REVIEW
OF
LITERATURE
Review of Literature

In the present era, the oral Submucous fibrosis drawn the attention of clinicians in the early fifties. However if we refer back to our ancient history of Indian Medicine, this disease was first described by SUSRUTA. In the classification of mouth and throat meladies, he mentioned a condition called “VIDARI” whose features were progressive narrowing of mouth, depigmentation of oral mucosa and pain while taking food. The same features precisely fit into modern clinical condition, oral submucous fibrosis (Shastri, 1924).

In modern era of medicine, clinicians came into consideration of this clinical entity from sixth decade of the current century. It was Schwartz (1952) who first described the disease as ‘Atrophica Idiopathica (Tropica) Mucosae Oris’. He found the disease in five ladies of Indian origin in East Africa and Kenya. One year later Joshi (1953) described the same clinical condition, reporting 41 cases from India and it was Joshi who coined the term ‘Submucous Fibrosis’.

Informations obtained from many part of the world lead to the believe that, this submucosal dyscrasia is particular to the people of Indian origin. But Su (1954) reported three cases from China (Taiwan) and showed its occurrence in different
population groups. Rao (1954) also found oral submucous fibrosis in some Europeans, living in Hyderabad. Turner (1966) found a typical case of Oral Submucous Fibrosis in an English woman married to a Pakistani individual in England. Lalchand (1962) reported 15 cases from Nepal during his visit for 25 days. Pindborg (1964) observed similar condition in two Danish patients also. Beside a few cases of other than Indians, it is of general belief that the disease is commonly found in Indian subcontinent or in persons of Indian origin settled abroad.

In 7th decade, multifactorial study was performed by Pindborg and associates (1962, 1964, 1966 and 1968) covering the aspects, epidemiology and geographical distribution to pathology and clinical behavior. Later on workers concentrated themselves on the pathogenesis and management of the disease.

**Definition:**

The oral submucous fibrosis was defined by Pindborg et al. (1966). “An insidious, chronic diseases affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by vesicle formation, it is always associated with Juxta-epithelial inflammatory reaction followed by a fibroelastic change of the lamina propria with epithelial atrophy leading to stiffness of oral mucosa causing trismus and inability to eat".
Geographical Distribution: -

Before the works of Pindborg et al. (1962), the disease was reported in Indians only, except few cases reported by Su (1954), Rao (1954). Some Europeans, suffering from this disease, living in Hyderabad, were reported by Rao (1954). Su (1954) reported oral submucous fibrosis in three Chinese. In early fifties first report came from Schwartz (1952) who described it in five Indian women from Africa and Kenya. He also reported one Indian student from Uganda and an English lady married to a Pakistani person. Pindborg (1962) reported two Danish patients having same clinical presentation. On his visit to Sri Lanka, Malaysia, Nepal, Thailand and South Vietnam, Pindborg (1964) saw a number of cases of oral submucos fibrosis. Shiau and Kwan (1979) reported 35 cases of oral submucous fibrosis from Taiwan. Laskaris, et al. (1981), described an unusual case of Non-Indian having oral submucous fibrosis. She was a sixty two years old Greek female.

Inspite of these reporting, it is now well accepted that oral submucous fibrosis is a disease of Indian sub continent and mainly occurs in populations of Indian origin. Most of the cases, reported out side of south East Asia i.e. from Europe and Africa, were migrated Indians.

In our country the disease is not having a definite trend of distribution but having slight predominance in Southern India as compared to Northern India (Pindborg, 1964). In Southern part, maximum number of cases have been reported
from Kerala and Andhra Pradesh. Pindborg (1964) studies the prevalence of disease and found that the incidence was more in Kerala, Andhra Pradesh, Tamilnadu, Eastern Uttar Pradesh and Bihar. Sirsat and Khanolakar (1962) reported large number of cases in Bombay. Yadav (1978) reported many cases from Eastern Uttar Pradesh and Bihar. Varghese et al. (1985), Bhonsle et al (1987) found that the disease is more prevalent in cashew workers of Kerala.

**Incidence & Prevalence**

Oral Submucous fibrosis has been reported as a pathological entity in several studies from India (Pindborg et al. 1966, 1964) De’Sa (1957; ) Joshi, (1953) and from abroad (Su, 1954) and Shiau, (1979) etc. It is an uncommon lesion which is confined to the oral mucosa and which is remarkable because it is found almost exclusively in Indians (Hammer and Shear et al. 1967). Possible exceptions are three cases from Formosa reported by Su (1954) who does not report the race of the patients and some ‘Europeans’ reported in 1962 by Rao.

Oral submucous fibrosis is a recognized and documented precancerous lesion. It occurs at an earlier age than the other oral precancerous lesions.

Submucous fibrosis as a condition was first described in the Indian medical literature just over 52 year’s age by Schwartz (1952). Since then it has been recorded occasionally under different names, but Pindborg et al in 1964 suggested that 1 in 1600 of the Indian population might be affected by this disease. All the recorded cases
have involved Indians apart from a few Asians and Europeans living in India and a recent case of a white South African woman reported by hammer and Shear (1967).

Age group falling between 20 and 40 years (Simpson, 1968) is slightly more susceptible, Rao from Hyderabad (1962) has reported 46 patients of this disease. In his series, most patients were in Second decade of life, the youngest being 12 years old and the eldest 64 years, 17 were men against 29 woman indicating a higher incidence amongst the females. Submucous fibrosis occurs more frequently than hitherto assumed. Recent epidemiological studies in Lucknow and Bombay in India, have shown a frequency of about 0.5 percent (Pindborg, 1965). It has been reported mainly from India but has also been diagnosed in Ceylon, Malaysia, Nepal, South Vietnam and Thailand by Pindborg (1966).

