

“ORAL LESIONS: TOPICAL MEDICATIONS, A CLINICO-PHARMACOLOGICAL STUDY”

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Abstract-Clinical Practice & Hence Medical Education & Clinical Research, Witnessed Recent Considerable Increase, In Oro-Pharyngeal Diseases, With Substantial Statistically Increased Emergence Of Smoke, Smokeless Tissue Reactions Clinical Entities E.g Various Stomatitis, Oral Mucositis, Frictional Hyperkeratosis & Sub-Mucous Fibrosis Etc., Comprising Variety Of Clinico-Morpho-Pathological Combinations And Differing Pre-Malignant / Malignant Transformations.

Present Study Includes More Than (2) Decades Of, Thousands Of Patients Management, Manifesting Different Stages Of Distinctly Variables / Mixed Clinical Presentations, Of Oral Cavity Diseases, Due To Traditional Betel, Tobacco Chewing Habits & More Recently Available Preparations Like PanMasalas & Others. Conducted Mostly, In The Eastern Parts Of India, As One Of The Maximum Incidence In The World Or Elsewhere.

One Of The Most Important Clinical Applicabilities Of Basics Of Clinico-Pathological Oncology Involving Severity, Chronicity & Transformations Of Oral Lesions, Because Of Constant Exposure To Aetiological Variants, While Management Of Initial Stages Of Oral Pathologies, By Implying 'Drug Delivery System(DDS)' Aspects Of Pharmaco-Therapeutics, Evolved The Situation Circumstance Of Using Available Systemic, Regional Relevant Medicines Together Safely, As A 'Local Application Preparation', To Achieve Significant Improvement In A Large Percentage Of Population, With Variety Oral Lesions Manifestations To Significantly High Proportions Closed Surveillance For Availability Of More Sophisticated Effective, Safe Alternative Pharmacological Substances, To Be Replacedly Included, As Basic Constituents Of Discussed 'Oral Preparation', Was Maintained To Maximize Patient Benefit.

Under Honest Discrete Supervision, Closely Monitored Observations Based Clinical Evaluations & Assessments, In Thousands Of Patients, Have Statistical & Logistic Support Of Usefulness, As Definitive Treatment Or Symptomatic Relief & Or As An Adjunct To Latest Modalities Of Management. Evidently Demonstrable Drastic Improvements In Associated Co-Existing 'Oral Lesion' Variables, Specially Of Recently More Common Infective, Inflammatory, Metabolic, Auto-Immune, Post Radiation, Chemotherapy & Other Similar Clinical Entities, Added Considerably To 'Oral Preparation' Usefulness.

Keywords- 1. Smoke & Smokeless Tobacco Tissue Reactions
2. Oral Reactive Lesions Variables, Oral Pre-Malignant Lesions (OPL I & II)
3. Local Chemoprophylaxis: Clinical Efficacy & Drug Delivery System(DDS)
4. Supportive Measures: Chemoprevention, Nicotine Dependence Treatments, Cancer Diagnostics, Surgical & Physiotherapy Interventions

1. INTRODUCTION Clinical Scenario During Last (25) Years, Is Overwhelmed With Gradual Statistically Considerable, Increased Evidence Of Clinical Entities Like Nicotine Stomatitis, Oral Mucositis Of Varying Aetiopathogenesis, Oral Mucosal Frictional Hyperkeratosis, Oral Lichen Planus, Candidiasis And Other Recently More Common Infective, Inflammatory, Nutritional, Metabolic, Auto-Immune, Post-Radiation, Chemotherapy Diseases Oral Affections, Besides Established Oral Pre-Malignant lesions (OPL I & II) and Oral Carcinoma.

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WHO Classification Categorized Diseases, In 1970s & 1980s Onwards.^{1,2,3} **Reactive Allergic Hypersensitivity Reactions**, Exhibit Different Severity, Recurrence, Relapse And Chronicity Variants, Have Variable **Premalignant (±) Malignant Transformation Potentials & Status Gradation As 'Risk Factors'**.

The Attributing **Aetiological Factors** Include **Oral Hygiene, Tobacco Smoke & Smokeless Tissue Reactions**, Different Methods Of **Intra-Oral Tobacco Applications**, Available By Different Names, Swedish Stuff Etc. Used in United States, Scandinavia & South Asia Including India And Other Parts Of Globe. Presence Of **Nonhomogeneous Group Of Compounds & Other Toxic Contents E.g. Aldehydes, Polycyclic Hydrocarbons, Nitrosamines, Heavy Metals & Other Chemicals** Are Believed To Be Responsible Causative Factors.

In The **Discussed Clinico-Pharmacological Study, The Aetio-Pathogenesis Based**

Scientific Pharmacological Help To These Lesions Had Been Achieved By A Combination Of Different Groups Of Available Systemic Medications, Belonging To Different Pharmacological Category. The Various Different Ingredients Have Been Constantly Replaced By Recent More Efficacious, Gradually Available Drug Molecules, **With Consideration Of 'Drug Delivery Pharmaco-Therapeutics**, To Achieve Maximal Available Medical Therapy Support, As Curetative & Or Palliative Management Or As Adjunct To Latest Treatment Modalities.

Clinico-Pathological Oncology Aspects Of The Study, Comprised **OverAll Control** Of Severity, Chronicity & Transformations Of Oral Lesions, Because Of Constant Exposure To Aetiological Variants, **By Management Of Initial Stages Of Oral Pathologies**, Minimizing The OverAll Mortality & Morbidity Of Significantly Prevalent Disease Processes.

