# Haematinic Deficiency in Recurrent Aphthous Stomatitis: its Prevalence and Response to Treatment

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**Purpose:** The purpose of this prospective study was to identify the prevalence of haematinic deficiency in a large panel of patients with recurrent aphthous stomatitis (RAS) and to ascertain the effect of replacement therapy.

**Patients and Methods:** 197 patients with RAS were recruited to the study. A detailed ulcer history, clinical examination and haematological investigations, including a full blood count, serum ferritin levels, red cell folate levels and serum vitamin B12 levels were carried out for each patient. In addition, a coeliac screen was performed for all patients under 12 years of age and those with any bowel symptoms. Patients with a deficiency state were referred to their general medical practitioners (GMPs) for management of the deficiency and reviewed six months later when the response to supplementation was ascertained and haematological investigations were repeated.

**Results:** A deficiency state was identified in 28.9% of RAS patients, with iron deficiency accounting for 96% of these; 4.6% of parents were vitamin B12 deficient, with 3.5% having a combined iron/vitamin B12 deficiency. No patient had a folate deficiency or a positive coeliac screen. Anaemia was present in only 10.5% of those patients with reduced haematinic levels. 8.6% of iron deficient patients were ulcer-free following supplementation, while 42.9% reported considerable improvement. Only 2 out of 6 patients with a combined deficiency had their iron and vitamin B12 levels corrected on review. However, this had resulted in complete ulcer resolution in one patient, and considerable improvement in the other.

**Conclusion:** The prevalence of haematinic deficiency was high in the study population. However few patients had complete resolution of ulceration following replacement therapy.

**Key words:** recurrent aphthous stomatis, oral ulceration, ferritin, folic acid, vitamin B12

*Oral Biosci Med 2004; 1: 259–266* *Submitted for publication 14 July 2004; accepted for publication 24 October 20004*

## INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a very common oral mucosal disease characterised by self-limiting painful oral ulcers which recur at various intervals. It is a common oral mucosal disease affecting approximately 20% of the population at some stage in their lives (Sircus et al, 1957; Axell and Henricsson, 1985). Its aetiology is unknown, although several predisposing factors have been implicated, such as a positive family history, stress, trauma to the oral mucosa, cessation of smoking, haematinic deficiency and systemic diseases, including coeliac disease, inflammatory bowel disease and HIV disease (Scully et al, 2003).

Patients with RAS are routinely screened for haematinic deficiency and given appropriate supplementation should they be deficient. However, few recent studies have been done to explore the effect of supplementation on the ulcer pattern in these patients (Rogers and Sutton, 1986; Porter et al, 1992). The aim of this study was to determine the prevalence of haematinic deficiency in a large case series of patients with RAS and to establish the effect of haematinic supplementation in those in whom a deficiency state was identified.

Serological screening for coeliac disease was also carried out in a subset of these patients.

## PATIENTS AND METHODS

Ethical approval for the study was obtained from the Research Ethics Committee of Tower Hamlets District Health Authority, London, UK. Patients were recruited in response to posters canvassing for volunteers who suffered with RAS. These posters were placed in the buildings of the Royal London Hospital and the London Hospital Medical College. They were also sent to general medical and dental practitioners in the East London area, along with explanatory letters suggesting the posters be placed in surgery waiting rooms. In addition patients were recruited from those referred to the Oral Medicine Clinic at the Royal London Hospital. All the patients were assessed by a single examiner (CMH). Inclusion criteria included: a 6 month or longer history of regularly recurrent episodes of oral aphthous ulceration and a clinical examination consistent with this history. Exclusion criteria included: (1) a confirmed history of systemic disease in which oral ulceration may be a feature e.g. Behçet's syndrome, coeliac disease, Crohn's disease, ulcerative colitis or AIDS; (2) a pattern of oral ulceration not consistent with recurrent aphthous stomatitis; (3) evidence of another ulcerative oral condition e.g. oral lichen planus.

A detailed ulcer history was obtained from each patient using a standard schedule with emphasis on the ulcer pattern and the possible role of predisposing factors. They were questioned about any associated eye, genital, skin, or gastrointestinal symptoms. The oral mucosa was examined thoroughly and the presence or absence of ulcers was recorded along with their location and average size. In addition scarring of the oral mucosa as a consequence of previous ulceration, tongue depapillation, angular cheilitis and other lesions of the oral mucosa were recorded.

