From The Norwegian Radium Hospital.
(Chief: Dr. Med. ROLF BULL ENGELSTAD.)

Leukoplakia Oris.

By

ANDREAS HOBÆK, M. D. L. D. S.

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»To a large extent, the decrease in the number of deaths from cancer of the oral cavity is in the hands of the dental profession.» J. C. BLOODGOOD.

Dental science during the last decades has shown a steadily growing tendency to expansion beyond its original domain: the teeth and their supporting tissues, to also involving the other oral organs and the numerous manifestations of diseases that these are capable of demonstrating. Up to the present time the development from odontology to stomatology has been clearest for the surgical disciplines, from dental to oral surgery, but it also is traced in the internal medicine: systemic diseases, blood-diseases, hypo- and avitaminosis, allergies — further in the dermato-venereology and the cancrology.

If not as surgeon and therapeutist the dentist on strength of his profession will necessarily have to play an important rôle as diagnostician, when he has learned to master the diagnostics of the numerous and often discreet oral facies morbi. Possibly the most important task with which he is faced, is the diagnosis of precancerous conditions and early forms of malignant oral tumours. An early diagnosed malignant tumour in the oral cavity gives, with the therapeutic possibilities of today, a relatively good prognosis, and it is obvious that the dentist may here render the patients inestimable services by unhesitatingly sending all ulcers tending to chronicity, papillomatous formations, tumours and leukoplakias on lip, tongue, gingiva, palate and buccal mucous membrane, for special examination and special treatment.

The earlier a malignant tumour in cavum oris arrives for treatment, the greater is the chance of permanent cure, or at least of a prolonged period free of recurrences. Most carcinomae in the oral cavity metastasize in an early stage, and already the presence of metastases in the regional lymph glands will considerably reduce the patient's chances.

The best thing would be to intervene already during the precancerous stage, before the development of the potential cancer has yet started. Therefore it is important to know the various types of oral precanceroses of which leukoplakia oris represents the most important and frequent form.

This disease has been known and described already at the beginning of the last century, chiefly by French and English clinicians. However, up to 1877, when SCHWIMMER (66) used the present term for the disease, it had no uniform designation, but was known as ichtyosis, tylosis or psoriasis oris. As early as in 1851 the disease was connected with the use of tobacco, when PAGET (50) named it "smoker's patch". In the recent literature synonymous terms, such as "Raucherflecke", "plaque de fumeur", after PRINZ (55) in Scandinavia called "rygepletter", are constantly encountered. The term leukoplakia from leukos: white, and plakos: patch, has since long been internationally accepted and used.

Leukoplakias occur on the mucous membranes of the upper air-ways, of the upper part of the digestive tract and of the urogenital tract. By far the greatest number of leukoplakias are found in the oral cavity. The location to pharynx-larynx is considerably rarer, whereas in oesophagus leukoplakias are found far more often than formerly assumed. LINDEMANN (39) has drawn attention to the phenomenon that leukoplakia in oesophagus often is found concomitant with chronic oesophagitis and varices. SCHAER (62) in an autopsy material from men above 40 years of age has found that leukoplakias in oesophagus occurred in 67 %, and also SHARP's (63) conception it is that leukoplakias in oesophagus is a very common pathologic condition that must be regarded as precancerous.

In the urogenital tract findings of leukoplakias are considerably rarer. Mostly they are here found in vulva, on glans penis or preputium, where as prodrome of cancer they are well known. Further they have been described from renal pelvis, ureteres, urethra and vagina.

Clinically the leukoplakias in the oral cavity mostly present

irregularly shaped, white patches, the distribution of which is more or less wide. Mc. CARTHY (41) has described the preliminary stages of leukoplakia in the form of localised, erythematous fields with a slightly granulated surface. That there do exist changes in mucosa of the oral cavity capable of being characterised as preliminary stages of leukoplakia is most probable. This assumption has inter al. found support in the condition that not rarely after treatment of leukoplakias it is observed the development of fresh formations with other locations in the oral mucosa. No well-defined clinical picture of such pre-leukoplakias has been described and such discreet changes in the mucous membrane will certainly only rarely be observed, because in the great majority of cases they presumably are clinically symptomless.

As a rule a single leukoplakic area will be found, however, a multiple occurrence is almost as frequent, and on rare occasions practically all of the oral mucosa may be found leukoplakically changed.

The colour of the leukoplakias usually is greyish-white to milkwhite, a certain opalescence [plaques nacrées (FOURNIER)] is not rare. Less commonly it is found of a pure grey colour, sometimes also with a brown or yellow tinge. The latter form may be found coinciding with quite milkwhite leukoplakias in the same mouth, and have been connected with the use of tobacco. However, this explanation seems hardly probable, as only a few of the leukoplakias have been stained. MICULICZ & KÜMMEL (44) believe minor hemorrhages to be responsible for the colour.

Broadly speaking, one may differentiate between 2 types of leukoplakias, of which the second type is merely a further development of the first, namely: leukoplakia plana and leukoplakia verrucosa. Every leukoplakia starts as a leukoplakia plana, that apart from its greyish-white colour is not to be distinguished from the rest of the oral mucous membrane. The leukoplakia lies on the mucosal level, and in the early stages it is not palpably infiltrated, or the infiltration is at most merely perceptible. The surface often is finely wrinkled, as the shrivelled skin of an apple. (Figs 1—6.)

Leukoplakia plana may remain stationary for years, in the literature up to 15 years has been mentioned. Transition into the verrucous form is fluid. After a shorter or longer period of time most leukoplakias will become thicker and infiltrated, rhagades or small ulcerations will form. The verrucous leukoplakia pro-

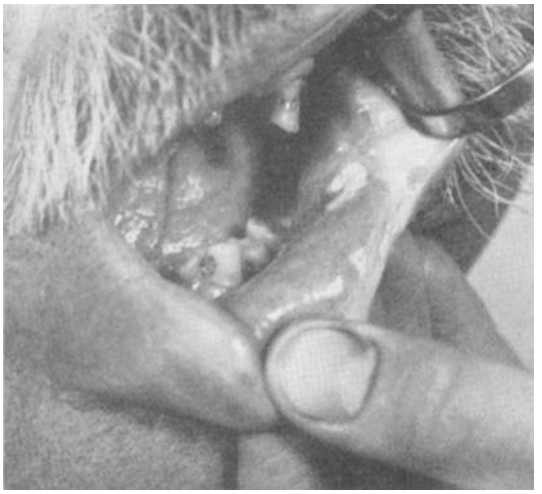

Fig. 1. Leukoplakia plana buccae.