2. MATERIALS AND METHODS

The Study Includes More Than (2^{1/2}) Decades Of, **Management Of Thousands Of Patients, In Different Stages Of Distinctly Variable Diseases / Mixed Clinical Pictures Of Oral Cavity Manifestations**. Largely Conducted In **The Eastern Parts Of India**, As One Of The Maximum Incidence In The World Or Elsewhere, Due To **Traditional Betel, Tobacco Chewing Habits** & More Recently Available Preparations Like PanMasalas, Guthkas etc. Besides **Other Conventional Tobacco Use Methods**.

The Study **Also Included Subjects Different Regions Of India, Europe, Africa, Middle East, South East Asia & Other Parts Of The World**.

Other Indications For UseFul Applications, Included Different Stages Of Radiation ChemoTherapy Induced Mucositis, Oral Manifestations Of HIV/AIDS, KidneyTransplant Patients, Other Immunosuppressive Conditions And Therapies Etc.

The Local Application Ingredients Included, Local Antiseptics, Local Anaerobs, Antimicrobials, Local Antifungals, Local Steroids ± Chemoprophylaxis Agents In Suitable Soothing Emollient Base.

The Use Of 'Oral Preparation', As Definitive Curetative Management, Symptomatic, Palliative Therapy, As An Adjunct To Latest Modalities Of PhysioTherapy; Oral Mouth Dilatation Devices Etc., Surgical Interventions; Submucosal Injections, CryoSurgery, Low Level Laser Therapy⁴⁰, Skin Grafting Etc. And Other Latest Modalities Of Oral Disease Manifestations Management Was **Done Under Expert Supervision**.

Referring The Needy Patients For Specific Specialized ManageMent, Depending Upon Available Resources Circumstances. OverAll Prognosis Explained Treatment Risk Consent Had Been Judiciously Retained With Proper AwareNess To Patients.

Supportive Measures: By Causative Factors Abstinence, Nicotine Dependence Treatments Etc., Along With Cancer Diagnostics (Oncosurgery Histopathology, Biomarkers & Imaging Etc.) For Premalignant And Malignant Transformations, Under Discrete Clinical Expertise Supervision, Were Incorporated As Available.

As Evident By Initial Phases Of Study, 'Recorded Prescription During 1980s'

"MOUTH LOTION"

A wonderful mouth lotion, prepared from available constituents as follows, has a dramatic immediate response after 1 to 2 applications in various types of stomatitis, aphthous ulcer, oral candidiasis and for other chronic oral lesions for which prolonged applications are required for example, submucous fibrosis and other oral lesions including arising from betel chewing, supplementing treatment with oral hygiene maintenance by repeated rinsing, and or use of available mouth wash.

PREPARATION

In one ounce boroglycerine following tablets are mixed in crushed form :

Rx

1. Tablet Dexamethasone/Prednisolone 10m.gm.
2. Tablet Metronidazole 400 m. gm
3. Tablet Mycostatin 250 m. gm. (Vaginal Tablet - Better Response).

**TO BE CRUSHED AND MIXED WITH 1 OUNCE
BOROGLYCERINE.**

For all three constituents of mouth lotion oral tropical preparations with least side affects following mucosal absorption required.

**DR. ANIL K. SAHNI
SURGEON**

PHOTOGRAPH-1

Ingredients Included Basic Essential Constituents In Those Forms, As Were Available About (25)Years Before, With An Inquest For More Sophisticated Effective Alternative Pharmacological Substances. Recently Availables Conveniently Effective Pharmacological Agents Were Replacedly Included To Maximize Patient Benefits.

Supplementary Treatment:

Included Oral Hygiene Maintenance By Repeated Rinsing, & Or Use Of Available Mouth Washes, Fortified B. Complex Lactobacillus Preparations. & Other Available Minerals & Nutrients.

The Comparative Therapeutic Assessment & Evaluation Of Various Ingredients Of Local Application; With Replacedly Better Available Alternatives, Having Comparable Mucosal Absorption, Minimal Side-Effects & Better Therapeutic Efficacy Results Had Been Timely Done.

VARIOUS INGREDIENTS

LOCAL ADMINISTRATION

AVAILABILITIES

- Local Antiseptics: Betadine, Povidone Iodine, cetrimide, chlorhexidine, benzydramines, glycols, thymols, menthols, KMNO₄ Etc.
- Local Anaerobic Antiseptics: Recent Availables; metronidazole Preparations Etc.

- **Local Antifungals:** Several Recent Preparations Including Antifungal Lozenges, nystatin, clotrimazole, Troches, fuconazole Preparations.
- **Local Steroids:** hydrocortisone, beclomethasone, triamcinolone Etc.
- **Local Anti-Allergic & Anaesthetic:** diphenhydramine and lidocaine Ointment Preparations
- **Spirulina Fusiformis** Therapy
- **Antimicrobials:** HSV – Antiviral Therapy,
- calcium phosphate Rinse (Caphosol), fluoride Gel, magnesium hydroxide, aluminium Hydroxide, silver Nitrate Solution, chamomile Mouth Wash, Coating Agents (sucralfate), Effervescent mucomelt; n-acetyl cysteine (600 Mgm.), glutathione Replenishers³⁹ Etc.
- **Traumeel S** (Homeopathy)

The Above Mentioned Gradually Available 'Better Alternatives', For 'Basic Ingredients Of Local Preparation', Were Assessed Evaluated For Safety Profiles, Convenience, Clinical Efficacy, Costs Etc. , And Were Replacedly Incorporated Into 'Oral Preparation' ^{34,35}.

