

Hospital Topics

Recurrent Aphthae: Treatment with Vitamin B₁₂, Folic Acid, and Iron

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Summary

A series of 130 consecutive outpatients with recurrent aphthous stomatitis were screened at the oral medicine department, Glasgow Dental Hospital, for deficiencies in vitamin B₁₂, folic acid, and iron. In 23 patients (17.7%) such deficiencies were found; five were deficient in vitamin B₁₂, seven in folic acid, and 15 in iron. Four had more than one deficiency. Out of 130 controls matched for age and sex 11 (8.5%) were found to have deficiencies.

The 23 deficient patients with recurrent aphthae were treated with specific replacement therapy, and all 130 patients were followed up for at least one year. Of the 23 patients on replacement therapy 15 showed complete remission of ulceration and eight definite improvement. Of the 107 patients with no deficiency receiving local symptomatic treatment only 33 had a remission or were improved. This difference was significant ($P < 0.001$). Most patients with proved vitamin B₁₂ or folic acid deficiency improved rapidly on replacement therapy; those with iron deficiency showed a less dramatic response.

The 23 deficient patients were further investigated to determine the cause of their deficiencies and detect the presence of any associated conditions. Four were found to have Addisonian pernicious anaemia. Seven had a malabsorption syndrome, which in five proved to be a gluten-induced enteropathy. In addition, there were single patients with idiopathic proctocolitis, diverticular disease of the colon, regional enterocolitis, and adenocarcinoma of the caecum.

We suggest that the high incidence of deficiencies found in this series and the good response to replacement therapy shows the need for haematological screening of such patients.

Introduction

Recurrent oral ulceration, unlike glossitis and angular cheilitis, seems to occur infrequently in association with deficiencies of iron, folic acid, and vitamin B₁₂. It has also been reported in patients with idiopathic steatorrhoea, though again glossitis is more common.^{1,2} In such cases it may be difficult to establish whether the oral lesions are directly due to the underlying disease or simply reflect co-existing deficiencies.

We have examined the relationship between recurrent aphthae, specific haematological deficiency, and malabsorption in 130 patients presenting consecutively at the oral medicine clinic at Glasgow Dental Hospital during the past five years. Our findings and the patients' response to treatment are reported here.

Patients and Methods

The 130 patients had suffered from recurrent oral ulceration of the aphthous type for periods of six months to 30 years. Their ages ranged from 8 to 83 years (mean 38.2 years); 78 were female (mean age 40 years) and 52 male (mean age 35.6 years) (table I).

TABLE I—Age and Sex Distribution of 130 Patients with Recurrent Aphthae

	Age (years):										Total
	-9	-19	-29	-39	-49	-59	-69	-79	-89		
Males ..	1	6	18	7	12	4	3	1	0	52	
Females ..	1	9	25	10	9	8	8	6	2	78	
Total	2	15	43	17	21	12	11	7	2	130	

The diagnosis was made from the clinical appearance and the history using the criteria of Lehner.³ The ulcers were typically 1-4 mm in diameter, with a grey base and a regular erythematous margin. Healing usually occurred in 3-21 days. The ulcers were present continuously or with varying periods of remission and occurred singly or in crops. Patients with bullae, traumatic ulcers, acute ulcerative gingivitis, herpes simplex and zoster, erythema multiforme, Reiter's syndrome, Behçet's syndrome, and other such conditions were excluded, as were those whose condition was related to the menstrual cycle.

A group of 130 controls matched for age and sex was obtained from patients attending Glasgow Dental Hospital for routine treatment.

