DEVELOPMENTS OF THE APPROACHES IN THE THERAPY OF VITILIGO*

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Vitiligo is a fairly common disease of acquired depigmentation occurring as well defined patches of loss of pigment The failure of pigment formation in the majority of cases is temporary but it may be permanent. This failure is attributed to depression of the tyrosinase system in the melanocytes.

The therapeutic use of the active extracts of the Egyptian Herb Ammi Majus Linn, marketed as Meladenine, Oxypsoralen and Methoxsolen; (each containing 10 mgm. of 8-methoxypsoralen; the former contains in addition 5 mgm, of 8 isoamyleneoxypsoralen per tablet), represents an important milestone in the treatment available at present.

It is now 14 years since my first report discussing the results of its clinical trials in 20 patients was published[1]. In this report, I discussed the specific results of oral medication, the favourable results of local painting of the alcoholic solution of the crystalline extracts and those of combined oral and local medication. It was made clear that the best results were obtained when both oral and local ways were followed together with sun or ultraviolet irradiation. In 1952, the second detailed paper[2] about the results of the treatment was published discussing details of treatment, dosage, specificity of response, and patterns of repigmentation. These patterns were described as: (1) follicular and (2) marginal. The first pattern shows hyperpigmented spots, that re-unite to fill the vitiliginous areas. The latter is less frequent, it shows repigmentation proceeding from the margin resulting in progressive narrowing of the depigmented area until it is completely repigmented. Both patterns of reactions were later proved through histological study[1,9] to be due to migration of the melanocytes either from the hair bulbs or from the margin involving the vitiliginous areas. The importance of sun or ultraviolet irradiation on the response of vitiliginous patches to Meladenine treatment was stressed. It was made clear that vesiculation is not essential in the process of repigmentation and that the majority of cases that responded favourably showed no vesiculation[2], on the contrary, some cases that showed severe reaction with repeated vesiculation did not show any improvement. This was later verified by other workers[1,3] through their clinical observation and remarks.

In this paper it was speculated whether the drug is playing its role through stimulation of the central or peripheral pigmentary mechanisms or whether it possesses both potentialitis.

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THE EFFECTIVENESS OF THE DRUG

The treatment of vitiligo with psoralens was documented by many workers and papers were published in France and the United States, and many other countries[1–12] proving that, it is effective when given orally, and when painted locally, small patches may respond to local paint alone helped by ultraviolet or sun irradiation. The best results are obtained when both oral and local ways are used together with solor or ultraviolet irradiation. The treatment should be given continuously and for long time.

The observations made by Funan[18] et al on in vitro studies of split-thickness of skin specimens of vitiliginous skin before and after treatment with 8-methoxy-psoralen and ultraviolet proved that no histochemically recognisable normal melanocytes was seen in the vitiliginous skin of 15 patients with typical vitiligo. When after treatment; normal silver positive, dopa positive and methylene blue positive melanocytes were seen in repigmenting areas. The histologic studies of Jarrett and Szabo[19] proved by specific effect of Meladenine in restoring pigmentation in vitiliginous skin when given orally or painted locally together with ultraviolet or sun irradiation. They proved the specific stimulating effect on the remaining Dopa positive melanocytes. They added that the response in the dark skin is more favourable than in the white skin.

THE POTENTIALITIES OF THE DRUG

I—*Its Photosensitising effect as a local paint;* when used as a local paint together with sun or ultraviolet irradiation, it leads to a severe and marked reaction, erythema, oedema with bullous formation. The reaction may be so severe that alarmed one of the early workers[4] on the field, and lead him to warn against its use followed by irradiation unless due care is taken. It was made clear through my clinical trials and exerience[13] that if the drug is given orally for about two weeks before the use of the local paint, such severe reaction can be avoided and never occurs. The use of the local paint together with irradiation without per-oral premedication is the cause of severe local reaction. This practical point in management of treatment of cases of vitiligo was later proved experimentally[14,15] showing that, if psoralens are painted on the skin of albino rats, photosensitisation to ultraviolet occurs[29]. Intraperitoneal injection of psoralen one hour before ultraviolet irradiation has got the same photosensitising capacity. In contrast, ingestion of psoralen for some-days before and together with ultraviolet irradiation diminishes the erythemal response and protects against the harmful effects of ultraviolet and lower tumour incidence tested in albino rats than in a control group[29].

