a variable within a risk group.
** Nonparametric statistics were used for all group comparisons.

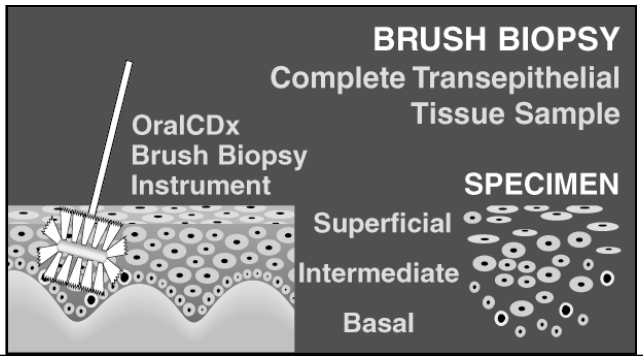



visual
vizilite
TB



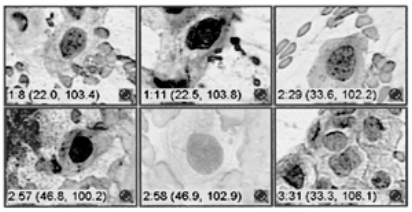



EXFOLIATIVE CYTOLOGY
Only Surface Cells Captured
Broom sweep
limited to superficial cells
SPECIMEN
Superficial
Intermediate
Basal


BRUSH BIOPSY
Complete Transepithelial
Tissue Sample
OralCDx
Brush Biopsy
Instrument
SPECIMEN
Superficial
Intermediate
Basal

OralScan Laboratories Inc

OralCDx™



OralCDx Slide ID: 90004323

Laboratory selected images from OralCDx Display. Refer to full OralCDx test report form.

Oral Brush Biopsy
OralCDX Test Report

PN: Submitting Clinician: Phone:

Biopsy Date: 12/13/1999 Barcode: Fax:

PATIENT INFORMATION

Last Name First Name Middle Name Sex

Social Security Number Date Of Birth Phone Number

Street Address

City State Zip

LOCATION OF ORAL LESION

Lateral Tongue Left

ORALCDx RESULTS

Microscopic Description:	Dysplastic epithelial cells
Cellular Representation:	Superficial, intermediate, and basal cells
OralCDx Result:	Positive for dysplasia or carcinoma

Matthew Klein M.D.
Cytopathologist

12/20/1999
Date

CLIA# 33D0952202
LABORATORY DIRECTOR, DR. STEPHEN FRIST
ORALSCAN LABORATORIES, INC.
2 EXECUTIVE BLVD., SUFFERN, NY 10901
PHONE NUMBER (914) 369-7096
FAX NUMBER (914) 369-7082

Monday, January 24, 2000

OralCDx®

Oral Brush Biopsy
OralCDx® Test Report

Confidential Patient Information
If you received this transmission in error please contact OralScan Laboratories Toll Free 877-672-5722

( ) -
020414A

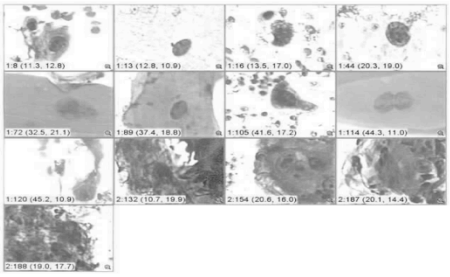
Dr.
Biopsy Date:
Rcv Date:
Phone:
Fax:
PN:

Patient:
Sex:
DOB:
SS#:
Lesion Site: Lateral Tongue
Case:

Microscopic Description: Mild atypia

Cellular Representation: Superficial, intermediate, and basal cells

OralCDx Result: **Atypical epithelial cells-warranting further investigation**



April 15, 2002

Dear Doctor:

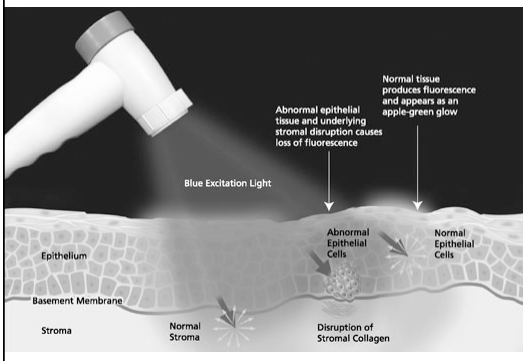
The OralCDx Display shows clusters of hyperplastic basal cells with loss of polarity and crowding, an increase in the nuclear to cytoplasmic ratio, and an increase in nuclear staining.