Epidemiological studies on the prevalence of submucous fibrosis have been done by Pindborg et al and shear et al. (1967). Pindborg et al (1963) and Zacharian et al. (1966) examined 35000 urban Indians seeking admission to Clinics at dental colleges in Lucknow, Bombay, Bangalore and Trivandrum and found the following prevalence figures respectively 0.5%, 0.5%, 0.2% and 1.2% Shear et al. (1967) who examined 1000 Indians in South Africa found a prevalence of 0.5%.

In 1962 Sirsat and Khanolkar reported age wise distribution in three series of submucous fibrosis of the palate in Bombay as seen in table No. 1.
Table No. 1

<table>
<thead>
<tr>
<th>Series</th>
<th>No of cases</th>
<th>Age group in Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1-10</td>
</tr>
<tr>
<td>I</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>64</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>85</td>
<td>2</td>
</tr>
</tbody>
</table>

The disease appears to have started in only four persons during the first ten years of life, whereas the majority of the patients belonged to the 20 to 40 age group.

In 1956 Pindborg reported 40 cases of oral submucous fibrosis with oral cancer with their sex and age distribution as seen in Table No. 2

Table No. 2

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age group in years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-29</td>
<td>30-39</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

In 1968 Pindborg reported age distribution in 63 patients of oral submucous fibrosis, as shown table No. 3.
Table No. 3

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age group in years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-29</td>
<td>30-39</td>
</tr>
<tr>
<td>Male</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

The youngest patient was 22 years old and the oldest was of 84 years, the peak frequency was between the ages of 40 and 60 years, the peak frequency was between the ages of 40 and 60 years. Females were more in number than the male patients.

In 1979, Shisu and Kwen reported age distribution in patients of oral submucous fibrosis in Taiwan as per details in table no. 4

Table No. 4

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age group in years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10-19</td>
<td>20-29</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>
In the above report the youngest patient was 17 years old and the oldest was of 64 years. The peak frequency was between the ages of 30 and 50 years. Male patients were more (97%) than female patients (3%).

Paymaster (1956) in study of buccal mucosa in 650 Indian patients found that younger persons were commonly affected by oral submucous fibrosis. Pindborg (1964) reported submucous fibrosis in an eight-year-old boy of Indian origin from Singapore. The youngest case was from India. She was an Indian girl aged four years, reported by Hayes (1985).

Information obtained from many parts of the world leads up to the belief that oral submucous fibrosis is peculiar to the people of Indian origin, although it was first reported in East-Africa by Schwartz, 1952.

**Table No. 5:** - Showing geographical distribution of oral submucous fibrosis in world.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Country</th>
<th>Age range</th>
<th>Peak age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz</td>
<td>1952</td>
<td>E. Africa</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lal</td>
<td>1953</td>
<td>India (M.P.)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Joshi</td>
<td>1953</td>
<td>India (Bombay)</td>
<td>-</td>
<td>40-60</td>
</tr>
<tr>
<td>Su</td>
<td>1954</td>
<td>China</td>
<td>-</td>
<td>30-40</td>
</tr>
<tr>
<td>Rao &amp; Raju</td>
<td>1954</td>
<td>Nepal</td>
<td>18-40</td>
<td>-</td>
</tr>
<tr>
<td>De’Sa</td>
<td>1957</td>
<td>India (Bombay)</td>
<td>19-55</td>
<td>-</td>
</tr>
<tr>
<td>Sharan</td>
<td>1957</td>
<td>India (Bihar)</td>
<td>13-62</td>
<td>-</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Location</td>
<td>Age Range</td>
<td>Effect/Comments</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-------------------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Rao</td>
<td>1962</td>
<td>India (Hyderabad)</td>
<td>12-64</td>
<td></td>
</tr>
<tr>
<td>Sirsat &amp; Khanolkar</td>
<td>1962</td>
<td>India (Bombay)</td>
<td>10-58</td>
<td>20-40</td>
</tr>
<tr>
<td>Pindborg</td>
<td>1966</td>
<td>India</td>
<td>22-77</td>
<td>44-50</td>
</tr>
<tr>
<td>Pindborg</td>
<td>1968</td>
<td>India</td>
<td>22-84</td>
<td>40-60</td>
</tr>
<tr>
<td>Shishu</td>
<td>1979</td>
<td>Taiwan</td>
<td>17-64</td>
<td>32-50</td>
</tr>
<tr>
<td>Present study</td>
<td>2000</td>
<td>India (Jhansi)</td>
<td>10-60</td>
<td>20-30</td>
</tr>
</tbody>
</table>

The above table indicates that oral submucous fibrosis has chiefly involved with an age group of 35-40 years.

The less ratio of incidence reported by (Wahi & Su, Wahi and associates), was 2:1 male to female and all of the three cases presented by Su involved male patients. However Joshi (1953), De’ Sa 91957) and Sirsat and Khanolkar (1962) reported more than 50 percent female victims.

**Religion:**

In India, the shaping of castes and communities is governed not only by the geographical location but also by their religion and language. Different communities resident in the same geographical area acquire different and divergent habits of living, such as those pertaining to (1) Nutritional Practices (2) Marriage Customs (3) Hygienic observations. It is a well established tenet of epidemiology that the etiology of disease can often be sought with success in the habits of the people. An analysis of
the incidence of submucous fibrosis of the palate was carried out by Sirsat and Khanolkar (1962) in 190 cases in Bombay as shown in Table No. 6.

Table No : 6

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of cases</th>
<th>Communities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hindu</td>
<td>Parsi</td>
</tr>
<tr>
<td>I</td>
<td>41</td>
<td>34</td>
</tr>
<tr>
<td>II</td>
<td>64</td>
<td>42</td>
</tr>
<tr>
<td>III</td>
<td>85</td>
<td>57</td>
</tr>
</tbody>
</table>

Aetiological Factors:

The exact causes of submucous fibrosis is obscure. The various hypothesis put forward so far suggest a multifactorial origin for this condition. Along side the role of local irritants such as capsicum (Sirsat SM, Khanolkar VR 1960), Tobacco (paymaster JC 1956), Areca nut(Canniff JP, Harvey W, 1981), pungent & spicy foods (Pindborg JJ, Sirsat SM) and alcohol (Wahi P. N. et al. 1966), an underlying systemic predisposition is likely because of the geographical and ethnic distribution of OSMF.