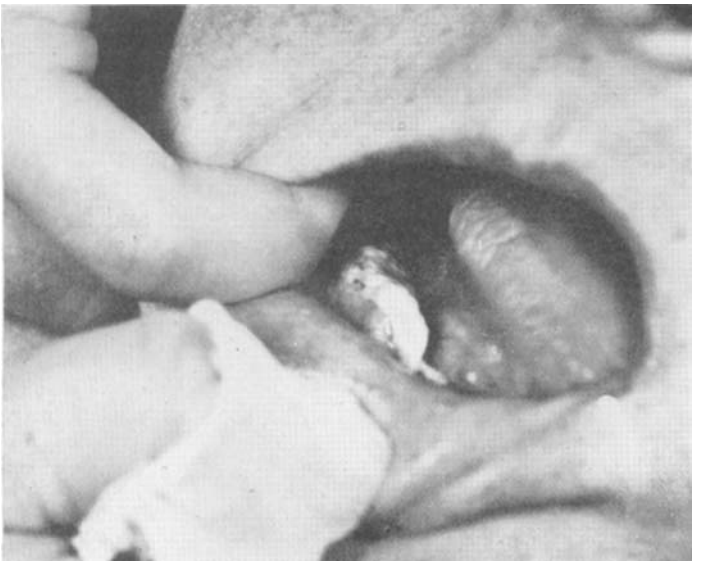

Fig. 2. Leukoplakia verrucosa gingivae.

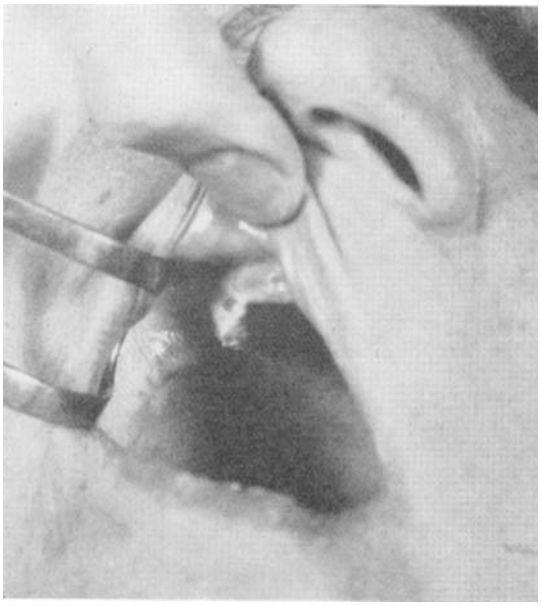

Fig. 3. Leukoplakia plana buccae et verrucosae gingivae.

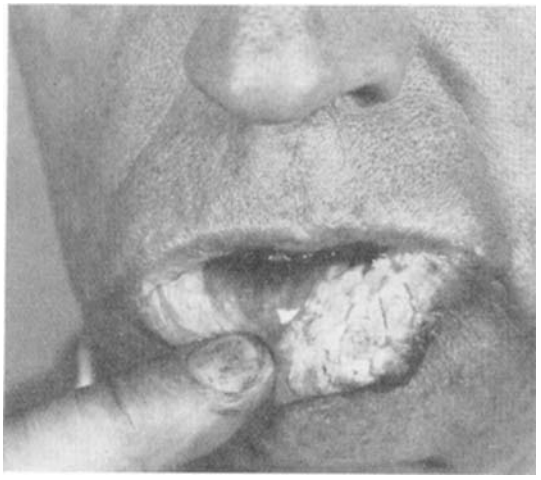

Fig. 4. Leukoplakia verrucosa labii.

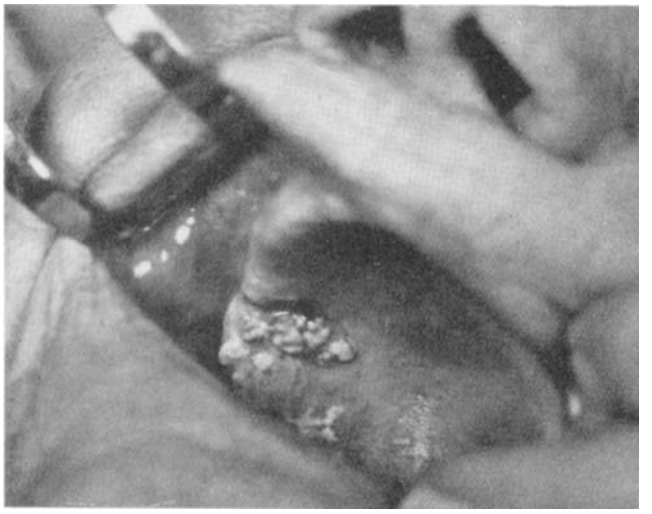

Fig. 5. Leukoplakia verrucosa palati.

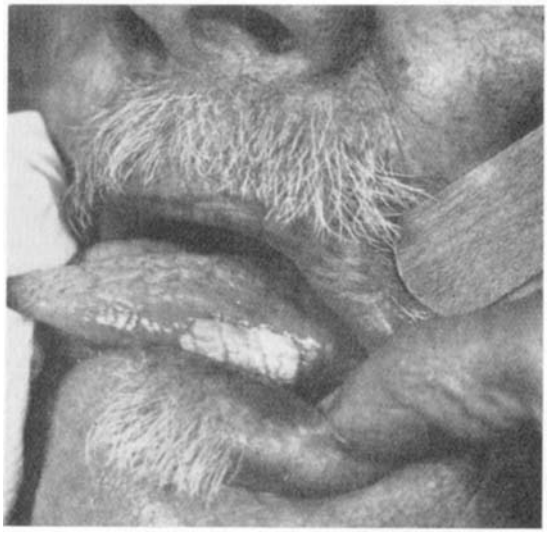

Fig. 6. Leukoplakia verrucosa lingvae.

inates more or less, the surface becomes papillomatous, and especially on the tongue it may present highly prominating, papillomatous greyish-white formations, that may be elevated several millimeters above the level of the surrounding mucosa. (Figs 7—8.)

Leukoplakia plana mostly presents no symptoms, and certainly many cases are mute from beginning to end, and never are diagnosed, or if so only by chance. Only the verrucous form with formation of rhagades, or in the later stages of ulcerations, gives smarting pain on smoking, on the intake of hot foods and drinks, spiced foods and alcohol in concentrated form. A patient who is not very observing will be apt to neglect these slight afflictions, and the leukoplakias may be prominent and distributed to an incredible degree before the patient realises that there is something wrong. How often the suffering is neglected appears to evidence from the material that here will be presented.

At the Norwegian Radium Hospital it has since 1932 been treated in all 77 cases of pure, uncomplicated leukoplakia. During the same period a total of 1272 cases of cancer in cavum oris, including the lips, have been treated. Of these cancers in all 176, *i. e.* 16 % have developed on basis of existing leukoplakias. Location of the leukoplakias will appear in Table 1.

It will be seen that the pure leukoplakias mostly occur on the tongue and in regio sublingualis, next on the lower lip, the buccal mucous membrane, the palate and gingiva. When collating the pure leukoplakias and leukoplakias with cancerous development the sequence will be: the lip, the tongue, the buccal mucous membrane, gingiva and the palate. On the tongue the seat of the leukoplakias mostly is back of the tongue or the lateral edges. On mucous membrane of the inner cheek they are as a rule found immediately inside commissura labii, not rarely bilaterally in form of a triangular formation pointing to the commisure, but also often further back, on a line opposite the occlusal surfaces of the teeth. In the palate they are mostly localised to the hard palate, not so often to the soft palate and uvula. On gingiva they are evenly distributed to both jaws. On the lower lip the leukoplakias are mostly found along the vermilion border, where the lip habitually is exposed to mechanical irritation in the form of pipe, cigar or cigarette.