ROLE OF OTHER MEDICATIONS⁶

- Vitamin 'A', Retinol Etc. Retinoids, β -Carotene, 13-Cis-Retinoids (Topical)^{13,14}, N-4-Hydroxy-Carbophenyl-Retinamide (4hr), Feneretinide.
- Vitamin 'E': α -Tocopherol, Gelenium
- Lycopene
- Lactoferrin
- Cyproxanthin
- Transforming Growth Factor Beta 1

As Primary/Adjuvant Chemo-Therapy Systemic & Chemoprevention Medications

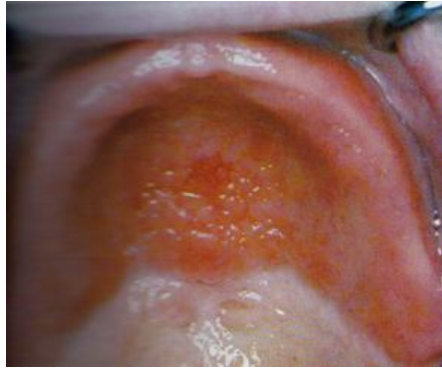
- Antioxidants, Anticholinergics & Coating Agents
- Antiinflammatory agents
- Aminoacids (Especially L-Glutamine with Enhanced Delivery Systems)
- Growth Factors: GM-CSF (Granulocyte Macrophage Colony Stimulating Factor), G-CSF (Granulocyte Colony Stimulating Factor), Topical & or Systemic Administrations. Most Effective Available e.g. Palifermin
- Protease Inhibitors, e.g. Bowman & Birk Inhibitor Concentrate (BBIC) etc.
- Bleomycin 5 FU Based Chemotherapy (Edatrexate etc.)
- High Dose Melphalan
- Tea and Tea Components, Especially Green Tea (Polyphenolic Compounds Called AS Catechins Most Abundant Epigallocatechin, -3 Gallate (EGCG).

Recent Availabilities Include:-

Amlexanox Oral Paste, 100Mgm Paste Contains (5)Mgm Amlexanox (Anti-Ulcer Agent) - Rebamipide, Anti-Ulcer Drug, (100)Mgms Tablet, TDS Orally

SCAR MANAGEMENT MEDICATIONS

- Centella Asiatica, Wheat Germ Oil, Lavandus, Aloe Vera, Tea Tree Oil & Honey Cream Etc.
- Other Herbal Preparations
- Chinese Medications
- Choline Salicylates, Tannic Acids, Tannins Etc.
- Recent Scarolytic Ointment; Contractubex Etc.



Chronic Stomatitis Type III
With A Granular Mucosa



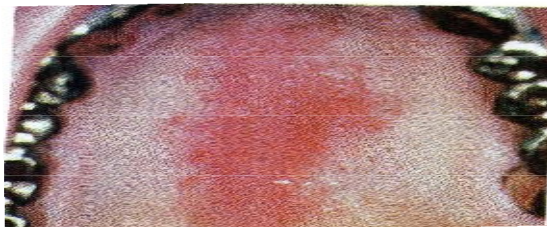
Dorsum Of Tongue, Stomatitis
With Erosions



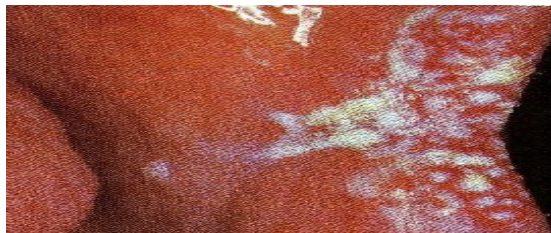
Nicotine Stomatitis



Partial Erosions
Caused By Smoking



Chronic Candidiasis



Chronic Nodular Candidiasis

**ACUTE(±) CHRONIC
ORAL PATHOLOGIES**

SUBMUCUS FIBROSIS

Schwartz(1952) Formulated The Term, 'Atrophica Idiopathica Mucosa Oris' to describe an oral fibrosing disease, While Joshi(1953),Used 'Oral Sub-Mucous Fibrosis (OSF)',

To Describe Diseases Characterized By,

- Fibrous Tissue reaction Beneath Oral Mucosa, Due To Variable Aetiological Variants Attributing Constant Prolonged Friction ; Irritation, ? Chemical, Repeated Trauma, Nutritional, Recurrent Infections & Inflammations Of Different Causes.
- Leading To Allergic Hypersensitivity Reactions ; Increased Fibrogenesis Beneath Oral Mucosal Layer. This Hypersensitivity Reaction May Often Results.

In A Juxta-Epithelial Inflammation That Leads To Increased Fibroblastic Activity Resulting In Formation Of Collagen Fibre In Lamina Propria. These Collagen Fibers Are Non Degradable And The Phagocytic Activity Is Minimized.

- "Oral **Submucous Fibrosis**--A Chronic Disseminated Intravascular Coagulation Syndrome With Local Coagulopathy.", Reports Are Available In Literature.

Prevalence & Aetiology:The Clinical Entity Being Well Recognized For Its Malignant Potential

Statistical Reports Of Prevalence, In (4 / 1,000) Adults In Rural India And As Many As (5) Million Young Indians Sufferers.

Known Causative Agents Include: Areca Nut, Betel Quid Chewing, The Ingredients And Nomenclature Of Betel Quid Vary By Region, All Though Basic Constituents In Different Combinations Are:

Areca Nut (Fruit Of The *Areca Catechu* Palm Tree, Erroneously Termed Betel Nut): Arecoline, An Alkaloid Found In The Areca Nut, Promotes Salivation, Stains Saliva Red, And Is A Stimulant.

