Cases of psoriasis improved by lowering homocysteine using 4-7 mg folic acid, vitamins B6 and B12 previously worsened using 1-2 mg daily folic acid, B6 and B12 folic acid

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Abstract
The daily intake of FA of 5% Americans age 50 and over and in one study of psoriatic American women is about 1 mg. A patient with plaque psoriasis on 10 mg lisinopril did not improve on vitamins B12 and B6 alone. When folic acid 5 mg daily was added PASI improved 50%. Three cases of plaque psoriasis flared when given 1-2 mg folic acid (FA), 100 mg vitamin B6 and 1000 mcg daily B12. When daily FA was increased to 4 to 7 mg daily all three cases improved their disease.

Introduction
Homocysteine (Hcy) affects neutrophil activity increasing superoxide release, IL-8 mRNA and growth related oncogene alpha causing reduction in spontaneous neutrophil apoptosis [1]. Hcy also increases intracellular H2O2 production by neutrophils and neutrophil migration [2,3]. Hcy reduces endothelial nitric oxide synthase causing endothelial dysfunction [4,5]. Five mg Folic acid week 1 followed by 1 mg for the next 3 weeks given to patients with plasma Hcy over 15 umol/L reduces chemokines from mononuclear cells [6]. Plasma Hcy correlates directly and FA levels inversely with psoriasis area and severity index (PASI) [7]. Plasma folic acid levels inversely correlate with PASI [8].

Homocysteine can be lowered by 1mg folic acid 500 mcg vitamin B12 and as little as 10 mg daily vitamin B6 over a 12-week period [9]. Other studies however use vitamin B6 at 100 mg daily [10].

A past study showed no benefit treating psoriasis with 6 weeks of twice daily FA 5 milligrams (mg) and 1-2000 micrograms (mcg) B12 [7]. We, however, have published case reports where FA (5-6 mg daily) with vitamins B6 (100 mg daily) and B12 (1000 mcg daily) improves psoriasis in two alcoholics and clears palmar plantar pustulosis, a disorder genetically related to some psoriasis through the CARD14 gene [11,12]. CARD14 mutations are associated with palmar plantar psoriasis through activation usually of NF-Kappa B. CARD 14 is found on epidermal keratinocytes as well as dermal cells [13,14]. Anti-inflammatory doses of folic acid reduce NF-kappaB [15]

In our study where 12 weeks of United States Pharmacopeia (USP) approved or NSF International certified [16,17] of daily 5mg FA, B6 and B12 were added to patients already on 16 weeks of adalimumab 4 of 7 subjects continued to improve, but 2 of 7 patients’ psoriasis worsened, and 1 did not change. Both patients who worsened initially has very high serum vascular endothelial nitric oxide synthase levels [18].

I present one psoriasis patient on lisinopril 10 mg daily who did not respond to vitamins B12 and B12 but who was improved when folic acid was added. Three psoriasis patients are then presented with elevated homocysteine who flared on FA 1-2 mg daily. These three subsequently improved with daily folic acid 4-7 mg, plus vitamin B12 1000 mcg and vitamin B6 100 mg.

Case reports
Case 1
Self-experimentation can lead to biased interpretations [19], but when good and ill comes from such experience, bias should be balanced if not minimized.

A 55-year-old man weighed 87 kilograms (kg) and had stage 3 chronic kidney disease. His psoriasis appeared initially at age 23. It had not been controlled using clobetasol ointment and calcipotriene cream (Figure 1). Fasting plasma homocysteine was 15.8 micromoles per liter (umol/L) (normal 4-14umol/L). Increasing to 16.9 and PASI 11.3 between weeks 4 and 9 (Figure 2).

Five mg FA was later discovered to be needed to lower hyperhomocysteinemia in patients with predialysis chronic renal failure [21]. Oral FA was increased from 5 then to 7-8 mg with B6 100 mg, B12 1000 mcg daily and, for 2 weeks, resveratrol at 10-37.5 mg

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81-year-old 90 kg, white male with psoriasis has a history of malignant melanoma in situ, other skin cancers and a cardiac stent. His homocysteine was slightly elevated (12.1 umol/L). He was on Lisinopril 10 mg daily. He had no response to topical medications alone. During the subsequent 8-week period and still on 10 mg, daily Lisinopril adding folic acid 5 mg to vitamin B12 and vitamin B6l resulted in week 3 BSA 7.7% falling to week 11 BSA 4.5% with improvement in lesion thickness and scale (PASI 50) (Figures 8 and 9). This response was not noticed by the patient except that his itching was reduced.