A full blood count (FBC), serum ferritin, serum vitamin B12 and red cell folate were determined in all patients. Serum ferritin was measured as its levels correlate well with total iron body stores (Lipschitz et al, 1974) and red cell folate represents the folate stores more accurately than serum folate (Tyldesley, 1983; Porter et al, 1988). All patients under 12 years of age and any other patients who complained of bowel symptoms were investigated for anti-α-gliadin IgG and IgA, anti-reticulin IgG and IgA and anti-endomysial IgA antibodies to explore the possibility of undiagnosed coeliac disease as a cause for their recurrent aphthous ulceration. The normal reference ranges for the FBC and haematinics were those adopted by the Department of Haematology at the Royal London Hospital and are indicated in Table 1. Normal ranges of ferritin, vitamin B12 and red cell folate had been established by testing a group of approximately 300 normal blood donors and the ranges for the FBC were those in common usage (Dacie and Lewis, 1984).

Blood for the estimation of serum vitamin B12 and serum ferritin was collected into Vacutainer© tubes, while samples for the measurement of red cell folate were collected into tubes containing 7.5% EDTA. Vitamin B12 and red cell folate were measured by radioassay using Quantaphase© 1 kits (Bio-Rad, California, USA). Ferritin was measured by immunoradiometric assay as described by Addison et al (1972) using a Quantimune kit© (Bio-Rad). Samples for the measurement of anti-α-gliadin IgG and IgA and anti-endomysial IgA were collected into plain tubes and the presence of the antibodies was determined by indirect immunofluorescence.

The general medical practitioners (GMPs) of those patients who had reduced haematinic levels on initial haematological investigation were informed by letter of these results. The patients were advised to attend their GMPs for appropriate investigation and supplementation of their condition. These patients were then reviewed approximately six months later. On review patients were asked about the investigations that had been carried out and whether their GMPs had established a cause for their deficiency state. Patients were asked if they felt that any change in ulcer pattern had occurred with supplementation and the degree of change was determined: complete cessation of ulceration, considerable improvement, slight improvement, no change, slight exacerbation or considerable exacerbation. Haematological investigations were repeated to determine if the reduced levels had been corrected.

## RESULTS

### *Patient Profile*

A total of 206 patients attended for assessment of which 197 suffered from RAS and fitted the inclusion and exclusion criteria. The remaining nine patients presented with lichen planus (3), speckled leukoplakia (1), homogeneous leukoplakia (1), denture-induced ulceration (1), burning mouth (1), a history suggestive of erythema multiforme (1) and geographic tongue (1). The RAS group consisted of 84 (42.6%) males and 113 (57.4%) females with a mean age (±S.D.) of 32.4

**Table 1 The investigations carried out in each patient and the normal range for each index**

| NORMAL POPULATION VALUES FOR HAEMATINIC INVESTIGATIONS | | |
|---|---|---|
| INVESTIGATION | POPULATION | NORMAL VALUES |
| White blood cell count (WBC) | Adult | 4.0-11.0×$10^9$/l |
| | Child 8-12 years | 4.5-13.5×$10^9$/l |
| | Child 4-7 years | 5.0-15.0×$10^9$/l |
| Red blood corpuscle count (RBC) | Male | 4.5-6.5×$10^{12}$/l |
| | Female | 3.8-5.8×$10^{12}$/l |
| | Child 3-12 years | 4.0-5.5×$10^{12}$/l |
| Haemoglobin (HgB) | Male | 13.0-18.0 g/dl |
| | Female | 11.5-16.5 g/dl |
| | Child 3-12 years | 11.5-14.5 g/dl |
| Haematocrit (Hct) | Male | 0.400-0.540 |
| | Female | 0.370-0.470 |
| | Child 3-12 years | 0.360-0.450 |
| Mean corpuscular volume (MCV) | Adult | 80-100 fl |
| | Child 3-12 years | 73-91 fl |
| Mean corpuscular haemoglobin (MCH) | Adult | 27.0-32.0 pg |
| | Child 3-12 years | 24.0-30.0 pg |
| Mean corpuscular haemoglobin concentration (MCHC) | Adult & Child | 30.0-35.0 g/dl |
| Serum vitamin B12 | Adult & Child | 200-900 ng/l |
| Serum ferritin | Adult & Child | >20 µg/l |
| Red cell folate | Adult & Child | 110-700 µg/l |

(±14.8) years (range 6-78 years). The majority (114, 57.9%) of the patients attended in response to poster canvassing within the Royal London Hospital and London Hospital Medical College; 13.2% (26) and 1% (2) attended after seeing the poster at their general dental practitioner's and GMP's surgeries respectively; 17.3% (34) were recruited from the oral medicine clinic and hospital staff members had referred the remaining 10.6% (21).

