Submucous Fibrosis of the Oral Cavity : 2. Studies on Epidemiology

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In recent years, submucous fibrosis has received considerable attention as a precursor to cancer of the oral cavity. Its prevalence in India has been reported as being from 0.2% to 0.5% in different population groups.[a] However, the etiopathogenesis of the condition is not understood, except that the disease is confined to the South-East Asian countries.

The present study embodies the observations on epidemiological factors in 104 histologically proved cases of submucous fibrosis.

The cases and comparable controls were obtained from the Department of Dentistry, S. N. Medical College, Agra. Controls were provided by 200 consecutive patients above 18 years of age attending the Department of Dentistry, selected after thorough intra-oral examination to exclude any detectable mucosal anomaly. The tobacco and dietary habits of patients and controls were recorded. The patients and the controls were examined for any clinical evidence of hypovitaminoses A, B and C, anaemia, Plummer-Vinson syndrome and other local or systemic diseases. Whenever possible, the haematological status (including absolute eosinophil count), serum proteins and serum vitamin A, were estimated in the patients. A tissue biopsy was obtained from all cases for histological study. The clinical features of the cases showing mucosal anomalies were recorded.

Observations

Of the 273 cases of precancerous oral lesions studied, 104 (38%) were diagnosed histologically as submucous fibrosis and constituted the largest group.

The cases were classified into three groups on the basis of clinical features, severity and extent of the disease, as mentioned in a previous communication.[b] It was found that 31 cases belonged to group I, 60 to group II and 13 to group III. The palate was the predominant site, being involved in 51.3% of the cases, while the buccal mucosa was involved in 44.2%, the tongue in 2.7% and the lips and gingivae each in 0.9% of the cases.

Sex and religion. It was found that 89 out of 104 patients were Hindus and the remaining 15 Muslims, while in the control group 180 of the 200 were Hindus and the remainder Muslims.

The male : female ratio was approximately 2 : 1 (70 males and 34 females) for the patients and 1.7 : 1 (126 males and 74 females) for the controls. Analysis of the sex-ratio distribution in Hindus and Muslims showed that females were more common among Muslim patients (male : female ratio 0.8 : 1, ratio in controls 1.4 : 1), while males were more common among Hindu patients (male : female ratio 2.4 : 1, ratio in controls 1.2 : 1). The number of Muslim patients is, however, too small to allow statistically significant conclusions to be drawn. The distribution of males and females in the three clinical groups is shown in Fig. 1. It will be seen that females predominate in clinical group III.

Age. Table 1 shows the age distribution of male and female patients with submucous fibrosis. The maximum prevalence (70%) was found between 30 and 49 years of age. Only one patient was below 20 years of age.

Table 2 gives the statistical analysis of the age distribution of patients with submucous fibrosis. No significant difference was found between the age distributions for the three clinical groups.

Socio-economic status. The distribution of the patients according to income and sex is shown in Table 3.

It will be seen that 72.1% of the patients had incomes of below Rs. 100 per month, in contrast to 39% in the control group. The prevalence of patients in this income group was significantly higher than those in the income group above Rs. 100 per month ($P<0.05$).

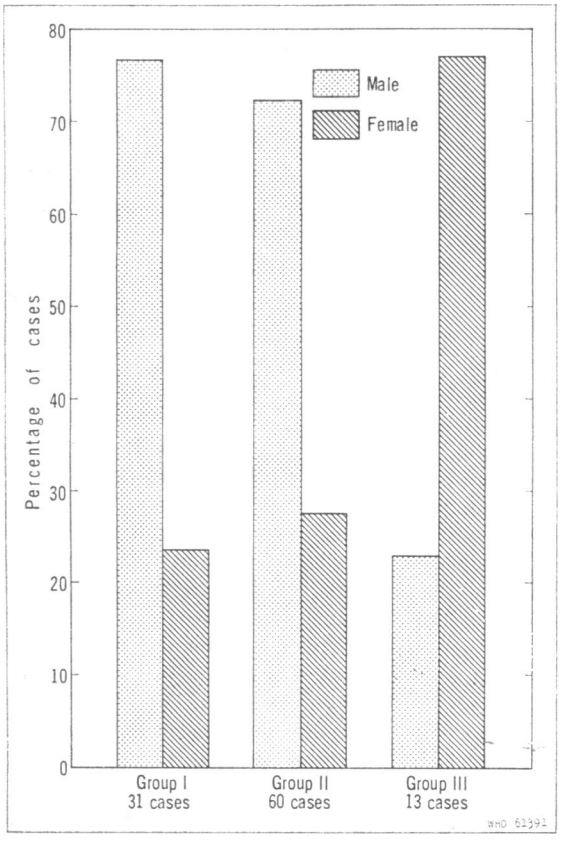
Occupation. The patients belonged to various occupational groups, e.g., farmers, labourers, clerks,

