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ALLERGY TO COPPER DERIVED FROM DENTAL ALLOYS AS A POSSIBLE CAUSE OF ORAL LESIONS OF LICHEN PLANUS*

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Lichen planus is an inflammatory disease of the skin and/or mucous membranes.

The clinical and histological features of oral lesions of lichen planus have been described by Cooke (14), Hällén and Sundberg (27), Shklar and Meyer (47), Shklar and McCarthy (48), Pindborg (43), Herrmann (25) and Abramova (1).

Colby, Kerr and Robinson (13) described the macroscopic appearance of lichen planus involving the buccal mucosa as slightly raised white, fine dots and thin lines (Wickham's striae). There may be extensive white plaques, nodules and erosive changes. The clinical appearance of lichen planus on the dorsal surface of the tongue is said to resemble that of leukoplakia (13). Lesions on the gingiva often form a reticular pattern, giving a lace lattice work appearance (14, 48). The various patterns of oral lesions of lichen planus usually occur on an erythematous mucosa (14). Cases have been encountered in which lichen planus involving the gingiva coexisted with desquamative gingivitis (14, 48).

At an early stage the histological changes in lichen planus involving the oral mucosa may be discrete resembling the changes seen in mild non-specific stomatitis. Characteristic changes in the epithelium and the inflammatory cell infiltrate do not occur until a later stage, the histological findings being then diagnostic.

Andreasen and Pindborg (3) reviewed the literature concerning lichen planus and found that several investigators had observed malignant changes in oral lesions, the frequency ranging from one to ten per cent. Koberg *et al.* (32) reviewed 48 published cases in which malignancy developed, adding 3 cases which they themselves had observed. However, the relationship between oral lichen planus and carcinoma has so far not been conclusively demonstrated. The clinical differential diagnosis between pre-cancerous lesions of oral tissues and non-precancerous lesions presents great difficulties and a thorough examination of the patient is most important.

The aetiology of lichen planus is not known. Drug reactions may manifest themselves as lichen planus lesions of the skin and mucous membranes [Baker, Hughes and Pegum (5), Baer and Kopf (4), Dinsdale, Ormerod and Walker (15)]. There is

* A short account of the history of this patient was presented at a post-graduate course for dentists organized by the Swedish National Board of Health and Wellfare (Socialstyrelsen) in April, 1967.

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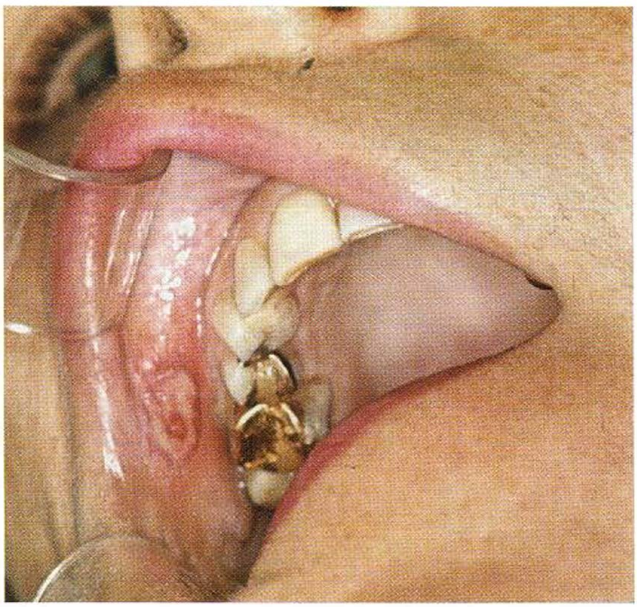


Fig. 1. Buccal lesion on the right side before treatment. Irregularly shaped, slightly raised grayish-white lesion, showing an eroded area in the centre and an area of redness along its borders. Grayish-white streaks in the adjacent mucosa.

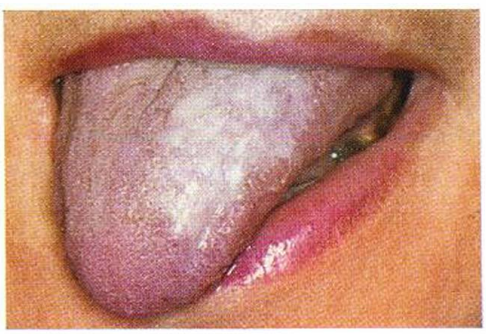


Fig. 2. Lesion on the left half of the dorsum of the tongue. Irregularly-shaped, grayish-white lesion. Papillae are absent.

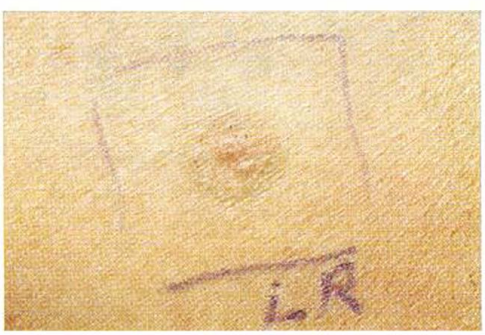


Fig. 3. Skin reaction to epicutaneous test with metallic copper confirming allergy to copper.

suggestive evidence that the condition may be of bacterial [Jacob and Helmbold (29), Brody (10)], spirochetal [Lennhoff (36)] or viral origin [Thyresson and Moberger (54)]. Galvanism and psychosomatic factors have also been reported to account for the disease [Ullman (56), Inovay and Bánóczy (28), Cooke (14), Koberg *et al.* (32), Midana and Ormea (38)].