The diagnosis of intraoral leukoplakias as a rule offers no special difficulties, particularly not in the verrucous form. Leukoplakia

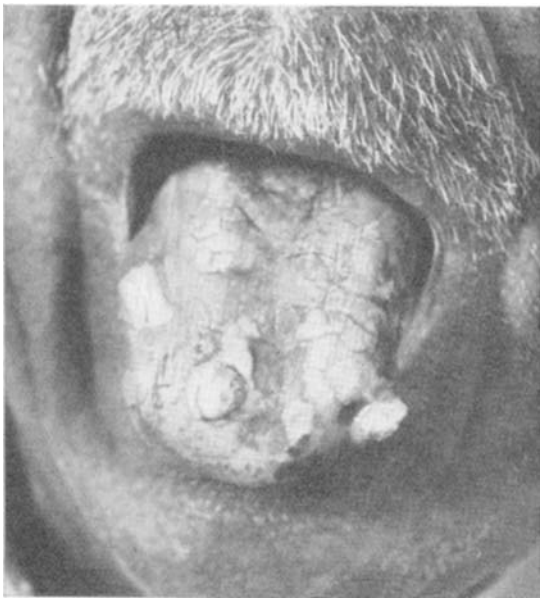

Fig. 7. Leukoplakia verrucosa lingvae. Lues.

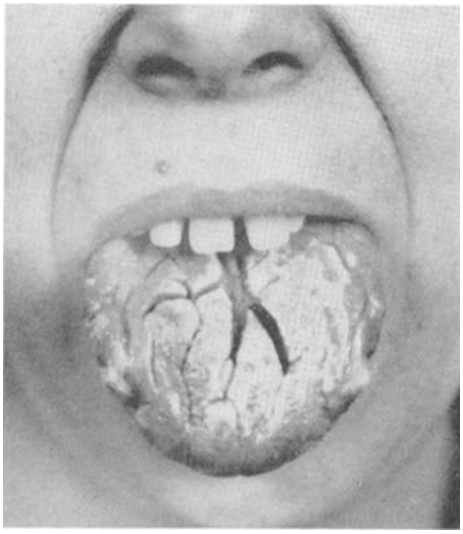

Fig. 8. Leukoplakia verrucosa lingvae. Non luetic.

Table 1.

Lokalization		♀	♂	Total number	Total number of cancer cases	Per cent of cancer cases developing leukoplakia
Bucca	Pure leukoplakia	6	12	18	93	25.8
	Leukoplakia developing into cancer	10	14	24		
Lingua et regio sublinguale	Pure leukoplakia	17	11	28	336	13.1
	Leukoplakia developing into cancer	12	32	44		
Gingiva	Pure leukoplakia	2	2	4	110	19.09
	Leukoplakia developing into cancer	10	11	21		
Palatum	Pure leukoplakia	2	3	5	89	11.24
	Leukoplakia developing into cancer	4	6	10		
Labium	Pure leukoplakia	0	22	22	645	10.85
	Leukoplakia developing into cancer	6	64	70		

plana is inter al. capable of being erroneously perceived as lichen planus, lupus erythematodes and as the so-called Fordyce's disease.

Lichen planus may sometimes show eruptions on the buccal mucosa or the tongue without simultaneous findings of cutaneous efflorescences. The oral manifestations of the disease usually offer a characteristic picture in form of a spider-web net-work of fine, crossing, white lines, partly ring-shaped, or as close-sitting white spots on mucous membrane of the inner cheek, more rarely on the tongue. The enanthema is not infiltrated. On tightening of the mucous membrane the typical streaky form will usually be clearly seen, in contrast to the smooth, coherent surface of leukoplakias.

Lupus erythematodes on the buccal mucous membrane is rare and practically always it is found coincident with a cutaneous eruption. The mucous membrane affections are characterised by

close-sitting, white spots often with a scar-like central area, and as a rule there are more prominent signs of inflammation in form of a red halo round the efflorescences. The so-called Fordyce's disease is ostensibly found more or less pronounced in about 60—70 % of all individuals, and is not the expression of any pathologic condition. Characteristic for the condition are numerous, close-sitting, pin-head-sized grains on the buccal mucosa, especially distributed along raphe buccalis from the commissure and backward. The grains represent small retention cysts in the sebaceous glands that are found here and on the inside of the lips. The grains are of soft consistency, are situated in epidermis of the mucous membrane, and often give to it a shagreened appearance. The grains are of a yellowish-white to pure yellow colour, and the appearance is so typical that the condition hardly is capable of causing differential-diagnostic difficulties, if once it has been seen. A few mucous membrane affections of more acute type, such as secondary luetic plaques muqueuses and thrush may sometimes cause differential-diagnostical complications. However, the white-coloured epithelium in these conditions is in contrast to the leukoplakias softened and easily scraped off. In cases of doubt bacteriological examination and the rapid disappearance of the suffering after specific treatment will reveal the true nature of the condition.

The histologic pictures presented by lichen planus and by leukoplakia are approximately identical. In cases of doubt will therefore a biopsy be of no particular differential-diagnostic value. On rare occasions cancers may arise on basis of a many years old lichen planus affection of the oral mucosa, and the differential-diagnosis will in such cases be of secondary importance, as the therapy is the same.

The disease has formely been considered as chiefly confined to the male sex. There were no women in NEDOPIL's (47) material. SCHOENGARTH (68), VON POLLNITZ (54), BOSSMANN (6), and GENSCHMER (24) found about 5 % of women in their materials. However, these numbers certainly are too low. In the present material there were in 246 cases of leukoplakia 65 women in all, making a percentage of 26.4. Also a number of late authors have found an increase in the percentage of women, and this has been connected with the extensive use of tobacco by women of today.

In the coloured races leukoplakias in the oral cavity are very rarely found. Thus PRINZ (55) has never observed leukoplakias

in American negroes, and only rarely in mulattoes, in whom melanoses in the oral mucosa represented by the so-called "blue gum" is a common occurrence. SHARP (64) has described a case of leukoplakia with transition into cancer on the tongue in a negress. The Eskimoes seem to form an exception, as PEDERSEN (53) amongst the Eskimoes on Greenland frequently observed leukoplakic changes in the oral mucous membrane.

The leukoplakias mostly occur in patients of 50—70 years of age. But they are not rare during the 30th, and are also observed in patients of more than 80 years. The average age in the present material was 60.1 years.

In spite of intensive experimental and clinical research work during decades the etiology of cancer is yet little known. As long as one has not reached beoynd the purely morphological, cellular points of view, one must temporarily rest contented with the assumption that the development of precancerous conditions, and in turn cancers, are due to an interplay between external irritaments and a predisposition in the individual.

Since Sir JAMES PAGET in 1851 drew attention to the importance of tobacco as an etiologic factor in cancer linguae, the use or abuse of tobacco has been mentioned as one of the main causes of leukoplakia oris. A number of former authors, such as ERB (15), NEISSER (48), FOURNIER (19, 20), SCHUCHARDT (67), JOSEPH (30), LIEVEN (38) et al. have mainly stressed the importance of tobacco as causal factor. Up to 100 % of the patients mentioned in the materials of these authors have been great smokers.

