THE EFFECT OF MELADININ IN THE TREATMENT OF VITILIGO*

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Vitiligo or primary acquired leucoderma is a condition which has been recognized for centuries, although probably in the past there has been considerable confusion between it and the various forms of secondary leucoderma. There is no need in this paper to give a detailed clinical description of the disease nor is it intended to go into the biochemistry of melanogenesis beyond to state briefly that melanin is formed by the enzymatic oxidation of tyrosine by tyrosinase, and the site of this reaction is the dendritic-shaped melanocytes lying at the epidermo-dermal junction. It has been suggested by Lerner and Fitzpatrick [1] that pigment-formation is controlled by adrenal hormones which through the pituitary-adrenal axis are secreted to inhibit the release of a pigment-hormone from the pituitary. This melanocyte-stimulating hormone (M.S.H.) has been shown in experimental work to cause temporary hyperpigmentation in normal human beings. It has not as yet been possible to relate these findings to vitiligo, and microhistological studies of the skin in this condition reveal no organic change in the melanocytes.

Although numerous hypotheses have been suggested to explain the aetiology of vitiligo, there has as yet been no supporting evidence to confirm these. As a result of clinical observations many workers have attributed the condition to some nervous shock in the form of a stress syndrome, and this might be supported by the suggestion of a pituitary-adrenal axis, but it is difficult to explain the patchy yet clear-cut distribution of the depigmented lesions.

In the past numerous treatments have been advocated, from the various forms of light therapy in use 50 years ago to the more recent use of gold sodium thiosulphate

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by Lindsay in 1929 [2] and its combination with 10% oil of bergamot and phototherapy by Burgess [3] in 1934; more recently thorium X has been suggested, and that overworked panacea for all ills, vitamin-B complex, in conjunction with dilute hydrochloric acid and para-aminobenzoic acid.

A recent report by Katchkovskiy [4] in Moscow (1953) claims that good results have been obtained with ultra-violet rays (U.V.R.) followed by painting with tincture of iodine.

Careful analysis has shown that none of these methods of treatment is likely to give at the best more than a 5% chance of cure, which may well be explained by cases of spontaneous remission, that are sometimes seen.

AMMI MAJUS

For many hundreds of years it has been known in the North African desert that certain extracts of the *Ammi majus* plant have the power of sensitizing the skin to sunlight, as a result of which an acute inflammatory reaction develops, leading frequently to normal repigmentation. But these crude extracts produce in quite a high percentage of cases certain severe side-effects such as abdominal pain, nephritis, cirrhosis of the liver, exfoliative dermatitis and coma. In 1941 Rogad Fahmy and Abou Shady,[5] in Egypt, prepared a soft alcoholic extract of this drug, which was given in enteric capsules. Although it was a definite advance on previous therapy toxic side-effects were still frequent, though less severe, and, as a result of further research by the same workers, 2 crystalline extracts were prepared, viz. ammoidin $C_2H_8O_4$ and ammidin $C_{16}H_{14}O_4$, neither of which exceeded 0.5% of the original powder. El Mofty [6] working with these extracts in 1948 treated a series of 20 cases, using 3 methods, viz. (1) local application of 1% ammoidin in glycerin and alcohol, (2) oral administration in a dose of 0.05 g. daily, and (3) a combination of (1) and (2).

In this series of 20 El Mofty reported 10 complete cures, 6 failures and 4 doubtful reactions, which were certainly most impressive results. The main feature noticed in repigmentation was the development of follicular pigmented islands which coalesced. All failures were treated for at least 3 months before being regarded as such.

Further extraction of the *Ammi majus* led to the isolation of another crystalline extract, majudin, ($C_{12}H_8O_4$), which is also present in large quantities in oil of bergamot.

A further series of 22 cases was reported by El Mofty [7] in 1952, which gave an even higher proportion of successful results.

Sidi and Bourgeois-Gavardin [8] (1953) reported a series of over 100 cases treated over a period of 2 years. They gave 3 or 4 tablets of Meladinin† daily, allowing 8 days' break each month. The paint was applied to all lesions 1 hour before exposure to sun or U.V.R. and the surrounding areas were painted with 10% para-aminobenzoic acid in 60% spirit to protect them. They found that in white skins an acute vesicular reaction prevented satisfactory pigmentation. Best results were obtained by daily short exposures, which caused a gradual repigmentation. Sensitive areas of skin were painted with a diluted solution, either half or quarter strength. Their analysis of cases showed that, out of 84 who persisted with treatment and were followed up, 7 were completely cured, 10 were almost completely repigmented, 17 showed definite improvement, and 50 showed partial repigmentation. They reported no complete failures. They found that children responded more satisfactorily than adults and also that the shorter the history, the better the prognosis.

