ORAL PREMALIGNANCY

Proceedings of the First Dows Symposium

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Introduction

The idea of a symposium on Oral Premalignancy arose during informal discussion between oral pathologists and research workers with an interest in oral epithelium. It was suggested that although premalignant lesions of the oral mucosa are of clinical importance, their nature is poorly understood and most investigation has focused on the clinical problems or on histopathological diagnosis. Consequently, it seemed worthwhile to bring together in a workshop setting a group of people who would be able to discuss some of the problems to be faced and whose interaction might stimulate a better understanding of the biology of premalignancy.

The general aims of the symposium were (a) to examine the concept of oral premalignancy; (b) to discuss what is known about the nature and behavior of premalignant lesions; (c) to explore which of the many recent advances in the basic sciences may offer hope of improving methods of diagnosis and prognosis, as well as providing direction for new areas of investigation.

The participants at the symposium were both pathologists with a particular interest in premalignancy and basic scientists whose area of research was related to various aspects of the problem. It was hoped that such a group would be able to generate free discussion and an interchange of ideas about concepts of oral premalignancy. The framework of the symposium was a series of presentations covering various facets of the problem so as to provide a general background of information for those participants who were not familiar with the whole field. They were arranged in a sequence expected to provide some order of progression for the discussion which was considered to be a most important feature of the meeting.

The discussion, in its unedited form, amounted to some 350 pages of typed transcript. Participants were encouraged to modify their original manuscripts to cover topics of importance raised during the discussion: many of the points raised during discussion have now been incorporated into the papers themselves. Remaining points of interest from the discussion have been grouped throughout the text in relation to the presentations concerned.

It was the hope of the organizers to extract from the symposium a balanced account of the present state of knowledge about oral premalignancy together with some rational ideas for future work. While the proceedings may go some way toward meeting the former objective, it

became clear that such large gaps exist in our knowledge of many aspects of oral premalignancy that a compilation of specific suggestions for future research would be impractical. For example, the meeting indicated that there is, as yet, a lack of a consensus concerning such basic problems as the definition and clinical significance of oral premalignant lesions. Many participants expressed concern about the subjective nature of present methods of histopathological diagnosis and about the uncertain reliability of a prognosis based on such procedures. Too little appears to be known about human premalignant lesions to allow their mechanism of development and progression to be clearly related to basic concepts, such as initiation and promotion in carcinogenesis, which have developed from animal studies. Further, no demonstrably suitable animal model for studying oral premalignancy appears to be available and work is only just reaching the stage where current ideas about control of normal epithelial differentiation and growth can be applied in attempting to understand the changes occurring in oral lesions. Such problems deserve examination and most of them require coordinated clinical and laboratory investigation. We therefore feel that there is still a strong need to further the exchange of ideas by means of meetings such as this one in which the basic scientist becomes aware of the problems of clinical diagnosis and patient management and the pathologist more familiar with progress in the laboratory in fields related to his or her specialty.

The organizers wish to express their gratitude for financial support for the workshop which was provided by grants from the International Union Against Cancer and the American Cancer Society, Iowa Division, and partly from funds made available to the University of Iowa College of Dentistry by gifts from the Sutherland and Frances Dows Trusts.

We have been ably assisted throughout the planning of the symposium, during the meeting itself and in the subsequent work on the manuscript by the secretarial staff of the Dows Institute. Our editorial assistant Nellie Kremenak assisted with every stage of the project and played a major part in producing the final manuscript. Without her help this volume would not have been possible.

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PART ONE
CLINICAL AND HISTOPATHOLOGICAL CONCEPTS

1

Lesions of the Oral Mucosa to be Considered Premalignant and Their Epidemiology

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1. INTRODUCTION

Many attempts have been made to define precancer and its synonym premalignancy. At a World Health Organization (WHO, 1973) "Meeting of Investigators on the Histological Definition of Precancerous Lesions" in Geneva 1972 a *precancerous lesion* was defined as "a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart." In an additional note it was mentioned that some lesions have a very high probability (20% or more) of developing cancer, others are much lower, while the potential of many is unknown.

Premalignant lesions include leukoplakia and erythroplakia (each of which can be divided into homogeneous and nodular types) and palatal changes associated with reverse smoking (Mehta et al. 1977). These palatal changes should not be confused with leukokeratosis nicotina palati (syn. nicotinic stomatitis).