[a] Pindborg, J. J., Chawla, T. N., Shrivastava, A. N., Gupta, D. & Mehrotra, R. M. L. (1964) *Acta odont. scand.*, 22, 679.

[b] Wahi, P. N., Kapur, V. L., Luthra, U. K. & Srivastava, M. C. (1966) *Bull. Wld Hlth Org.*, 35, 789-792.

FIG. 1

DISTRIBUTION OF MALES AND FEMALES IN THE THREE CLINICAL GROUPS OF SUBMUCOUS FIBROSIS



government officials, technical personnel, etc. None of the occupations predominated to a significant extent.

Nutritional status and diet. Poor nutritional status was evident on clinical examination in 28% of the male and 35% of the female patients. The prevalence of malnutrition in cases of submucous fibrosis was significantly higher than in the control group ($P < 0.05$).

The diet consisted predominantly of cereals (wheat, rice and pulses) and vegetables, and was occasionally supplemented by meat, eggs or fish in the patients classed as non-vegetarian. All the Muslim patients

FIG. 2

APPROXIMATE AMOUNT OF CHILLIES CONSUMED PER MONTH BY SUBMUCOUS FIBROSIS PATIENTS AND CONTROLS

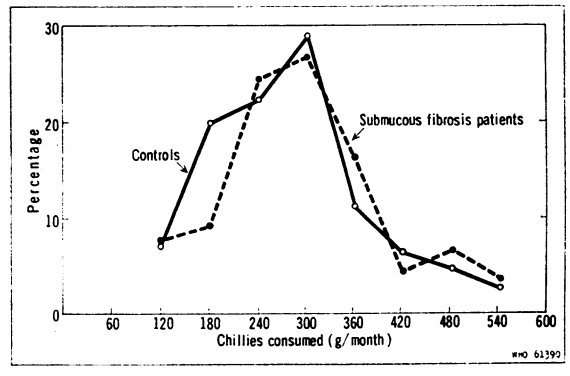


TABLE 1

AGE DISTRIBUTION IN MALE AND FEMALE PATIENTS WITH SUBMUCOUS FIBROSIS AND IN CONTROLS

Age-group (years)	Males		Females		All patients		Controls	
	No.	%	No.	%	No.	%	No.	%
15-19	—	—	1	2.9	1	0.9	3	1.5
20-24	4	5.7	2	5.8	6	5.7	9	4.5
25-29	7	10.0	1	2.9	8	7.6	19	9.5
30-34	12	17.2	6	17.7	18	17.5	35	17.5
35-39	11	15.7	2	5.8	13	12.6	10	5.0
40-44	14	20.0	12	35.7	26	25.0	39	19.5
45-49	6	8.6	2	5.8	8	7.6	23	11.5
50-54	4	5.7	2	5.8	6	5.7	18	9.0
55-59	5	7.1	1	2.9	6	5.7	16	8.0
60-64	3	4.3	4	11.8	7	6.8	19	9.5
65 and above	4	5.7	1	2.9	5	4.9	9	4.5

TABLE 2
STATISTICAL ANALYSIS OF AGE DISTRIBUTION IN CASES OF SUBMUCOUS FIBROSIS

	Age (years)		
	Male	Female	Both sexes
Mean	40.6	40	40.5
SD	14.0	12.4	13.2
Range [a]	26.6-54.6	27.6-52.4	27.3-53.7
Median	40	38	40
Standard error of mean	1.7	2.1	1.3

[a] Range = Mean ± SD.

