Vitamin B status and response to replacement therapy in patients with burning mouth syndrome

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The aim of the study was to determine, in a group of patients with therapy-resistant burning mouth syndrome (BMS), the possible deficiency of vitamins B_1, B_2, and B_6 and the effect of proper vitamin replacement therapy. Sixteen individuals, aged 47 to 81 years, participated in the study. All underwent a base-line examination comprising anamnestic information, subjective assessment of symptoms, dietary registration, salivary analysis, and serum analysis of thiamine (B_1), riboflavine (B_2), and pyridoxine (B_6). Fifteen individuals had low thiamine and/or riboflavine levels in accordance with suggested levels in the literature and were given replacement therapy. No effect on BMS of vitamin replacement therapy or placebo therapy could be demonstrated. □ *Clinical study; placebo effect; visual analog scale; vitamin analysis*

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Burning mouth syndrome (BMS), as a clinical entity, has been described in the literature over a long period. It is, for most of those affected, a very troublesome disorder. In typical cases the patients complain of a burning sensation in the oral cavity and the pharynx. Certain parts of the oral cavity, such as the tongue and the palate, are often involved, but the mucous membranes of the cheek and lips may also be affected. Several possible causative factors have been proposed in the literature, such as stomatognathic disorders, low salivary secretion, oral candidosis, oral lichen planus, gastrointestinal disturbances, iron deficiency and pernicious anemia, manifest endocrinologic diseases, allergies towards dental materials, and psychiatric disorders (1–14). A comprehensive review of clinical appearance, causative factors, and treatment modalities has been published by van der Waal (15).

There are few epidemiologic studies on the frequency of BMS in the population. In an English study a frequency of 2.6–5.1% was mentioned (16). The symptoms were reported to be five times more common among women aged 40–49 years than among other groups. In a Swedish investigation of dental health in 654 individuals aged 20–80 years in the borough of Jönköping, BMS was found in 3.9%. Among women aged 40 and 50 years the frequencies were 4% and 10%, respectively (A. Hugoson, B. Thorstensson. Unpublished observations).

Many patients with burning mouth syndrome are relieved of their symptoms after thorough odontologic and medical examination and proper treatment (12, 17). In several patients, however, the symptoms are unchanged despite all treatment efforts. In a recently published study by Lamey et al. (18) the effect of vitamin B therapy in a group of BMS patients deficient in vitamins B_1, B_2, and/or B_6 was studied. Vitamin replacement therapy gave encouraging results. However, a proper control group for assessment of a possible placebo effect was lacking in the investigation.

The aim of the present study was to determine, in a group of patients with therapy-resistant BMS, the possible deficiency of the vitamins B_1, B_2, and B_6 and the effect of proper vitamin replacement therapy. The placebo effects were evaluated as a control.

Materials and methods

The subjects included 16 individuals, 14 women and 2 men aged 47 to 81 years (mean 63), with therapy-resistant BMS. BMS is defined as a burning, smarting, pricking, or aching sensation located in any of the oral mucous membranes, including the tongue, the lips, and the pharynx, without any clinical manifestations. One patient had full upper and lower dentures, one had a full lower denture, and one had a removable partial upper denture. The other patients were completely or partially dentate and without any removable partial dentures. Before the start of the investigation all individuals were examined and treated for possible dental causes of their symptoms—for example, stomatognathic, endodontic, periodontal, and prosthetic factors. At their own request, four patients had had their amalgam fillings replaced by composite. In a few cases an allergologic dental screening test (19) and calculations of intraoral currents were performed (20). All patients also had a routine clinical/chemical blood analysis and an analysis of the serum iron and folic acid/cobalamin content. When indicated, a medical check-up had been performed and treatment given. All patients underwent a base-line examination, comprising anamnestic information on health and drug consumption and determination of the onset and duration of the BMS. The daily variation of BMS and its location and severity were charted, and the results were registered on a special chart. On a 200-mm visual analog scale (VAS) (21) each patient marked the severity of the symptoms, ranging from 'not at all severe' to 'more severe than anything else'. The location of the symptoms was marked by the investigator on the oral cavity figure on the chart in accordance with each patient's description (Fig. 1). In addition, taste alterations such as 'bad' taste, metallic taste, and battery taste were registered. The base-line examination further included a 3-day dietary registration, analysis of saliva (stimulated saliva: rate of secretion, buffering pH), and serum analysis of the vitamins thiamine (B_1), riboflavine (B_2), and pyridoxine (B_6).