If this report is a fax, then the original report with color images will be forwarded.

Sincerely,

Dr. Matthew Klein
Cytopathologist
(Electronically Signed)

ORALSCAN LABORATORIES,INC 2 EXECUTIVE BLVD. SUFFERN,NY 10901 PHONE 845-369-7096 FAX 845-369-7082 LABORATORY DIRECTOR DR. STEPHEN FRIST CLIA# 33D0952202



VELscope – example of autofluoresence technology

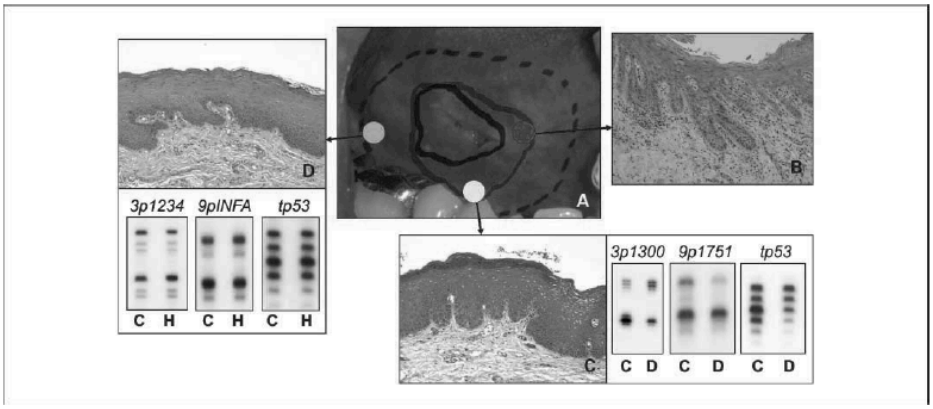


Fig. 3. Presence of high-grade histology or molecular clones in FVL margins outside of clinically apparent tumor. *A*, mapping of surgical field showing three boundaries: clinically apparent tumor (*blue*), FVL boundary (*green*), and boundary of surgical specimen (*red*). *B*, photomicrograph of FVL margin (*red circle*) showing high-grade dysplasia. *C*, photomicrograph and LOH images of FVL margin (*yellow circle*) showing mild dysplasia with LOH at *D3S1300*, *D9175*1, and *tp53*. *D*, photomicrograph and LOH images of FVR margin (*green circle*) showing no dysplasia and heterozygosity (no LOH) at *D3S1234*, *D9INFA*, and *tp53*. Magnification, ×100.

Fluorescence Visualization Detection of Field Alterations in Tumor Margins of Oral Cancer Patients

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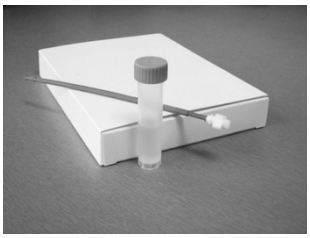
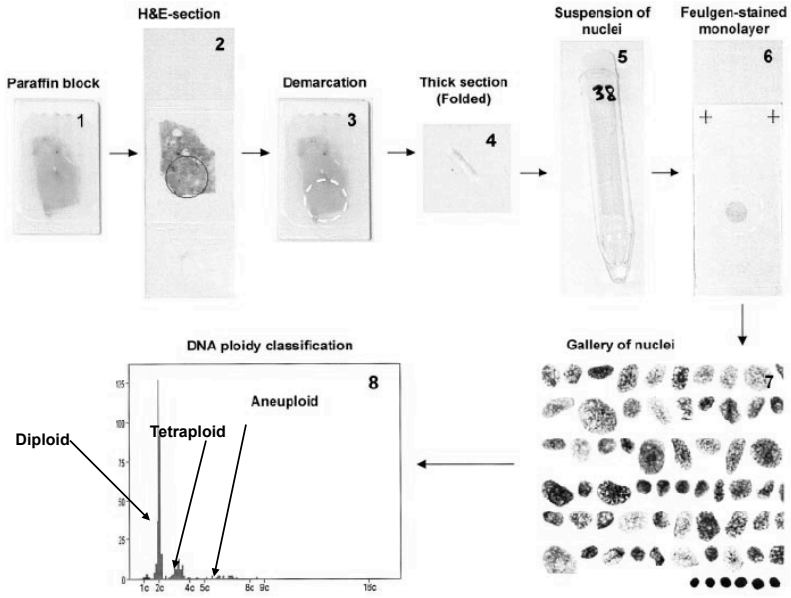
DNA Ploidy