Vitamin status. Clinical features indicative of deficiency of vitamin A, B and C were noted as shown in Table 5. Table 6 shows the frequency of vitamin deficiencies observed in patients and controls.

In 40 cases of submucous fibrosis (38.4%), deficiency of more than one vitamin was evident while only 6% of the controls had evidence of multiple vitamin deficiency. The greater frequency of clinical manifestations of deficiencies of vitamins A, B and C and multiple vitamin deficiency in cases of submucous fibrosis than the controls was found to be statistically significant ($P<0.05$).

Serum vitamin-A levels. The serum vitamin-A level in the patients varied from 36.8 IU/100 ml to 154 IU/100 ml, the average being 75.23 IU/100 ml with a standard deviation of 25.7 IU/100 ml. The serum vitamin-A content was below the normal range [d] in all cases of submucous fibrosis but one.

TABLE 3
SOCIO-ECONOMIC STATUS IN MALE AND FEMALE PATIENTS WITH SUBMUCOUS FIBROSIS AND IN CONTROLS

Monthly income	Cases of submucous fibrosis				Controls	
	Males	Females	All patients		No.	%
			No.	%		
Below Rs. 100	48	27	75	72.1	78	39.0
Rs. 101 to Rs. 200	20	4	24	23.1	103	56.5
Above Rs. 200	2	3	5	4.8	19	9.5

were non-vegetarian, as compared with only 32.6% of Hindu patients. On the whole, the diet was poor in animal proteins and fats, and varied in adequacy with the income group. Seasoning of food with chillies and other condiments such as black pepper, ginger, onions, garlic, etc., was an almost universal feature of the dietary habits of both patients and controls. Fig. 2 shows the approximate amount of chillies consumed per month by the patients and the controls; no significant difference was found between the two groups. The age of starting consumption of chillies was between 5 years and 8 years in both groups.

Serum proteins. Table 4 shows the total serum proteins, albumin and globulin in patients with submucous fibrosis. In none of our patients was an increase in globulin content or an altered albumin:globulin ratio observed. The values for all patients with submucous fibrosis were within the normal range for the population of this region.[c]

Haematological findings. Clinical examination showed 6% of the male patients and 11% of the female patients to be anaemic. The haemoglobin content varied from 7.5 g per 100 ml of blood to 10 g per 100 ml of blood in these cases. The frequency of anaemia did not, however, differ significantly from that for the control subjects ($P>0.05$).

The absolute eosinophil count ranged between 60/mm³ and 675/mm³ of blood. The average absolute eosinophil count was 322.7/mm³ of blood (SD, 178.32/mm³). The absolute eosinophil count was slightly above the normal range in 30% of the patients.

Orodental hygiene. The orodental hygiene was poor in 90.5% of the patients, and oral sepsis was

[c] Chatterjee, P. C. (1963) *Electrophoretic studies of serum proteins in metastatic malignant disease*, Agra (Thesis).

[d] Wahi, P. N., Bodkhe, R. R., Arora, S. & Srivastava, M. C. (1962) *Indian J. Path. Bact.*, 5, 1.

TABLE 4

TOTAL SERUM PROTEIN, ALBUMIN AND GLOBULIN IN PATIENTS WITH SUBMUCOUS FIBROSIS

	Total serum protein (g/100 ml serum	Albumin (g/100 ml serum)	Globulin (g/100 ml serum)
Mean	6.8	3.9	2.1
SD	1.3	1.1	0.8
Range [a]	5.5-8.1	2.8-5	1.3-2.9

[a] Range = Mean ± SD.

present in 44.2%. However, these figures were not significantly different from those for the control group.

Tobacco habits. Table 7 shows the tobacco habits in patients and controls. While 72.6% of the patients used tobacco, only 55.5% of the controls did so. This difference is statistically significant ($P<0.05$). The types of tobacco habits in patients and controls are analysed in Table 8.