The vitamin analyses were performed at Näringslaboratoriet, Statens Livsmedelsverk, Uppsala (B_1, B_2) and at Klinisk kemiska laboratoriet, Sahlgrenska Sjukhuset, Gothenburg (B_6). Five milliliters of frozen untreated serum were transported to the respective laboratories. S-thiamine and S-riboflavine were determined by a fluorimetric method modified from that of Bötticher & Bötticher (22) and Johnson et al. (23), respectively, and S-pyridoxine by an enzymatic method (24).

The experimental plan is described in Fig. 2. All the evaluations were carried out double-blind; that is, neither the examiner nor the patient had any knowledge of which therapy had been prescribed. After the base-line examination on day 0, all patients received a placebo treatment (placebo 1; one tablet per day for 30 days). The result of the placebo treatment was evaluated after 30 days (evaluation 1), at which time the results of the vitamin analysis were also available. At this evaluation, as at all consecutive evaluations, the severity and location of the BMS were recorded. Separate record sheets were used, to prevent previous results from influencing the patients.

Those patients who had persisting symptoms and deficiency of vitamins B_1, B_2, and/or B_6 at evaluation 1 (group A), received replacement therapy as shown below. Serum concentrations of $B_1 < 2.0\ \mu g/100\ ml$, $B_2 < 3.2\ \mu g/100\ ml$, or $B_6 < 15\ nmol/l$ were considered deficient (25).

The dosage of the various replacement therapies was as follows: vitamin B_1, one 300-mg Benerva® (thiamine) tablet daily for 30 days; vitamin B_2, one 10-mg Bevitotal® comp tablet twice daily for 30 days (thiamine, riboflavine, nicotinamide, calcii pantothenas, pyridoxine, and ascorbic acid); and vitamin B_6, one plus one plus two 40-mg Benadon® (pyridoxine) tablets daily for 30 days.

Bevitotal, a multivitamin product, was

Fig. 1. Chart for patients with burning mouth syndrome. One patient's data are filled in. The location of the symptoms is marked by black crosses or lines. The data are filled in from a separate autoanamnestic form. The patient has no access to the previous data when completing the form.

Burning Mouth Syndrome chart

Occasion	1	2	3	4	5
Date	illegible	illegible	illegible	illegible	___

Name

Date of birth

Address

Telephone

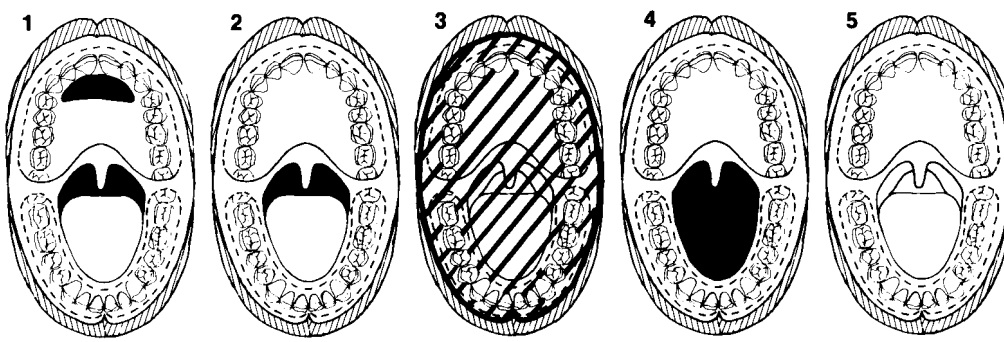
Type of problem

	1	2	3	4	5
Ache	X	X	X	X	
Smarting			X	X	
Burning sensation				X	
Pricking					
Bad taste		X	X	X	
Metallic taste				X	
Battery taste				X	