On the basis of the patient history and clinical examination, minor RAS was diagnosed in 97.0% (191) of patients according to the criteria proposed by Lehner (1969). Only 2.0% (4) and 1.0% (2) of patients suffered from major and herpetiform ulceration respectively.

**Table 2 The effect of decreased ferritin alone, vitamin B12 alone and ferritin and vitamin B12 combined on FBC parameters is shown. n = number of patients with each deficiency**

| Reduced Haematinic | n | ↓ RBC | ↓ HgB | ↓ Hct | ↓ MCV | ↓ MCH | ↓ MCHC |
|---|---|---|---|---|---|---|---|
| Ferritin<10 µg/l | 16 | 1 | 1 | 6 | 0 | 2 | 0 |
| Ferritin 10-15 µg/l | 19 | 0 | 3 | 4 | 1 | 1 | 0 |
| Ferritin 16-19 µg/l | 13 | 0 | 2 | 3 | 0 | 0 | 0 |
| | | ↓ RBC | ↓ HgB | ↓ Hct | ↑ MCV | ↑ MCH | ↑ MCHC |
| Vitamin B12 alone | 2 | 0 | 0 | 1 | 0 | 0 | 0 |
| | | ↓ RBC | ↓ HgB | ↓ Hct | ↓/↑ MCV | ↓/↑ MCH | ↓/↑ MCHC |
| Ferritin & Vitamin B12 | 7 | 0 | 0 | 4 | 0 | 0 | 1↑ |

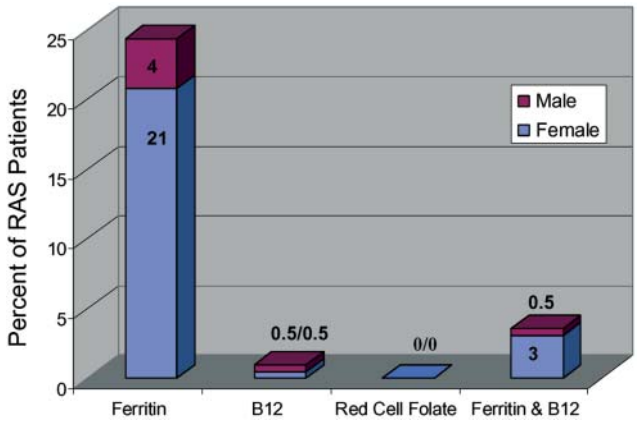


**Fig. 1** The proportion of RAS patients with reduced levels of haematinics. The purple part of the bars represents male patients and the blue part female patients. The numbers given over the bars are the numbers of male and female patients in each category. The total number of RAS patients was 197.

No patient suffered from Behçet's syndrome but 0.5% (1) of the patients had oro-genital ulceration. The oral ulceration in this patient was of the minor type.

### *Haematological Investigations*

In total 28.9% (57) of all patients investigated had reduced haematinic levels, of whom 84.2% (48) were female. The majority (55; 47 female, 8 male) of these had reduced ferritin levels (Fig. 1): 7.1% of all patients (14; 1 male, 13 female) had a ferritin level in the 16-19 μg/l range; 11.2% (22; 4 male, 18 female) had a ferritin level in the 10-15 μg/l range, and 9.6% (19; 3 male, 16 female) had a level less than 10 μg/l. 4.6% of all patients had a reduced serum vitamin B12 level, with 3.6% having a combined ferritin and vitamin B12 deficiency and only 1.0% having an isolated vitamin B12 deficiency (Fig. 1). Of those patients with a combined vitamin B12/ferritin deficiency, 1 had a ferritin level in the 16-19 μg/l range, 3 had a level in the 10-15 μg/l range and 3 had a level less than 10 μg/l. None of the 197 patients had a reduced red cell folate level (Fig. 1).