Betel Leaf (From The *Piper Betel*, A Pepper Shrub), Tobacco,

Slaked Lime (Calcium Hydroxide): Maintains The Active Ingredients In Its Freebase Or Alkaline Form, Thus Facilitating Their Entrance Into The Bloodstream Via Sublingual Absorption

Catechu (Extract Of The *Acacia Catechu* Tree): Stains Saliva Red.

The Habit Practiced Predominately In Southeast Asia And India, From Thousands Of Years.Similar To Tobacco Chewing In Westernized Societies.

The Increased Popularity Of The Habit Of Chewing Pan Masala(Mixture Of Spices Including, Betel Nuts, Catechu, Menthol, Cardamom, Lime And Others), With Mild Stimulating Effect ,Often Eaten At The End Of The Meal To Help Digest Food And As A Mouth Freshner.



**Submucous Fibrosis Leading To Restricted Mouth Opening Ability,
Buccal Mucosa Has Marbling Appearance**



**Submucous Fibrosis Tongue:
Atrophy, Erosions**



**Submucous Fibrosis Tongue With
Squamous Cell Carcinoma
Development**

The Present Study Includes Available Statistical Evidence Of, Relation Between Differential Uses Of Variety Of Tobacco Products, Especially Recent Availabilities Of Different PanMasalas, Gutkhas, Containing Increased Concentrations Of Various Chemicals ? Synthetic Substances ? Adulterations, Cheap Alternatives Etc. With Localized & Or Generalized Nature Of Oral Manifestations, & Different Clinical Histories Of Severity, Chronicity, Previous Episodes, Recurrences, Relapses Etc.

Aetiopathogenesis;

- ❖ Dose Dependence Between Areca Quid Chewing Habit & SMF
- ❖ Areca Nut: Alkaloids; Arecoline (Most Imp.)
- Modulation Metal Proteinases, Lysal Oxidases & Collagenases
Effect Collagen Metabolism: Increased Fibrosis
- During ↑ Fibrosis : Water Retaining Proteoglycans
→ Increased Collagen Type 1 Production
→ Genetic Predisposition: Aetiological Importance
- Gene Polymorphism: Coding For Tumor Necrosis Factor- α (TNF- α) :
Fibroblast Stimulation → Fibrosis
 - Other Cytokines Aberrations
→ Transforming Growth Factor-Beta & Interferon- γ
→ Collagen Production & ↓ Degradation
- Genetic Predisposition
→ Human Leukocyte Antigen Molecules: HLA-A10, -B7 & DR-3

Clinical Manifestations;

Wrinkles, White Leathery Lesion¹¹, Ulcer (\pm), Hyper Keratinization, Acanthosis, Epithelial Fibrosis + Atrophy & Hyper-Plasia, Overlying Epithelium, Epithelial Dysplasia, Epithelial Vacuolations, Gingival Reactions (\pm)

Including Progressive Difficulty In Opening Mouth Of Variable Extents, Diffuse, Localized Fibrous Bands, Adhesions Formation At Various Folds & Sulci Of Oral Cavity, With Differing PreMalignant & Or Malignant Transformations.

PINDORG J.J: (3) Clinical Stages

- **Stage 1:** Stomatitis
- **Stage 2:** Fibrosis
 - A- Early Lesions, Blanching Of The Oral Mucosa
 - B- Older Lesions, Vertical And Circular Palpable Fibrous Bands In And Around The Mouth Or Lips, Resulting In A Mottled, Marble-Like Appearance Of The Buccal Mucosa
- **Stage 3:** OSF Sequelae
 - A- Leukoplakia
 - B- Speech And Hearing Deficits

Treatment; Depends On The Degree Of Clinical Involvement.

- Early Disease Detection, Cessation Of The Habit Is Sufficient.
- Most Patients Present With Moderate-To-Severe Disease.
Moderate-To-Severe OSF Is Irreversible.
- **Medical Treatment;** Symptomatic, Predominantly Preventive & Aimed At Mouth Movements Improvements.

Pentoxifylline (Trental), A Methylxanthine Derivative With Vasodilator Properties, Increases Mucosal Vascularity, Recommended As An Adjunct Therapy In The Routine Management

o **Submucosal injections:**

-Hylase⁷
-Hydrocortisone
-Human Chorionic Gonadotrophins (Placentrax)^{8,9,10}
2-3 ml per sitting twice or thrice in a week for three to four weeks.

Aim To Achieve Similar Results By Using 'Steroidal Constituent' Of

The 'Oral Lotion', Had Been Practiced For Years, With Differentially Successful Result Outcomes. The Latest Availability Of 'Topical Steroid'

E.g triamcinolone Etc. ,The Clinical Efficacy, Safety Profile , Local & Systemic SideEffects Are Comparatively Convincingly Acceptable.

o **Surgical Treatment:** Indicated In Progressive Fibrosis, When Inter-Incisor Distance Becomes Less Than 2 Centimetres (0.79 In).

Multiple Release Incisions Deep To Mucosa, Submucosa And Fibrotic Tissue And Suturing The Gap Or Dehiscence By Mucosal Graft Obtained From Tongue And Z-Plasty Multiple Deep Z-Shaped Incisions Are Made And Then Sutured In A Straighter Fashion To Gain Length.

Excision Of Bands & Adhesions Etc.

Stem Cell Therapy: Autologous BoneMarrow Stem Cells Intralesional Injection, Is A Safe And Effective Treatment Modality . Induces Angiogenesis In The Area Of Lesion Decreasing The Disease Extent(Fibrosis), Leading To Significant Increase In Mouth Opening.

