

# Improvement of Vitiligo after Oral Treatment with Vitamin B12 and Folic Acid and the Importance of Sun Exposure

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The aim of this 2-year study was to test the hypothesis that folic acid, vitamin B12 and sun exposure could be helpful in treating vitiligo. One hundred patients with vitiligo were treated with oral folic acid and vitamin B12 after being informed that sun exposure might enhance repigmentation. They were requested to keep a record of sun exposure in summer and UVB irradiation in winter. The minimal treatment time suggested was 3–6 months but should be longer if improvement was achieved. Clear repigmentation occurred in 52 patients, including 37 who exposed their skin to summer sun and 6 who used UVB lamps in winter. Repigmentation was most evident on sun-exposed areas, where 38% of the patients had previously noted repigmentation during summer months. Total repigmentation was seen in 6 patients. The spread of vitiligo stopped in 64% of the patients after treatment. Folic acid and vitamin B12 supplementation combined with sun exposure can induce repigmentation better than either the vitamins or sun exposure alone. Treatment should continue as long as the white areas continue to repigment. Further studies are needed to determine ideal minimal dosages of vitamins and UV exposure, as well as treatment time.

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Vitiligo causes destruction of melanocytes in the skin and mucous membranes in about 1% of the population. The aetiology is unknown. At present the most common treatments are topical steroids and PUVA (psoralens with UVA irradiation) (1). We were prompted to investigate the effect of oral folic acid and vitamin B12 on vitiligo by a report from Buenos Aires in 1992 (2). They found low serum levels of folic acid and/or vitamin B12 in 15 patients with vitiligo and treated 8 of them for 3 years with oral folic acid and ascorbic acid and vitamin B12 intramuscularly every 2 weeks. The progression of vitiligo stopped within weeks of starting treatment and significant repigmentation was visible after 3 months. After 2 years 80–100% of the vitiligo had repigmented. We now report a 2-year study of 100 patients with vitiligo who were treated similarly with oral folic acid and vitamin B12, but who were also encouraged to expose their skin to sunlight and UVB irradiation.

## MATERIAL AND METHODS

### Patients

Thirty-three men and 67 women (age 9–79 years) were treated for vitiligo from October 1994 to 1996. All but 6 were Caucasians and they had had vitiligo for 1–43 years, beginning at age 1–65 (Fig. 1). They were in good general health, although 6 took levothyroxine for thyroid deficiency. In 64 patients the vitiligo was actively extending, while it had been stable in 31 patients for at least 1 year and uncertain

in 5 patients. PUVA treatment had failed in 10 patients, who had used it 4 years earlier. Most patients had previously been advised to avoid sun exposure due to the risk of sunburn and the increased visibility of their white spots with tanning.

Prior to starting treatment, serum levels of vitamin B12 and folic acid were determined in 53 patients and found to be normal. As the study progressed these levels were investigated only in elderly patients.

### Treatment and follow-up

Patients were given tablets containing vitamin B12 (1 mg cyanocobalamin) and folic acid (5 mg) to be taken twice daily for 3 months. They were also encouraged to expose their skin to the sun in summer and UVB irradiation in winter, to induce a slight reddening of the white areas. They were requested to inform us later about their light exposure.

All patients were seen or contacted after 3 months. If they wished to continue, they were seen again after 6–12 months and answered a questionnaire about repigmentation and UV exposure.

### Statistics

The chi-square distribution was used.

## RESULTS

Repigmentation was clearly noted in 52 patients (Fig. 1). It was significantly more common ( $p < 0.01$ ) in those younger than 26 years. Patients with vitiligo for less than 10 years repigmented significantly more often ( $p < 0.01$ ) than those who had had it for a longer time. Total repigmentation was seen in 6 patients on sun-exposed skin.

Repigmentation was the same in active versus stable vitiligo. It usually started around hair follicles and then spread. In 54% it was most evident on sun-exposed areas. During the 6–12-month observation period the new pigmentation remained in all patients except in 2, who were treated for only 1–2 months.