†'Meladinin' is the trade name of the extract of *Ammi majus* prepared by the Memphis Chemical Co., Cairo.

PRESENT SERIES OF CASES

The series of 20 cases to be discussed in this paper was started in 1953. The cases were selected as showing the typical clinical features of vitiligo. They consisted of 17 Indians, 2 Africans and 1 European. In each case a Wassermann test was performed to exclude syphilis, and the lesions were photographed. All treatment was carried out in the Department of Physical Medicine at King Edward VIII Hospital, Durban.

As a result of a warning in a personal communication from Dr. Louis Forman of London on the strong photosensitizing powers of Meladinin, the initial approach was cautious and this caution appeared to be more than justified in several cases by the acute reaction which developed after initial irradiation.

Initially a paint was applied having the following percentage formula:

Ammoidin	0·75
Ammidin	0·25
Acetone	10
Propylene glycol	10
90% alcohol	79

Thrice weekly this was painted on the lesions and the patient then exposed to the midday sun for about 15—20 minutes; if the reaction was mild U.V.R. was then used. In the 1 European and 7 of the Indians this caused an extremely acute oedematous and vesicular reaction in the areas treated, as a result of which the treatment was modified. This modification consisted of suspending treatment until the reaction had subsided and then renewing with the paint diluted with S.V.R. to form a 25% or 50% solution.

The present series of cases is too short for statistical deductions. Individual case details are given in Table I and the results are summarized in Table II. General impressions are recorded, particularly as experimental trial was necessary to find the best combination of topical and oral administration of the drug and the best type and dosage of irradiation.

As, so far as we know, there have been no previously published results regarding the treatment of vitiligo in the deeply pigmented races, who tolerate vastly heavier dosage of ultra-violet irradiation than do Europeans or lightly pigmented peoples, the details of physical treatment given in the earlier series of cases (see above) were of little assistance.

In general, with non-pigmented patients, the dosage of ultra-violet is based on the development of the earliest perceptible erythema on the untanned skin

TABLE I

Case No.	Race Age and Sex	Duration	Areas Affected	Method of Treatment	Duration of Treatment	Method of Irradiation	Reaction	Signs of Repigmentation	Remarks
1.	I.F.14	3 mths.	Lips and arms	Paint Pills Both	6 wks. 2 wks. 4 mths.	T.W. 6″ 3—6 mins. T.W. 6″ 2—6 mins. No U.V.R.	Oedema and vesiculation of lips (4th degree erythema)	Islands	Complete repigmentation. Acute light sensitization developed temporarily during treatment.
2.	I.M.10	'Years'	Forehead, abdomen, ant. surfaces of both legs	Paint and Pills 1/day	6 mths.	T.W. 6″ 3—30 mins.	4th degree erythema	Islands	Acute vesiculation in leg lesions within 48 hrs. in spite of no treatment with U.V.R. Developed islands of pigmentation on legs which had not been irradiated or painted. Poor response on forehead. Abdomen repigmented.
3.	E.F.15	8 yrs.	Forehead, neck, angles of mouth, axillae	Paint only	1 mth.	Sun 5 mins. daily. No U.V.R.	Acute eczematous eruption	Nil	An extreme acute sensitization to sunlight on local application of paint. Suggestion of early repigmentation but parents stopped treatment.
4.	A.M.24	10 yrs.	Face, neck, L. pectoral area	Paint Paint and Pills (b.d. or t.d.s.)	4 wks. 4 mths.	Hanovia 18″ 3—25 mins.	2nd degree erythema	Nil	No repigmentation.
5.	I.M.21	3 mths.	Circular patches on eyelids	Paint only	2 wks.	Sun ½ hr. after paint		Islands	Completely repigmented within 1 wk.
6.	I.F.2	6 mths.	Both legs below knee	Paint Paint and Pills 1/day	7 wks. 3 mths.	Hanovia 18″ 5—15 mins.		Islands	Completely repigmented.
7.	I.F.13	2 mths.	Lower 3rd right leg	Paint and Pills 1/day	2 wks.	T.W. 6″ 5—10 mins.		Islands	Rapid and uneventful repigmentation.
8.	I.M.22	3 yrs.	Upper and lower lip	Paint and Pills j.b.d.	7 mths.	Kromayer up to 10 mins.	4th degree acute vesiculation		No sign of repigmentation in spite of acute and repeated vesicular reactions in areas treated.
9.	I.F.35	3 mths.	Shin area and between shoulders	Paint and Pills j.b.d.	3½ mths.	Hanovia 18″ or T.W. 6″ 5—25 mins.	2nd degree erythema	Islands	Back area (covered) completely repigmented after 3 mths. No vesiculation or oedema. Little or no signs of repigmentation in legs.
10.	I.F.16	3 yrs.	Outer aspect thighs, deltoid areas, elbows	Paint and Pills j.b.d.	5 mths.	T.W. 6″ 5—20 mins.	2nd degree erythema	Islands	Hyperpigmentation of shoulder areas. Pigmentation started after 1 wk. and complete in 8—10 wks. Lesions on thighs not treated owing to extent of affected areas.
11.	I.F.14	5 mths.	behind L. ear and between shoulder blades	Paint and Pills b.d.	6 mths.	T.W. 6″ 4—20 mins.	3rd to 4th degree erythema	Islands	This patient reacted well initially but failed to continue treatment. When seen 4 mths. later original lesions had extended.
12.	I.M.18	not known	L. scapular area	Paint and Pills b.d.	5 wks.	Hanovia 18″ 5—25 mins.	2nd degree erythema	Islands	Repigmented steadily with small islands. When last seen progressing well. Not seen after intermediate stage; patient disappeared.
13.	I.F.13	not known	Forearms and temples	Paint only		sun 20 mins.	4th degree erythema	Islands	Steady repigmentation.
14.	I.M. 14	not known	Periorbital region and ant. hair margin	Paint only		sun 5 mins.	4th degree erythema	Islands	Repigmented.