Among systemic factors the main ones incriminated are chronic iron and vitamin B-Complex deficiency, anaemia (Rajendran R et al 1990) and a genetic predisposition to the disease (Canniff JP et al. 1986).
1. Local Factors:

In the pathogenesis of submucous fibrosis might lie the continuous prolonged action of mild irritants. Since the disease occurs predominantly among Indians a possible allergen has been suspected in their common diet. Spices being an essential ingredient in Indian diet, would attract attention, especially chilli papers, which are universally used in all parts of India. Support for this theory that chillies are the irritating factor is found in the occurrence of submucous fibrosis among Indians living outside India but maintaining Indian dietary habits. A number of cases of submucous fibrosis have been diagnosed in such countries as Ceylon, Nepal, Thailand and South Vietnam where chillies are commonly used in the diet. Sirsat and Khanolkar (1960) demonstrated changes similar to human submucous fibrosis after painting palate of the rat with chillies lotion.

Chronic irritation has been thought to be the local factor to induce the pathological changes in the oral mucosa. Among the possible irritants, tobacco, liquor, chillies and betel nut have been regarded the most important causative agents.

In the study of Shisu (1979), involving patients of submucous fibrosis 5 were liquor users, 18 were smokers and 21 were betel nut chewers. In this study betel nut chewing was more common in-patients of oral submucous fibrosis. The history of betel nut chewing among in twenty one patients was varied. The duration ranged from
as long as 20 years or more to as little as 1 year before submucous fibrosis was clinically diagnosed.

According to Su (1954) the mode of action of betel nut over the buccal mucosa could be a continuous and prolonged action of an alkeloid, Arecoline, on the nerve endings in the oral mucosa with consequent neurotrophic disorder of the area.

According to Pindborg (1965) the most important etiological factors for producing oral submucous fibrosis and oral cancer are tobacco and betel nut. In his study on 40 patients of oral submucous fibrosis and oral cancer, all patients except one, had the habit of consuming tobacco mixed with betel nut and lime, Sinha (1980) reported the presence of oral submucous fibrosis is more in those areas where the habit of consuming tobacco in prevalent. This fact also suggests that consumption of tobacco is an etiological factor for oral submucous fibrosis.

**Betel and Betel Nut:**

The habit of chewing of betel nut is very common practice in India. Betel nut is either taken alone or in the form of PAN & GUTKIA. PAN is a preparation of betel leaf, betel (Areca) nut (raw or crushed), slaked lime and catechu. It may or may not be combined with tobacco. The bolus, formed by chewing the preparation is swallowed, spat or kept in the mouth for some time even during sleep. Bolus of PAN is usually kept in lower buccal sulcus.
Khaini (Tobacco Chewing)

Khaini is a common practice among Indians. Bolus of pieced raw tobacco leaves are mixed with lime and it is kept in lower labial or buccal sulcus. Though the Khaini habit is common in rural and urban both, it has slight predominance among the rural population.

Gutkha:

This rank first in local factors. This is commercially powder containing betel nut, tobacco and catechu, preservative with certain chemical ingredient (e.g. leather tinning agent). Gutkha is most commonly used local irritant factor in all over India, mainly in Bihar, Uttar Pradesh, Madhya Pradesh, Rajasthan, Maharastra. This is easily available in attractive pouches containing about 5 to 10 grams of commercial powder. Few companies use various types of chemicals (e.g. Gambiar) instead of catechu because these chemicals are cheaper. These chemicals are more irritant to buccal mucosa.

Smoking:

Although Cigarette smoking is common all over the world Bidi, Chutta, Chilam are smoked in Indian sub continent only. Bidi is a locally made cigarette prepared by tobacco (0.30-0.36 gm.) rolled in Tendu leaves. Chutta is a preparation similar to Bidi and practiced in Tamilnadu. In some regions of Andhra Pradesh, reverse smoking (keeping burning end inside the mouth) is commonly done. Chilam is another method
of smoking, which is done with the help of a conical clay pipe of about 10cm in length. It is smoked from its narrow end keeping a piece of cloth covering it. Wider end is filled either with tobacco or with cannabis. The wider end is flamed before smoking and the cotton serves as filter.

**Hokka:**

It is an Indian pipe. Upper end of hokka is attached to Chilam, described above, but the material being smoked, is always tobacco (not the cannabis). In hokka the smoke is filtered through the water before reaching to smoker. It is commonly found in every rural home of Northern India.

**Spices and Chillies:**

Spices are the essential ingredients of Indian foods. Almost all of the Indian food preparations are spiced. The choice of preparation may differ but the spices are invariably used. Most of the Indians are very fond of chillies too. Spices and chillies both act as continuous irritants to oral mucosa when they are used for prolonged period. Beside the smoking and food habits, oral hygiene and nutritional status of patients play an important role in the development of the disease process. Pindborg (1964) quoted poor oral hygiene in most of the patients observed by his team. Sirsat and Khanolkar (1962) observed that majority of the patients was under nourished.

Rajendran et al. (1986) working on cell mediated and humoral response in oral submucous fibrosis, came to conclusions of disease being an autoimmune disorder.
Seedat et al. (1988), in their recent work on oral submucous fibrosis were off the opinion of genetic predisposition, playing an important role in the development of the disease.

2- Blood Chemistry and Haematological Variations:

Rajendran R et al (1990) stated that the deficiencies of vitamin B12 folate and Iron can affect the integrity of the oral mucosa.