Case 3

A 40-year-old 60 kg man had psoriasis was on maintenance phototherapy with over 18 treatments of narrow band ultraviolet B phototherapy (nb-UVB) and calcipotriene 0.005% -betamethasone dipropionate 0.064% ointment. Hcy was 15.1 umol/L (normal 4 to 14 umol/L). His body surface area (BSA) involvement was 1.5 percent (%). Still on nb-UVB, he was told to take the 3 B vitamins but he took 1 mg FA daily plus B6 (100 mg) And B12 (1000 mcg). His psoriasis flared 10 weeks later (5% BSA).

Over the next 6 weeks on 4 mg FA his BSA improved 22%.

Case 4

This man was 56 years old, weighed 104 kg, and was 67 inches tall. He had diffuse plaque psoriasis despite a trial of NB-UVB and then alefacept. On week 13 of alefacept with Hcy 17 umol/L (normal 4-14 umol/L ) he was begun on daily FA 1 mg, B6 (100 mg) and B12 (1000 mcg). He was also on calcipotriene 0.005% - betamethasone dipropionate 0.064% ointment and tacrolimus 0.1% ointment. After 16 weeks of alefacept, his BSA was still 15-20%. Seven weeks off alefacept but still on the 3 B vitamins, his BSA was 28%.
Etanercept 50 mg twice weekly was begun with daily FA 1 mg, B6 and B12 added. Four months later his psoriasis BSA was 4.8%. He required aspirin 325 mg three times daily for joint pain. Ten months after starting etanercept and aspirin and still on 50 mg once weekly and for the next year he had 1% BSA involved. His weight had increased to 250 pounds. Six months later his joint pain worsened and his psoriasis has increased to 3% BSA. Shortly thereafter had a respiratory infection with etanercept held for 1 month, restarted one month later and then held for 3 months. When etanercept was again started, topical clobetasol ointment was also started. His legs and buttocks had larger plaques with scattered trunk and arm plaques as well. His weight was 247 pounds. When seen two months later Ibuprofen 800 mg daily to twice daily had been added along with colchicine 0.6 mg bid for joint pain rethought as secondary to gout. FA had been increased to 2000 mcg daily. BSA had increased to 9% BSA. Three weeks later while ibuprofen and colchicine were continued, his FA was increased to 5 mg daily. Twenty weeks later his psoriasis had almost cleared (BSA 0.1%) (Figure 10).

**Comment**

Regulatory T (TReg) cells expressing the transcription factor forkhead box P3 (Foxp3+ cells) are naturally present in the immune system. They are indispensable for the maintenance of dominant self-

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**Figure 6.** After Lisinopril 2.5 mg on 5 mg FA, B6 and B12.

**Figure 7.** After Lisinopril 2.5 mg on 7 mg FA, B6 and B12.

**Figure 8.** Patient 2. Before vitamins.

**Figure 9.** Patient 2 on vitamins.

**Figure 10.** Patient 4 BSA on alefacept and then on etanercept.
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Vascular endothelial growth factor (VEGF) is elevated in models of psoriasis [42]. Patients with severe psoriasis and those with onset of psoriasis between the ages of 20 and 40 are thought to have elevated plasma levels of VEGF, VEGF alleles and VEGF receptors [42]. In our study where 5 mg FA, 100 mg B6 and 1000 mcg B12 daily was added to adalimumab for 16 weeks [18], Adalimumab alone caused all study patients to lower their VEGF. The addition of the B vitamins caused mild rise in VEGF. Two of three patients with high baseline VEGF (147 and 259 pg/ml) and who had BMIs of 23 and 24.9 (and thus less leptin to stabilize the anti-inflammatory activities of coupled eNOS) flared their psoriasis when 5 mg FA, B6 and B12 were added. One of these patients also developed H. pylori antibodies which may have prevented full ingestion of the B vitamins causing the dosing to possibly promote uncoupled eNOS [43]. One patient in this same study had his Hcy increase while on the B vitamins and despite his high initial VEGF his psoriasis continued to improve on adalimumab [12]. In vitro Hcy reduces expression of VEGF-A and VEGFR [44]. Reducing Hcy with 1-2 mg daily FA may have also promoted psoriasis by allowing VEGF effect to increase in patients 1 and 3.