Of the 52 patients repigmenting, 37 had been exposed to sunlight from April to September in Sweden, and 6 had been exposed to UVB lamps once or twice weekly in the winter (Table I). A history of prior repigmentation in the summer sun was obtained from 20 (38%) of those who repigmented with sun exposure in this study, compared to only 6 (15%) of those not repigmenting. Successful repigmentation was seen in 9 of 36 patients with no UV exposure, with another 5 being uncertain. None of them had previously seen any repigmentation of their vitiligo.

In 64% of the patients, vitiligo stopped spreading after treatment. The inhibition of spread was most marked ( $p < 0.05$ ) in patients who had been exposed to UV irradiation. No increase in vitiligo was seen in the 31 patients with stable vitiligo or in 4 of the 5 patients with initial uncertain activity.

## DISCUSSION

Vitamin B12 and folic acid were given together, since derivatives of these vitamins interact in the one-carbon cycle. N-N-

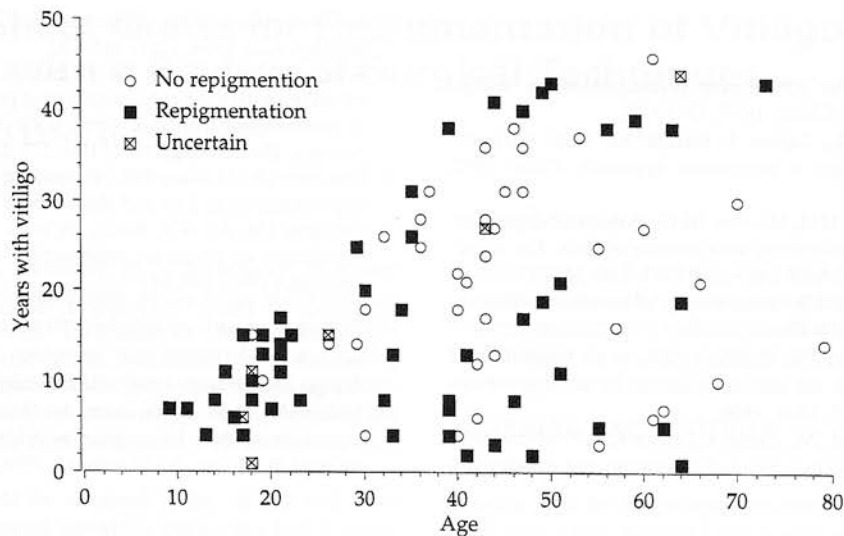


Fig. 1. Age of patients and the number of years they had had vitiligo in those repigmenting or not.

Table I. Results in 100 patients treated for 1 to 12 months with oral vitamin B12 and folic acid

Figures show number of patients. Repigmented UV-exposed skin versus non-exposed,  $p < 0.001$

Months treated	UV exposure	Repigmented	No repigmentation	Uncertain if repigmentation
1-2	yes	6	6	1
	no	2	9	3
3-6	yes	18	13	1
	no	5	10	1
7-12	yes	19	—	—
	no	2	3	1
Total		52	41	7

methylene tetrahydrofolate, the most common form of folate in human plasma, donates a methyl group to homocysteine in the vitamin B12-dependent formation of methionine, so that this enzymatic reaction partly governs the level of homocysteine. Since patients with genetic homocysteinuria have blond hair and fair skin, often described as pigmentary dilution (3), depigmentation in vitiligo could be a consequence of the build-up of local homocysteine due to deficient methionine biosynthesis.

Another possible explanation for the therapeutic effect could be that the pteridine part of folic acid is responsible for repigmentation in combination with UVB irradiation. Pteridine deficiency, which could decrease tyrosine and result in inhibition of pigmentation, was first suggested by Lerner & Fitzpatrick (4). Schallreuter et al. (5) have also shown that 5,6,7,8-tetrahydrobiopterin (6-BH<sub>4</sub>) regulates the tyrosine supply needed for melanin formation and that patients with active vitiligo overproduce 7-tetrahydrobiopterin, which may initiate depigmentation. The uncoupling of phenylalanine hydroxylase and BH<sub>4</sub> reductase also produces hydrogen peroxide in the epidermis (6). It seems possible that the non-reduced pteridine group in folic acid could block or interfere with the recycling of the reduced pterins in vitiligo. Schallreuter et al. reported the stop of progression of vitiligo and a good effect on repigmentation, using a pseudocatalase cream to remove

hydrogenperoxide in combination with UVB irradiation twice a week (7).