From other quarters it has been claimed that plaques de fumeurs must be read as a special form for leukoplakia and essentially different from the true leukoplakia, as not by far so often it is supposed to show transition into malignancy, and also is characterised by a capacity for spontaneous regression on removal of the irritament. This conception is maintained inter al. by SCHERBER (65), VON WURMB (80), and EMERY and LACAPÈRE (18). Amongst the Greenland Eskimoes PEDERSEN (53) found a few cases of typical leukoplakia, but considerably more often a bluish-white to greyish-white colour of the mucous membrane, that probably must be interpreted as incipient leukoplakia plana. The changes were especially found in sulcus bucco-alveolaris inf. and on gingiva, and occurred in male individuals only. PEDERSEN also frequently observed a grave form of paradentitis marginalis

("toxica"), and connects this with the peculiar smoking customs of the Eskimoes. These have been described by FRIDTJOF NANSEN (45). "On the western coast the tobacco is mostly smoked and chewed . . . his chewing-tobacco the West-Greenlander prepares in a manner that seems somewhat surprising to us. Tall, Danish porcelain-pipes are half charged with smoking-tobacco that next is soaked by pouring water over it, and then the pipe is filled up with dry tobacco, whereafter it is smoked until the fire reaches the moisture, and it is extinguished. The ashes are then emptied, whereupon as much oil as possible is scraped out of the oil-container, stem of the pipe, the old crusts of the pipe-bowl etc., and are then added to the, because of the smoking already well juiced, remains in bottom of the bowl, and these are then ready for chewing. This strong candy is particularly appreciated as provision in the kayak."

This form for chewing-tobacco is called "imakut", and is still being used. The scrapings from the pipe rolled up in moist tobacco leaves are called "eroq", and this is smoked as a cigar. Though leukoplakic changes in the oral mucous membrane to all evidence has considerable distribution amongst the Eskimoes, only 2 cases of cancer oris have been reported from Greenland.

Also a number of more recent authors, such as EICHENLAUB (16), FOX (23), MC. CARTHY (41) point out the tobacco as the most important cause of leukoplakias. AHLBOM (1) found that between 86 and 99 % of male patients with cancer in cavum oris, pharynx, larynx and oesophagus were using tobacco in some form or other.

However, lately there seems to be a distinct tendency toward reducing the etiologic importance of the use of tobacco. MARTIN & PFLUEGER (40), QUICK (56), BLOODGOOD (5), and COOK (12) indeed stress the importance of the tobacco as a cancer provocative factor, but are of the opinion that it comes second to other forms of irritaments. BLOODGOOD and QUICK both emphasies that it is the excessive use of tobacco that plays a part: "The striking feature is the excessive use of tobacco of any form" (BLOODGOOD). "It is the excess of smoking for any given individual that does the harm rather than just smoking in general." (QUICK).

NIELSEN (49) maintains that the abusus tabaci may act as a cancerogenous irritament in predisposed individuals, especially by producing or aggravating leukoplakias, but warns against overrating the importance of tobacco, especially when considering

the extensive use of tobacco today, and the comparatively rare occurrences of leukoplakias and intraoral carcinomae.

During smoking, that may be described as a sort of dry destillation, there is released besides heat, a number of chemical substances, such as pyridin bases, nicotin, tar-substances, phenol derivates et. al. ROFFO (60) who has pursued the problem of tobacco as a cancerogenous factor, has produced hyperkeratotic carcinoma on rabbits ear in the course of 8 months by painting with various extracts of tobacco. He arrived at the result that neither the nicotin nor the tobacco-tar per se were significant, but that the cancerogenous agent consisted of a substance nearly related to the cancerogenous agent contained in coal-tar. Later researchers such as MC. NALLY (43) and SUGIURA (72) have not been able to produce hyperkeratosis nor carcinoma on mice by painting with tobacco-extracts. As the cancerogenous substance of the coal-tar is destilled only at a temperature of about 550° C, the temperature on the burning of tobacco in pipes has been determined. This has been found to be varying between 370 and 590° C, all according to the sort of tobacco and to intensity of the smoking, and after this it seems hardly reasonable to believe that large amounts of an eventual cancerogenous agent in the tobacco would pass into the smoke.

On the other hand, hot smoke of tobacco through short pipes may be thought in the long run possibly to have an irritating effect. PRINZ claims that pipe-smokers are more liable to leukoplakias than are cigar- or cigarette-smokers, further that long pipe or the oriental Nargileh are far to be preferred to the short pipe. No statistical material for illumination of this problem has been presented in the literature.

As for the use of tobacco it is necessary to build on anamnestic informations, that always to a certain extent will be encumbered by uncertainty and inaccuracy. Therefore no attempt has been made to give any statistical account of frequency of the tobacco habit in the present material. The author is content to establish the fact that most of the men were moderate to heavy smokers, several at the same time were using chewing-tobacco or snuff, and that none of the women smoked.

The habitual chewing of betel-nut, so prevalent on Ceylon and in India, as well as in the Malay-states, is of interest in this connection, because the substance chewed is a mixture of buyo-leaves, betel-nuts, slaked lime and tobacco, and further, because

development of cancer buccae often is seen in connection with an abuse during years. Buyo-cancer is found oftener in women than in men. DAVIS (14) in 49 cases of cancer buccae found that the chewing of betel-nuts in all cases was responsible and that seat of the tumour corresponded to the spot in the mouth where the betel-nut habitually was placed. BALENDRA (2) found that 94 % of all cases of malignant tumours in the oral cavity in India are due to betel-nut chewing, but his opinion is that the direct cause is that the teeth become brittle and jagged, such that they constantly are irritating the mucous membrane.

The use of tobacco in any form through a prolonged period of time produces a chronic irritative condition of the mucous membrane of the mouth, further also of larynx, pharynx and oesophagus. Several authors, inter al. NIELSEN (49) have pointed to the custom of chewing or snuffing tobacco as particularly harmful, as the irritament here habitually is localized to the same place in the oral cavity. It can hardly be doubted that the danger element involved in this form for abuse of tobacco is greater than that in smoking. The paradentitis marginalis toxica in the Eskimoes, observed by PEDERSEN (53) is an example hereof. That also smoking throughout decennia produces similar chronic irritative changes in the oral mucous membrane, is shown by the so-called stomatitis nicotina. This affection, that has been commented on by THOMA (73, 74) in 1936, is characterised by a hyperkeratosis in the palate with formation of small retention cysts in the mucous glands, sometimes with formation of small papillomae and leukoplakically changed mucous membrane.

If the use of tobacco qua such hardly can be eliminated as a cancerogenous factor, the importance hereof seems to be somewhat exaggerated. Considering the enormous number of individuals who are using or abusing tobacco, especially in the form of smoking-tobacco, compared to the relatively rare occurrences of precancerous and cancer conditions in the oral cavity, it seems reasonable to presume that there should be a certain individual predisposition for the use of tobacco to lead to leukoplakia and this in its turn to cancer.

It is a well-known fact that a chronic abuse of alcohol, especially in concentrated form is considered as an important causal factor in sufferings in the oesophagus. Importance of the abuse for leukoplakia oris has repeatedly been suggested, but no statistical material has been published.

Table 2.

