measles, mumps, and rubella, are powerful modifiers of the immune response and might be related to the onset of several autoimmune disorders, including type 1 diabetes. However, the link between vaccination and subsequent autoimmune disorders has not been strong.

Diabetes now frequently develops at younger ages, and it has been argued that the total incidence of type 1 diabetes is increasing and that high socioeconomic status, a cleaner environment, and a decreasing frequency of infections may play a role. These factors, in turn, are correlated with increasing immunization coverage. Small studies have suggested possible relationships between the onset of diabetes and immunizations. However, these studies have not been supported by more rigorous epidemiologic examinations.[4,5] In this issue of the *Journal*, Hviid and colleagues (pages 1398–1404) report a retrospective review of a cohort of Danish children born between 1990 and 2000; they conclusively demonstrate that there is no relationship between vaccination history and the development of type 1 diabetes. Neither the administration of live attenuated vaccines nor the administration of killed vaccines was correlated with the development of type 1 diabetes in a relatively high-risk Scandinavian population. This study will, one hopes, be the last one that is necessary to disprove an association between immunization and diabetes. The scientific community should now move on to the most important tasks: identifying the genetic, immunologic, and environmental phenomena that are actually responsible for the development of diabetes and finding the means to prevent and treat this chronic disorder.

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The White Lesion That Kills — Aneuploid Dysplastic Oral Leukoplakia

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Perhaps the earliest link between oral leukoplakia and cancer was made by James Paget, for whom Paget's disease was named; he also recognized the connection between oral leukoplakia and smoking. Leukoplakia is a clinical term that refers to an oral mucosal white patch that will not rub off and is not attributable to any other known disease. It is considered to be potentially malignant, with a transformation rate in various studies and locations ranging from 0.6 to 18 percent. Clinically, oral leukoplakia is in the same spectrum of disease as the more sinister red or speckled lesion erythroplakia, which has a much higher transformation rate and is more often found on biopsy to be squamous-cell carcinoma.

The leukoplakia we are discussing here should be distinguished from oral hairy leukoplakia, the lesion associated with Epstein–Barr virus and seen in immunosuppressed persons, predominantly but not exclusively those with human immunodeficiency virus infection. White patches in the mouth may have other causes, including chronic trauma such as friction and mucocutaneous diseases such as white sponge nevus, lichen planus, or lupus erythematosus. However, the lesion that is the subject of the article by Sudbø et al. in this issue of the *Journal* (pages 1405–1413) is more commonly associated with tobacco-related habits — notably, smoking and the use of some other forms of tobacco, including moist snuff (smokeless tobacco) and pan (betel nut). Another form of precancer, proliferative verrucous leukoplakia, is predominantly found in those who do not use tobacco, but it has a high rate of transformation to cancer.

Here is where the histopathological changes known as dysplasia enter the picture. On biopsy, most leukoplakias show histologic features of epi-

thelial dysplasia, including basal-cell hyperplasia, bulbous rete ridges, loss of polarity of basal cells, abnormal keratinocyte stratification, an increased nuclear:cytoplasmic ratio, nuclear hyperchromatism and pleomorphism, abnormal keratinization, and abnormally increased numbers of mitoses and suprabasal mitoses (see Figure). Unfortunately, the recognition of these features is subjective, and there is wide variation in the degree of interexaminer agreement and intraexaminer reproducibility in the diagnosis. Yet a microscopical diagnosis of oral epithelial dysplasia is still one of the few indicators of an increased risk of oral cancer that we have, despite the reality that most dysplasias do not progress to cancer.

Transformation rates, like those associated with a clinical diagnosis of leukoplakia, vary, ranging from 16 to 33 percent. Differences in the transformation rate may reflect differences in criteria for histologic grading, clinical follow-up, and populations of patients. Therefore, a search has long been under way for molecular markers that may indicate an increased likelihood of malignant transformation. The possibilities that have been explored include DNA aneuploidy, loss of heterozygosity as assessed on the basis of microsatellite markers, mutations in the *p53* gene and aberrant expression of p53 protein, inappropriate expression of other oncogenes such as cyclin D1, and differentiation markers such as keratins, blood-group antigens, and other cell-surface carbohydrates. Some assays for these markers have shown promise in modeling the risk of cancer, but their use has been hampered by technical difficulties that make their wide-scale application challenging. Others have proved to be of limited predictive value for individual persons, thus necessitating a search for new markers of risk and methods of risk assessment.

As demonstrated by Sudbø et al., aneuploidy is emerging as one of the most promising prognostic indicators for the study of oral cancer. The authors have previously shown that the DNA content of dysplastic oral leukoplakia predicts the development of oral squamous-cell carcinoma. In these studies, nuclear DNA content or ploidy was classified as diploid (normal nuclear content), tetraploid (double the normal amount of DNA and number of chromosomes), or aneuploid (an amount of DNA that was not an exact multiple of the diploid number). DNA was measured by means of optical examination of cell nuclei obtained from thick paraffin sections of biopsy samples. Taking advantage of the superb comprehensive Cancer Registry of Norway to follow for several years the same group of patients with dysplasia on biopsy, the authors previously showed that oral squamous-cell carcinoma was significantly more likely to develop in persons with dysplastic leukoplakias showing aneuploidy than in those with diploidy or tetraploidy. The only other predictor of squamous-cell carcinoma, according to multivariate analysis, was tobacco use.