Hypersensitivity to dental restorative materials as a possible cause of oral lichen planus has to our knowledge so far not been reported. The following case is therefore presented.

Case Report

History

The case concerns a Scandinavian woman, born in 1920, married to a business man and living in Switzerland. She had previously been healthy and not experienced allergic reactions. There was no familial history of allergy. She had three healthy children, 10, 18 and 20 years old. The presenting symptoms, including pain in the regions of the right eye, temple and forehead, appeared in 1962. The pain was intermittent in character, and the episodes lasted from a few days up to four weeks. She was free from pain during the intervals which were of about two-weeks' duration.

With a view to relieving the pain, the impacted teeth 3+ and +3 had been surgically removed two years before her admission. The pain then changed in character and radiated upwards and downwards, involving the upper and lower jaws on the right side, but the source of the pain could not be localized.

It could not be excluded that the pain was caused by pulpitis involving the tooth 7+. Therefore the root channels were filled. However, the pain persisted and was described as severe. Moreover, additional symptoms in the form of an intense burning sensation of the anterior part of the palate and a peppery taste of the tongue appeared.

Four months before admission, the patient attended a hospital in Sweden. Radiography of the maxillary sinus did not reveal any abnormality. She was not relieved of her complaints.

On her own initiative the patient had some laboratory tests done two months later. Apart from a mild sideropenia [47 μg%] which was rapidly overcome, they did not disclose any abnormality.[1]

Examination

When first seen at the School of Dentistry (April 1965) the following teeth were present: 6+ . . . 4+, 2+ . . . +2, +4, +6, +7, 7− . . . −6. The majority were restored with amalgam, silicate, gold or acrylic resin. The latter material had been used for the face of a bridge involving three teeth. A few moderately deep gingival pockets and some soft and hard deposits were present. Radiography revealed five root-filled teeth including the tooth +2 which showed a periapical bone destruction the size of half a pea, the lumen of the root canal being visible at the apical end of the root filling. The apical periodontal spaces at the apices of the teeth 5+ and 4+ appeared to be widened; the marginal bone was markedly retracted between the teeth 4+ and 2+; in the region of the latter tooth it was retracted to about half of the length of the root. The jaw bone in the region of the teeth 3+ and +3 showed areas of lesser density the size

[1] The laboratory findings were as follows: sedimentation rate, 15 mm per hour; haemoglobin, 14.4 %; haematocrit, 44 %; white blood cells, 4100; differential blood count: rods, 0; segmented cells, 66 %; eosinophils, 2 %; basophils, 0; lymphocytes, 27 % and monocytes 5 %.

S-GOT (Glutamate oxalacetate transaminase in serum), 13 units/ml (normal values, 8–25); S-GPT (Glutamate pyruvate transaminase in serum, 10 units/ml (normal values, 10–40; S-LD (Lactic dehydrogenase in serum), 130 units/ml (normal values, 100–400). Urine: protein 0; glucose 0. Serum protein: 6.7 %; serum albumin: 4.3 %; serum globulin: 2.4 %. Serum electrophoresis: albumin, 64.4 % $alpha_1$ globulin, 4.2 %; $alpha_2$ globulin, 6.3 %; beta globulin, 9.2 % gammaglobulin, 15.9 %; TIBC, 357 μg%.

of a bean, resulting from a previous operation. A few teeth showed caries. Radiography of the maxillary sinuses revealed deep recesses into the alveolar processes on both sides but did not disclose any abnormality. A few mandibular lymph nodes were enlarged but were not tender.

One month later a revision of the root filling of the tooth +2 followed by periapical curettage was performed.[2]

The treatment of the tooth +2 did not result in relieving the patient's complaints. The peppery taste of the tongue and palate persisted, occasionally alternating with a metallic taste. The intermittent pain involving the palate and several teeth in the upper jaw, also persisted. The intensity of the pain varied but she was never free from pain. She had not noticed any triggering stimulus. When applying pressure on the right cheek, the severity of the pain decreased. There was no evidence of teeth-grinding or tongue-thrusting.

Five months after admission the patient experienced a burning sensation of the buccal mucosa on both sides. At that time the first objective signs appeared as patches of intense redness with whitish streaks on the buccal mucosa (Fig. 1). On occlusion the sites of these patches appeared to correspond to the sites of the restored teeth +2 to +8 and 2+ to 4+. Moreover, a whitish lesion, about 1.5×3 cm in size, was noted on the left anterior part of the dorsum of the tongue. The lesion was not raised above the level of surrounding normal tissue; it was not indurated and could not be scraped off (Fig. 2).

Microscopy of a biopsy specimen of the buccal mucosa showed it to be covered with stratified squamous epithelium with some degree of hyperkeratosis in association with a varying degree of parakeratosis (Fig. 4). In some places the epithelium was slightly hyperplastic with some elongation of the rete pegs towards the connective tissue; in others it was thin and slightly atrophic. Within these areas the epithelium tended to separate from the corium. There was no evidence of dyskeratotic cells or spongiosis in the stratum spinosum. Markedly degenerated cells and cells showing vacuolization were present in the basal cell layer. An inflammatory cell infiltrate with a well-defined lower border was identified below the epithelium. The majority of the cells were differentiated lymphocytes and histiocytes. Only a small number of neutrophils and a still smaller number of eosinophilic leukocytes were present. Plasma cells were absent. The number of melanin-containing chromatophores under the inflammatory infiltrate was not increased (Figs. 4 and 5). The changes in the epithelium, the extent and configuration of the inflammatory cell infiltrate, the types of cell present and the marked degree of degeneration of the cells in the basal layer of the epithelium corresponded to the histological changes observed in lichen planus [Colby *et al.* (13), Herrmann (25), Fasske and Morgenroth (16)].