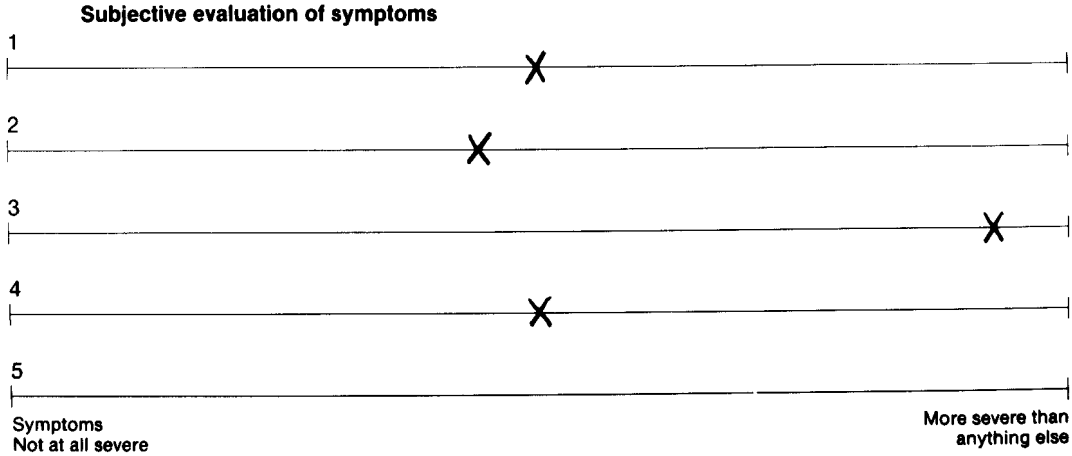
Time when symptoms are worst

	1	2	3	4	5
Early morning	X	X		X	
Late morning			X		
Noon			X		
Afternoon			X		
Evening					
Night					
Continuously					

Location of problem



Subjective evaluation of symptoms



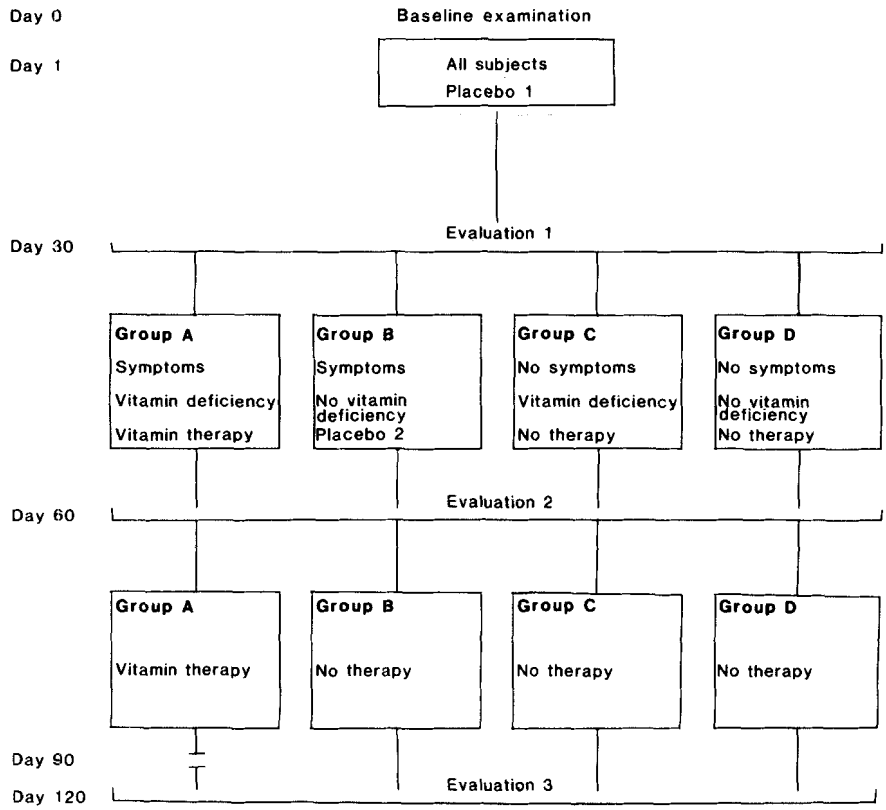


Fig. 2. Experimental design.

prescribed for vitamin B_2 deficiency, as no product containing only B_2 was available. Those patients who had persisting symptoms but no vitamin deficiency (group B), received a second placebo treatment (placebo 2; one tablet per day for 30 days). It was planned that those patients who were free of their symptoms were not to receive any treatment irrespective of the presence (group C) or absence (group D) of vitamin deficiency.