MUCOSITIS
(MUCOSAL INFLAMMATION)

Aetio-Pathogenesis: Besides Various Etiological Variants Of Vivid Clinical Disease Entities Including Metabolic, Nutritional, ImmunoCompromised States, Tranplant Patients Chemotherapy (Standard & Or Marrow Ablative), Radiation Therapy, Drugs, Chemicals Induced Are Important.

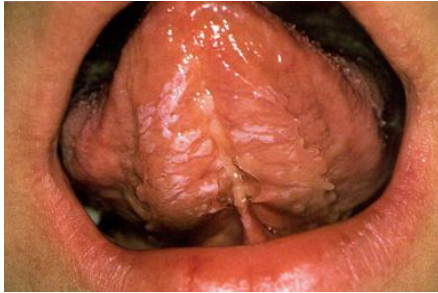
Clinical Manifestations: Beside Other Presentations, 'Dysgeusia' Or An Alteration In Taste Perception Or "Taste Blindness," Temporary Condition, Because Of Effects On Taste Buds.



Aspirin Burn



Antibiotic Induced Stomatitis



"CHEMICAL / CONTACT ORAL INFLAMMATORY LESIONS"

Agricultural Compounds Contact Stomatitis, Erosions

MUCOSAL INJURY PATHOPHYSIOLOGY

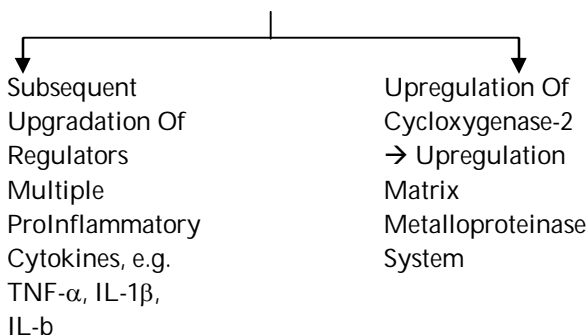
Mucosal Injury & Subsequent Healing Process Involves All Mucosal Layers Including Extracellular Matrix Besides Epithelium Only.

(5) Stages Process Involve Complex Molecular, Cellular & Histopathological Events

(1)Initiation Phase: Oxidative Stress Due To Different Mechanisms Being Basic Causative Factor.

(2) Upregulation Of Transcription Factors & Messenger Signals Generation Phase:

NK- κ beta (Central vital role)



In Addition Sphyringomyelinase & Ceramide Pathways, Fibronectin Break-Up And Macrophagic Activities (Complex Events) Lead To, **Further Mucosal Injury & Apoptosis.**

(3) Additional Signaling & Amplification

Phase: Enhancement Synergism Of Previous Pathways Leading To Generation Of Additional ProInflammatory Cytokines. Upto This Stage Mucosal Anatomy Being Intact.

(4) Symptomatic, Ulceration Phase: Clinical Manifestations Including Ulcerations, Pain, Bleeding, Complicated By Microbial SuperInfections & Decreased Salivary Function Leads To Enhance Mucosal Injury

(5) Healing Phase: Process Depends Upon Angiogenesis And Increased Biological Activity Of Extracellular Matrix. In **Myeloblastic Conditions** Healing Phase May Not Begin Until Leucocyte Recovery.

All (5) Phases Does Not Necessarily Follow Linear Progression, But May Occur Simultaneously At Different Locations.

Mucositis Assessment Evaluators: Scales Commonly Used, Combined Information From Both Patient's **Signs And Symptom Scores**, With Patient's **Functional Status & Ability To Eat.**

NICOTINE DEPENDENCE TREATMENTS

(A) Non-Pharmacologic Treatments

- 1) **Self Help, Intervention & Counseling Etc.** By Print, Live & Various Electronics Media Aids Including Telephone Based Cessation Counseling & Others.
- 2) **Behavioural Therapies** Include Guidance And Instructions On Elements Of Nicotine Fading Quit Date Contracting, Management Of Smoking Triggers, Relaxation Techniques Strategies, Trigger Management & Relapse Prevention In Various '**Cognitive-Behavioural Smoking Cessation Programme**' & '**Educational Control Condition**', Schedules.

(B) Pharmacologic Treatments³

- 1) **FDA (Food & Drug Administration)-Approved Nicotine-Replacement Therapies:**
US-FDA Approved (5) Nicotine Replacement Therapies (NRTs):
(i) Transdermal Patch, (ii) Gum, (iii) Nasal Spray, (iv) Inhaler, (v) Lozenge, While 6th NRT (vi) The Sublingual Tablet Is Used Only In Europe.

NRTs Are Tolerable, Safe With Results Achieved By:

- (i) **Ameliorating Withdrawal Symptoms** Due To Initial Physical & Psychological Reactions To Cessation, E.g. Irritability, Restlessness, Depressed Mood & Poor Concentrations
- (ii) **Reducing Nicotine Craving Experience** & Limiting Possible Weight Gain (For Gum & Patch)
- (iii) Providing Safer Way To Experience **Neurobiological & Psychophysiologic Effects Of Nicotine.**

For Quit Rates Relapse Intervals, Rapid Release Formulations Have Better Efficacy For Post Cessation Cravings.

Overall NRT Efficacy In Various Subgroups Including Different Smoking Characteristics Varying Mild, Moderate, High Dependence Levels, Body Weights, Ethnic, Racial Groups & Genders, By Various NRT Preparations, Studies Are Available & In Process.