Author	Year	Number of cases	Lues in percent
Bockhardt	1902	60	100
Kopp	1907	29	100
Pandy	1918	—	100
Kaposi	1875	400	100
Guszmann	1908	181	ca. 95
Erb	1892	240	» 80
Fournier	1900	324	» 80
Schoengarth	1902	596	66
Bloodgood	1929	—	21
Sturgis & Lund	1934	520	» 30
v. Wurmb	1935	—	» 50
Fox	1925	40	2/3
Belote	1930	92	29.3
Eichenlaub	1924	70	17.1
Present material	1945	246	» 8.1

Besides tobacco has lues always been mentioned as an important etiologic factor in connection with leukoplakias. Especially by French authors has lues been regarded as important, and by several, mostly by former authors it has been regarded as a conditio sine qua non for the rise of leukoplakias. FOURNIER (19, 20) interpreted leukoplakias as a parasyphilitic disease, which went to explain why leukoplakias were not influenced by antiluetic therapy. EMERY and LACAPÈRE (18) and LANDOUZY (37) claim the diagnosis of lues to be permissible in every case of leukoplakia oris, and KOPP (31) without reservation states: "Der Kranke mit einer Leukoplakia buccalis war früher mit Syphilis infiziert". But from the following table (Table No. 2), in which the lues percentage has been calculated for a series of published materials, it will be found that no longer is the same importance attached to lues as was formerly the case. In 246 cases of leukoplakia I have found only 20 patients with positive WR, or with informations of previous lues in the anamnesis, giving 8.1 %. NIELSEN (49) found in a Danish material from the Radium Station in Copenhagen 27 cases with positive WR or positive anamnestic informations in a material of 256 intraoral cancers, which makes 10.5 %. SHARP (64) found amongst 121 cases of leukoplakia that 18, *i. e.* 14.8 % had positive WR, 7 others had negative WR with positive histories of the disease. This gives a total percentage of 21.4. A number of recent authors, such as CAHN (9, 10), MC. CARTHY (41), MARTIN & PFLUEGER (40), BELOTE (3) and BLOOD-

GOOD (5) do not deny the importance of lues as an etiologic factor, but claim its importance to have been considerably overrated. QUICK (56) and EICHENLAUB (16) are of the opinion that the origin of most leukoplakias is not luetic.

However, the leukoplakia linguae here seems to form an exception, as lues here apparently plays a greater predisposing rôle. NIELSEN (49) in 108 cases of cancer linguae found a total of 20 who had gone through luetic infection, *i. e.* 18.5 %. Of 276 lingual cancers in the present material 44 had developed from leukoplakias. Of these 8 had lues, *i. e.* 18.2 %. COOK (12) claims that just for leukoplakia linguae lues plays a prominent part, as the leukoplakias develop on basis of a chronic interstitial glossitis with endarteritis, that produces atrophy of the lingual papillae, in this way making the surface of the tongue more exposed to irritation, as *e. g.* by constant smoking. Also as a clinical type leukoplakia linguae of luetic origin show peculiar characteristics. The leukoplakias often have a wide distribution, sometimes covering the entire back of the tongue, they soon become verrucous with rhagade and ulcer formations, besides which all experience shows that they more rapidly become manifest malignant. (Fig. 00.)

Only on rare occasions are leukoplakias found in individuals with good oral hygiene and well-kept teeth. Lately greater importance has been attributed to the chronic mechanical irritation produced by jagged, carious teeth as the cause of precancerous conditions and cancer in cavum oris, besides severe forms of marginal paradentitis ("Schmutzpyorrhoe") and injury from prosthesis. As long as it has not been produced reliable statistical material founded on accurate records of state of the teeth in oral cancers and precanceroses, it is not possible numerically to express the frequency with which these conditions actually do cause leukoplakias, other precancerous conditions or cancers. Undoubtedly they play an important rôle. 81 % of EICHENLAUB's 70 cases of leukoplakia had carious teeth and poor oral hygiene, and he often observed that leukoplakias on the mucous membrane of the inner cheek was localised immediately opposite to jagged, carious teeth. FOX (23) reports 40 cases of leukoplakia, whereof 18 were produced by jagged teeth. BLOODGOOD (5) strongly emphasises the importance of carious teeth, as he found that 47 of 160 cases of cancer linguae were due to mechanical irritation by carious teeth. FIGI (21) claims that leukoplakias and cancer oris are intimately connected with oral sepsis, carious

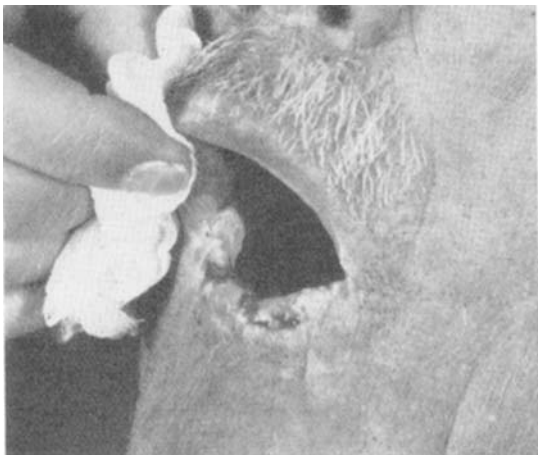

Fig. 9. Leukoplakia buccae et labii with cancer development.

teeth and badly fitting prostheses. MARTIN and PFLUEGER have found a certain connection between carious teeth and cancer buccae in 23 %.

As cause of leukoplakias in the present material of 246 cases I have found jagged, carious teeth in 12 cases in all, and badly fitting prosthesis in a total of 29 cases. These numbers certainly are too low, as reliable anamnestic informations often have been lacking, and here only have been included cases in which the connection between the developed leukoplakia and the mechanical

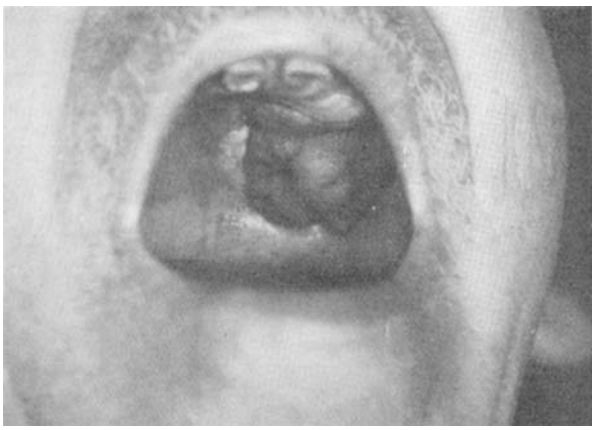

Fig. 10. Leukoplakia palati with cancer development.

irritation by carious teeth or prostheses was obvious. The injury from prostheses indeed makes a large and interesting group, that will be treated in a later publication. Here mucosal injuries in form of the so-called "rubber sore mouth" caused by contaminations from the prosthetic material will be disregarded. Grosser prosthetic injuries such as leukoplakias and cancer certainly are due to a mechanical irritament in form of direct chafing.