TABLE I (CONTIN.)

Case No.	Race Age and Sex	Duration	Areas Affected	Method of Treatment	Duration of Treatment	Method of Irradiation	Reaction	Signs of Repigmentation	Remarks
15.	I.M.42	1 mth.	Angles of mouth	Paint Paint and Pills	10 wks. after 6 wks.	T.W. contact 5—10 mins.	4th degree with vesiculation		Some encroachment of pigment from periphery. 50% repigmentation.
16.	I.F.13	not known	L. ear area L. elbow both legs	Paint and Pills b.d.	10 wks.	Hanovia 18" 5 mins.			Complete repigmentation of all areas except legs which when last seen were showing islands of pigment.
17.	I.M.32	5 yrs.	Forearms, hands, chin, forehead, between shoulder blades, legs	Paint and Pills j.b.d.		Kromayer contact 35 mins.			Beginning to repigment after 4 mths. intensive treatment.
18.	A.M.24	1 mth.	Patchy on hands	Paint and Pills j.b.d.	2 mths.	Hanovia 10" 10—20 mins.	1st degree erythema		No sign of repigmentation.
19.	I.F.17	1 wk.	Back of neck. L. ankle	Paint only	6 wks.	sun 20 mins.			No reaction so far but has only had two treatments.
20.	I.F.14	not known	L. knee behind R ear	Paint only	5 wks.	Hanovia 10" 10—20 mins.			Absented after promising initial response.

TABLE II. ANALYSIS OF RESULTS

Distribution	No. of Cases	No. Repigmented	Failures	Doubtful
Face, head, neck	14	6 (43%)	6 (43%)	2 (14%)
Trunk	7	3 (43%)	4 (57%)	—
Arms	6	4 (66%)	1 (17%)	1 (17%)
Legs	7	3 (43%)	1 (14%)	3 (43%)
Total	34	16 (47%)	12 (35%)	6 (18%)

of a person of average pigmentation. The duration of exposure required to produce this erythema, at a given distance of the source from the skin, is regarded as the 'minimal erythemal dose'. This is determined for every lamp and serves as a standard by which ultra-violet dosage may be estimated and prescribed.