Significant haematological abnormalities have been reported in Oral Submucous fibrosis, including an increased blood sedimentation rate (ESR), anaemia & eosinophilia (Pindborg JJ. Sirsat SM 1966).

A significant depression of the lactate dehydrogenase isoenzyme ration (LDHIV/LDH II) is reported at the tissue level in Oral Submucous fibrosis. A significant reduction in the serum copper and zinc ratio is also reported (Varghese I et al. 1987).

Decreased Serum Zinc and Iron level are also reported as Bioindicators of precancerous nature of Oral Submucous Fibrosis. (Paul et al 1996).

Role of multiple micronutrients Supplementation in the management of Oral Submucous Fibrosis is carried out in Karachi, Pakistan. (Maher R, et al 1997)

3- AutoImmunity:

Canniff JP et al in 1986 reported high incidence of anti nuclear antibodies together with autoanti bodies to gastic parietal cells, thyroid microsomes, reticulin and smooth muscle in Oral Submucous Fibrosis.

The increased frequency of HLA halotypic pairs A 10/DR3 B8/DR3 and A 10/B8 in OSMF and scleroderma suggets on MHC mediated immunological derangement operating in this disease.

4- Cytogenetics:

Ghosh P. K. et al (1990) stated that sister (?) chromatid exchange (SCE) levels are raised in the peripheral blood of patients with Oral Submucous Fibrosis. This may be attributed to the genotoxic effect of the constituents of betal nut.

Clinical Features:

The onset of oral submucous fibrosis is incidious. It usually spreads over a period of years. In most of the observations, the earliest symptom was burning sensation which made the eating of spicy food, painful and difficult (Paymaster, 1956 and Pindborg et al, 1964). Pindborg (1968) described blistering and ulceration of oral mucosa and recurrent stomatitis as early symptoms. There after a variety of symptoms may appear. Su (1954) and DeSa (1957) described trismus being commonest symptom of oral submucous fibrosis, followed by tightness and loss of elasticity of oral mucosa. This fibrosis spreads to submucosal layer and involves underlying
muscle layer. If pharyngeal muscles are involved, it causes ankyloglossia. Severely affected palate produces symptoms of nasal speech and nasal regurgitation.

Rao (1962) found earache associated with oral submucous fibrosis when pharynx was involved in the disease process. This might lead to deafness, depending upon degree of involvement of pharyngotympanic tubes. In his observation, the commonest affected sites were palate and pillars of fauces. The buccal mucosa and tongue were also involved frequently.

Paymaster (1957) observed that the typical appearance of affected buccal mucosa was lusterless and pearly white. This condition was progressive to a dull white appearance of mucosa with areas of band of scar tissue, giving a reticular pattern. These patterns were best seen along the edge of soft palate. There was contraction of uvula also. Soft palate became hard and immobile. The immobility (or reduced mobility) of the palate resulted into nasal voice and nasal regurgitation. In the patients having prolonged history of disease, the reticular pattern of fibrous spread lead into the pillars of fauces and posteriorly into pharynx. Sometimes this spread was more extensive, even covering pyriform fossa. Buccal mucosa was showing same appearance of fibrous band and further spread occurred towards lips (Bhatt 1986). There was often atrophy of the papillae and appearance of patchy baldness of the dorsum of tongue (Soni et al., 1981). The lingual sulcus appeared to be lost if the floor of mouth became involved.
Soni et al. (1981) also reported the loss of taste papillae and presence of patchy baldness of tongue. After doing electrogustometry, they found some degree of impairment of taste sensation in 24% cases. They emphasised atrophy of taste buds as possible cause of impairment of taste in oral submucous fibrosis. They classified the disease into four categories based on observation of electric gustometry.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Severity of the disease</th>
<th>Electrogustometric observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mild</td>
<td>50 - 100 uA</td>
</tr>
<tr>
<td>2.</td>
<td>Moderate</td>
<td>100 - 200 uA</td>
</tr>
<tr>
<td>3.</td>
<td>Severe</td>
<td>200 - 300 uA</td>
</tr>
<tr>
<td>4.</td>
<td>Eugesia</td>
<td>above - 300 uA</td>
</tr>
</tbody>
</table>

**Classifications:**

Depending upon severity and extension of disease, DeSa (1957) classified oral submucous fibrosis into three stages.

**Stage I : (Early Stage)**

It is an early stage of the disease where the patients complaint of fibrotic bands. There is no trismus and Tongue is not invoved (no ankyloglossia).

**Stage II : (Established Stage)**

In this stage patients complaint of trismus along with the presence of fibrotic bands. Tongue is involved but not grossly.
Stage III: (Advanced Stage)

In third stage of oral submucous fibrosis, there is gross involvement of tongue resulting ankyloglossia along with severe trismus. Palpable fibrotic bands are also present.

Rao (1962), after series of studies on oral submucous fibrosis put following symptoms forward, covering most of the clinical features of the disease.

1. Inability to open mouth.
2. Inability to take pungent food and intolerance to chillies.
3. Inability to blow out candle or inability to whistle.
4. Inability to protrude tongue.
5. Pain in the ears.
6. Swelling and pain around the lower jaw & neck.