The concept "oral sepsis" includes not merely caries, especially the highly destructive forms, but also and perhaps oftener, chronic infectious processes in gingiva in form of marginal paradentitis. At the present time it is difficult to make out the importance of the chronic oral sepsis as a cancerogenous factor. Nevertheless, it is a generally accepted clinical experience that leukoplakias and cancers in the oral cavity rarely are found in connection with well cared-for teeth and thorough oral hygiene. A chronic marginal paradentitis will certainly only in extremely rare cases lead to the development of gingival cancer. However, it is not unlikely that the enormously developed bacterial flora accompanying this suffering in the long run may have a predisposing influence upon the mucous membrane of the mouth, throat and oesophagus. NIELSEN (49) claims that chronic gum sufferings are particularly frequent in patients with cancer labii and preliminary stages hereof. BULL ENGELSTAD (8) and BERVEN (4) consider poor oral hygiene one of the main causes of oral cancers.

Plummer-Vinson's syndrome, that by AHLBOM (1) has been emphasised as an important cancer-predisposing suffering, seems not by far to be as common in Norway as in Sweden, where AHLBOM found that well above 50 % of oral carcinomae in females occurred in patients with Plummer-Vinson's syndrome. The development of cancer does apparently as a rule not happen via any leukoplakic preliminary stage, as in the present material I have found only very few cases in which leukoplakia coincided with Plummer-Vinson's syndrome.

Already CHASE (11) and PALMER (51) have mentioned the possibility that teeth that were filled with metals or metal alloys of various kinds might act as small galvanic batteries in the oral cavity, the soft parts of the mouth acting as conductor. In the mouth the fillings are bathed in saliva that makes a good electrolyte through which the metal electrones may circulate freely from the higher to the lower electrical potential. The greater is the difference in potential between the various metals used in

the fillings, the greater will be the chance of the rising of galvanic currents. It is not conditional that the metals should occur in pure form. In usual silver-amalgam as a rule it enters three or more of the following components: silver, tin, zink, copper and mercury. In the commonest gold alloys used for fillings and crown constructions there are found besides gold: copper, often also platinum, nickel and silver.

REINHARD & SOLOMON (58) and REINHARD, SOLOMON and GOLTZ (59) point out that in a gold alloy containing copper, potential changes easily may arise around the gold and copper crystals in the filling, because of the considerable difference in potential between gold and copper, such that through mediation of saliva weak currents may arise. LAIN (34, 35, 36) measured strength of currents up to 100 microampere, whereas REINHARD & SOLOMON found currents of 80 microampere, that were merely initial, however, and after a few seconds fell to 10 % of its initial strength, because of polarization and the formation of an isolating film over the fillings. NIELSEN (49) has measured the difference in voltage between the amalgam and the gold fillings and has found values up to 0.4 volt.

LAIN (35) examined 300 patients picked at random, who had fillings or prostheses of varied metals in the mouth, and found in 41 % of these small erosions or ulcers, and 21 % with leukoplakias in form of small grey patches on the mucous membrane in palate, on gingiva or tongue. In 150 of these patients a restoration was made, such that fillings of heterogenous metals were replaced by a certain filling material, and he found that in 56 % of the patients the mucosal lesions disappeared completely, only in 11 % they remained unchanged. Also from other quarters it has been claimed that this form of leukoplakias, by ULLMANN (75, 76) called leukoplakia electrogalvanica, more readily disappear than do leukoplakias from other etiology. This condition has chiefly been mentioned in the American literature, inter al. by LAIN (34), LAIN, SCHRIVEN & CAUGHRON (36), REINHARD & SOLOMON (58), REINHARD, SOLOMON & GOLTZ (59), HOLLANDER (28), HOLLANDER, SHONFIELD & FISHER (29), REED & WILLMANN (57), ROONE & DAHLBERG (61), and by QUICK and BLOODGOOD.

In the experimental investigations that have been made in order to measure the strength of the current arising between 2 fillings of various metals in the mouth, a metal wire has been

used, that has been brought in contact with the fillings, and then connected with a galvanometer. Evidently, data obtained in this way give no expression of the true conditions, as the contact between the various fillings only is capable of being conducted by the soft parts of the mouth, that have a power of resistance many times that of the metal wire. In case a galvanic battery actually is established in the oral cavity, the strength of the current will in any case certainly only come to a fraction of the experimentally measured voltage, because of the great resistance offered by the soft parts, polarization phenomena and film formations. REED & WILLMANN (57) have thus found the strength to be less than 1 microampere, and claim that the oral mucous membrane hardly is capable of being harmed hereby.

Leukoplakia electrogalvanica has been observed in very few cases in the present material. Its importance must be regarded as considerably overrated, it is hardly a common condition.

QUICK (56) connects some not specified leukoplakic forms with a liver insufficiency, like glossitis Hunteri. He has observed results from liver therapy. Further, improvement has been reported after vitamin B preparations, especially after Panthothenic acid and nicotinic acid. NATHANSON & WEISBERGER (46) have reported total disappearance of leukoplakia after treatment with oestrogenous hormones.

From what at the present time it is known of etiology of the leukoplakias it must be presumed that underlying the suffering there is a certain predisposition, that possibly is activated by a luetic affection. In favour of such predisposition speaks first the condition that leukoplakia develops in only a few of the millions of individuals who through years and decennia are exposed to a chronic irritation of the oral mucous membrane by the use of tobacco, alcohol in concentrated form, prostheses, oral sepsis, and dental fillings of varied metals. Leukoplakia has been named hyperkeratosis of the oral cavity, but there is no indication that the predisposition for development of leukoplakia has anything in common with predisposition for the formation of skin-hyperkeratosis. THOMA indeed emphasises that stomatitis nicotina mostly is found in blond, blue-eyed individuals with sensitivity of the skin to sun-light, and liability to keratosis. The great majority of patients in the present material belong to the blond Nordic type, but as to the percentage, these are hardly more strongly represented than corresponding to the Nordic constituent of the

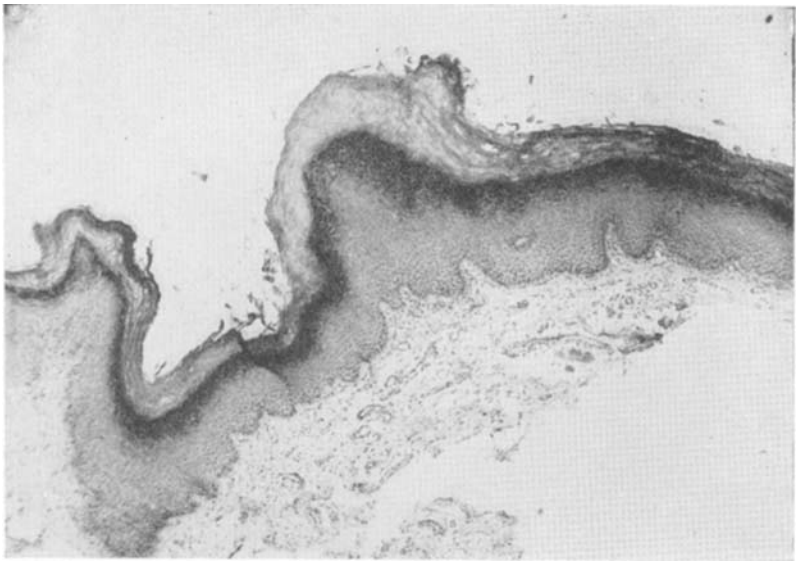

Fig. 11.

total population of the country. Neither is there any good reason to believe that leukoplakia is a more frequent occurrence in Scandinavia than in other countries. Concerning the predisposition for leukoplakia formations nothing is known outside the hypothesis of its existence. The main point in etiology of the leukoplakias is a chronic irritation of a predisposed mucous membrane by a mechanical, less often by a thermic, chemical or electrogalvanic irritament.