In the present series of cases all but one were darkly pigmented, making the detection of a true erythema not impossible but of unreliable accuracy. Further the position was complicated by the common tendency of this series of cases, when exposed to sunlight, to exhibit the so-called Meirowsky phenomenon,[9] i.e., the skin fairly rapidly undergoes a process of primary pigmentation or pigment darkening. Kooij and Scott,[10] working recently on primary pigmentation of normal skin in the African, along similar lines to the earlier work on Europeans done by Henschke and Schulze [11] and others [12] have found that the long ultra-violet wave-lengths of sunlight (2,900—3,900 Angstrom units) did not produce in their cases that erythema which precedes secondary pigmentation and is produced by the short wave-lengths (1,800—2,900). This being so, attempts to standardize the ultra-violet dosage in terms of time or wave-length appeared futile since exposed areas of vitiligo, normally unaffected by sunlight, when painted with Meladinin and exposed to the sun, developed in some cases a 4th-degree erythemal reaction after only 10 minutes exposure; whilst in other cases, or even in other areas on the same case, no visible reaction occurred after as much as 30 minutes contact-exposure to an efficient artificial short-wave ultra-violet source, emitting a known 2,537 Angstrom-unit wave-length. This variability of reaction to ultra-violet led to a cautious process of graded trial with each case and of each area to be treated.

The initial routine adopted in this series, particularly with areas which would be expected to react briskly to irradiation, was to apply the paint and advise the patient to expose himself to the midday sun for 15—20 minutes; if there was no appreciable reaction to this the painting was repeated in 2—3 days using U.V.R. from a Kromayer, a Westinghouse thin window, or a Hanovia lamp. Where possible treatment was given thrice weekly and, if there was little reaction, pills containing 10 mg. of ammoidin and 5 mg. of ammidin were also given in dosage of 1 or 2 daily. An exception was one African (case 18) who received the pills t.d.s., was painted thrice weekly, and received U.V.R. from a Hanovia lamp at 10 inches up to 30 minutes; the only reaction to this was an erythema with no sign of repigmentation.

The degree of repigmentation not only varied from patient to patient but from lesion to lesion and even in different parts of a lesion. One interesting anomaly was observed in case 2. When first treated he was given paint alone on the abdominal lesion followed by U.V.R. to that area; within 3 weeks he developed an acute

Fig. 1. Case 1 before treatment.

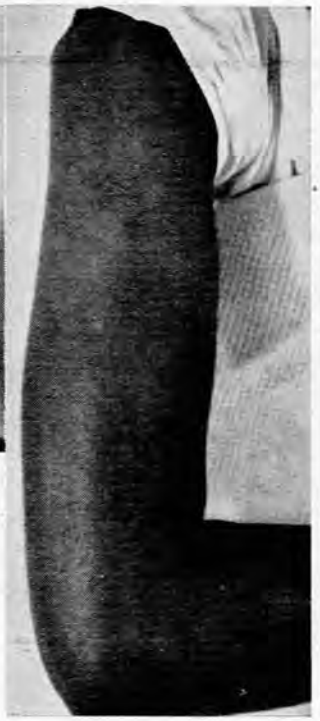

Fig. 2. Case 1 after 8 weeks' treatment.

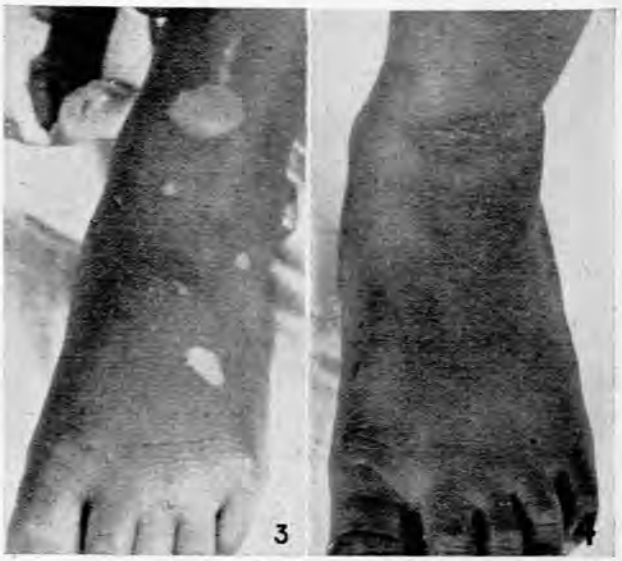

Fig. 3. Case 6 before treatment. *Fig.* 4. Case 6 after 2 weeks' treatment.

vesicular eruption over the leucodermic areas on the shins in spite of the fact that these had received no treatment in any form and were protected from sunlight by long trousers. Repigmentation developed in these areas in the usual 'island' way but was not complete, leaving some depigmented areas. There was no repigmentation in his forehead in spite of intensive treatment there. The lesion on the abdomen after receiving 30 minutes of 'thin window' U.V.R. treatment (at contact distance instead of the normal 6 inches) eventually developed an acute vesicular eruption which led to the development of islands of pigment within 24 hours; repigmentation then continued in the usual way. Case 9 showed complete repigmentation of a lesion on the back, but no response on the legs.