Inability to Open the Mouth:

In very early stage, the disease remains asymptomatic completely. Whitish appearance of the palate due to fibrosis is limited to soft palate. The blanching appearance of soft palate and fibrosis is being diagnosed accidentally during the examination of patients for some other disease. It the condition is overlooked, over a period of years (usually two to three) patients develop inability to open mouth. This inability leads to clinical condition called trismus. It is the stage of trismus when
patients first report to otolaryngologist. The other associated findings at this stage may be as follows:

a) **Trismus** being so severe, leads to progressive narrowing of mouth opening. The average distance between upper and lower incisors may be reduced to 4-6 mm. The patient maintains his nutrition with great difficulty because his ability of taking food is reduced to semisolid and liquids only.

b) The soft palate becomes whitish and arched. The fibrosis extends to the buccal area on both sides. It is extent and contraction of the fibrous tissue, underneath the mucosa, over the inter alveolar region and behind molar and pterygomandibular raphe, which produce trismus.

c) The fibrosis progresses to the lateral wall of pharynx via the pillars and it may extend down to the pyriform fossa. The uvula may become small and contracted due to fibrosis. The cheek, when palpate bimanually from outside with support of fingers inside of oral cavity, gives impression of tough feeling and increased thickening. The soft palate showes restricted mobility and has hard rubbery feel. Some times the restricted mobility results into nasal speech and regurgitation.

**Inability to Take pungent Food:**

As the disease advances, the patients becomes unable to tolerate pungent hot
food. The problem becomes more severe when the foods are spicy and seasoned with chillies (Capsicum anum and Capsicum frutescens). In fact intolerance is the first symptom in many cases, which is followed by trismus after few months. It is believed that the fibrosis is the natural outcome of the continuous prolonged irritation of oral mucosa (Pindborg et al, 1964).

**Inability to Blow out Candle or Inability to Whistle:**

It is a qualitative evaluation of the fibrosis and movement of tongue, cheek and palate together. Patients of oral submucous fibrosis, are usually unable to blow a candle out at a distance where normal individual can do so (aprox. Half feet) or unable to whistle. It is due to severity of fibrosis, producing hard and immobile cheeks, palate and tongue. Though the palate is as fibrosed as cheek (or some time more fibrosed) yet its mobility is maintained up to some degree and nasal regurgitation and nasal speech are resulted only in very advanced cases of oral submucous fibrosis.

**Inability to Protrude Tongue:**

This symptom develops when the contracting fibrosis extend to the tongue. Severe fibrosis involves the muscular layers and reduced the mobility resulting ankyloglossia. Some time baldness of tongue is also seen (Soni et al, 1978). Which results in taste impairment.
Pain in the Ears:

It is a referred symptom, presented when pharyngeal fibrosis occurs. Severe fibrosis to this area may result in contraction and scarring of Eustachian tube opening, causing conductive deafness in some cases of oral submucous fibrosis.

Swelling & Pain Around Lower Jaw and Necks:

Continuous trismus is bound to affect oral hygiene. It may lead to ulceration in oral mucosa. Due to ulcers, infections and reduced hygiene, pain and swelling may develop around the jaw and neck. This symptom is presented in very advanced stage of the disease (Pindborg et al, 1954 an Sirsat et al, 1962).

Investigations:

Various investigations have been tried but none found to be diagnostic. Pindborg et al. (1964) found mild iron deficiency anaemia in 40% of the patients. They also noted mild neutropenia. Percentage of anaemia patients in oral submucous fibrosis was even higher (Sirsat and Khaolkar, 1962). Rao (1962) and Sirsat & Khanolkar (1962) found eosinophilia in most of the cases of oral submucous fibrosis. These observations were confirmed by Mukherjee and Biswas (1972) and Phatak (1978). Erythrocyte sedimentation rate (ESR) was found raised in most of the cases (Rao, 1962), Sirsat & Khanolkar, 1962, Pindborg et al. 1964 Mukherjee and Biswas, 1972 and Phatak, 1978).
Rao (1962) studied bone marrow spectrum in-patients of Oral Submucous fibrosis. His findings were suggestive of picture of an allergic reaction, marrow being hypercellular and eosinophilic. These were negative for L E Cells. Urine and gastric tests too were non-contributory (Rao, 1962).

Mukherjee et al. (1972) conducted series of investigations to establish diagnosis of oral submucous fibrosis. They found that there was significant elevation of serum mucoproteins and serum mucopolysaccharides. According to him these elevations represented the reactions in active stage of disease, where breakdown of tissue and degeneration of collagen were taking place.

ASO titre was measured by Mukherjee et al. (1972) showed its rise in all cases. They concluded that immunologic response in the form of localised collagen disorders was responsible for the disease. Phatak (1978), analysing serum proteins and immunoglobulins in oral submucous fibrosis, agreed with the results of Mukherjee et al (1972). In his observations, he found that in oral submucous fibrosis:

1. Total proteins were elevated as compared to control.
2. Total globulins were elevated.
3. Total immunoglobulins were significantly elevated.
4. The fraction, which showed elevation in immunoglobulins, was IgG.
5. IgA fraction was unaltered.
6. IgM fraction did not show any alternation.
Phatak (1979), in another study of fibrin factors, found that there was a strong fibrin precipitating factor present in the saliva of the patients of oral submucous fibrosis. Plasma fibrinogen levels were elevated. Precipitable fibrinogens were also noted.

Immunological studies performed so far, suggested an increase in Null cells population (Phatak, 1979), hyperglobunaemia (Magdun, 1970, Mukherjee et al, 1972) and increase in mononuclear cells observed in microscopic study of fibrous tissue (Phatak and Gosavi, 1975, Adhvanu, 1986).

Gupta et al. (1985) estimated major immunoglobulin profile by immunodiffusion. They observed that severity of oral submucous fibrosis was directly proportional to estimated elevated level of major immunoglobulins. This may be a pointer to know the gravity of disease.

Rajendran et al. (1986) assessed cell mediated and humoral responses in oral submucous fibrosis. The number of high affinity rosette forming cells (ARFC) was found significantly decreased in oral submucous fibrosis and oral cancer. Where as the number of total rosette forming cells (TRFC) remained unaltered, levels of serum IgA, IgD and IgE were found elevated both in oral submucous fibrosis and in oral cancer.