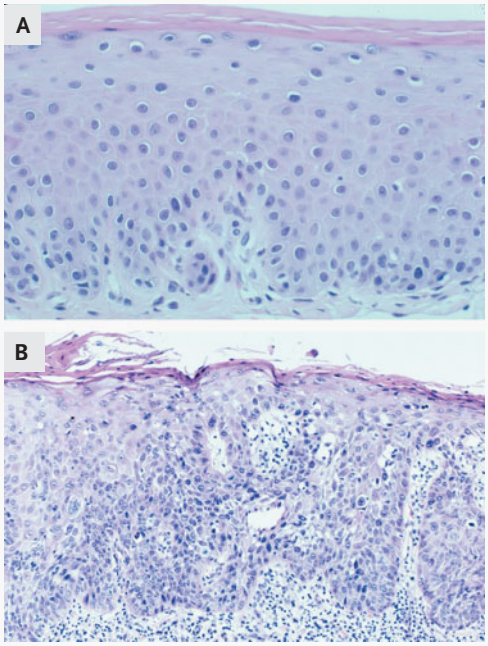

Figure. Microscopical Appearance of Normal Oral Mucosa (Panel A; Hematoxylin and Eosin, ×100) and of Oral Epithelial Dysplasia with Hyperkeratosis, Irregular and Bulbous Rete Processes, and Numerous Atypical Keratinocytes (Panel B; Hematoxylin and Eosin, ×40).

In the present study, Sudbø et al. show that further oral cancers consistently developed in patients whose dysplastic leukoplakia was characterized by aneuploidy; this group also had poorer survival than the other two groups. Furthermore and most intriguingly, the removal of lesions with histologically clear margins did not lead to an improved outcome, challenging a central dogma that oral dysplasia can be managed surgically. The investigators begin to answer the question that has rarely even been asked — not which oral white lesions become cancer, but rather which oral white lesions are likely to kill. They conclude that it is aneuploidy that best predicts poor survival.

However, several questions remain. For example,

it is not clear how practical and reproducible the complex methods that Sudbø et al. have used will be in other settings or in the clinical rather than the research arena. Presumably, other and larger studies will be conducted to confirm or refute the intriguing findings. Why should cancers arising from aneuploid dysplastic oral leukoplakia be more lethal than cancers arising from diploid or tetraploid oral leukoplakia? What is happening in the epithelium that appears to be clinically and histologically normal in these persons? Should we change our views about pathogenesis? Until now, we have associated aneuploidy with invasion or at least carcinoma in situ. We must now recognize that it occurs earlier, during a process that we currently call dysplasia, and its initiation may be a turning point or sentinel event in the transformation from normal to malignant oral epithelium. There is already evidence that aneuploidy is not merely a byproduct of a cell gone wrong but that the process itself most likely contributes to neoplasia. What is the role of the assay for aneuploidy in the assessment of proliferative verrucous leukoplakia or even lichen planus? The observation that the lethality associated with aneuploid dysplastic oral leukoplakia appears not to be ameliorated by excision suggests that the procedure may be of little more than palliative or cosmetic value. Are its effects perhaps analogous to those of retinoids on epithelial dysplasia — an improvement in the clinical appearance that often does not reflect a change in the underlying molecular abnormalities or an improvement of the clinical outcome?

The primary and most perplexing question that the article by Sudbø et al. raises is what treatment we can offer persons with aneuploid dysplastic oral leukoplakia. Is this situation hopeless, or will effective chemopreventive or chemotherapeutic agents be developed that can interfere with the molecular and metabolic events leading to aneuploidy? One promising area may be the use of inhibitors of cyclooxygenase-2, an enzyme that Sudbø et al. have shown in another study[1] to be more frequently overexpressed in aneuploid oral dysplasia than in diploid or tetraploid dysplasia. The future assessment of oral leukoplakia may involve the routine assessment of ploidy in persons with oral leukoplakia. It is even possible that this could lead to the screening of apparently clinically normal mucosa in persons or populations thought to be at risk.

Where do we go from here? The study by Sudbø and colleagues raises important questions about our current approaches to the diagnosis and management of dysplastic oral leukoplakia. Although the investigators address current tobacco use in the population they studied, it remains unclear how smoking cessation can modify the natural history of the lesions. Until that question is answered, there seems to be no reason to reduce our current emphasis on the cessation of both smoking and the use of smokeless tobacco. Moreover, tobacco use causes or exacerbates a number of other oral diseases, including periodontal disease, candidiasis, and xerostomia. Histopathological examination to establish the presence or absence of epithelial dysplasia or carcinoma will continue to have an important role in the assessment of oral leukoplakia. However, in the light of this study, the importance attached to the establishment of histologically clear surgical margins in the excision of dysplasia must be reassessed, for the implication is that the genetic aberrations within the epithelium may not be reflected in the clinical or microscopical appearance. What we do know from the work presented here is that the determination of the prognosis for persons with oral leukoplakia will never be quite the same again.

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Counterfeit Drugs

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In May 2002, thousands of vials of Procrit (epoetin) labeled as containing 40,000 units were found to contain only 2000 units, and later that year, other vials of Procrit were found to contain nothing but Miami tap water. In the spring of 2003, there were reports that some Lipitor (atorvastatin) pills tasted bitter, caused a burning sensation on the tongue, and were too large. In February 2004, several Web