Case 11 started to respond well but then ceased to come for treatment, and when the patient was seen 4 months later the previous lesions had extended although the repigmented areas had not relapsed. Further treatment was producing good results when the patient again disappeared and has not been seen again. Case 5 showed the most dramatic response of all and repigmented completely after 1 treatment. Case 6 also repigmented very quickly, giving an excellent result in less than 2 weeks. Case 12 was reacting very well to treatment and had reached the 'island stage' when treatment had to be stopped for 6 months while the patient retired to prison; he is therefore labelled as 'doubtful' in the assessment of figures.

It will be seen, therefore, that some of the cases described as failures have hardly given the treatment a fair trial, while two or three of the more recently treated cases have not been under observation long enough to be regarded as outright failures although they may show as yet no signs of repigmentation. The analysis therefore in Table II, is a very conservative one and probably underestimates the effectiveness of the treatment. One significant observation was the complete failure to repigment in the African cases in spite of the most intensive and protracted treatment. The one European case was also a failure; although she stopped treatment after 2—3 weeks, there was very little suggestion of repigmentation even after an acute vesicular response.

As already observed, an acute vesiculation was obtained with 40% of the cases, which led to some modification in the treatment. After surveying the results the general impression was that the best results were obtained in cases in which an acute near-vesiculation reaction was deliberately provoked and the maximum safe dosage was given as early in the course as possible before the skin had time to acclimatize itself to the photodynamic effect of the drug.

The method of repigmentation was in most cases by the development of minute perifollicular islands of pigment which gradually coalesced; this phenomenon is well shown in the photographs. The other method of repigmentation is that of peripheral encroachment which was well illustrated in case 15, where the lesions round the angles of the mouth materially decreased in size but where no small islands developed.

One or two cases did develop larger 'freckle-like' lesions which came to nothing and disappeared as soon as the U.V.R. was stopped. This was particularly noticeable in case 9 on the legs, which failed to repigment, and in case 2 on the forehead.

As a result of these observations it is planned in future to use more intensive treatment initially, trying to avoid a reaction of such severity that it interferes with regular treatment. Before it is possible to estimate the optimum dosage for each case and lesion, considerable experience is required; from the present results it is suggested that,