At evaluation 2, 60 days after the baseline examination, the recording of BMS symptoms was repeated, and a second serum analysis of the B vitamins was performed.

This second serum analysis was performed for all patients including those who had received only placebo treatment after evaluation 1. As the results of the serum analysis took several weeks to produce, those patients who had received replacement therapy after evaluation 1 (group A) continued this therapy for a further 30 days after evaluation 2, in case they were found still to be vitamin-deficient. It was planned that the rest (groups B, C, and D) should not receive any therapy.

At evaluation 3, 60 days after evaluation 2, the recording of BMS symptoms was repeated, and a third serum analysis was performed for those patients who had not reached normal vitamin serum values at evaluation 2.

Results

General health and medication

A list of general diseases seen in the trial participants is given in Table 1. Of the six allergic patients, one was allergic to nickel,

Table 1. Anamnestic information on the medical background of the 16 investigated patients. The number of patients with each condition is given in parentheses

Heart and vascular diseases (5)
Pernicious anemia (1)
Diabetes mellitus (2)
Allergies (6)
Asthma (1)
Anxiety, depression (7)
Joint problems, muscle pains (4)
Gastrointestinal illness (2)
Eye problems (2)
Others (2)

one to formalin, one to cobalt and colophony rosin, and one to *p*-tolyldiethanolamine. Two patients reported diffuse eye symptoms. Fourteen patients regularly took one or more drugs. Seven of these took drugs for central nervous system disorders, mainly analgetics and antidepressive drugs. Five patients took drugs for gastrointestinal or metabolism disturbances. Among these drugs were antacids and antidiabetics. Four took antihypertensive drugs and/or diuretics. Another four took drugs for disorders of the respiratory tract, mainly antiasthmatic drugs. One patient took vitamin B_{12} for pernicious anemia. All the laboratory values of the clinical/chemical blood analysis and the analysis of serum iron, folic acid, and cobalamin were normal.

Dietary registration

The frequency of principal meals varied from one to three meals per day, and the frequency of snacks between meals varied from one to six times per day. The diet of six of the patients was not satisfactory with regard to the intake of ascorbic acid. Otherwise no marked deviations from the recommended food intake were registered (26).

Salivary tests and dry mouth

Eight of the patients reported frequent or constant dry mouth problems. Six patients had a salivary secretion rate <0.7 ml/min. Two of these had <0.4 ml/min. Twelve patients had a buffering pH value of <5.0.

Presence, location, and severity of BMS at the base-line examination

All patients had had BMS for 2 years or more, and for 13 of them the symptoms had developed gradually. Four patients reported a sudden symptom debut, in all cases directly connected with the insertion of crowns, dentures, or fillings.

The commonest symptom location was the tip of the tongue, the anterior palate and/or the pharynx. Next most involved were the rest of the tongue and palate and the inside of the lower lip.

Symptoms from the cheeks, the upper lip, and the gingiva were less common. The location of the symptoms was relatively constant in the group as a whole at the different registrations. For some individuals, however, the location varied from time to time. The location of the symptoms for one of the patients is described in Fig. 1.

The most frequent types of symptom were smarting, burning, and pricking sensations. Taste alterations were less frequent (Fig. 3). Many of the patients reported variations in their symptoms from day to day. Furthermore, it was often stated that application of cold water and saliva eased the symptoms, whereas heavily spiced and sour food aggravated them.

In seven patients, symptoms varied throughout the day: mildest in the mornings, increasing somewhat during the day, and worst during the evening. The other patients had different or no daily symptom variation.

The subjective assessment of the severity of the symptoms is shown in Fig. 4. At the base-line examination the severity of the symptoms varied from moderate to close to intolerable.