HAEMATOLOGICAL STUDIES

Venous blood was taken from each of the patients and controls at two consecutive clinic visits. The serum iron and total iron-binding capacity (T.I.B.C.) were measured by an automated method.⁴ A consistent iron saturation of the T.I.B.C. of less than 16% was regarded as indicating iron deficiency.⁵ The serum folate and, later, the whole blood folate were measured using a technique modified

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from that of Waters and Mollin.⁶ Folic acid deficiency was diagnosed when the serum folate was less than 2.5 µg/l or the whole blood folate was less than 80 µg/l. Serum vitamin B₁₂ was assayed using *Euglena gracilis*,⁷ values consistently below 120 ng/l being regarded as abnormal. Routine haematological measurements and blood film examinations were performed using standard methods.⁷

Patients found to have iron, folic acid, or vitamin B₁₂ deficiency were investigated further by A.W.H. and J.H.D. to determine the cause of the deficiency and initiate treatment. Malabsorption was diagnosed when the faecal fat exceeded 5 g daily, when the serum xylose two hours after a standard oral dose related to body weight was less than 2.0 mmol/l (30 mg/100 ml), and when intestinal clumping of barium was seen on follow-through examination. In two patients with malabsorption intestinal biopsy failed for technical reasons; in another five cases, diagnosed as adult coeliac disease, intestinal biopsy confirmed the presence of subtotal villous atrophy. A clinical response followed the introduction of a gluten-free diet in these patients. Pernicious anaemia was diagnosed on the basis of blood and bone marrow findings, histamine-fast achlorhydria, the presence of gastric parietal cell antibodies, a characteristic Schilling test result,³ and a therapeutic response to vitamin B₁₂.

TREATMENT

Patients with vitamin B₁₂ deficiency were given 1000 µg hydroxocobalamin intramuscularly followed by a further 1000 µg every two months. Folic acid was taken by mouth in doses of 5 mg thrice daily during follow-up. Iron was also taken only by mouth and given continuously for at least six months. During treatment all patients used a zinc chloride/zinc sulphate mouthwash (*B.P.C.*). Triamcinolone 0.1% in dental paste (*B.P.C.*) or hydrocortisone lozenges (*B.P.C.*) were also used for symptomatic relief.

In assessing the response to treatment, complete absence of ulcers for at least one year after treatment constituted a remission, and only occasional ulcers after treatment (one to six a year) constituted a definite improvement.

Results

HAEMATOLOGICAL DEFICIENCIES

Altogether 23 patients with recurrent aphthae (17.7%) were found to be deficient in iron, vitamin B₁₂, or folic acid compared with 11 (8.5%) of the controls. This difference was significant ($P < 0.025$). Of the 23 patients 15 were deficient in iron (four having iron deficiency anaemia and 11 iron deficiency without anaemia), seven in folic acid (four showing the characteristic morphological changes in blood and bone marrow and three showing no such changes), and five in vitamin B₁₂ (all with evidence of megaloblastic change in the bone marrow but two having apparently normal peripheral blood). Four patients had more than one deficiency (table II).

Of the 11 deficient controls, seven were deficient in iron, only one showing overt anaemia. Three had reduced blood folate levels and one had latent Addisonian pernicious anaemia. No control had more than one deficiency. Thus iron and folic acid deficiencies were over twice as frequent in the patients as in the controls, and vitamin B₁₂ deficiency was five times more common in the patients than in the controls.

RESPONSE TO TREATMENT

Fifteen of the 23 patients (65%) showed complete remission and eight (35%) definite improvement. Of the remaining 107 non-deficient patients, who received only local treatment, 12 (11%) had a complete remission and 20 (19%) were improved. Only 30% of the non-deficient patients, therefore, showed a response comparable to that of the 23 deficient patients ($P < 0.001$).

Four of the five patients with vitamin B₁₂ deficiency were promptly relieved of symptoms and remained free of ulcers during follow-up; the fifth was definitely improved (table III). Of the seven patients with folic acid deficiency, six were completely relieved of ulcers and remained symptom-free during follow-up and one was much improved. Of the 15 patients with iron deficiency, eight showed remission and seven were definitely improved after iron therapy. Three of

the iron-deficient patients had co-existing folic acid deficiency, however, and one had ascorbic acid deficiency; they had received folic acid and ascorbic acid respectively with remission of symptoms before iron therapy was instituted. In addition, one iron-deficient patient underwent resection of a caecal adenocarcinoma. Of the remaining 10 patients with uncomplicated iron deficiency, five were cured and five definitely improved with iron replacement alone (table III).