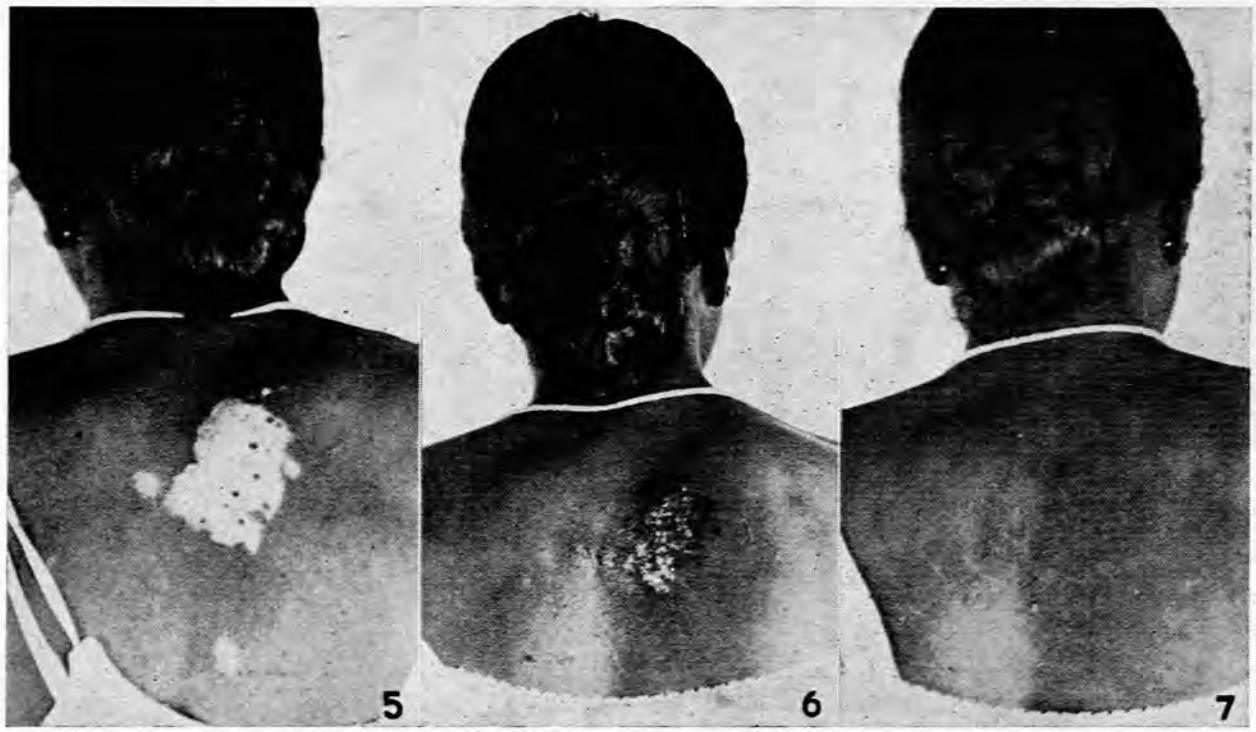

Fig. 5. Case 9 before treatment. *Fig.* 6. Case 9 after 6 weeks' treatment. *Fig.* 7. Case 9 after 14 weeks' treatment.

unless there is some definite sign of repigmentation following vesiculation within 2 weeks, a satisfactory result is unlikely to follow. It also appeared that better results were obtained when both paint and pills were given from the beginning, in addition to the maximum dosage of U.V.R. which the skin could tolerate.

It is not possible as yet to hazard more than a guess as to the mode of action of this drug. It is possible that it inhibits the action of certain substances containing the sulph-hydryl group which antagonize the enzymatic action of tyrosinase in the normal formation of melanin, but as yet there is no supporting evidence for this.

CONCLUSION AND COMMENTS

In summing up our results and trying to give rough statistical figures, the lesions are divided into 4 groups. The reason for doing this is that it is extremely difficult, as already explained, to regard a patient with several lesions as cured, because while some lesions have repigmented others may show no change; the extreme example was shown in case 2 where repigmentation took place in the greater part of the leg lesions, but an area of depigmentation remained which in spite of extensive treatment would not repigment. In Table II cases have been classified according as the vitiligo affected (i) the head and neck (14), (ii) the trunk (7), (iii) the arms (7), and (iv) the legs (8).

The only justifiable comment to be made on these results is that this drug offers a means of treating vitiligo with a reasonable prospect of success. One observation made in these cases was that the soft satin-like type of skin appeared to react very well while the coarse hyperkeratotic areas or type of skin was less likely to repigment. Attention is drawn, however, to certain discrepancies between these results and those of the original Egyptian and French workers. In this series a brisk inflammatory reaction in the skin has been almost a necessity to produce repigmentation. This observation, so contrary to those of Egyptian and French workers might be partly due to the well-known tolerance of pigmented skins to U.V.R. It has also been found that smaller and more recent lesions have reacted best and it would appear that if patients could be treated early on in the course of the disease before lesions had become extensive, results would improve considerably.

The method is rather laborious and it is felt that it should only be carried out under regular supervision and with carefully regulated U.V.R. exposures. It is obviously more convenient, and safer, to treat such cases in a special hospital department under the supervision of a trained physiotherapist.[7] Casual and occasional treatment with the drug, followed by haphazard irradiation, is very strongly deprecated and the result in case II, with its extension of lesions, supports this view. There is also some possibility that the drug can provoke a permanent light sensitization. Sidi and Bourgeois-Gavardin [8] in Paris report 5 such cases in a series of 106 cases, and in this country of sunshine that is hardly a desirable condition to bring about.

This paper is in the nature of a preliminary report, but the results would seem to justify further and more complete trials of this treatment.

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SUMMARY

A report on the result of treatment of 20 cases of vitiligo with Meladinin is presented. Two long-standing African cases failed to respond and treatment was unsuccessful in the one European case. The remaining Indian cases responded well to treatment, showing repigmentation in more than 50% of the lesions.

POSTSCRIPT

Since this paper was written further work has been carried out by the authors along these lines particularly with European cases. It has been found that white skins show a much more marked photosensitization in areas where Meladinin paint has been applied than do Indian or African skins. As a result of this it is strongly recommended that in treating such cases an initial application of a 25% solution of the paint in S.V.R. be used and exposure of treated area be limited at first to a maximum period of 5 minutes, the strength of the paint and the duration of exposure can then be gradually increased.

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