On the other hand, the histological changes differed from the type of epithelial hyperplasia which may be found in so-called leukoplakia and from the type of hyperplasia associated with mechanical irritants in the mouth.

A part of the same biopsy specimen was also examined in the electron microscope [for details of the method see Frithiof and Wersäll (20)].

Two different areas of the lesion each containing epithelium and part of the connective tissue, were sectioned and examined with special reference to the possible presence of micro-organisms. On examination of the epithelium and the inflammatory infiltrate no structure suggesting the presence of bacteria, spirochetes or any kind of virus were identified within the sections.[3] The basement membrane was seen

[2] Microscopy of the biopsy specimen of soft tissue derived from the apical bone defect showed it to be very dense coarsely fibrillar tissue containing a relatively small number of cells and staining like collagen.

[3] The examination of eleven biopsy specimens from other cases of oral lesions of lichen planus carried out by one of us (L. F.) did not disclose the presence of micro-organisms.

Fig. 4. Photo-micrograph of the lichen planus lesion on the buccal mucosa on the right side. Typical hyperplasia of the epithelium and characteristic inflammatory reaction (×65).

to be detached from the basal cells and numerous fragments of basement membrane were identified in the connective tissue (Fig. 6). These findings correspond to those of Johnson and Fry (30).

Measurements of electrical potential differences* betwen different restorative metallic materials revealed the highest potential (650 mV)** between a gold inlay and a palatine amalgam filling in the same tooth (6+). There were no mechanical irritants in the form of rough edges of teeth, fillings or crowns. Saliva produced in response to stimulation and resting saliva were tested for rate of secretion, pH and buffering capacity on several occasions. The secretion rate was normal, pH values rather low and buffering generally very law.

With a view to determining whether the patient was hypersensitive to restorative dental material patch tests were carried out in December 1965. Reactions in the form of redness of the skin were observed to copper-II-hydroxide,[4] copper-II-oxide[5] and copper-I-oxide[6] at 72 hours. In order to avoid non-specific traumatic reactions the test with metallic copper was carried out by means of a piece of the material with smooth and rounded edges and conforming in shape to that of a watch glass.[7] The first reading at 48 hours was negative but on the following day small, pale and slightly shiny papules had developed within the exposed area; there was no redness of the skin. A further fourteen tests including tests with $CuSO_4$,[8] different gold alloys

* Electrodes of platina.

** Radiometer type pHM22 (Radiometer Ltd., Copenhagen, Denmark).

[4] Kebo S 5895, Katalog 5 (1955), Kebo, Stockholm, Sweden.

[5] Merck 2766, E. Merck AG, Darmstadt, Germany.

[6] Matheson, Coleman & Bell CX2225. Norwood (Cincinnati), Ohio, U.S.A.

[7] Diameter 11 mm: Copper, Heavy foil "Bakers Analyzed Reagent" No. 1714, J. T. Baker, Philipsbury, N.J., U.S.A.

[8] $CuSO_4 \cdot 5Aq$. 1 %. E. Merck AG, Darmstadt, Germany. No. 2790.

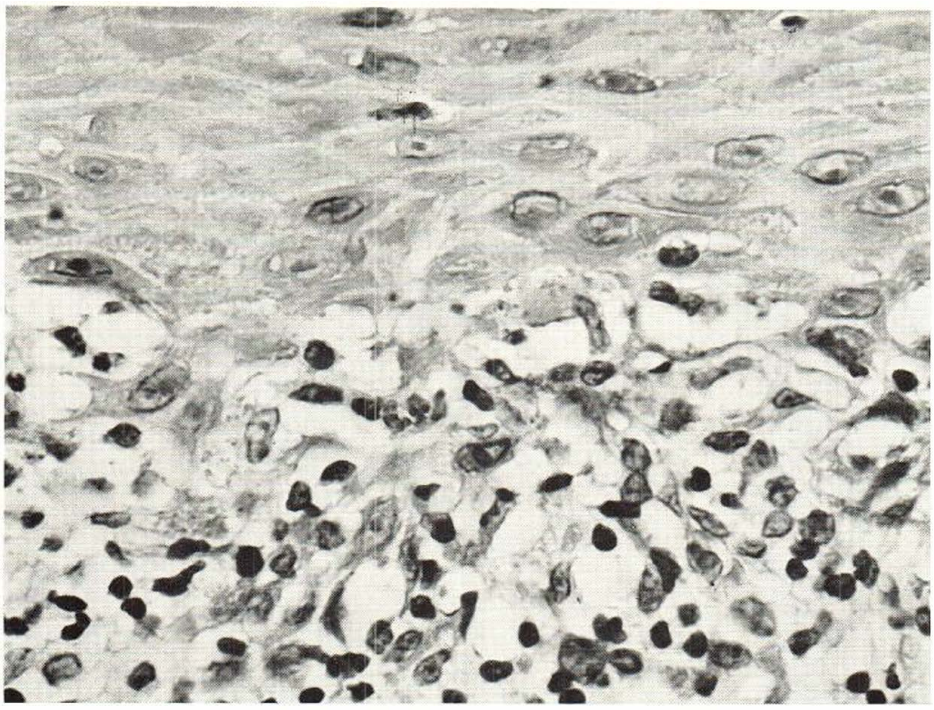


Fig. 5. Photo-micrograph of the same specimen as shown in Fig. 4. Cellular degeneration of the basal cell layer of the squamous epithelium. Inflammatory infiltrate in which lymphocytes predominate (×665).