Varghese et al. (1987), analysed serum levels of Copper and Zinc in cases of oral submucous fibrosis and oral cancers. Both were significantly reduced in oral submucous fibrosis. However, Copper/Zinc ratio was found to be elevated in oral
submucous fibrosis. Borle and Jagtap (1987), estimated complement C'3 in oral submucous fibrosis and found its level was unaltered.

Some genetic studies have also been undertaken to throw light on the genetic susceptibility in this disease. Cannif et al. (1985), taking into consideration that all autoimmune disease shows disturbance in the frequencies of HLA antigen, performed HLA typing of the patients of oral submucous fibrosis and controls of the same ethnic origin. They observed raised frequencies of A-10 and D-R3. Their findings supported the concept that oral submucous fibrosis is a chronic autoimmune disease, initiated by constituents of betel nut and occurring in genetically susceptible individuals. Genes situated in the HLA region are important determinants of genetic susceptibility in oral submucous fibrosis.

These immunological observations suggest that oral submucous fibrosis fulfil the criteria of autoimmunity. Laid down by Mackey and Burnet (1963).

**Pathological Study Of Oral Submucous Fibrosis:**

The majority of studies Sharan (1959), Rao (1962), Sirsat and Khanolkar (1957 and 1962) and Wahi (1966) have described the histological changes of the subepithelial tissue in oral submucous fibrosis. Sharan (1959) described hypertrophy with occasional areas of atrophy, Rao (1962) described tobacco tar paintings on the skin to induce progressive epithelial hyperplasia followed by areas of cellular atypism.
Sir sat and Khanolkar (1957 and 1962) described a thickened epithelium with deep invagination into subjacent lamina propria.

**Epithelial Changes:**

An evaluation of epithelial changes in the different grades of Oral Submucous Fibrosis shows that increase in the clinical severity of the disease may be accompanied by epithelial hyperplasia or atrophy, which is associated with an increased tendency for keratinizing metaplasia (Bulletin of WHO 1994).

Wahi et al (1966) correlated the type of keratinizing metaplasia with the site of lesion and the habits of the patients. Lesions involving the palate showed predominantly orthokeratosis and those of the buccal mucosa, parakeratosis. The high mitosis count in parakeratotic epithelia, which is more common with Oral Submucous Fibrosis and the association with parakeratotic leukoplakia predisposes to carcinoma.

**Sub Epithelial Changes:**

In oral submucous fibrosis the Juxta epithelial tissue shows dense hyalinization and fibrosis. Some may have other different combination of type of juxta epithelial tissue. i.e., dense and fibrillar, loose and fibrillar, and loose and hyalinized. In Majority, the blood vessels in juxta epidermal connective tissue are constricted, but in some instances they may be dilated; Constriction of blood vessels is more in tobacco users than in non tobacco users.
The more advanced lesions had an increased frequency and severity of epithelial hyperplasia and atypism. Hyperchromatism, variation in nuclear/cytoplasmic ratio, spindling of nuclei and downward projection of basal cells are the prominent features of submucous fibrosis. Connective tissue changes in submucous fibrosis have been variably interpreted, Sirsat, and Khanolkar (1957 and 1962) Sharan (1959) and Rao (1962) have described marked increase in dense collagen in subepithelial tissue. Sirsat and Khanolkar (1962) and Sharan (1959) have also described hyalization of connective tissue. The changes in connective tissue have been interpreted as fibronoid degeneration by Sharan (1959) and elastic degeneration by Sirsat and Khanolkar (1962) Rao (1962) on the other hand did not find elastic or fibronoid degeneration. It is suggested that the connective tissue changes may proceed any epithelial anomaly or may be concomitant. The epithelial and connective tissue changes seem to depend on the effect of tobacco on tissues preconditioned by vitamin deficiencies (Wahi, et al. 1966). However, the epithelial changes may be aggravated by the abnormalities of underlying connective tissue and blood vessels, which may act interfering with metabolic exchange or by the direct effect of the products of degeneration of altered metabolism. The products of degeneration have been considered to have growth promoting properties (Varoni, 1951) and thus the epithelial changes may be secondary to the connective tissue changes.
Histology According to Stage:

On the basis of the histopathological appearances of stained sections, the surgical specimens from Oral Submucous Fibrosis can be grouped into four clearly definable stages (Sirsat SM, Pindborg JJ, 1967) i.e., very early, early, moderately advanced and advanced. These stages are based not only on the amount and nature of the subepithelial collagen but also on the following criteria –

(a) Presence or absence of oedema

(b) Physical state of mucosal collagen

(c) Overall fibroblastic response (number of cells and age of individual cells)

(d) State of blood vessels

(e) Predominant cell type in the inmatory exudate.

Very Early Stage: -

It is characterized by finely fibrillar collagen dispersed with marked oedema. The fibroblastic response is strong with plump young cells containing abundant cytoplasm. The blood vessels are sometimes normal, but more often they are dilated and congested. Inflammatory cells, mainly polymorphonuclear leucocytes with an occasional eosinophil are present.

Early State: -

The Juxta epithelial area shows early hyalinization. The collagen is still seen as separate bundles, which are thickened. Plumps young fibroblasts are present in
moderate numbers. The blood vessels are often dilated and congested. The inflammatory cells are mostly mononuclear lymphocytes, eosinophils and an occasional plasma cell.

**Moderately Advanced Stage:**

The collagen is moderately hyalinized, the amorphous change starting from the juxta epithelial basement membrane. Occasionally thickened collagen bundles are still seen separated by slightly residual oedema. The fibroblastic response is less marked, the cells present being mostly fibrocytes with elongated spindle shaped nuclei and scanty cytoplasm. Blood vessels are either normal or constricted as a result of increased surrounding fibrous tissue. The inflammatory exudate consists of lymphocytes and plasma cells although an occasional eosinophil is also seen.