TABLE II—Deficiencies Found in 23 Patients with Recurrent Aphthae

Case No.	Age	Sex	Iron Deficiency	Folic Acid Deficiency	Vitamin B ₁₂ Deficiency
1	32	F.		+	
2	60	M.		(+)	
3	18	M.	(+)	+	
4	75	F.		(+)	(+)
5	50	F.	(+)	+	
6	37	F.	(+)	(+)	
7	68	F.	(+)		
8	83	F.	(+)		
9	28	F.		+	
10	48	M.			+
11	68	F.			+
12	30	F.			+
13	13	M.	(+)		
14	65	F.	+		
15	31	M.	(+)		
16	71	M.	(+)		
17	31	M.	(+)		
18	57	F.			(+)
19	13	F.	+		
20	72	F.	+		
21	47	F.	(+)		
22	79	F.	+		
23	20	F.	(+)		
Total			15	7	5

Symbols in parantheses in this and tables III and IV indicate latent deficiency—that is, deficiency without anaemia or detectable blood film abnormality.

TABLE III—Response to Replacement Therapy

Case No.	Iron Deficiency	Folic Acid Deficiency	Vitamin B ₁₂ Deficiency	Remission	Marked Improvement
1		+		+	
2		(+)		+	
3	(+)	+		+	
4		(+)	(+)	+	
5	(+)	+		+	
6	(+)	(+)		+	
7	(+)			+	+
8	(+)			+	+
9		+		+	
10			+	+	
11			+	+	
12			+	+	
13	(+)			+	
14	(+)			+	
15	(+)			+	
16	(+)			+	+
17	(+)			+	+
18			(+)	+	+
19	+			+	+
20	+			+	+
21	(+)			+	+
22	+			+	+
23	(+)			+	+

AETIOLOGY OF DEFICIENCIES

We attempted to define with greater accuracy the cause of the deficiencies in the 23 patients (table IV). Seven (30%) were shown to have a malabsorption syndrome, which in five proved to be adult coeliac disease (gluten enteropathy). In addition, four patients were found to have Addisonian pernicious anaemia, one was found to have idiopathic proctocolitis, one had diverticular disease of the colon, one had Crohn's disease (regional enterocolitis), and one had an adenocarcinoma of the caecum.

ROLE OF LOCAL TREATMENT

All 130 patients were given local symptomatic treatment. Most received a zinc chloride/zinc sulphate mouthwash (*B.P.C.*) and were given topical steroids if this proved ineffective. Though steroids are beneficial,^{9, 10} clinical improvement continues only if treatment is maintained,¹¹ and in no case have the ulcers been eradicated.¹² In

this series when a patient was given specific replacement therapy such local treatment was stopped. Any lasting clinical improvement seen in the 23 deficient patients was thus unlikely to have resulted from local treatment.

TABLE IV—Associated Conditions in Patients with Deficiencies

Case No.	Iron Deficiency	Folic Acid Deficiency	Vitamin B ₁₂ Deficiency	Associated Condition
1		+		Malabsorption, adult coeliac disease
2		(+)		Malabsorption
3	(+)	+		Malabsorption, adult coeliac disease
4		(+)	(+)	Malabsorption, adult coeliac disease
5	(+)			Malabsorption, adult coeliac disease
6	(+)	(+)		Malabsorption
7	(+)			Diverticular disease of colon
8	(+)			Adenocarcinoma of caecum
9		+		Malabsorption, adult coeliac disease
10			+	Pernicious anaemia
11			+	Pernicious anaemia
12			+	Pernicious anaemia
13	(+)			Latent iron deficiency
14	+			Iron deficiency anaemia
15	(+)			Latent iron deficiency
16	(+)			Crohn's disease
17	(+)			Idiopathic proctocolitis
18			(+)	Latent pernicious anaemia
19	+			Iron deficiency anaemia
20	+			Ascorbic acid deficiency
21	(+)			Latent iron deficiency
22	+			Iron deficiency anaemia
23	(+)			Latent iron deficiency

Discussion

In all but three of the 23 deficient patients oral ulceration was the only presenting complaint, and the underlying haematological abnormality or gastrointestinal disease was found only on further investigation. Of the other three patients, one had been known to have idiopathic proctocolitis for three years, one had Crohn's disease, and the third had a history of treatment for coeliac disease in childhood; even in these cases the clinical picture was dominated by oral ulceration. In most cases, therefore, associated haematological deficiency or gastrointestinal disease would have remained unsuspected without further investigation. Indeed, many of the deficiencies were themselves latent (table II)—that is, they had produced no recognizable abnormalities in the peripheral blood; screening by peripheral blood examination alone would have been thus insufficient to detect an underlying abnormality in these patients.