Sun-induced or spontaneous repigmentation has been reported to occur in 0-44% of patients with vitiligo, but rarely at a significant degree (8 for ref). Of all our patients 26% had previously seen repigmentation during a sunny summer. Eight of them spontaneously remarked, however, that repigmentation during treatment with the vitamins was much more evident. Vitamin B12 and folic acid alone induced a clear repigmentation in 25% of our non-UV-exposed patients. Our findings indicate that a combination of the vitamins and sun exposure is better than either treatment alone.

From where do the melanocytes needed for repigmentation come? In vitiligo the melanocytes are not detectable in the epidermis with histological techniques. After PUVA treatment the areas of vitiligo with dark hairs can respond, but not those areas with white hairs, suggesting that the necessary reservoir of melanocytes is in the hair follicles (1). Regrettably we have no exact documentation of the hair colour in the repigmented skin areas of our patients. Recently, c-kit protooncogene (mast/stem cell receptor) reactive cells that appear similar to melanocytes have been demonstrated in the lower half of the follicular infundibula (9 for ref). They presumably form a precursor melanocyte reservoir, which could colonize the vitiliginous skin after stimulation. The c-kit positive cells are absent in lesional vitiligo epidermis but can be seen in the dermis of patients with vitiligo (10, 11). In the perilesional skin c-kit expression was reduced (11). Presumably, our treatment with oral vitamin B12 and folic acid, in combination with UVB exposure, somehow stimulated the precursor melanocytes and/or hair follicle melanocytes to become active and migrate into the epidermis of vitiligo skin. Since our patients had normal serum levels of vitamin B12 and folic acid, it appears that deficiency of these vitamins is not a significant factor in inducing vitiligo.

#### ACKNOWLEDGEMENT

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REFERENCES

1. Nordlund JJ, Majumder PP. Recent investigations on vitiligo vulgaris. *Dermatologic Clinics* 1997; 15: 69-78.
2. Montes LF, Diaz ML, Lajous J, Garcia NJ. Folic acid and vitamin B12 in vitiligo: a nutritional approach. *Cutis* 1992; 50: 39-42.
3. Shelley WB, Rawnsley HM, Morrow III G. Pyridoxine-dependent hair pigmentation in association with homocysteinuria. The induction of melanotrichia. *Arch Dermatol* 1972; 106: 228-230.
4. Lerner AB, Fitzpatrick TB. Biochemistry of melanin formation. *Physiol Rev* 1950; 30: 91-126.
5. Schallreuter KU, Wood JM, Pittelkow MR, et al. Regulation of melanin biosynthesis in the human epidermis by tetrahydrobiopterin. *Science* 1994; 263: 1444-1446.
6. Schallreuter KU, Wood JM, Ziegler I, Lemke KR, Pittelkow MR, Lindsey NJ, et al. Defective tetrahydrobiopterin and catecholamine biosynthesis in the depigmentation disorder vitiligo. *Biochim Biophys Acta* 1994; 1226: 181-192.
7. Schallreuter KU, Wood JM, Lemker KR, Levenig C. Treatment of vitiligo with a topical application of pseudocatalase and calcium in combination with short-term UVB exposure: a case study on patients. *Dermatology* 1995; 190: 223-229.
8. Ortonne JP, Mosher DB, Fitzpatrick TB. Vitiligo and other hypomelanosis of hair and skin. New York: Plenum Press; 1983.
9. Grichnik JM, Ali WN, Burch JA, et al. KIT expression reveals a population of precursor melanocytes in human skin. *J Invest Dermatol* 1996; 106: 967-971.
10. Dippel E, Haas N, Grabbe J, Schadendorf D, Hamann K, Czarnetzki BM. Expression of the C-kit receptor in hypomelanosis: a comparative study between piebaldism, naevus depigmentosus and vitiligo. *Br J Dermatol* 1995; 132: 182-189.
11. Norris A, Todd C, Graham A, Quinn AG, Thody AJ. The expression of the c-kit receptor by epidermal melanocytes may be reduced in vitiligo. *Br J Dermatol* 1996; 134: 299-306.