The dominant features in the histologic picture of leukoplakias are the epithelial hyperplasia with hyperkeratosis, acanthosis, and in the great majority of cases a chronic inflammatory infiltration in corium, preferably of plasmacells and lymphocytes, more rarely of polynuclear leukocytes. (Fig. 11.)

Normally the oral mucous membrane only has a fairly thin, superficial parakeratotic zone. A stratum corneum is found on gingiva and certain areas of the hard palate only. More pronounced hyperkeratosis is only seen as an expression of chronic tissue irritation with formation of epithelial thickenings in places that are exposed to prolonged irritation, as *e. g.* by prostheses. In its most pronounced forms the epithelial layer gets a greyish to white appearance, as in leukoplakia. All according to duration

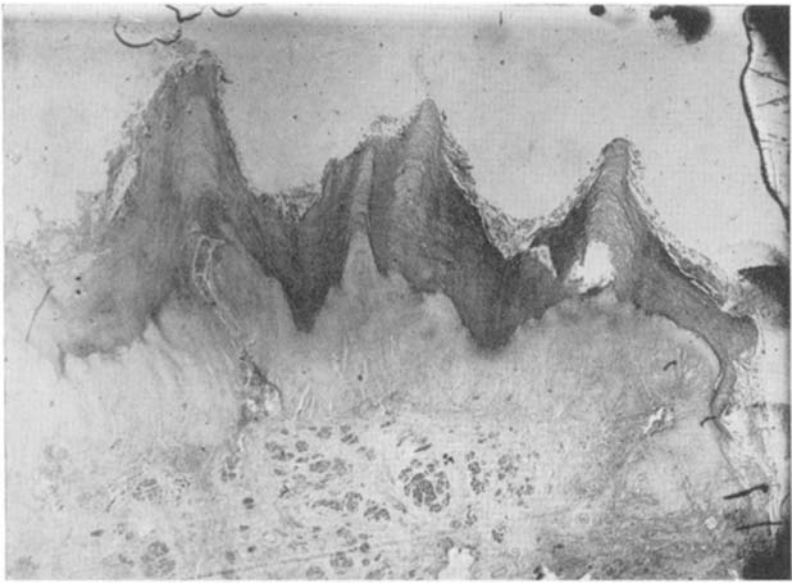

Fig. 12.

of the irritation and the clinical type of the suffering the horny layer may be found more or less developed. Thus in the verrucous leukoplakias it often forms heavy pads. (Fig. 12.)

From pathologic-anatomical quarters attempts have been made to differentiate between leukokeratoses and epithelial hyperplasias. The border-line is vague however and very difficult to maintain. SIEGMUND-WEBER (70) makes a distinction between a "true" leukoplakia, in which the inflammatory infiltration in corium is lacking, and the so-called "Reiz-leukoplakias", in which the subpapillar inflammation is found more or less advanced, and with a greater tendency toward spontaneous disappearance. MEEKIE (42) on the other hand claims that just the plasma-cell infiltration in corium is primary in the development of leukoplakias.

In the histological picture of an uncomplicated leukoplakia mitotic formations are rarely found. The border-line between a "true" leukoplakia and leukoplakia with incipient development of cancer is far from clear. The transition into cancer is first of all marked by an increase in the number of mitoses, next by an incipient loosening of the cellular borders and breaking through of the basal cellular layer. How fluid the transition may be often

Table 3.

Author	Year	Number of cases	Cancerdevelopment in percent
Nedopil	1877	15	100
Fournier	1900	324	29.9
Bloodgood	1929	160	25.6
Schoengarth	1902	277	22.2
Meekie	1932	100	10 (Buccae)
Fox	1925	40	10
Sturgis & Lund	1934	248	54.5
Ullmann	1935	67	29.8
Wassink	1935	300	20 (Lingua: 40 %)
Hedrich	1923	266	21
Schønbauer, Kautek, Friedel	1931	172	10.4
Martin & Pflueger	1935	—	70 (Buccae)
Partsch	1924	—	50 (Lingua)
Present material	1945	246	16

appears from the microscopical pathologic-anatomical diagnosis that for the transitional forms as a rule runs: Epithelial hyperplasia with atypia or carcinoma incipiens.

Already early one has been aware that leukoplakia oris represents a precancerous condition. As the first, FINNIGAN in 1869 has described a transition into cancer from a leukoplakia linguae. The problem has later been pursued by a number of authors. A summary of the obtained results from the study of some larger materials is given in Table 3.

From the table it appears that a development from leukoplakia into cancer is found in between 10 and 100 percent. HAASE (26) has construed a similar table and has found an average value of 25.9 %. KRONFELD finds the percentage to be about 25, and PRINZ (55) has arrived at the same result. LAZARUS describes leukoplakias as cancer in the incubation stage, and BROPHY (7) claims that all lingual cancers develop on leukoplakic basis. Without giving more exact numbers, KÜTTNER (33), HAYES & MARTIN, QUICK and EWING consider leukoplakia oris a very significant precancerous condition. NIELSEN (49) believes that more than 50 % of the intraoral cancers start from leukoplakically changed mucous membrane, WALDRON (77) describes the leukoplakia as the most frequent oral form for precancerosis and GESCHICKTER (25) thinks that 20 % of all oral cancers are of leukoplakic origin.

In the present material it was found that a total of 168 of 1272

cases of intraoral cancers and cancers of the lip had developed on leukoplakic basis. The fact that the percentage was no higher than 16 may be attributable to the circumstance that all doubtful cases have been eliminated, further to incomplete informations in the anamneses, and to a number of cancer cases having arrived for treatment so late that possible leukoplakic fields long ago have been invaded by tumour.

Some authors, such as COCCHI (13), ELLER & ANDERSON (17), v. WURMB (80) et al. do not deny that the leukoplakia should be described as a precancerous condition, but have only rarely observed transition into cancer.

To secure certain informations of the frequency with which leukoplakias in the oral cavity develop into manifest cancer would require an opportunity to observe a rich selection of leukoplakias for a number of years. In spite of the leukoplakias being capable of remaining stationary for years, possibly for decennia, an agreement seems to prevail that the suffering represents the most common form for oral precancerous condition. The percental transition into cancer varies highly with the many authors, and is at the present time not capable of any exact numeral expression. The value of 16 % that is found in the present material, because of the above mentioned reasons, lies possibly on a very low level. To judge by the literature it seems that about 20 % of all intraoral carcinomae develop on leukoplakic basis. (Figs. 9, 10.)

It appears from Table 1 that leukoplakia buccae in the present material has an exceptional position, as more than 25 % of the total number of cancer buccae cases are of leukoplakic origin. MARTIN and PFLUEGER (40) have found that cancer buccae develops from leukoplakia in as much as 70 %, whereas MEEKIE (42) only found 10 %.