- 2) **FDA-Approved Non-Nicotine Pharmacologic Treatments:**
 - (i) **Bupropion SR (Zyban)** – An **Anti-Depressant**, Exact Action Mechanism Not Fully Known, Efficacy Mediated By Reduction Dopamine & Norepinephrine Uptake & Or Nicotine Receptor Antagonist Effects. The Second Mechanism May Involve Drug Ability To Prevent / Diminish Post Cessation Negative Effects & Weight Gain, Cited As Causes Of Relapse Among Smokers.
 - (ii) **Varenicline (Chantix)** – Is An **$\alpha 4\beta 2$ Neuronal Nicotinic Acetylcholine Receptor (nAChR) Partial Agonist**, By Activation Of These Receptors Widely Expressed On Dopamine & GABA Neurons In The Ventral Tegmental Area, Varenicline Has Attenuation Effect On Dopamine Release While Maintaining Dopaminergic Tone, Thus **Minimizing Nicotine Craving & Withdrawal By Agonist Function**, While **Antagonist Properties** May Attenuate Reinforcing Nicotine Effects, Leading To Reduced Smoking Satisfaction And Relapse Likelihood.
Tobacco Dependence Treatment & Clinical Oncology, Have Different Versatile Aspects.

If Tobacco Is The Choice, Chewing May Be Preferred Over Smoking, With Assured Oral Hygiene Maintainence.

Overall Assessment And Management Of Generalized Body Affections Of Tobacco

⁴Including Atherosclerosis, Peripheral Vascular Diseases Etc, Being Important Constituent Of **Nicotine Dependence Management.**

DIAGNOSTIC AIDS¹⁵

Include:

- (A) **Surgical Pathology** ³²

- FNAC, Histopathology: Excisional, Incisional Biopsy, Exfoliated Cell Sampling^{25,26,27}
 - (1) Global Obtained by Mouth Rinse, Swabs Etc.,
 - (2) Specific, e.g. Scrapes of Leucoplakia Or Other Lesions.
- Immuno-Histochemistry (IHC)
- For Deciding Type, Nature Of Lesions, Tissue Of Origin, (±) Metastasis, Including Dysplasia Presence With Severity Degree, Loss Of Heterozygosity (LOH), Allelic Imbalance (AI), CIS Being Important Predictive Parameters.
- For Confirming Various Benign Lesions, Premalignant (OPL I & II), Malignant Lesions & Course Of Disease Process.

(B) Molecular Diagnostics^{19,20}

Circulating Tumor Markers Detection^{26,27,28}, Tumor NDA, Circulating Tumor Related Antibodies, Mutant P53 Gene Sequences, Viral DNA - ELISA Test For Serum IgA Response To EBV-related diseases, Anti-TK (Thymidine kinase) Antibodies, Fluorescence Spectroscopy, Mid-InfraRed Fibreoptic Spectroscopy Attenuated Total Reflectance Spectroscopy, Being Important Tool For Differentiating Between Benign & Malignant Oral Mucosa^{21,22,23,24}

(C) Imaging

For Size And Other Details Of Lesion, Stage Migration By Plain X-Ray Films, CT, Angiography, USG, MRI & MR Spectroscopy Nuclear Medicine And Positron Emission Tomography (PET) Especially FDG (Radiolabelling)-PET.

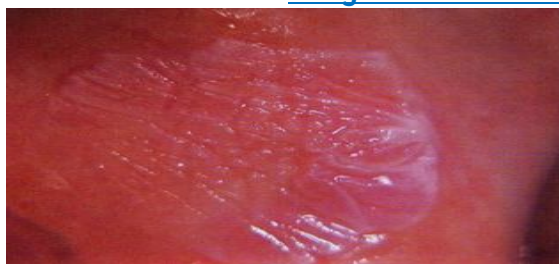
HEAD & NECK CARCINOMA²⁸

RISK FACTORS:

- Alcohol , Tobacco, Areca Nut / Quids / Pan Masalas, Various Other Chewing Tobacco Preparations, Snuffs Etc. Alone Or Concurrent Use. Precipitated By Poor Dento-Oral Hygeine, Sumps, Sore Teeth, Susceptibility, Leucoplakia Etc.
- Human Papilloma Virus & Other Viral Infections Human Simplex Virus-1 (HSV-1), EBV, IG-18, E6 PRO,+P3 Tumor Suppressor Gene P53, Leading to P53 Degradation Tumorigenesis, P53 Tumor Suppressants, Plummer-Vinson & Paterson Kelly Syndrome
- Poor Nutrition, Carcinogen Exposure, Genetics.



Sanguinaria-Associated Oral Leukoplakia



Homogenous Leukoplakia Buccal Mucosa

MALIGNANT TRANSFORMATIONS^{29,30}

(A)
High Risk Lesions

- Speckled Erythroplakia
- Erythroplakia

(B)
Medium Risk Lesions

- Syphilitic Glossitis
- Oral Submucous Fibrosis

(C)
Low Risk/ Equivocal Risk Lesions

- Discoid Lupus Erythematosus

POTENT

POTENTIALS FOR MALIGNANT CHANGE

- ↑ With ↑ Age Of Pt.
 - ↑ With ↑ Age Of Lesion
 - ↑ In Smokers
 - ↑ In Alcohol Consumption
 - Anatomical Site Dependence
 - Floor Of The Mouth
 - ↑ With Leucoplakia¹²
 - Ventral Surface Of Tongue
 - Esp. Younger ♀
- Even Without Associated Risk Factors