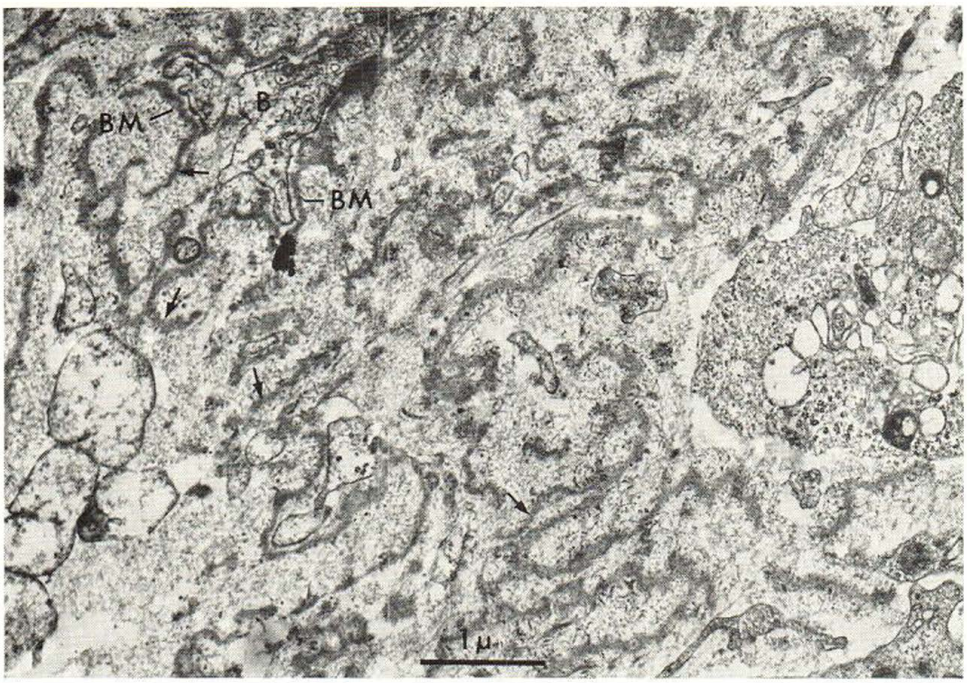


Fig. 6. Electron micrograph of the region of the basement membrane in the same specimen as shown in Figs. 4 and 5. Cytoplasmic processes from basal cells (B) are partly covered with basement membrane (BM). Numerous detached fragments of the basement membrane are seen in the connective tissue (arrows). Embedded in Vestopal (×16,500).

(20-carat, 22-carat, C-gold,[9] Auro-platin[10]), metallic highly pure gold[11] and sublimate[12] gave negative readings. The tests carried out with the above substances on 20 individuals serving as controls, gave negative readings.

Treatment

On the basis of the results of the measurements of electrical potential differences some amalgam fillings were removed (September 1965) and potential differences eliminated. The replacement of some of the larger amalgam fillings with silicate cement resulted in a marked improvement in the patient's subjective symptoms and in particular the pain decreased in severity. One month after the treatment was initiated, the pain in the upper and lower jaw on the right side had subsided. The burning sensation in and the metallic taste on the tongue and the burning sensation in the palate just behind the front teeth persisted.

On the basis of the results of the patch test (December 1965) the treatment was extended to include the removal of all metallic restorations containing copper i.e. restorative amalgam and gold. These materials were removed and replaced with porcelain and copper-free gold[13] homogenized by heat treatement [Hedegård (24), Björn and Hedegård (8)]. Silicate cement was used temporarily until the permanent restorations were in place.

A transient recurrence of the pain six months later was believed to be due to sinusitis but explorative puncture of the maxillary sinuses failed to confirm its presence.

Further restoration of the patient's dentition, including the removal of an amalgam abutment from the tooth -6, mitigated the burning sensation in and the metallic taste on the tongue.

Outcome of the initial treatment

After removal of the remaining metallic fillings the symptoms decreased in severity. Six months after the treatment had commenced the only persisting symptom was an unpleasant sensation involving the tongue. The lesions on the buccal mucosa and the tongue had then decreased in size.

Follow-up

Tests with gold and amalgam were carried out in May 1966, using specimens derived from the patient's dental restorations. They were all negative. The reaction to copper was weaker than that observed previously.

The patient was tested for the third time in October 1966. The reactions to gold crowns, metallic copper and copper-II-oxide were remarkably delayed, appearing in the form of redness of the skin on the fourth day.

A marked redness of the buccal mucosa was noted in conjunction with the skin tests, the involved area facing the buccal surfaces of the teeth $7-$ and $6-$. This symptom disappeared after a few days.