The frequency of combined smoking and chewing in patients with submucous fibrosis was significantly higher than in the controls. The distribution of

TABLE 5

CLINICAL FEATURES OF VITAMIN A, B AND C DEFICIENCY IN PATIENTS WITH SUBMUCOUS FIBROSIS

Hypovitaminosis	No. of cases	%	Clinical features	No. of cases	%
Vitamin A	20 [a]	19.2	Dryness of eyes	18	90.0
			Photophobia	2	10.0
			Night blindness	6	30.0
Vitamin B	56 [b]	53.8	Chelosis	53	94.6
			Soreness of mucosa	18	32.1
			Atrophic glossitis	2	3.5
			Skin changes	6	10.7
Vitamin C	54 [c]	51.9	Swollen gums	52	96.3
			Haemorrhage from gums	50	92.6

[a] Six patients showed more than one feature.
[b] Twenty-three patients showed more than one feature.
[c] Fifty patients showed both clinical features.

TABLE 6

FREQUENCY OF VITAMIN A, B AND C DEFICIENCY IN PATIENTS WITH SUBMUCOUS FIBROSIS AND IN CONTROLS

		Hypo-vitaminosis A	Hypo-vitaminosis B	Hypo-vitaminosis C	Multiple vitamin deficiency [a]
Patients with submucous fibrosis (104)	No.	20	56	54	40
	%	19.2	53.8	51.9	38.4
Controls (200)	No.	11	38	33	12
	%	5.5	19.0	16.5	6.0

[a] These cases have also been included in the individual vitamin deficiencies.

TABLE 7
TOBACCO HABITS OF PATIENTS WITH SUBMUCOUS FIBROSIS AND OF CONTROLS

		No chewing or smoking	Betel nuts and/or betel leaf chewing	Tobacco chewing or smoking or both
Patients with submucous fibrosis (104)	No.	22	6	76
	%	21.6	5.8	72.6
Controls (200)	No.	74	15	111
	%	37.0	7.5	55.5

tobacco habits in the three clinical groups of submucous fibrosis and the controls is shown in Table 9.

The use of tobacco was found to be significantly more frequent in group III than in either group I or group II, and also more in group II than in group I ($P<0.05$). There is an apparent predominance of cases of combined tobacco chewing and smoking in group III as compared with groups I and II, but the number of cases is too small to allow definite conclusions to be drawn.

The duration of the tobacco habit in the three clinical groups of submucous fibrosis and the controls is shown in Table 10.

Tobacco habits of more than 20 years' duration were found in 12.5% of the controls as compared with 44.8% of the patients. The analysis by clinical group shows durations of more than 20 years in 25.8% of group-I, 50% of group-II and 77% of group-III cases.

Discussion

The possible role of various etiological factors in 104 histologically diagnosed cases of submucous fibrosis has been presented above. This forms the largest single group of cases reported so far.

In the present series, males predominated over females in the ratio of 2 : 1. This is at variance with

TABLE 8
TYPES OF TOBACCO HABITS IN PATIENTS WITH SUBMUCOUS FIBROSIS AND IN CONTROLS

	No. of subjects using tobacco		Tobacco smoking	Tobacco chewing	Both smoking and chewing tobacco
Patients with submucous fibrosis	76	No.	47	16	13
		%	61.8	21.0	17.2
Controls	111	No.	83	24	4
		%	74.8	21.6	3.6

TABLE 9
DISTRIBUTION OF VARIOUS TOBACCO HABITS IN THREE CLINICAL GROUPS OF SUBMUCOUS FIBROSIS

Clinical group		No chewing or smoking	Betel nuts and/or leaf chewing	Tobacco smoking	Tobacco chewing	Tobacco chewing and smoking or both	Total
I	No.	13	2	10	4	2	31
	%	41.2	6.4	32.3	12.8	6.4	
II	No.	9	3	36	7	5	60
	%	15.0	5.0	60.0	11.6	8.4	
III	No.	0	1	1	5	6	13
	%	0	7.7	7.7	38.5	46.3	
Controls	No.	74	15	83	24	4	200
	%	37.0	7.5	41.5	12.0	2.0	