**Advanced State:**

The collagen is completely hyalinized and is seen as a smooth sheet, with no separate bundles discernable. Oedema is absent. The hyalinized areas are devoid of fibroblasts, although a thin elongated cell or a vestigial nucleus is seen at same interval along the fibre bundle. Blood vessels are completely obliterated or narrowed. The inflammatory cells are lymphocytes and plasma cells.

**Oral submucous Fibrosis: A Precancerous Condition**

The possible precancerous nature of oral submucous fibrosis was first reported by Paymaster in 1956. While working on oral submucous fibrosis in Bombay he
described development of slow growing squamous cell carcinoma in one third of the cases of this disease. But Sirsat and Khanolkar (1962) could not support Paymaster’s findings. Pindborg et al. (1965) demonstrated leukoplakia of oral cavity in 26.9% patients of oral submucous fibrosis. Their findings were based on observations made on 101 patients of oral submucous fibrosis in Northern India. Where as, they reported, the incidence of oral leukoplakia without oral submucous fibrosis was only 3% (19,899 patients were observe). Zacharia and associates (1964) found frequency of oral cancer as 1.2% in patients of oral submucous fibrosis. In Cancer Institute, Trivandrum, they found that the oral cancers share was 36.6% of all reported cancer (1963 observation) and most of the oral cancers patients were having the clinical findings of oral submucous fibrosis.

In order to clarify a possible relationship between oral cancer and oral submucous fibrosis, Pindborg and Zacharia (1965) examined 100 patients with oral cancer and found that 40 of them were having clinical signs and symptoms of oral submucous fibrosis. In their report Pindborg et al. (1965) found leukoplakia, which is an established precancerous condition in 46.7% cases of oral submucous fibrosis. He observed several cases of oral cancer and oral submucous fibrosis occurring together not only in India but in Sri Lanka, Malaysia, Nepal, Thailand and South Vietnam also. They came to conclusion that oral submucous fibrosis was possibly serving as precancerous condition for oral malignancies.
The findings described by Pindborg et al. (1965) lend support to the concept that oral submucous fibrosis is a precancerous condition. In supports of conclusions made by them, they explained the pathogenesis of oral submucous fibrosis based on histopathological observations. In patients of oral submucous fibrosis, the oral epithelium became atrophic and thus more vulnerable to carcinogens which, in India, are not infrequently present in the form of chewing tobacco, spices, chilies, betel leaves and betel nuts. The atrophic epithelium first became hyperkeratotic (Clinically leukoplakia) and later inters cellular oedema and basal cell hyperplasia developed. From these precancerous developments oral carcinoma could develop at any time.

Working, over a period of seventeen years, on malignant transformation rate in oral submucous fibrosis in Kerala, Murti et al. (1985) found that oral cancers were presented in 7.6% cases. The malignant transformation rate in the same sample was 4.5%. Their findings imparted a high degree of malignant potential to this disease. Laskaris et al. (1981) described the potential of disease as a predisposing factor for the development of the malignancies of oral cavity and reported one case of transformation of oral Submucous fibrosis in carcinoma. Mc Gruk and Craig (1984) also demonstrated malignant transformation of oral submucous fibrosis in two Asians immigrants to the United Kingdom. Their observation also, supported high malignant potential to oral submucous fibrosis.
Murti (1985) found co-existence of oral cancer in 10% cases of oral submucous fibrosis. When, co-existence and malignant transformation were considered together, this incidence was 13.5%. He found leukoplakia in 26% cases. Observation of histopathological reports of all oral submucous fibrosis patients brought the picture squamous cell carcinoma in 12%, epithelial dysplasia in 26% and atrophic epithelium in 76% cases.

Rajendran et al. (1986) assessed cell-mediated immunity and humoral response in oral submucous fibrosis and oral cancer and found similar pattern of changes in both conditions. They indicated that oral submucous fibrosis could be an intermediary stage in the malignant transformation of normal cells. These findings reinforced the hypothesis that oral submucous fibrosis is a precancerous condition.

Differential Diagnosis:

In the differential diagnosis Scleroderma must be excluded. Other conditions from which oral submucous fibrosis must be distinguished include leprosy, Hyalinosis cutaneous mucose, Intra oral scarring from epidermolysis bullosae and an extension of the pharyngeal lesion sometimes seen in case of iron deficiency anemia. Oral submucous fibrosis bears a resemblance to localized Scleroderma, which is also a disease of unknown etiology affecting the connective tissue. In each of these two diseases females are affected more often than males. The age range is 70 to 50 years, in duration and hyperpigmentation are clinical features, chest radiographs are normal,
the red blood cell count also decreases. Hyalinized material is deposited in the connective tissue, and abnormal light staining collagen fibres are characteristic. Both disease give response to steroids and hylase therapy. The salient difference between the two conditions is that oral submucous fibrosis is localized to oral mucosa and pharynx and does not affect cutaneous structures, where as scleroderma lesions can occur throughout the body.

Other white lesions of oral mucosa are Leukoplakia, Leukoderma, Lichen planus and oral cancer, Pindborg (1968). Which can be distinguished easily even on clinical examination. In this survey in Bangalore, Lucknow, Bombay the commonest lesion of oral cavity was Leukoplakia, and other lesions were Leukoderma submucous fibrosis, lichen planus and oral cancer.

Table 8 – Frequency of various oral mucosal lesions in different cities of India.

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Bangalore</th>
<th>Lucknow</th>
<th>Bombay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Cancer</td>
<td>37</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>155</td>
<td>328</td>
<td>284</td>
</tr>
<tr>
<td>Leukoderma</td>
<td>164</td>
<td>166</td>
<td>96</td>
</tr>
<tr>
<td>Submucous fibrosis</td>
<td>18</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>2</td>
<td>19</td>
<td>22</td>
</tr>
</tbody>
</table>
Treatment:

In early days, the treatment was purely imerical and consisted of injections of vitamin A & E, Gold injections, injection of fibrinolysin and Iodine.