A *precancerous condition* was defined as "a generalized state associated with a significantly increased risk of cancer." Examples of precancerous conditions are syphilis, sideropenic dysphagia, oral submucous fibrosis, discoid lupus erythematosis, and xeroderma pigmentosum. Apart from these groups are some generalized diseases (for example, lichen planus) which may make the mucosa more susceptible to action of carcinogens and the development of cancerous lesions.

When the above definitions are applied to the oral mucosa a classification emerges, which is shown in Table 1.

2. PREMALIGNANT LESIONS

2:1 LEUKOPLAKIA

In this paper leukoplakia is defined as a white patch which cannot be removed by scraping and cannot be attributed to any other diagnosable disease.

2:1:1 *Epidemiology of oral leukoplakia*

House-to-house studies of oral leukoplakia are rare except in India. Table 2 summarizes the available studies. In India, 176,000 people have

TABLE 1

Classification of Oral Precancerous Lesions and Conditions

Precancerous lesions
- Leukoplakia
  - Homogeneous
  - Nodular (speckled)
- Erythroplakia
  - Homogeneous
  - Nodular (speckled)
- (Palatal changes associated with reverse smoking)

Lichen planus

Precancerous conditions
- Syphilis
- Sideropenic dysphagia
- Submucous fibrosis
- Discoid lupus erythematosus
- Xeroderma pigmentosum

TABLE 2

Prevalence of Oral Leukoplakia in Unselected Populations

Country	*Investigator*	*Size of sample*	*Prevalence*
India			
Villages	Mehta et al. (1969, 1972a)	152,000	0.2-3%
Suburban	Zachariah and Pindborg (unpublished material)	24,000	2%
Sweden	Axéll (1976)	20,000	3.6%
Hungary	Bruszt (1962)	5,000	4%

been surveyed in unselected populations, mostly among villagers, but also including a large suburban sample. The prevalence rates of leukoplakia in India vary between 0.2 and 3%; and are similar to findings in Hungary. The most extensive study in the West is that of Axéll (1976) in Sweden who found a prevalence of 3.6% in adults. It is pertinent to ask whether the same diagnostic criteria have been applied in all these surveys so that a comparison is permissible. It should be noted that the criteria in all the Indian surveys were identical, and that the Swedish investigator calibrated with the author who initiated the Indian surveys.

In India, it has also been possible to make incidence studies in some states, for example in Gujarat and Kerala (Table 3). The incidence (rate) of leukoplakia is much higher in Kerala than in Gujarat, especially among females.

TABLE 3
Annual Incidence of Leukoplakia in a 7-year period.
After Mehta, Pindborg, Bhonsle, and Sinor (1976).

		No. new leukoplakias per 100,000 per year	
	Follow-up rate	*Females*	*Males*
Gujurat	61%	0	190
Kerala	71%	400	330

2:1:2 *Follow-up studies of oral leukoplakia*

The premalignant nature of a given lesion or condition may be demonstrated by the simultaneous occurrence of the lesion (condition) and cancer, or through follow-up studies of presumed premalignant lesions and conditions.

Clinical follow-up studies

The simultaneous occurrence of leukoplakia and oral cancer has been reported by Silverman et al. (1963), who found that this ranged from 11 to 60% in 10 studies. The range reveals more about difference in criteria applied by the investigators than about true differences in the populations examined.

Follow-up studies can be done in two ways: (1) a sample of leukoplakias (with or without matched controls) can be followed over a number of years, (2) a sample selected on the basis of histologic criteria (e.g. epithelial dysplasia) can be followed.

The most frequent approach is to follow a sample of leukoplakias, and this has been carried out in a number of countries. The malignant transformation rate can be expressed as (1) oral cancer development as a percentage of the entire sample, (2) the yearly oral cancer incidence rate, (3) oral cancer development per 100,000 persons, or (4) oral cancer development per 1,000 lesion person years.

Table 4 gives published information as to oral cancer development as a percentage of the entire sample since 1960 and comprises a sample of more than 100 patients. The malignant transformation rate ranges from 0.8 to 9.9%, these very different figures both coming from India. If, however, these two samples are compared it turns out that the police material of Mehta et al. (1972b) is very homogeneous and is comprised of well-fed individuals who lead a much more regular life than the individuals in Gangadharan and Paymaster's sample (1971). When comparing the six groups from Table 4 it should be kept in mind that the various institutions will have different opinions as to when an oral leukoplakia should be kept

TABLE 4

Oral Cancer Development in Percent of Entire Sample.