TABLE 10
DURATION OF TOBACCO HABIT IN PATIENTS WITH SUBMUCOUS FIBROSIS ACCORDING TO CLINICAL GROUPS AND IN CONTROLS

Duration of tobacco habits (years)	Cases of submucous fibrosis								Controls	
			Clinical groups							
			I		II		III			
	No.	%	No.	%	No.	%	No.	%	No.	%
0-5	11	14.4	7	63.6	4	36.4	—	—	21	18.1
6-10	11	14.4	8	72.7	3	27.3	—	—	28	25.2
11-15	10	13.2	4	40.0	5	50.0	1	10.0	38	35.2
16-20	10	13.2	4	40.0	4	40.0	2	20.0	10	9.0
21-25	13	17.5	6	46.1	4	30.7	3	23.2	8	7.2
26-30	7	9.1	1	14.3	5	71.4	1	14.3	4	3.5
31-35	7	9.1	1	14.3	3	42.8	3	42.8	1	0.9
36 and above	7	9.1	0	—	4	57.1	3	42.8	1	0.9
Total	76		31		32		13		111	

the reports of Schwartz,[e] Rao & Raju,[f] Rao[g] and Pindborg,[a] who found a definite preponderance of female cases, and with those of Joshi,[h] DeSa[i] and Sirsat & Khanolkar,[j] who found nearly equal proportions of males and females. Sharan [k] reported a predominance of males, while all the three cases reported by Su [l] were in males. However, in group-III cases there was a preponderance of females (Fig. 1). Since this group comprises cases at an advanced clinical stage, it may be that the high incidence of females in the other reports was due to selection of clinically advanced cases.

The etiology of submucous fibrosis is not understood. It has been suggested that this condition belongs to the group of collagen diseases.[l] None of our cases showed any evidence of systemic or skin involvement. Hypergammaglobulinaemia has been reported in cases of submucous fibrosis.[i, j] In the present series, the levels of total proteins and of albumin and globulin were within normal limits. Rao [g] also reported similar findings.

In 30% of our cases of submucous fibrosis, the absolute eosinophil count was above the normal range. Sirsat & Khanolkar [j] have also reported eosinophilia in cases of submucous fibrosis. Pindborg,[a] DeSa [i] and Rao [g] did not find eosinophilia in their studies. Since other causes of eosinophilia such as parasitic infestations have not been excluded, much significance cannot be given to this observation.

Histomorphologically, the lesions were characterized by dense hyalinized juxta-epithelial connective tissue which showed metachromasia with alcoholic toluidine blue (indicative of acid mucopolysaccharides.[m] Constricted blood vessels were also a conspicuous feature. These changes in the dermal connective tissue are comparable to those described in skin carcinogenesis.[n-p] An increase in the acid mucopolysaccharide content of connective tissue in general has been reported in guinea-pigs after in-

[e] Quoted by Sirsat, S. M. & Khanolkar, V. R. (1962) *Indian J. med. Sci.*, **16**, 189.

[f] Rao, R. V. & Raju, P. R. (1954) *Indian J. Otolaryng.*, **6**, 81.

[g] Rao, A. B. N. (1962) *Brit. J. Surg.*, **50**, 23.

[h] Joshi, S. G. (1953) *Ind. J. Otolaryng.*, **4**, No. 3, p. 1.

[i] DeSa, J. V. (1954) *Ann. Otol. (St. Louis)*, **66**, 1143.

[j] Sirsat, S. M. & Khanolkar, V. R. (1962) *Ind. J. med. Sci.*, **16**, 189.

[k] Sharan, J. (1959) *Indian J. Path. Bact.*, **2**, 150.

[l] Su, I. P. (1954) *Arch. Otolaryng.*, **59**, 30.

[m] Pearse, A. G. E. (1960) *Histochemistry : theoretical and applied*, 2nd ed., London, Churchill, p. 251.

[n] Prodi, G. & Maltoni, C. (1957) *J. Path. Bact.*, **73**, 355.

[o] Prodi, G. (1963) *Brit. J. Cancer*, **17**, 504.

[p] Orr. J. W. (1963) *The role of the stroma in epidermal carcinogenesis.* In: Urbach, F., ed., *First International Conference on the Biology of Cutaneous Cancer*, Washington, D.C., US Government Printing Office, p. 531 (National Cancer Institute Monograph No. 10).

halation of tobacco smoke.[q] In the present study the use of tobacco, in particular for long periods (more than 20 years), was found to be significantly more frequent in patients than in controls, and increased significantly from clinical group I to group III.