- Refers to quantitative DNA content within cell nuclei
- A normal nucleus in interphase has diploid DNA content (2N)
- Polyploidy refers to an increase in DNA content by whole number multiples of the entire set of chromosomes (eg tetraploidy (4N) in S-phase
- Aneuploidy indicates a deviation from the normal 2N complement of chromosomes that is usually accompanied by structural losses/gains of chromosomes



Perceptronix Oral Advance System™ using ClearCyte™ automated image cytometer

Workflow for ploidy analysis from tissue block



	Sensitivity			Specificity		
Test Type	Sample size (# lesions)	Point Estimate	95%Confidence Interval	Sample Size (# lesions)	Point Estimate	95%Confidence Interval
Clinical Examination	142	0.70	(0.62, 0.78)	234	0.74	(0.68,0.80)
Vizilite	142	0.61	(0.53, 0.69)	234	0.41	(0.34,0.48)
Toluidine Blue	142	0.81	(0.73, 0.87)	234	0.56	(0.49, 0.63)
Brush Biopsy	133	0.62	(0.52, 0.70)	226	0.83	(0.77, 0.88)

Table 13. Summary of results of logistic regression models to identify dysplasia or cancer based on the worst lesions identified on the scalpel biopsy. All patients (N=258), dysplasia and cancer (N=108).

Model Components	CLINICAL EXAM		CLINICAL EXAM, VIZILITE		CLINICAL EXAM, TOLUIDINE		CLINICAL EXAM, BRUSH BIOPSY		CLINICAL EXAM, VIZILITE, TOLUIDINE		CLINICAL EXAM, VIZILITE, BRUSH BIOPSY		CLINICAL EXAM, TOLUIDINE, BRUSH BIOPSY		CLINICAL EXAM, VIZILITE, TOLUIDINE, BRUSH BIOPSY	
	Coeff-icient	p	Coeff-icient	p	Coeff-icient	p	Coeff-icient	p	Coeff-icient	p	Coeff-icient	p	Coeff-icient	p	Coeff-icient	p
Intercept	-1.31	<.0001	-1.45	<.0001	-1.66	<.0001	-1.58	<.0001	-1.81	<.0001	-1.70	<.0001	-1.79	<.0001	-1.91	<.0001
Clinical exam	2.00	<.0001	2.02	<.0001	1.64	<.0001	1.38	<.0001	1.66	<.0001	1.39	<.0001	1.18	0.0006	1.20	0.0005
Vizilite			-0.07	0.44					0.24	0.42	0.18	0.56			0. 19	0.54
Toluidine stain					0.82	.02			0.82	0.02			0.52	0.15	0.52	0.14
Brush biopsy							1.61	<.0001			1.61	<.0001	1.53	<.0001	1.52	<.0001
Model Fit Statistics																
	Chi-Square	p	Chi-Square	p	Chi-Square	p	Chi-Square	p	Chi-Square	p	Chi-Square	p	Chi-Square	p	Chi-Square	p
Likelihood ratio test	55.89	<.0001	56.50	<.0001	61.70	<.0001	80.64	<.0001	62.35	<.0001	80.97	<.0001	82.71	<.0001	83.09	<.0001
Score Statistic	54.13	<.0001	54.61	<.0001	58.64	<.0001	75.92	<.0001	59.08	<.0001	76.15	<.0001	77.40	<.0001	77.62	<.0001
Wald	49.58	<.0001	49.79	<.0001	51.87	<.0001	62.26	<.0001	51.98	<.0001	62.61	<.0001	63.26	<.0001	63.25	<.0001
AUC																

Combining tests…. Only the BB improves the Clinical Exam Outcome