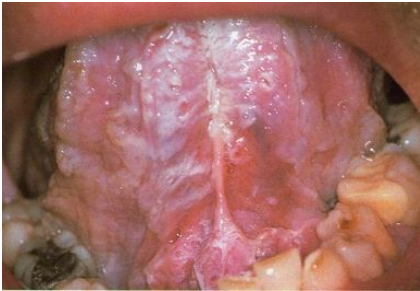
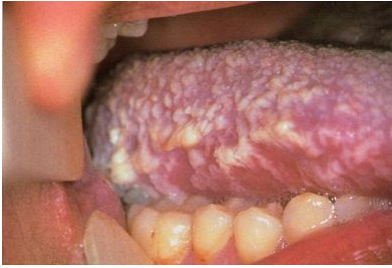
LOCAL MEDICATIONS: OTHER INDICATIONS

With The Use Of Discussed Preparation:
Reasonably Good Results Achieved, In
Following Conditions:

- (1)HIV AIDS Oral Manifestations
- (2) Other Immunosuppressive
Conditions
- (3) Immunosuppressive Therapies
- (4)KIDNEY TRANSPLANT PATIENTS

[Leuko-Erythematous Lesions](#)

[Ulcerative Lesion](#)



[Uremic Stomatitis,](#)

[Gray-Pseudomembranous Lesion](#)

[Hyperkeratotic \(White\) Lesion](#)



[Necrotic Pseudomembrane](#)

[Covered Ulceration](#)

[UREMIC MANIFESTATIONS](#)

- (5) Radiation Mucositis Of Different Aetiopathogenesis³⁸, Chemotherapy Induced^{34,35,36,37}
- (6) Drug Reaction Manifestations, Metal Poisonings Etc.
- (7) Dentition And Denture Related Lesions

(8) Difficult Endo-Tracheal Intubation Conditions,

? (Decreased Mouth Opening) Oral SMF Extending To Oro-Naso-Pharyngeal Regions Re-Assessment during Pre-Anaesthetic Checkup Or Otherwise Important Cause

“RESULTS”

- **The Discussed Clinico-Pharmacological Study Involves, Successful Overall Management Of Thousands Of Patients, >(2500) Cases, Comprising Large Variety Of ‘Oral Lesions’ Variables,** Clinical Distinct & Or Mixed Clinical Manifestations, Differing In Regards To Cure, Definitive, Symptomatic Management, Of Varying Disease Severity & Chronicity, Recurrence, Relapse & Or Progression To Pre-Malignant & Or Malignant Lesions.
- Gradually **Better Available Pharmacological Substance Alternatives,** For The **Basic Constituents Of The ‘Oral Preparation’,** Were Replacedly Administered, During >2 **Decades (20-25 Years) Continuing Study Duration.**
- **Augmentation Support** By; Newer Efficacious Systemic & Or Local Medications, Chemoprevention Measures, Abstinence Control Management Regulations Of Various Causative Factors, E.g Nicotine Dependence/Replacement Treatments Etc. Gradually Available In Due Course Of These Many Years, Were **Appropriately Incorporated.**

- **Retaining Discrete Expert Clinical Assessment As The Basic Diagnostic And Therapeutic Tool In Regards To Treatment Efficacy End Points,**
Various Surgical, Histo-Pathologies, Molecular Diagnostics (Different Bio-Markers) & Imaging Techniques, Assessments^{32,33} Were **Colloborated**, In The Disease Management Plan As And Where So-Ever Needed And Practically Available In **Consideration Of Resources.**
- After Properly Conveyed Needed **'AwareNess', 'Prognosis Explained Treatment Consent',** Was Sought, From Almost Every Patient, Especially In The Situations Of **Clinically Evident Suspicion.**
- Repeated **Referral Advise,** With Awareness Of **Expert Management Resources,** Well Before, Within Time, Especially In Peripheries Were **Emphasized,** In Demanding Situations.

"DISCUSSION"

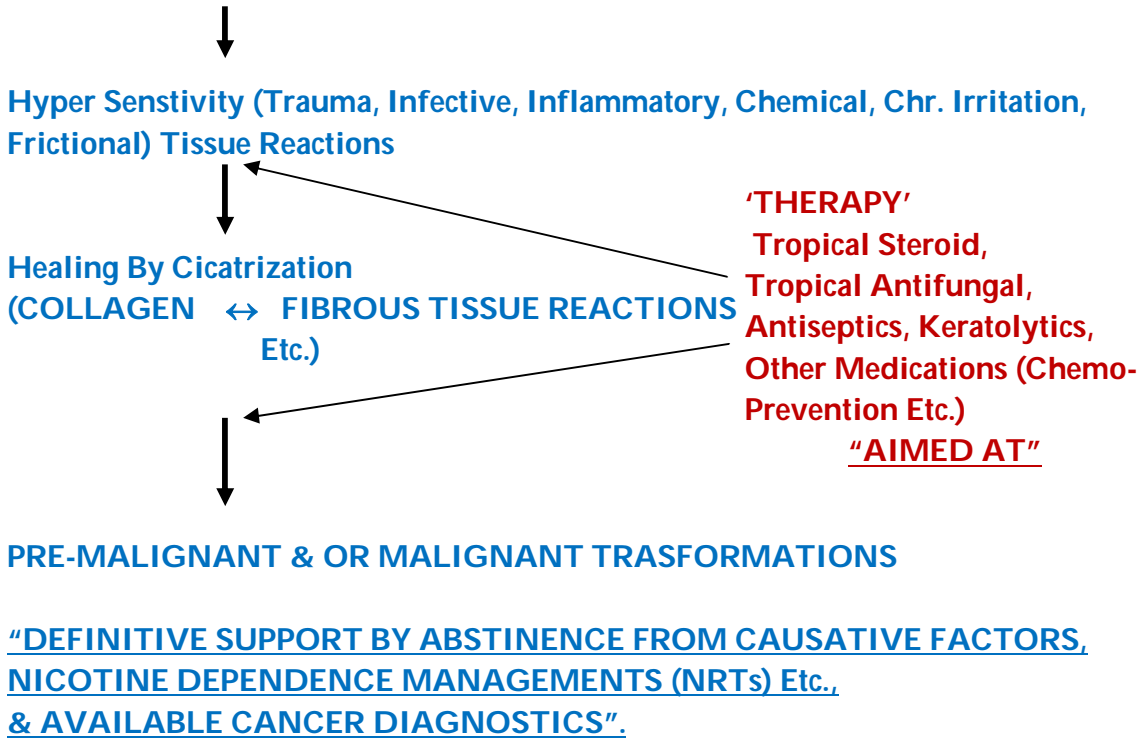
Retaining The **Very Basic Aim Of The Study, Initiated More Than (25) Years Ago,** To **Definitively Treat & Or Provide Maximal Relief** In The Usually Mixed Combinations Of **'Oral Lesions'** & Or Solitary Variables, Under Closed Observation Clinical Expertise Supervision, With The Then Available Constituent Ingredients & Supplementary Therapy. **Witnessed Gradually Available Efficacious Medication Alternatives,** **Supportive** Chemo-Preventive Therapies, Surgical & Physiotherapy Procedural Supports,