The frequency of vitamin-C deficiency was significantly higher in cases of submucous fibrosis than in control cases. Florey [r] has reported homogeneous appearance, increased mucopolysaccharide content and decreased vascularity of connective tissue during healing in vitamin-C-deficient animals and humans. The morphological appearance of the connective tissue was found to be very much the same in cases of submucous fibrosis.[s]

In submucous fibrosis, the overlying epithelium showed predominantly hyperplasia with or without cellular atypism; in only a few cases was atrophy observed. Tobacco extracts and tobacco smoke are also known to produce hyperplasia of the oral epithelium.[t, u] Muir & Kirk [v] have reported development of oral carcinoma in mice treated with crude tobacco extract.

Epithelial hyperplasia, atrophy and excessive keratinization have been described in vitamin-A deficiency.[w] Low serum vitamin-A levels, comparable to those observed in cases of oral cancer,[d] were found in our cases of oral submucous fibrosis. Atrophy of the epithelium has been described as a feature of deficiency of vitamins of the B complex.[w, x] Waravdekar et al.[y] have described clinical signs of mild vitamin-B deficiency in cases of oral precancerous lesions and oral cancer. A significantly high frequency of clinical manifestations of vitamin-B deficiency was found in cases of submucous fibrosis.

No significant difference in the amount and the duration of the consumption of chillies was found between patients with submucous fibrosis and the controls, so that no definite etiological role can be assigned to this factor. However, the experimental studies of Sirsat & Khanolkar [z] suggest that the mild irritant action of chillies might reinforce other factors.

On the basis of these observations, it seems possible that the chemical, thermal and/or mechanical factors associated with the use of tobacco may act in conjunction with the vitamin deficiencies to lead to the development of submucous fibrosis. However, this hypothesis does not account for those cases where there was no history of the use of tobacco, or without manifest hypovitaminosis. In such cases other unknown irritants or altered tissue responses, acting in conjunction with one of the above-mentioned agents or independently, might have led to the development of the lesion.

[q] Lupu, N. G. & Velikan, K. (1962) *Arkh. Pat.*, **24**, 2.

[r] Florey, H. (1962) In: *General pathology*, 3rd ed., London, Lloyd-Luke, p. 489.

[s] Wahi, P. N., Luthra, U. K., & Kapur, V. L. (1966) *Brit. J. Cancer* (in press).

[t] Roffo, A. H. Quoted by Florey, C. M. (1941) *Cancer Res.*, **1**, 262.

[u] Divekar, V. D., Ambayo, R. K., Rane, T. B. & Khanolkar, V. R. (1961) *Proc. Indian Acad. Sci.*, **54**, Sect. B (No. 2), p. 57.

[v] Muir, C. S. & Kirk, R. (1960) *Brit. J. Cancer*, **14**, 597.

[w] Wolbach, S. B. & Bessey, O. A. (1942) *Physiol. Rev.*, **22**, 233.

[x] Abels, J. C., Reckers, P. E., Martin, H. & Rhodas, C. P. (1942) *Cancer Res.*, **2**, 281.

[y] Waravdekar, V. S., Mangaonkar, V. G. & Khanolkar, V. R. (1950) *Acta Un. int. Cancr.*, **6**, 1017.

[z] Sirsat, S. M. & Khanolkar, V. R. (1960) *Arch. Path.*, **70** 180.

New Antigenic Variants of Avian Influenza A Viruses

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Influenza A viruses of avian origin have been divided by Pereira, Tůmová & Law [b] into four antigenic groupings represented by the following strains: (1) classical fowl plague virus (Dutch strain), Turkey/England/63 (Langham strain) and virus N; (2) Duck/England/56; (3) Duck/Czechoslovakia/56 (Kosice) and Duck/England/62, and (4) Chicken/Scotland/59 (Smith strain) and Tern/South Africa/61.

[a] Work performed while on leave at the College of Agriculture, University of Massachussetts, Amherst, Mass., USA.

[b] Pereira, H. G., Tůmová, B. & Law, V. G. (1965) *Bull. Wld Hlth Org.*, **32**, 855-860.