Vitamin status

The serum concentrations of vitamins B_1, B_2, and B_6 at the three analyses (base-line examination, evaluations 2 and 3) are listed in Table 2. At the base-line examination the serum concentration of vitamin B_1 was between <1 and 3.0 μg/100 ml. For vitamin B_2 the corresponding values were 1.7 and 5.2 μg/100 ml. The B_6 values were between

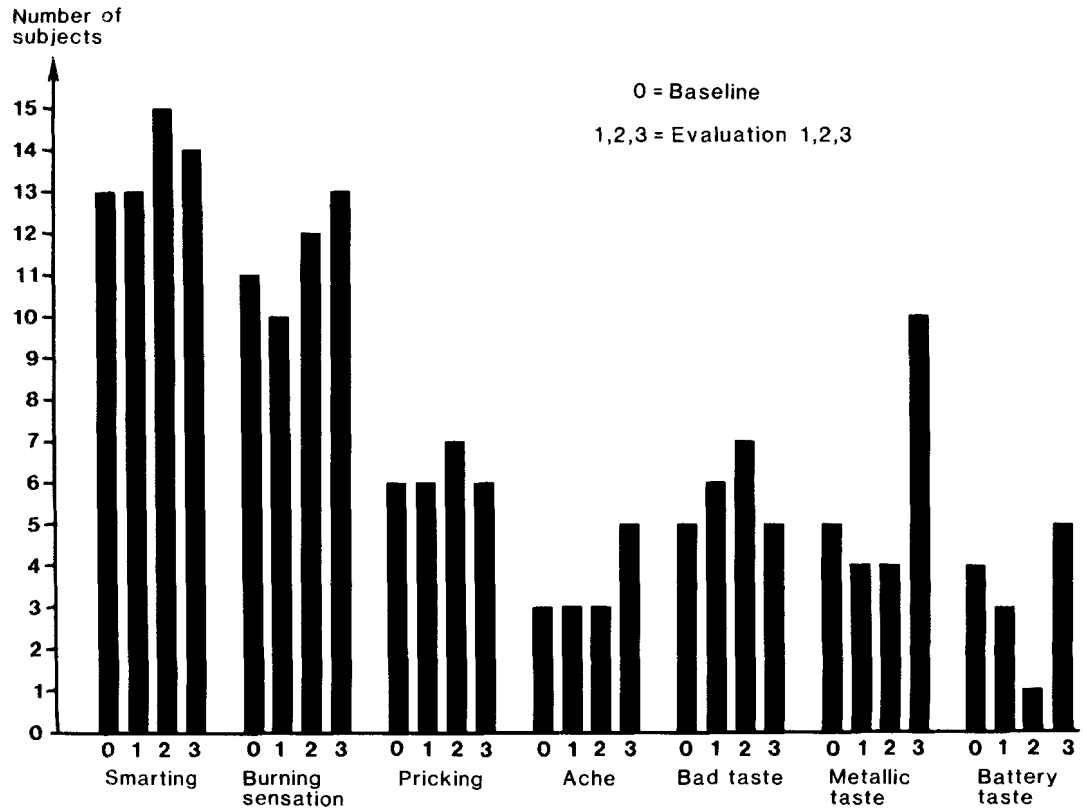


Fig. 3. Anamnestic information on the presence of smarting, burning, and pricking sensations, ache, bad taste, metallic taste, and battery taste in the studied patients at the different examinations. 0 = base-line examination; 1 = evaluation 1; 2 = evaluation 2; and 3 = evaluation 3.

31 and 600 nmol/l. At evaluation 1 those 15 patients who at the base-line examination had a B_1 and/or B_2 deficiency were given vitamin replacement therapy (group A). One patient had neither B_1 nor B_2 deficiency (group B). No patient was vitamin B_6-deficient. At evaluation 2 the serum values were between <1 and 8.2 µg/100 ml for vitamin