Deficiency of vitamin B₁₂ is not generally recognized as a cause of recurrent aphthae, though isolated cases have been reported.¹³⁻¹⁴ Four patients with Addisonian pernicious anaemia, one at the latent stage, were diagnosed in this series. A fifth patient had slight vitamin B₁₂ deficiency associated with adult coeliac disease, though his main deficiency was in folic acid. Other causes of vitamin B₁₂ deficiency were not found. In the patients with pernicious anaemia there was a particularly striking response to treatment; three had permanent remissions after replacement and one had marked improvement.

Folic acid deficiency as a cause of recurrent aphthae is not generally accepted, though several cases of folic acid deficiency with oral ulceration have been reported.¹⁵⁻¹⁹ Isolated cases of idiopathic steatorrhoea with oral ulceration have also been reported.²⁻¹¹ Farmer²⁰ found folic acid ineffective for treating unselected cases of recurrent aphthae, and Sircus *et al.*²¹ also found folic acid of no benefit in (five or six) randomly selected patients with ulcers. There were seven patients with folic acid deficiency in this series, all associated with underlying malabsorption states, mostly adult coeliac disease. Folic acid replacement alone produced a complete cure in five of these and a marked improvement in two. In one of the two patients who had had recurrent aphthae for 30 years complete cure did not occur with replacement therapy alone but promptly followed the institution of a gluten-free diet (case 2, table IV).

The dramatic response to vitamin B₁₂ and folic acid in those patients in whom such a deficiency was adequately shown suggests a direct role for these substances in the pathogenesis of recurrent

apthae. The role of iron deficiency is much less clear, though recurrent ulceration has been described rarely among the oral manifestations of iron deficiency.²² Eleven patients with latent iron deficiency and four with overt iron deficiency anaemia were diagnosed in this series. In four of these patients co-existing deficiencies were present, and treatment of these rather than iron therapy was probably responsible for the clinical improvement. A further patient with iron deficiency improved after resection of an adenocarcinoma of the caecum. Of the remaining 10 patients with uncomplicated iron deficiency, five had a complete remission and five markedly improved; the poorer response of the iron-deficient patients to specific replacement therapy may reflect the greater difficulty in reconstituting body stores with iron as compared with replacement of folic acid and vitamin B₁₂. Indeed, three of these 10 patients still had a saturation of the T.I.B.C. in the iron-deficient range after several months of iron therapy.

The 23 deficient patients on replacement therapy showed a significantly better response to treatment than the 107 patients without such deficiencies. These 130 patients, however, may not have been representative of all patients with recurrent aphthae. Hospital patients tend to have severe recurrent oral ulceration and to have been referred because they presented a problem in management to their general dental or medical practitioners. Possibly, therefore, the prevalence of underlying disorders in an unselected group of patients with recurrent oral ulceration would be lower than in this series. Interestingly, however, the age and sex distribution of our patients was closely similar to the series of hospital outpatients with recurrent aphthae described by Sircus.²¹

Isolated cases of steatorrhoea associated with recurrent aphthae have been reported.²⁻¹¹ In our series, the incidence of malabsorption and gluten enteropathy was strikingly high—5.3% of the whole series and 30.3% of the group with proved haematological deficiencies; the estimated prevalence of coeliac disease in central Scotland is only 0.054%.²³ Apart from one patient who was known to have had coeliac disease in childhood, this diagnosis was unsuspected before investigation. In most cases the ulcers responded to replacement therapy alone, though in one (case 2) complete cure did not occur until a gluten-free diet was instituted.