A leukoplakic preliminary stage to cancer linguae was in the present material shown only in 13.1 %, with is in good accordance with statements by FOX (23), SCHØNBAUER (69) et al. WASSINK (77) on the other hand found 40 %, PARTSCH (52) 50 %, BLOODGOOD (5) 25 % and BROPHY (7) even 100 %.

WASSINK (77) found for gingiva 14.5 %. The number in the present material is definitely higher, almost 20 %. For cancer palati and labii the percentage lies about 10, decidedly lower than for the other groups.

According to these numbers it seems as if leukoplakias mostly give cause to development of cancer when localised to buccae,

gingiva and the tongue. Possibly the sequence in reality will prove different.

Presuming that the theory is correct, that leukoplakia oris is attributable to a chronic irritation of an already predisposed mucous membrane, the therapy will first be directed toward removal of the irritament, next toward treatment of the already formed leukoplakia.

In order to prevent the formation of fresh leukoplakic plaques most authors agree that the patient should be denied all use of tobacco. If unmistakable symptoms are found that the irritation is due to a jagged, carious tooth, chafing by a prosthesis, or to an electrogalvanic process, this eventual causal factor must be removed as soon as possible. As yet there is no agreement as to how drastically the process of clearing up should be performed. The irritational moment of a jagged, pointed tooth may be eliminated without sacrifying the tooth, but as a rule extraction will be made. Chafing by prosthesis will convey denial for the patient of any use of his prosthesis, and permission to wear a newconstructed prosthesis is given only after a prolonged period of observation. As long as the problem of the importance of oral sepsis as a cancerogenous factor has not been clarified, a total clearing up of oral cavities with severe destructive caries or irreparable, far advanced forms of marginal paradentitis seems to be overshooting the mark. On the other hand, this will in many cases certainly be a considerable advantage to the patient.

To judge by the literature, in cases of positive WR, or with anamnestic informations of a previous luetic infection has antiluetic treatment had no effect on leukoplakias. All luetic patients in the present material have received antiluetic treatment, without it being possible to decide whether this has had any influence on the result of the treatment.

At the Norwegian Radium Hospital has the principle, since the opening of the hospital in 1932, been closely followed, that all leukoplakias that histologically show signs of gross atypia should betreated as if they were manifest cancers. The treatment has in the great majority of cases been radium intubation, or electrocoagulation with subsequent radium intubation in cancericide doses.

If the histologic picture of the leukoplakia proves this to be an uncomplicated epithelial hyperplasia, eventually epithelial hyperplasia with chronic inflammation without gross signs of atypia,

one has as a rule been satisfied with electro-coagulation. However, this method must be reserved for the more localised forms of leukoplakia where the end as a rule is gained without the occurrence of recurrences. In cases of more extensive leukoplakic fields, or multiple larger leukoplakias, one has after the removal of possible irritative causes been obliged to rest content with close observation of the patient at short intervals. In these cases frequent biopsies are taken from eventually occurring suspect parts, in order, at the earliest possible time, to intervene in case of the development of manifest cancer. The same principles for treatment of leukoplakias are maintained inter al. by WISE (79) and DE FOREST (22).

As it has been mentioned, recurrences from radium-treated or electro-coagulated leukoplakias have not been frequent. But fresh occurrences of leukoplakias with other locations are not rare, as expression of the special mucosal predisposition.

Prognosis of the uncomplicated leukoplakia on a whole must be considered good. But the danger for these patients of transition into cancer is always lurking. The moment the development of cancer is a fact the prognosis of the leukoplakia will be identical to that of the intraoral cancer.

Summary.

After a brief discussion of the clinics, diagnosis and differential diagnosis of leukoplakia oris, an account is given of its most important etiologic factors. Next there is accounted for a material of patients from the Norwegian Radium Hospital, consisting of 246 cases. Of these 77 were uncomplicated cases of leukoplakia, whereas amongst 1,272 cases of intraoral cancer treated in the period 1932—1945 there were found 168, *i. e.* 16 % that had developed on leukoplakic basis.

Of the various forms of intraoral cancer it seems that cancer buccae and cancer gingivae most frequently develop from leukoplakias, namely in 25.8 and 19.9 % respectively, whereas for cancer linguae there was found a definitely lower percentage, 13.1. Cancer palati and cancer labii are found on the same level, 11.24 and 10.85 % respectively.

Histology of the leukoplakias and the principles for the therapy used at the Norwegian Radium Hospital are briefly discussed.

The author emphasizes that leukoplakia oris must be described as the most common precancerous condition in the oral cavity.

Zusammenfassung.

Nach einer kurzen Besprechung der Klinik, Diagnose und Differentialdiagnose der Leukoplakia oris, wird über ihre wichtigsten ätiologischen Faktoren berichtet. Darauf wird über ein 246 Fälle umfassendes Patientenmaterial aus dem Norwegischen Radiumkrankenhause berichtet. Hiervon waren 77 Fälle unkomplizierte Leukoplakiefälle, während unter 1,272 Fällen von intraoralem Krebs, die in der Zeitspanne 1932—1945 behandelt wurden, 168 Fälle gefunden wurden, die auf Leukoplakiebasis zur Entwicklung gekommen waren.

Von den verschiedenen Formen von intraoralem Krebs scheint es, dass der Wangen- und Zahnfleischkrebs sich am häufigsten aus einer Leukoplakie entwickelt, und zwar in 25.8 bzw. 19.9 %, während für den Zungenkrebs eine bedeutend niedrigere Prozentzahl (13.1) gefundenen wurde. Gaumenkrebs und Lippenkrebs wurden in derselben Häufigkeit (11.24 bzw. 10.85 %) gefunden.

Die Histologie der Leukoplakien und die im Norwegischen Radiumkrankenhause zur Verwendung kommenden Behandlungsprinzipien werden kurz besprochen. Verf. betont, dass die Leukoplakia oris als die gewöhnlichste präkanzeröse Vorbedingung in der Mundhöhle zu bezeichnen ist.

Résumé.

A une brève discussion du tableau clinique et du diagnostic, différentiel aussi, de la leucoplasie de la bouche, fait suite un relevé de ses facteurs étiologiques les plus importants. Puis est présenté le matériel de l'Hôpital Norvégien du Radium, constitué par 246 malades. 77 de ceux-ci étaient atteints de leucoplasie simple, alors que sur 1,272 cas de cancers intrabuccaux traités pendant la période de 1932 à 1945 on en avait trouvé 168 *i. e.* 16 % qui s'étaient développés sur la base d'une leucoplasie.

Des diverses formes de cancers intrabuccaux il semble que ce soient ceux de la bouche proprement dite et ceux de la gencive qui se développent le plus souvent à partir de leucoplasies, à savoir respectivement dans 25.8 % et 19.9 % des cas, tandis que

pour le cancer de la langue on trouva une proportion nettement moindre, 13.1 %. Le cancer du palais et celuis de la lêvre sont au même niveau de fréquence, soit 11.24 % pour l'un, 10.85 % pour l'autre.

L'histologie des leucoplasies et les principes du traitement en usage à l'Hôpital Norvégien du Radium font l'objet d'une courte discussion. L'auteur souligne que la leucoplasie buccale doit être caractérisée comme la lésion précancéreuse la plus courante de la bouche.

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Address:

Det Norske Radiumhospital,

Oslo,

Norway.