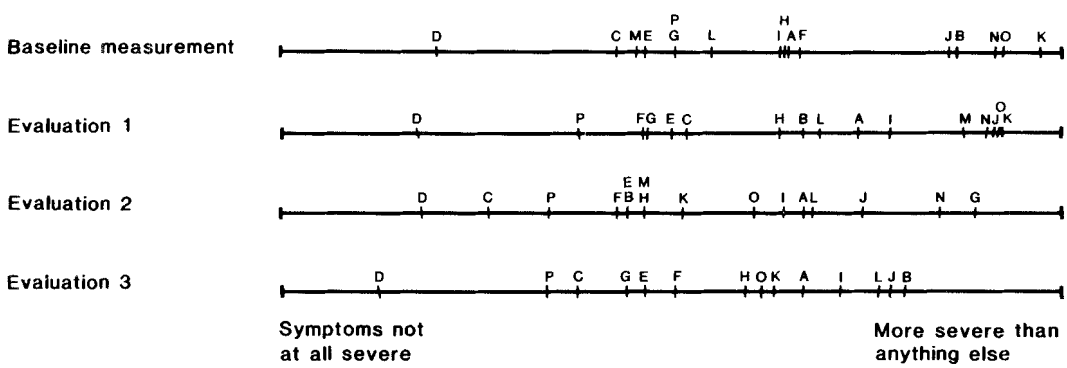


Fig. 4. The individual patient assessment (VAS) of the severity of the symptoms of burning mouth syndrome at the different examinations. The 16 patients are denoted alphabetically from A to P.

Table 2. Results of serum vitamin B_1, B_2, and B_6 analysis (0 = base-line measurements; 2 = evaluation 2; 3 = evaluation 3)

	B_1 (μg/100 ml) analysis			B_2 (μg/100 ml) analysis			B_6 (nmol/l) analysis	
Patient	0	2	3	0	2	3	0	2
A	<1.0	1.4	1.0	2.0	2.3	1.9	38	23
B	1.0	2.2	—	2.7	3.2	—	57	55
C	<1.0	<1.0	1.1	2.1	2.8	1.1	35	26
D	1.0	1.6	1.0	2.2	2.4	1.9	60	31
E	1.0	3.8	—	2.3	6.9	—	34	34
F	<1.0	1.2	<1.0	1.8	2.4	1.7	70	21
G	3.0	4.6	—	3.6	14.2	—	600	310
H	<1.0	7.0	—	2.3	6.8	—	54	32
I	<1.0	1.4	1.2	2.6	2.3	2.3	47	50
J	1.0	2.1	1.4	2.3	2.6	1.9	79	22
K	1.5	1.4	1.2	4.6	5.1	3.7	64	18
L	1.0	5.4	—	2.7	10.6	—	185	294
M	<1.0	8.2	—	5.2	8.1	—	51	16
N	1.5	2.1	—	2.4	3.3	—	52	32
O	1.0	2.7	1.2	1.6	2.4	2.1	31	39
P	1.0	1.2	<1.0	2.8	3.5	2.1	64	70

B_1, between 2.3 and 14.2 μg/100 ml for vitamin B_2, and between 16 and 310 nmol/l for vitamin B_6.

The serum analysis at evaluation 3 was carried out only for those individuals who were deficient in vitamins B_1 and B_2 at evaluation 2. There were still no patients deficient in vitamin B_6 at evaluation 2. The serum values at evaluation 3 were between <1 and 1.4 μg/100 ml for vitamin B_1 and between 1.7 and 3.7 μg/100 ml for vitamin B_2. At evaluations 1 and 2 one patient was B_1-deficient but had normal B_2 values. For practical reasons a serum analysis of vitamin B_2 was carried out anyway at evaluation 3, at which stage the B_2 value was still normal.

Presence, location, and severity of BMS after placebo therapy

At evaluation 1, after 30 days of placebo therapy, six patients had unchanged or almost unchanged symptoms compared with the base-line examination. Six patients had worse and four patients had reduced symptoms (Fig. 4).

Presence, location, and severity of BMS after replacement therapy

At the base-line examination and evaluations 1, 2, and 3, the mean values for the entire patient group were 128, 132, 117, and 121, respectively, as measured in mm from the left end-point of the VAS scale. In Fig. 4 the results of the individual ratings of the severity of the symptoms on all four occasions are given. When the base-line examination was compared with evaluation 3 for each individual, five of the patients had equal or almost equal symptoms on both occasions, five had milder symptoms at evaluation 3, and four had worse symptoms. Two patients were unable to attend at evaluation 3. The daily symptom variation at evaluation 3 was unchanged from that seen at the base-line examination. There were no side effects registered either from replacement or placebo therapy.

Discussion

On a population level individuals with BMS are relatively scarce, and the number of subjects in this clinical study was also small. The 16 patients were all thoroughly examined odontologically and, when required, medically. They were treated before the start of the investigation, without any effect on their BMS. In several of the patients general

symptoms such as fatigue, loss of appetite, anxiety, and generalized muscle and joint pain were present. These general symptoms are well in accordance with symptoms described by other investigators for patients with BMS. At the same time there is a lack of homogeneity of the patient population with regard to specific disorders and medication that might explain the symptoms. The location of the BMS is also in good agreement with previous reports (13, 16, 18, 27).