Years in which material was observed	*Investigator*	*Size of material*	*Observation period*	*Sex distribution*		*Malignant transformation in per cent of entire sample*
				M	*F*	
1959–69	Mehta et al. (1972)	117	10 yrs.	100%	0	0.8
1920–60	Einhorn and Wersäll (1967)	782	11.7 yrs.	522	260	10 yrs.: 2.4
				67%	33%	20 yrs.: 4
1955–64	Pindborg et al. (1968)	248	3.7 yrs.	62%	38%	4.4
1946–76	Bánóczy (1977)	670	9.8 yrs.	76%	24%	6
1955–66	Silverman and Rozen (1968)	117	1-11 yrs.	57%	43%	6
1941–69	Gangadharan and Paymaster (1971)	626	8.9 mos.	82%	18%	9.9

under observation and when it should be treated, either surgically or by removing possible irritants. With these considerations in mind it is remarkable that the figures for malignant transformation are uniform when compared with estimates made some decades ago.

In an analysis of the Copenhagen material from 1974 (Table 5) it was found that the annual incidence (rate) of malignant transformation was 0.75% based upon a follow-up rate of 96.6% (Roed-Petersen and Pindborg, unpublished material).

Oral cancer development from oral leukoplakia given as cancers per 100,000 persons has been determined by Silverman et al. (1976) in material from 6,718 Indian industrial workers with oral leukoplakia. After 2 years 71% of these patients were reexamined and development of oral cancer established in six individuals, which is 0.13% of the entire sample. This equals an annual incidence of 63 oral cancers per 100,000 persons.

Finally, oral cancer development in leukoplakias has been calculated using the person-year method (Mehta et al. 1976a). The investigators found that 6.5 oral cancers developed per 1,000 leukoplakia years. Table 6 from the same study shows the distribution of oral cancers according to type of leukoplakia and other lesions and conditions. The findings confirm previous observations that the nodular (speckled) type of leukoplakia is more prone to malignant transformation than homogeneous leukoplakia. Table 7 also from the same study shows that leukoplakias caused by chewing habits are more likely to become malignant than leukoplakias caused by other habits.

Histological follow-up studies

In 1972, Mincer et al. published the first study of the natural history of oral epithelial dysplasia. Since then four more studies have been reported on the behavior of oral epithelial dysplasia. Table 8 summarizes the results of these investigations. As for the clinical follow-up studies, a direct comparison is difficult, because it is not easy to standardize the criteria for epithelial dysplasia, although an attempt has been made in that direction (Smith and Pindborg 1969). Moreover, patients with epithelial dysplasia in their leukoplakias have been variously treated, sometimes with excisional biopsy. Even with these reservations, it is interesting to note some common trends: e.g., (1) the malignant transformation rate does not exceed 13%, (2) a substantial number of the lesions associated with epithelial dysplasia remain unchanged during the observation period, and (3) there may even be a reduction of the lesions in some patients. It is noteworthy that the

TABLE 5

Results from the 1974 Analysis of the Copenhagen Oral Leukoplakia Material (Roed-Petersen and Pindborg, unpublished material).

Rate of follow-up	96.6 (451/467)
Median observation period	5.5 years
Cancer development	4.1%
Annual cancer incidence	0.75%

TABLE 6

Malignant Transformation of Oral Lesions in 1 to 8 Years Follow-up in Kerala. From Mehta et al. (1976a).

Previous diagnosis	*Number*	*New oral cancers detected*
Leukoplakia		
Homogeneous	321	7
Nodular (speckled)	21	3
Traumatic	59	–
Preleukoplakia	380	2
Other oral lesion		
Submucous fibrosis	44	1
Lichen planus	303	1
Normals	6,686	–

TABLE 7

Rate of Malignant Transformation of Oral Leukoplakia According to Tobacco Habits in 1 to 8 Years Follow-up. From Mehta et al. (1976a).

Tobacco habits	*Leukoplakia person-years*	*New oral cancers detected*	*Rate of malignant transformation per 1,000 leukoplakia years*
Smoking	388	–	–
Chewing	523	6	11.5
Mixed	623	4	6.4
Total	1,534	10	6.5

malignant transformation rate in India is well below the rate in the U.S.A. and Hungary, despite the absence of surgical treatment.