Oral ulceration is associated with various gastrointestinal disorders, especially Crohn's disease, ulcerative colitis, and idiopathic proctocolitis.²⁴⁻²⁸ In this series, Crohn's disease (case 16) and idiopathic proctocolitis (case 17) were diagnosed before the appearance of recurrent aphthae, though the latter dominated the clinical picture; both patients responded well to iron therapy. Case 8 was an elderly woman who presented with recurrent aphthae and was found to be iron deficient. Physical examination showed a mass in the right iliac fossa, subsequently confirmed to be an adenocarcinoma of the caecum. Removal of the lesion and iron treatment brought about a definite improvement in the ulcers.

The precise role of iron, vitamin B₁₂, or folic acid deficiency in the pathogenesis of recurrent aphthae is speculative. Though atrophic glossitis and angular stomatitis have long been recognized as complications or iron deficiency, attempts to correlate these changes with depletion of iron enzymes such as cytochrome oxidase in buccal mucosa have been unsuccessful.²⁹⁻³⁰ Iron enzyme studies in recurrent aphthae will be reported later.

Defects of cell-mediated immunity have recently been reported in iron-deficient patients,³¹⁻³² but attempts to show infection as a fundamental cause of aphthae have not been convincing.

The oral ulceration which occurs with folic acid antagonist drugs such as methotrexate is also well recognized and responds to topical folic acid; interestingly, Dreizen *et al.*¹⁹ induced oral ulceration in marmosets by feeding them a diet free of folic acid though changes in the cells of the tongue and buccal mucosa analogous to those found in the blood and bone marrow have been reported in vitamin B₁₂ deficiency.³³⁻³⁶ The DNA content of buccal mucosal cells, however, has been found to be

normal³⁷ and it is uncertain by what precise mechanism deficiency of vitamin B₁₂ may be implicated in the pathogenesis of recurrent aphthae. It seems clear from our study, however, that treatment of demonstrable deficiencies of folic acid or vitamin B₁₂ is likely to result in a permanent cure of such ulcers; the role of iron seems less well defined.

It was not possible by clinical examination of the ulcers to separate patients with an underlying deficiency or disease from those with no such abnormality. Our findings, therefore, have significant implications for the management and treatment of patients with recurrent aphthae. Since there is a one in five chance of patients with persistent recurrent aphthae having some form of haematological deficiency or malabsorption syndrome, all patients presenting in this way should undergo haematological screening.

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Letter from . . . South Australia

Birth Pangs of Medibank

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Medibank is the major excitement on the medical scene. It is the strange name of the new health service funded from government taxes. The new system will begin on 1 July but such are the complexities of Australian government and politics that, though Medibank will begin on that day, it will only be effective in South Australia, Tasmania, and Queensland. The first two have Labour governments in tune with the federal government of Mr. Gough Whitlam, and Queensland has a fiery premier who does not like the central government, but who is willing to take any generosity which is handed out to his state. The states with the largest populations, New South Wales, Victoria, and Western Australia, have not yet decided whether to join the national scheme. There have been political cries for rejecting the scheme outright, and one or two of the leaders of the opposition parties have tentatively tried to use the issue to force a general election.

Mr. Whitlam has let it be known that he would be delighted to accept this particular challenge. He is sure he would win. Nevertheless, he does not want an election at all and wishes to run his full term. The last election was not long ago, and though the people appear to be heartily sick of the national state politicians with their posturings, vapourings, and attempts to drum up causes for no other purpose than to harass their opponents, there seems to be no desire to go through all the paraphernalia of an election this year. Meanwhile, there is the usual anxiety that the politicians fiddle as the country rushes to perdition, mainly because of inflation.

The present system of health care is essentially one in which the patient pays the doctor on a fee-for-item-of-service basis. The doctor can charge what he likes, but usually sticks to the rates agreed nationally. The patient pays the fee, and if he is insured he can recover almost all of it. The insurance funds are separate from those of government. They function well for those who can afford to insure. The rates of premium are flat ones, and they cover whole families, or only a single person. The poorer sections of the community, therefore, inevitably pay a larger percentage of their disposable income in health insurance than the richer. And the Medibank advertising stresses that over one million people in the country are not covered by health insurance. They gamble on remaining healthy, for if they fall ill they may have to face enormous bills. Even if they go into hospital to avoid paying a general practitioner's fee they still have to pay

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