The fourth series of tests were carried out in May 1967. The test with metallic copper gave a vesicular reaction (Fig. 3), whilst those with copper-II-hydroxide and copper-II-oxide gave negative readings.

Microscopy of the biopsy specimen taken from the skin area exposed to metallic copper disclosed a mild non-specific dermatitis with folliculitis in places, moderate spongiosis of the stratum spinosum of the epithelium, a serous exudate in the corium and a few eosinophilic leukocytes in the connective tissue. The histological changes resembled in character an allergic reaction (Fig. 7).

In May 1967, apart from a slight feeling of discomfort in the region of the tooth

[9] C-Guld (Sjöding & Co., Solna, Sweden). Principle constituents: Au, Ag, Cu (11.5 %), Pt. Trace metals: Ir and others.

[10] Auro-platin I, II and III (Ädelmetallbolaget AB, Malmö, Sweden). Principle constituents: Au, Ag, Cu (7.4 %), Pt, Pd. Trace metals: mostly Zn which disappears during the process of melting.

[11] Johnson, Matthey & Co., 73–83 Hatton Garden, London, E. C. 1, No. 1207, foil, 0.2 mm thick.

[12] 0.1 % $HgCl_2$. Svenska Farmakopén, 1946.

[13] Beslagsclasp, Sjöding & Co., Solna, Sweden.

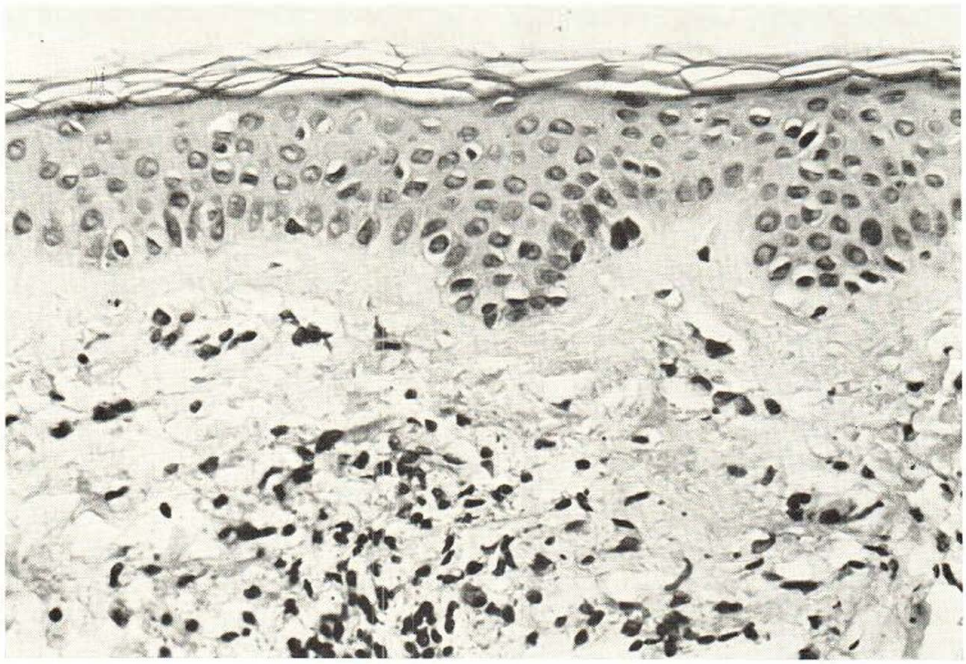


Fig. 7. Photo-micrograph of histological section from skin reaction to copper. Moderate spongiosis of the epidermis and mild inflammatory reaction of the connective tissue (×145).

+ 4 and some tenderness of the palate, the patient was virtually without subjective symptoms. The lesion on the buccal mucosa had further regressed and the whitish lesions on the tongue had almost disappeared.

The second measurement of potential differences was performed in March 1968. The highest value was 30 mV *i.e.* less than 1/20 of the original. A second saliva test was also performed. The low buffer capacity was unchanged.

In May 1968 she had no symptoms and the appearance of the oral tissues had reverted to normal.

Analyses of the metallic structures of one of the removed gold inlays (tooth 5 +) disclosed a casting of hard gold, coarse-grained (4–8 grains per mm^2), inhomogeneous and porous (Figs. 8 and 9). Several attempts to homogenize the alloy by heat treatment were unsuccessful. That such a heat treatment is adequate was demonstrated by a successful homogenization of another dental gold alloy (Fig. 10).

Discussion

The cause of the patient's symptoms was at first obscure and as long as these remained subjective some doubt existed if they were actually experienced. The patient gave the impression of being intelligent and balanced and a psychogenic cause seemed to be unlikely. This was supported when objective signs in the form of lesions on the oral mucosa appeared which were found to be spacially related to the metallic restorations.

Both the clinical and histological findings corresponded to those associated with lichen planus (25). There was no clinical evidence of candidosis [Cawson (11)]. Mechanical irritants as the cause of the patient's symptoms could be excluded. Salivation was sufficient as confirmed by measurements. The low values of buffering capacity may have provided favourable conditions for the migration of metallic ions. The persistance of these low values after healing disprove their primary etiological importance.

Fig. 8. Photo-micrograph of a polished cross-section from the gold crown of the tooth+4. Porosities are seen some being filled with a substance which could not be identified (×100).