The tongue, hard palate, lips, and pharynx are the most affected sites. The daily symptom variation is also in agreement with previous studies (13, 27). The symptoms tend to increase during the course of the day and reach their peak in the afternoon and evening.

The BMS has been described in the literature over a long period. Various causal connections and therapies have been suggested, but no clear-cut cause of the disorder has been established. Investigation and treatment of BMS therefore constitute a severe clinical problem in individual cases.

Among the possible causes of BMS, different vitamin deficiencies, such as thiamine (B_1), riboflavine (B_2), and pyridoxine (B_6) have been discussed (10, 16, 18). Thiamine is present in all vegetable and animal tissues. It is lost to a great extent in the handling of raw materials. Initial thiamine deficiency manifestations are loss of appetite, fatigue, and irritability. Eventually paresthesia and anesthesia of the body and extremities may appear.

Riboflavine is generally abundant in vegetable and animal products. Deficiency symptoms may be angular cheilitis, glossitis, dermatitis, and eye irritations.

Pyridoxine is present in vegetables, meat, and fish but is lost to a great extent in the handling of the raw material. Common deficiency symptoms are emotional lability, fatigue, and mental depressions. Pyridoxine deficiency may lead to secondary iron deficiency anemia with oral mucosal lesions (28, 29).

Thus, according to the literature, deficiency of the above-mentioned vitamins might directly or indirectly give rise to various oral symptoms. There are great variations in the published normal serum values for the vitamins in question, and what should be considered the limit of deficiency states is open to discussion. Nor are there any representative reference values available for age groups equivalent to the patients in this study. We have chosen to make a readjustment of the values presented in the Ciba-Geigy scientific tables (24). On the basis of this, the lower limits for serum concentrations would be ≥ 2.0 µg/100 ml for thiamine, ≥ 3.2 µg/100 ml for riboflavine, and ≥ 15 nmol/l for pyridoxine.

At the base-line analysis all patients but one had thiamine serum values less than the lower limit, 13 had riboflavine serum values less than the lower limit, but all had normal pyridoxine serum values. Thus, despite a grossly adequate and nutritious diet, a great number of the patients had low thiamine and riboflavine serum values. On the basis of these results thiamine and riboflavine replacement therapy was instituted.

In the study presented by Lamey et al. (18), promising results from vitamin B therapy in BMS patients were reported. Twenty-five of 28 patients deficient in thiamine, riboflavine and/or pyridoxine were completely relieved of their symptoms after replacement therapy. However, that investigation can be criticized as being without a proper placebo-treated control group. In the present study the experimental design has been different. Placebo therapy has been included.

No effect of vitamin replacement therapy could be demonstrated. It is true that at the second evaluation, after 30 days of replacement therapy, eight patients reported milder symptoms, but the changes were small. At the third evaluation, when the replacement therapy had continued for a further 30 days followed by 30 days without any treatment, seven patients reported worse symptoms than at evaluation 2. Individual comparisons of symptoms and vitamin serum values showed that in certain patients the symptoms got worse despite increased vitamin serum values, whereas others were somewhat relieved of their symptoms despite unchanged serum values. Thus the objectively registered changes of vitamin serum values were not followed by a corresponding change of the sub-

jective symptoms from the oral cavity. The risk of these results being a consequence of the patients not following given prescriptions is judged unlikely. All vitamin bottles and boxes were collected after treatment, and the remaining pills were counted.

In contrast to Lamey et al. (18), we could find no lasting increase in the vitamin serum values after replacement therapy. Instead, after 2 months the serum values had returned to the base-line level. These results are in good agreement with a normal uptake and excretion of therapeutic vitamin doses, in which a temporary surplus of vitamins is soon excreted via urine and feces (30). The registered decrease of the vitamin serum values after finishing vitamin therapy might indicate that the base-line values were normal for these patients and thus not an expression of a true deficiency state. Grushka (13) has previously expressed similar points of view and has stated that there is little support that factors such as nutritional deficiencies are important causative factors in BMS.

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