Joshi (1953) tried Arsenotyphoid injections without any significant regression of the disease. However, cortisone therapy achieved remarkable success (Rao, 1954). De Sa (1954) too noted a similar experience with corticosteroid administrated by parental or oral routes. However, they noted better response only in early stage of the disease (Stage I & stage II).

Schwartz (1952) also found cortisone produce alleviation of symptoms in one case treated by him in Kenya. De Sa (1957) observed 64 cases and found that on two years follow up after treatment, there was a gradual recurrence of symptoms in majority of the patients. He treated cases with systemic administration of hydrocortisone.

Sirsat and Khanolkar (1962) came to conclusion that cortisone affords temporary relief from the disabling symptoms in the early stage of this long standing disease. Rao (1961) concluded that cortisone and its other purified derivatives (Hydrocortisone, Deltacortisone Triaminolone, Dexamethasone) in the form of tablets, systemic injections and local injections were of great help. Rao (1961) advocated definite course of treatment which consisted of 7 weeks treatment with Triamcinolone or Dexamethasone in gradually decreasing dose, starting with 600 mg Triamcinolone
or 90 mg Dexamethasone. This was supplemented with hydrocortisone local injections of 25 mg per time biweekly into the affected area (usually 15 to 20 injections). Since the hydrocortisone was fibrinolytic, antiallergic and anti-inflammatory reduced the oedema. With the above course of treatment Rao (1961) found remarkable improvement in the disease.

In early days of treatment with corticosteroids, Rao (1961) found glycosuria, moon face and generalized oedema. But as the treatment advanced with latest derivatives of corticosteroids, these unwanted symptoms were negligible. He advocated three injections of ACTH (20 IU) to be given for three successive days before the treatment was concluded.

Moos (1968) strongly advocated eradication of chronic irritation of any form, either mechanical (sharp jagged tooth) or chemical (betel nut and beta chewing, alcohol, smoking and tobacco chewing), along with the subjective treatment. Since most of the cases, reported from India, were anemia, a balanced diet was essential. He was of the strong opinion of the supplementation of vitamins in the initial phase of treatment. Though the vitamin supplementation therapy had been proved of little value by itself (Sirsat and Khanolkar, 1962), but along with other treatments, the improvement was found to be much better, Moos (1968) also tried hydrocortisone therapy and surgical cutting of fibrous band but came to conclusion that these two management gave good result initially but the long term result of such management
still remained doubtful. Fibrous contracture might resulted at the operated site resulting more severe symptoms.

Sinha (1978) tried intra oral injections of hydrocortisone and placental extracts (Placentrax) and paid attention to the improvement of disease. He found improvement in both of the regimes but it was far superior with cortisone as compared to placental extracts. The improvement in Symptomatology, like improvement in suppleness of oral tissue, regaining of pink coloured buccal mucosa, burning sensation, improvement in protrusion of tongue as well as in inability to open mouth and reduction in fibrous bands of oral cavity were found to be better in hydrocortisone therapy.

Beside the improvement with hydrocortisone treatment, Sinha (1978) observed that failure rate was four times higher with placental extract. When the failure cases of placentrax were switched over to hydrocortisone therapy the result was quite good while the hydrocortisone failure case could not got improvement with placental extract.

Two years later Sinha (1980) conducted another therapeutic study. He compared the treatment with intra oral injection of hyaluronidase (hylase) and hydrocortisone, and combination of these two drugs in the treatment of oral submucous fibrosis. He found that there was better response in patient treated with hydrocortisone as compared to hylase. The failure rate was less with hydrocortisone
treatment. When the treatment of failure cases were exchanged, they found that the success rate in hylase failure case (i.e. treated with hydrocortisone) was far better than hydrocortisone failure cases (i.e. treated with hylase). Above all, Sinha (1980) obtained best result with combination of hylase and hydrocortisone therapy.

Kakar et al. (1986) tried four regimens and compared the improvement. These regimens were local dexamethasone, local combination of hyaluronidase and dexamethasone and local placental extract. They found that there was quicker response with hyaluronidase but long term and better response was obtained with combination of dexamethasone and hyaluronidase. They recommended this regimen for the management of oral submucous fibrosis.

Considering it as a collagen disorder some workers tried collagenase for the management of oral submucous fibrosis. Chen and Lin (1986) used intra oral injections of collagenase in the treatment of the disease. They found remarkable success in the improvement, but the remission was not complete.

Sharma et al. (1987) searched a new dimension of treatment, giving emphasis to the incomplete remission of by treatment. They advocated vasodilators for the management of oral submucous fibrosis. Nylidrin hydrochloride, a peripheral vasodilator, was experienced for over 10 years. There was reportedly no side effect except complaints of flushingly warm skin. Supportive therapy of vitamin A, E & B,
complex, iodine and placental extract were given. They found success rate of 62.07% in cases of oral submucous fibrosis.

**Surgical Treatment:**

Moos (1968) advised surgical cutting of fibrous bands of oral submucous fibrosis. The patients improved immediately from severe trismus. But long standing results were not so good because symptoms reappeared due to scarring at the operated site. Kavarana et al. (1984) tried nasolabial flaps in oral submucous fibrosis to improve trismus. They used bilateral full thickness nasolabial flaps and set it into the defects created by incision in oral mucosa. They compared postoperative rehabilitation with other methods and advocated this technique for all cases of oral submucous fibrosis requiring correction of severe trismus.

The malignant transformations of oral submucous fibrosis were treated according to site and size of the growth and histopathological reports. Almost all workers suggested excision of the growth followed by chemotherapy or radiotherapy depending upon the requirements.

Most of the workers like Sirsat & Khanolkar (1962) and Pindborg et al. (1968) suggested regular follow up of the patients of oral submucous fibrosis, keeping high malignant transformation rate of the disease into mind.