The past history of the patient included a transient mild sideropenia. As the patient's symptoms persisted two years after the condition had subsided, it is most unlikely that this was an aetiological factor. This assumption was supported by the fact that there was no recurrence of the lesions or of symptoms at the time of recurrence of the sideropenia in the autumn of 1967. Moreover, the clinical appearance of atrophic changes in the oral mucosa produced by certain forms of sideropenia differs from

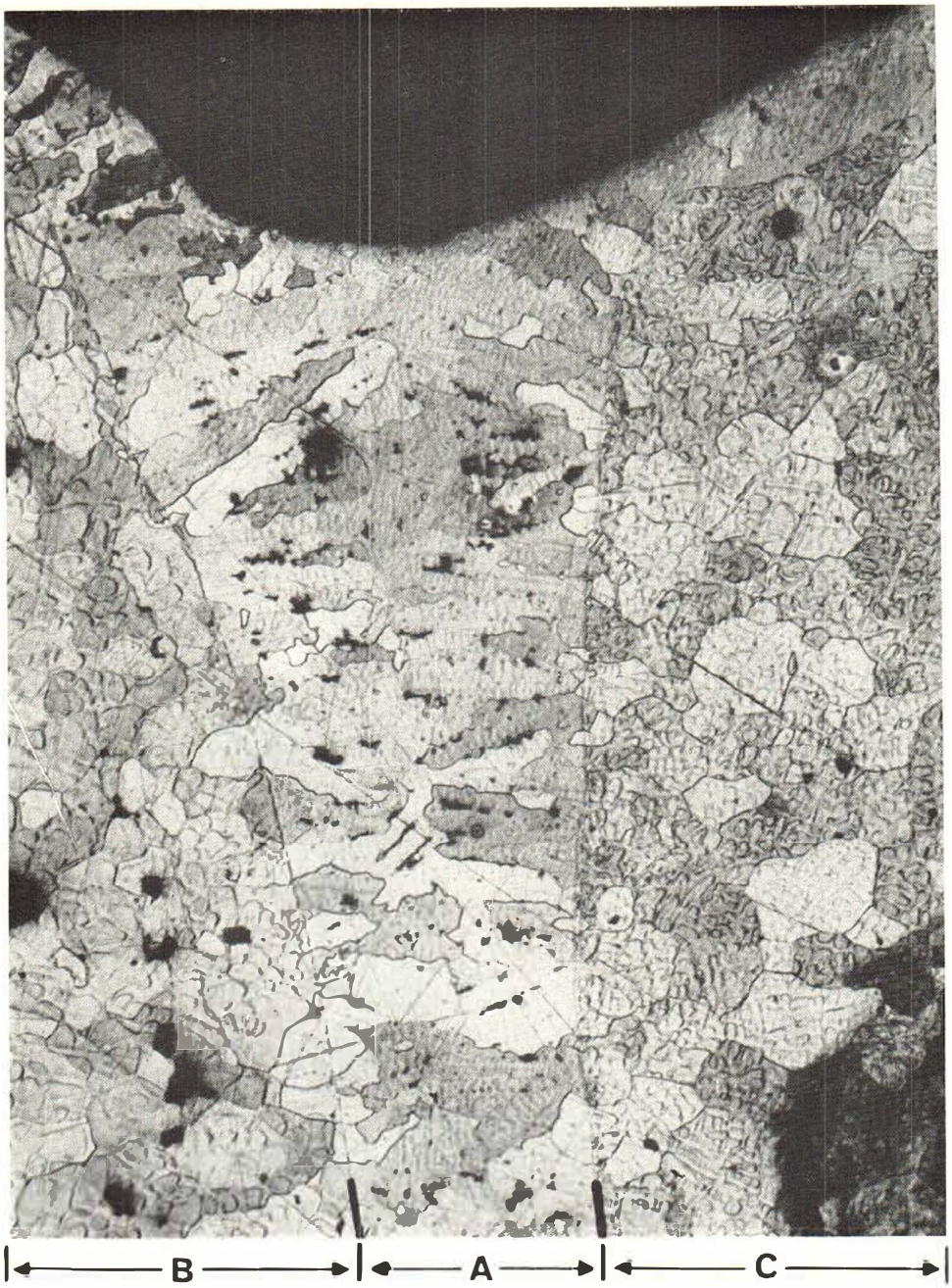
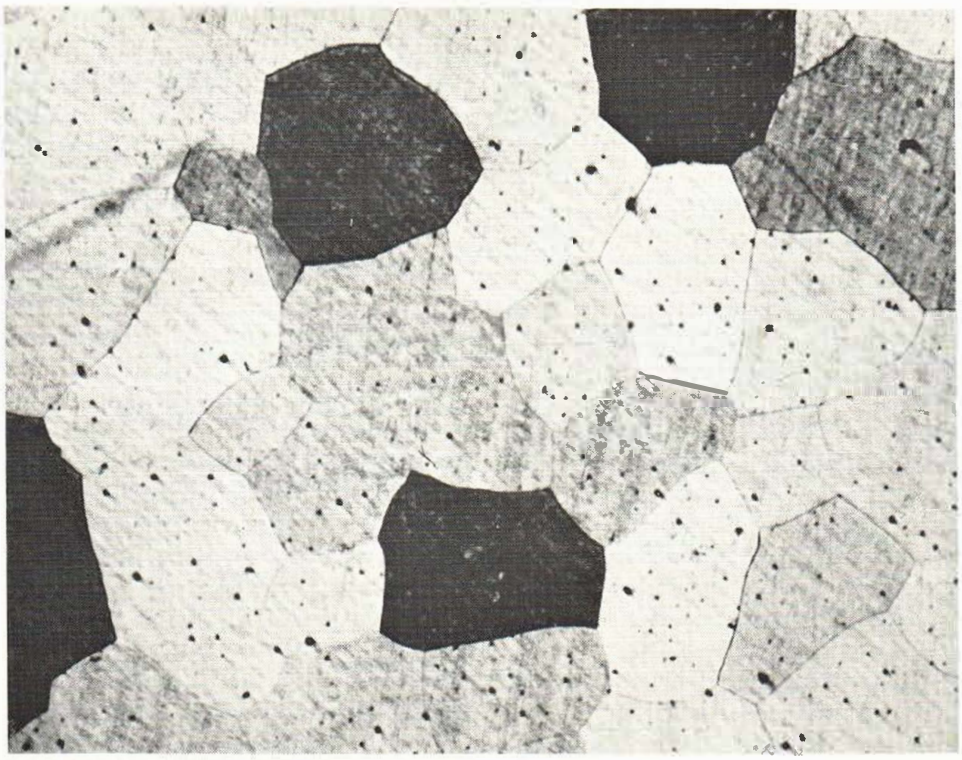
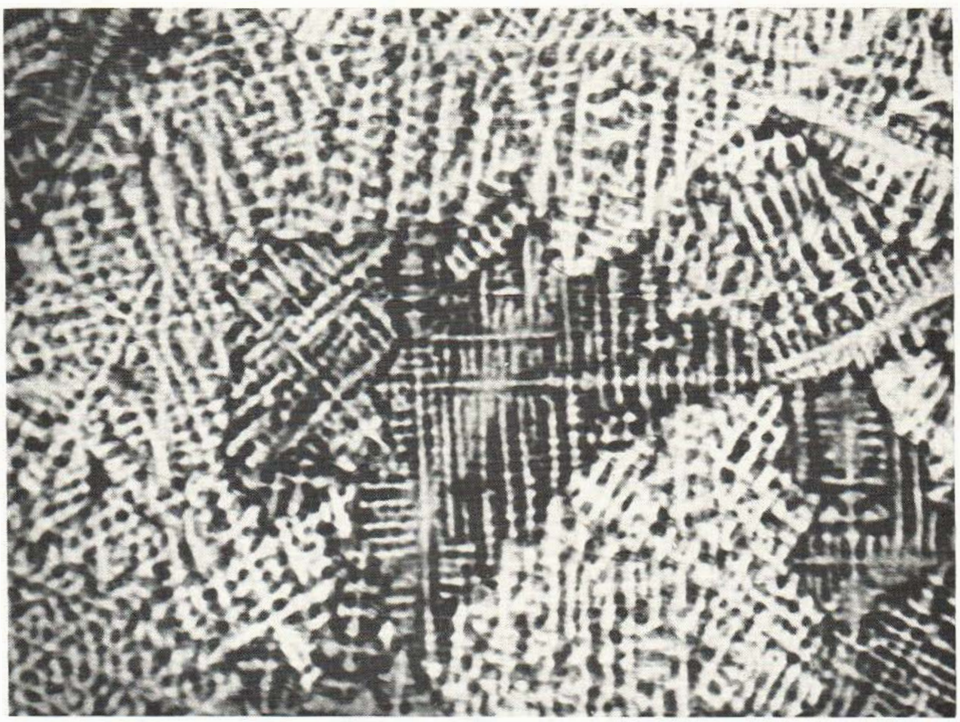