Most of the patients with reduced ferritin and/or vitamin B12 levels had no associated changes in their FBC and in those that did, the changes were usually slight (Table 2). Anaemia was present in 6/57 (10.5%) patients with a deficiency state, all of whom had ferritin deficiency. The parameter most frequently affected was the haematocrit, which was often the only change in the FBC. Not surprisingly red cell parameters were most frequently affected in the patients with the most reduced ferritin levels.

Two patients out of a total of 24 tested were positive for anti-α-gliadin IgG. However a repeat test several months later was negative in both these patients without the institution of a gluten-free diet. Neither of these patients or any of the other 22 patients tested were positive for anti-endomysial IgA.

### *Review of Patients with Reduced Haematinic Levels*

Of the total 57 patients in whom reduced haematinic levels were identified at initial assessment, 47 (82.5%) were available to attend for a review appointment.

Forty of the 48 patients who were deficient in ferritin alone were available for review; 37 patients had been prescribed iron supplementation and 1 other had adjusted her diet to include more foods rich in iron at the suggestion of her GMP. The remaining 2 had not attended their GMPs and had received no active treatment. 33 (82.5%) had ferritin levels within the normal range on review. A further 4 patients had dramatically improved levels although still marginally outside the normal range, while in 3 the levels were not increased. 5 patients were excluded from analysis of the effects of supplementation on RAS: those 3 whose level had not improved, 1 patient whose ulcer pattern had significantly improved with pregnancy and another whose ulcer episodes were too infrequent to assess the benefit of supplementation. Interestingly most patients had not been questioned by their GMPs about possible causes for their reduced ferritin levels. In those patients that were, the presumed reason was dietary lack in 3 patients and menorrhagia in 2 others. Three (a child, a post-menopausal woman, and a 37-year-old man) had been referred to hospital by their GMPs for investigations and in none of these was an underlying cause found.

Three patients (8.6%) were completely ulcer-free following supplementation, 15 (42.9%) reported considerable improvement, 10 (28.6%) reported slight improvement, and 7 (20%) reported no change in their ulcer patterns (Table 3). In no patient did supplementation result in worsening of ulcer pattern.

Only one of the two patients who had an isolated vitamin B12 deficiency was available for review and his level had been corrected with intramuscular vitamin B12 injections. Despite investigation no cause was elucidated. Supplementation resulted in considerable improvement in his ulcer pattern (Table 3). Of the seven patients with combined ferritin and vitamin B12 reduction, six were reviewed. However, both levels were now normal in only two of these. Four of these patients had been referred by their GMPs to a consultant gastro-

**Table 3 The response of ulcer pattern to correction of underlying reduced haematinic levels**

| Reduced Haematinic | Ulcer-free | Considerable improvement | Slight improvement | No change |
|---|---|---|---|---|
| Ferritin | 3 | 15 | 10 | 7 |
| Vitamin B12 | | 1 | | |
| Combined | | | | |
| Both corrected | 1 | 1 | | |
| Ferritin corrected | | 1 | 1 | |
| Vitamin B12 | | 1 | 1 | |

enterologist or haematologist and had undergone extensive investigations. These showed evidence of a malabsorption syndrome in only one patient but a jejunal biopsy excluded coeliac disease. Two other patients also had negative jejunal biopsies. A definitive diagnosis was not reached in any of these patients. The response of their ulceration to supplementation is indicated in Table 3.

## DISCUSSION

Of all patients assessed, 28.9% had an underlying deficiency state. It is interesting that such a high prevalence of haematinic deficiency was found in this largely self-referring population. The prevalence is higher than that found in other UK studies with one exception in which 37% of 75 patients referred to an oral medicine unit had low serum ferritin (Porter et al, 1993). Iron deficiency was the most common deficiency state affecting 27.9% of this study population, thus accounting for 96% of all deficiencies. Challacombe et al (1983) reported that 8.5% of 105 patients with RAS had reduced serum ferritin levels. In their study serum ferritin less than 15 μg/l in females and less than 20 μg/l in males was considered reduced while in this study all patients with levels less than 20 μg/l were regarded as iron deficient regardless of gender. However if the criteria of Challacombe et al (1983) had been used in this study, the prevalence of iron deficiency would have been 21.3%, which is still considerably higher than in their RAS population. In two Bristol studies the prevalence of iron deficiency in RAS, as determined by serum ferritin, was 11.6% in 1988 and 37% in 1993 but the normal reference values used were not indicated so direct comparison is not possible (Porter et al, 1988; Porter et al, 1993). This study and the study of Porter et al (1993) suggest that the prevalence of iron deficiency in RAS may be increasing.