While The **Successful Use Applicabilities** Also **Increased Several Folds For Oral Lesions** Accompanying Recently More Prevalent Infective, Inflammatory Conditions, Immuno-Compromised Situations, Renal Transplant Patients, & Several Others Clinical Entities.

The Fundamental Need To Have All The Necessary Basic Ingredients (Anti-Septic, Anti-Microbial Specially For Anaerobes Flora, Anti-Fungal & Tropical Steroid In A Suitable Welcoming Use Flavour Base), Constituted For Efficient Delivery Convenient Preparation Module, Demands Intensive Pharmaco-Therapeutics Research To Provide Safe, Efficient Medications Effective By Local/Tropical/Regional Route Of Administration, With Maximally Effective Mucosal Barrier Absorption & Minimal Local & Or Systemic Side-Effects.

The Convincing Rendered Help By Combining Age-Old Herbal & Or Other School Of Medicines Effective Preparations, Being An Important Part Of The OverAll Management Module, For Oral Disease Manifestations. While The Safe Oral Application Use Of Classical Scarolytics Applications, Available Topical Steroids, To More Recent Applications With Similar Pharmaco-Kinetics Like Contractubex, Amlexanox, Along With Advent Of Successful Intra-Oral Appliances For Cryo-Surgery & Laser Applications & Physio-Therapy, At Appropriate Time, Stage Of Disease Process, May Offer Necessary Remedial Solution For Controlling Basic Underlying Patho-Genesis Of Ac./ Sub-Ac./ Chronic Inflammatory Changes, Conversion Processes Of Cicatrization Involving Fibrin, Collagen & Other Similar Stimulating Tissue Reactions.

ACUTE (±) CHRONIC ORAL LESIONS



**'Oral Lesions: Clinico-AetioPathogenesis
& Pharmaco-Kinetics Aspects'**

"TABLE"

"SUMMARY"

As Discussed The Study,
Being One Of The Most Needed,
Important, Clinical Research,
Of Present Times,
With An Aim To Control (Minimize),
Considerably Prevalent Oral Disease Entities,
More Disabling Due To Non-AwareNess,
'No' & Or Unproper Treatment,
ManageMent GuideLines,
Recurrence, Relapse, Chronicity,
With Or Without Pre-Malignant & Or
Malignant Transformations.

Incorporating Replacedly Better Available Safe
Pharmacological Agents,
For Various Constituent Ingredients Of The
'Oral Topical Application',
With Efficacious Oral Mucosal Absorption,
Clinically Justifiable Result Outcome,
& Minimal Side-Effects(Local/Systemic Etc.)

Supported By Various Gradually Available Systemic & Or Local Therapies. Surgical & Physiotherapy Interventions Etc. Prevention And Or Regulation Management Of Basic Aetiological Factors, E.g Nicotine Dependence/Replacement Managements Etc. Judiciously, Expert Regular Clinical Assessments, In Collaboration With Various Histopathologies (Invasive, Minimal/ Non-Invasive ...), Tumor Markers, Biological Assays, Imaging, And Various Diagnostic & Or Therapeutic Tools.

The Fundamental Management Guidelines Of, Proper Awareness & 'Prognosis Explained Treatment Risk Consent', With Timely Emphasized No-Delay, Referral Of The Cases For Expertise Management, As Needed, Minimizing The Morbidity & Mortality In A Large Group of Population, With Significant Disease Prevalence.

OverAll Control Of Severity, Chronicity & Transformations Of Oral Lesions³¹, Because Of Constant Exposure To Aetiological Variants, By Management Of Initial Stages Of Oral Pathologies, Minimizing The OverAll Mortality & Morbidity Of Significantly Prevalent Disease Processes.

The Pharmacological Aspects Of The Study Demands, Needed Appropriate Medications, Satisfying Parametres Of Therapeutics, Based Upon The Principles Of 'Drug Delivery System', Research Of Modern Pharmaceuticals, Supported By Causative Factors Abstinence Regulations & Other Recent Management Modalities For Prevalent Versatile 'Oral Disease Manifestations' Of Vivid Aetio-Pathogenesis.

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