Fig. 9. Photo-micrograph of a polished and etched specimen of gold derived from the patient's gold bridge, showing the soldered joint. The structure is inhomogeneous and porous. The vertical zone (A) represents the soldered joint which shows elongated grains and a dendritic structure, suggesting inhomogeneous solder. The areas marked B and C respectively represent parts of the gold bridge showing relatively large grains, suggesting a palladium-containing and very inhomogeneous gold alloy (×100).



A



B

Fig. 10 A–B. Photo-micrograph of two polished and etched specimens derived from the same casting of a 20 carat dental gold alloy. Specimen A shows the effect of adequate heat treatment at 800°C for 45 minutes which resulted in homogenizing the crystalline structure. Note inhomogeneity of the crystalline structure of the untreated specimen B (×100).

that of the lesions in the present case inasmuch as they involve the entire mucosa [Ahlbom (2)].

The patient refused to have another apical curettage of the tooth +2 done. Nevertheless, the symptoms subsided. It may therefore reasonably be assumed that the process involving the apex of that tooth was of no aetiological importance.

According to the literature skin tests with sublimate 0.1 % give positive reactions in cases of allergy to mercury in amalgam [Frykholm (21), Fernström, Frykholm and Huldt (17), Juhlin and Öhman (31) and others]. In our case there was no reaction to sublimate.

Cutaneous tests with copper gave reactions such as redness of the skin, papules and vesicles which are identical with those given by tests in cases of contact dermatitis which is a delayed hypersensitivity (eczematous) reaction. The patient's positive reaction to pure copper metal and oxides and her negative reaction to copper sulphate may be explained by the low concentration of copper sulphate of the test solution (45) or by sensitivity to corrosion products of metallic copper.