Of all patients, 3.5% were vitamin B12 deficient, a prevalence similar to that of other UK studies (Wray et al, 1975; Hutcheon et al, 1978; Porter et al, 1988; Porter et al, 1993). Most previous studies have reported that iron, folate and vitamin B12 deficiencies occur in this decreasing order of frequency (Wray et al, 1975; Challacombe et al, 1977; Hutcheon et al, 1978; Tyldesley, 1983; Field et al, 1987; Porter et al, 1993). However an interesting finding in this study was that none of the patients was folate deficient. The reason for the lack of folate deficiency in this group is unknown but may be related to an increasing awareness in the general population of the importance of an adequate intake of green vegetables, which are folate-rich as a part of a balanced diet. If so, this finding is unlikely to be specific to this study as East London is not an affluent area. An increase in vegetarianism may also contribute, but only 5.1% of the RAS patients were vegetarians.

Most studies exploring haematinic deficiency in RAS have been carried out in the UK. Two studies carried out in the USA showed markedly different prevalence rates. One disputed the role of deficiency states in RAS showing a prevalence of just 3% (Olson et al, 1982) while the other had a very high prevalence of 37% (Rogers and Sutton, 1986). The response to supplementation was not determined in either study. In recent years two studies have been carried out in mainland Europe, the results of which conflict with this and other UK studies. The earlier of the two was carried out in Spain and found that folic acid deficiency was the commonest deficiency in 80 RAS patients (Barnadas et al, 1997). A more recent study from Turkey has conflicted with this and other studies, in that Vitamin B12 deficiency was the most frequently found haematinic deficiency (Piskin et al, 2002). In both studies serum folate was measured, and not red cell folate, and in the Spanish study serum iron, and not ferritin, was measured which makes comparison with this study difficult. However, the prevalence of vitamin B12

deficiency is much higher than seen in this and other UK studies. Unfortunately, the reason for B12 deficiency was not determined in these patients, nor was the response to supplementation.

Iron and vitamin B12 deficiency often occurred in the absence of changes in the FBC in this study and only 10.5% of those with deficiency (3% of total study population) had associated anaemia, all of whom had iron deficiency. This confirms the necessity for specific haematinic screening in RAS (Hutcheon et al, 1978; Tyldesley, 1983). One patient with mild iron deficiency anaemia had angular cheilitis but no other patient with haematinic deficiency had other oral signs and symptoms. This is contrary to a previous study in which both angular cheilitis and glossitis occurred with a prevalence of 21% in RAS patients with deficiencies (Hutcheon et al, 1978).

The response to supplementation was assessed in 82.5% of those who had deficiency states. In many earlier studies patients have been managed in collaboration with medical or haematology hospital units and consequently have been thoroughly investigated (Wray et al, 1975; Challacombe et al, 1977; Hutcheon et al, 1978). This study differed in that patients were referred to their GMPs for management of their deficiencies, which may reflect routine procedure better. It was surprising how few iron deficient patients were questioned by their GMPs about possible causes of their deficiency. However, two thirds of the patients with combined iron and vitamin B12 deficiencies were referred by their GMPs for hospital management. A definitive diagnosis was not made in any of these patients but one showed evidence of a malabsorption syndrome. Treatment regimes differed between GMPs and patients had repeat haematological investigations on review to ensure that the deficiency state had been corrected.