Patient 3 improved 22% on 4 mg FA, B6 and B12. The 4-mg dose lowered additionally by NB-UVB seems too low a dose for much improvement despite the NB-UVB also lowering his VEGF [45]. Since he was 40 years old when he flared and his BMI was low, the risk of having elevated VEGF was high [43] possibly making him a poorer candidate for the effects of a high FA dose.

Neutrophil activity was enhanced by rising Hcy in patient 1 when given low FA. When lisinopril was added VEGF effect may have reasserted its effects.

Patient 2’s PASI only cleared 50%. He was on 10 mg daily lisinopril; Patient 1 flared when lisinopril 2.5 mg daily was added being already on low dose carvedilol but improved again when folic acid was increased from 5 to 7 mg daily. Patient 4 flared when ibuprofen was added despite being on etanercept. Patient 4 nearly cleared on etanercept when 1 mg FA was increased to 5 mg FA without stopping the ibuprofen. Ibuprofen and third generation beta blockers like carvedilol preserve or promote ROS or VEGF of VEGF and/or Both [46–48]. Theoretically depending on which type of VEGF is present these drugs could improve or worsen psoriasis. Homocysteine is lowered by ACE inhibitors and betas blockers which by itself should improve psoriasis [49]. A case control study did not associate beta blocker use with psoriasis flare [50]. However, a case control study however did associate psoriasis flares to ACE inhibitor and non-steroidal anti-inflammatory drug ingestion [51]. How ACE inhibitors flare psoriasis is not known unknown Wilkin et al., followed by Coulter suggested that ACE inhibitors not only inhibit angiotensin II production, but also inhibit kinin catabolism. Thus ACE inhibitors potentiate the activity of kinins and thus may cause exacerbation of kinin-associated skin disorders [52]. Possibly relevant to case 4 is that at least in mice, ibuprofen doses of 1.0 mg/kg or more raise VEGF levels [53].

Relevant to future cases would be attempts to treat patients the methylenetetrahydrofolate reductase deficiency and mutations. Conversion of homocysteine to another amino acid methionine requires Methylenetetrahydrofolate reductase. This enzyme converts a molecule called 5,10-methylenetetrahydrofolate to a molecule called 5-methyltetrahydrofolate [54].

Patients with severe MTHFR deficiency have elevated homocysteine and low blood methionine and variably present in childhood or at older ages with neurological and vascular abnormalities. A milder MTHFR...
deficiency, is associated with a thermolabile enzyme, may increase susceptibility for cardiovascular disease and for neural tube defects [55].

Methylenetetrahydrofolate reductase has two common mutations. For example, Incidence of MTHFR 677T mutations are between 10 and 36% of the population [56]. The 677T or 677T mutation patients commonly show elevated total Hcy and low plasma folate. A high oral dose of folic acid can between 23% and 40% of patients depending on specific genotype reduce tHcy [57]. Additional causes of reduced homocysteine metabolism are the A1298C MTHFR mutations [58].

Homocysteine is elevated in alcoholics. Moderate alcohol intake and low MTHFR activity, and the MTHFR677 genotype, (but not he MTHFR1298 genotype) have adverse effects on tHcy, but those effects may be overcome by sufficient folate intake [59,60]. High dose folic acid appears to be a treatment for at least some patients who need folic acid [61,62].

Conclusions

Daily FA 1-2 mg can flare psoriasis. This doe is common in the US population over 50 and in the psoriasis population.

Four or more mg daily FA appears to variably improve psoriasis in these same patients. Reducing or stopping FA 4-8 mg daily may place a patient at risk for comborbid events due to the passage through FA levels that would promote pro-inflammatory side effects. The safety of stopping and the safety of continuing this therapy requires study.

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