The late appearance of the skin reactions (from 24 to 96 hours) is characteristic of "a delayed allergic reaction". The late appearance and the fact that the tests carried out on the controls gave negative readings mitigates against the possibility of a toxic reaction. The flare-up of the patient's symptoms in conjunction with the skin tests can be compared to the exacerbation of the eruption in allergic dermatitis if the patient is exposed to the appropriate allergen by cutaneous tests. This supports the view that there was a causal relationship between the patient's symptoms and allergy to copper.

Electro-potential differences may occur under certain conditions not only between restorative amalgam and gold but also between two individual amalgam or gold restorations, the saliva being the electrolyte. There may also be potential differences between different parts of the same metallic restoration, due to inhomogeneity of their crystalline structure (24). The highest potential registered in the present case was 650 mV. A potential difference may result in a galvanic current under certain conditions [Skinner and Phillips (49), Schriever and Diamond (46), Köhler (33), Spreng (53), Frykholm and Hedegård (22)]. The inhomogeneity of the gold casting (Fig. 9) may have provided favourable conditions for galvanism in our case. The sites of the mucosal lesions in relation to the gold restorations support this assumption.

A potential difference between the epithelium and connective tissue is maintained by the basement membrane [Ottoson, Sjöstrand, Stenström and Svaetichin (42)] and related to oxidative metabolic processes within the epithelium. It may be possible that foreign exogeneous galvanic potentials have a direct influence on this mechanism.

Several investigators have expressed the view that electrogalvanic potentials may be involved in conditions such as leukoplakia [Lain (35), Nielsen (40)], glossitis, cheilitis, perléche, different forms of neuralgia and lichen planus (28). Galvanic currents have also been reported to be carcinogenic irritants [Reinhard and Solomon (44), Nielsen (41), Hertz (26)].

The pain in the teeth and jaws gradually subsided and the appearance of the oral mucosa reverted to normal during the treatment of the patient. Occasionally, the patient's condition improved markedly from one day to the other following the replacement of some of the amalgam restorations. This suggests that the cause of the pain, the burning sensation, the offensive taste, and of the developing lesions of lichen planus was thereby eliminated. The prolonged persistence of the symptoms, the gradual decrease of their severity and the observation that they did not recur during the follow-up of the patient are additional evidence in support of this view.

According to Bergenholtz (7) and others galvanism may result in the migration of metallic ions to adjacent tissues. We are inclined to believe that this is an essential factor in the development of hypersensitivity to constituents of dental alloys. Both

restorative gold (5–15 per cent copper) and restorative amalgam (4–5 per cent copper) may be sources of copper.

The conclusion that allergy to copper was an aetiological factor in the patient's subjective and objective symptoms was based on the following observations: (i) the patient's positive reaction to the copper tests; (ii) the exacerbation of the oral symptoms in conjunction with the skin tests; (iii) the unquestionably delayed skin reactions; (iv) the disappearance of the patient's symptoms following the substitution of copper-containing restorations for copper-free materials.

As the treatment of the patient resulted in reducing the existing potential differences, *i.e.* from a maximum value of 650 mV before treatment to a maximum value of 30 mV after treatment, the possibility cannot be excluded that galvanism was the sole cause of the patient's complaints. If this assumption holds good she may have aquired allergy to copper as a result of copper being released by galvanism. On the other hand, the exacerbation of the oral symptoms in conjunction with the skin tests strongly suggested that allergy was an essential aetiological factor.

Spreng 1944 (50) has assumed copper to be the cause of intolerance of dental restorative gold alloys. The mechanism was regarded to be allergic or toxic or both. In 3 of his 7 published cases (50, 51, 52, 53) the intolerance was interpreted as allergic reactions. These 3 patients had skin symptoms, such as eczema or unspecific skin eruptions which healed when certain dental gold alloys were removed. The assumption of allergy was not confirmed by skin tests.

Authors using skin tests [Charpy 1952 (12), Kozák and Krčpelka 1953 (34), Törnell 1962 (55)] found allergy to the gold component of dental gold alloys. Their findings correspond to the results of skin tests in patients with intolerance to golden jewelry (19, 23) and to gold-alloy implants (18). In our case skin tests excluded the gold component and suggested copper allergy to be an aetiological factor.

The existence of copper allergy has previously been demonstrated by skin tests in patients with occupational dermatitis (6, 9, 37, 39) and contact dermatitis due to a metallic watch band (45), but, to the best of the authors' knowledge, not in patients with intolerance of dental restorative alloys, nor has allergy to metallic restorative dental materials been described as the cause of oral lichen planus.

SUMMARY

A woman, aged 45, suffered from persistent pain in the jaw and an offensive taste on the tongue for several years. Eventually, she developed lesions of lichen planus on the oral mucosa and on the tongue. Examination of the patient disclosed inhomogeneity of dental gold alloys and great electropotential differences between these materials and amalgam restorations. Allergy to copper was demonstrated by positive skin tests and a flare-up of the patient's complaints in association with the test.

The replacement of all metallic dental restorative materials with copper-free material and the alleviation of the potential differences resulted in cure.

Galvanism, migration of metallic ions, sensitization and copper allergy are discussed. The galvanic release of metallic ions was suggested as a possible mechanism for sensitization to metals.

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