Of the reviewed patients, 23% still had haematinic values below the normal range. Very few patients (9.5% of those reviewed) had complete remission following supplementation but 73.8% of the reviewed group experienced some improvement; 16.7% of those reviewed, all of whom had iron deficiency, reported no benefit but none reported worsening of their ulceration. This response is similar to that found in some previous studies (Challacombe et al, 1983; Porter et al, 1992) although the proportion who had complete remission was less than that in other studies (Wray et al, 1975; Hutcheon et al, 1978; Rogers and Sutton, 1986). This is probably because the patients were predominantly iron deficient and RAS associated with iron deficiency appears to be less responsive to replacement therapy than folate or vitamin B12-associated RAS (Wray et al, 1975; Challacombe et al, 1977). As this was an open trial, it is important to bear in mind the high placebo effect in RAS trials but the proportion of patients that benefited far exceeded the expected placebo effect (Donatsky et al, 1983). There are obvious ethical problems in carrying out a placebo-controlled trial in these circumstances. It is important to bear in mind that any improvement with supplementation may be only temporary and it would be interesting to reassess these patients 1-2 years following cessation of supplementation. An additional factor that is impossible to control is the natural course of RAS. In many patients it is a self-limiting disease and a proportion of these patients may have had an improvement in ulcer pattern in the intervening period between initial assessment and review without supplementation. Furthermore this and previous studies have been dependent on patient recollection of ulcer pattern prior to supplementation. Completion of ulcer diaries both before and after supplementation may be preferable in assessing possible benefits, although it has the drawback of delaying the institution of replacement therapy.

The mechanisms by which haematinic deficiencies predispose to RAS are still unclear. Vitamin B12 and folic acid are important in DNA synthesis and their deficiency affects red blood cell production initially but then affects other dividing cells. Oral epithelium is atrophic in patients with haematinic deficiency (Jacobs, 1961) sometimes manifesting as glossitis (Hutcheon et al, 1978; Tyldesley, 1983). Thinning of the epithelium is likely to make it more vulnerable to trauma and to enhance penetration of exogenous antigens, which may be implicated in RAS. However one study has demonstrated normal DNA content of oral epithelium in vitamin B12 and folate deficiency which was unaltered by correction of the deficiency state (Atkin et al, 1962). Reversible defects in cell mediated immunity have been reported in iron deficiency both in the presence and absence of anaemia (Joynson et al, 1972; Chandra, 1976). These defects include reduced T lymphocyte number, reduced lymphocyte transformation in response to mitogen stimulation and depressed delayed-type hypersensitivity reactions, and it is possible that they may play a role in the pathogenesis of RAS. Impairment of the metabolic activity and bactericidal ability of neutrophils also occurs and it has been suggested that this is because iron is a co-factor in leucocyte enzymes (Chandra, 1976). Depletion of iron-containing enzymes has been well-documented in iron deficiency (Dagg et al, 1966; Jacobs, 1969).

Serological screening for coeliac disease was confined to those who were perceived to be most likely to have the disease, i.e., children under 12 years of age

and older patients with any bowel symptoms, but it was not identified in any of the 24 patients tested. The target autoantigen for endomysial antibodies has been identified as the enzyme tissue transglutaminase (Dieterich et al, 1997), so in many centres enzyme-linked immunosorbent assay detection of anti-tissue transglutaminase has replaced anti-endomysial antibody testing. Three of the patients with dual deficiencies had jejunal biopsies, which were negative. Folate deficiency is commonly detected in coeliac disease and, in this context, it is interesting to note that no patients in this series were folate deficient

Testing for coeliac disease in RAS is a matter of some debate. It may be that serological testing for coeliac disease should only be done in those patients where folate and/or iron deficiency has been identified and in those with bowel symptomatology. However, a degree of caution is required as it appears that coeliac disease is often silent and is more common than previously thought with a prevalence of 0.5-1% (Green and Jabri, 2003; McLoughlin et al, 2003), resulting in calls for mass population screening (Fasano, 2003). Therefore the role of serological testing for coeliac disease in RAS requires further elucidation.

## SUMMARY

This study found that the prevalence of haematinic deficiency in a large cohort of RAS patients, the majority of whom were not attending an oral medicine clinic, was high (28.9%). In general these results corroborate the findings of previous investigations although folic acid deficiency and coeliac disease were not identified in any patients in this study. The response to haematinic supplementation varied considerably among patients. While the majority experienced some improvement in their pattern of ulceration, some had complete resolution. This study also confirmed the benefit of performing specific investigations for haematinic deficiencies, particularly iron and vitamin B12 deficiency, and correcting these as part of the management of RAS.

## ACKNOWLEDGEMENT

This research was supported by Unilever Dental Research.

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