II—*It increases tanning capacity when given orally* It has been repeatedly proved that exposure to sun or ultraviolet radiation with oral psoralen medication increases the tanning capacity of the skin by actual potentiation seen clinically[16]. This phenomenon of increased tanning capacity was one of the early observed

phenomenon both by patients and by volunteers on taking Meladenine[16]. This was later verified histologically[14]. The melanocytes and their dendrites have been found to be full of melanin granules in active pigment formation. A process of melanisation of the stratum corneum is taking place at a faster speed as well as a large amount of melanin is retained in the basal cell layer[17]. Pigment retention due to slower desquamation and increased adherence of the stratum corneum has been shown to take place.

III.—*Oral Psoralen Increases the Tolerance to Sun and Ultraviolet light and Decreases Sun Burn Reaction:* The per-oral medication of psoralen increases the tolerance of the skin to sun ultraviolet irradiation. It has been noticed clinically[16] and experimentally[30,14] that 8-methoxypsoralen decreases the sensitivity to ultraviolet light of normal people and vitiliginous patients. It also decreases the sun burn reaction of albinos[5]. It increases their tolerance to sun and makes them able to work in the field.

By histological studies, it has been proved that this increased tolerance to the drug was due to increased density and thickness of the stratum corneum and lucidum of the skin and increased adherence of the stratum corneum[15]. This protecting mechanism is initiated in albino, vitiliginous and normal skin after the ingestion of psoralens. Beeker Jr. reported that a stratum lucidum was formed in the skin after it was irradiated with either an ultraviolet light or with sun light, two hours following ingestion of 20 mgm, of methoxsolen[14]. Zimmerman[15] studied the histologic changes in irradiated skin, he confirmed the formation of thicker stratum corneum and lucidum as a response to irradiation after oral psoralen medication. He proved that such formation does not take place after psoralen treatment in the skin unless it is irradiated. Increased density and thickness of stratum corneum and stratum lucidum is the cause of protective effects of oral psoralen against sun burn. This shows that the mode of administration of the drug is the all important factor in influencing the response of the skin to ultraviolet and solar radiation.

POTENTIALITIES OF PSORALEN

I. *Local Paint*—Photosensitisation.

II. *Oral Psoralens*—increases tanning capacity

1. Stimulation of melanocitic activity.
2. Rapid melanisation of stratum corneum and basal cells.
3. Pigment retention due to slower desquamation and increased adherence.

III. *Oral Psoralens*—Increases skin tolerance to solar and U. V. R, radiation and decreases sun burn reaction.

Even in Albinos
1. Increased density and adherence of stratum corneum.
2. Increased thickness of stratum lucidum.
3. Potentiation of pigmentation.

IV. *The Psoralen and Copper Metabolism* :—Copper has a role in melanin for mation. It is essential for tyrosinase activity in mammalian tissues including human epidermis. There is hypercupraemia[20,21] in addison's disease, Leukaemia and Hodgkins disease and pregnancy, all conditions are known to be accompanied by hyperpigmentation.

Breathnach[22] found that the addition of dilute copper sulphate solution to the tyrosinase, leads to a speeding up of the action in the melanocytes of both freckles and pale epidermis[22].

We tried since 1954 the addition of copper sulphate in doses of 15 mgm. by mouth daily to the meladenine treatment. It was found that this addition raised the percentage of cure in a group of patients[13]. This stimulated us to estimate the serum copper in normal and vitiliginous patients. We found it is ranging in normal persons between 100-244 microgram percent with a mean average 157[23].

That of vitiliginous patients ranged between 62-190[23] with an average mean of 143 for adult males. Figures studied by Lerner[20] for vitiligo patients ranged from 56-132 micrograms percent with an average of 109. Cases studied by Behl et al[30] recorded average of 105 micrograms of copper percent for normal individuals and only 66 micrograms per 100 ml. serum of vitiliginous patients. On analysis of the copper content of the skin, Behl[30] found 65 micrograms per 100 mgm. of dried epidermis in the normal persons and normal skin of vitiiiginous patients while that of vitiliginous areas scored only 26+5 microgram copper per 100 mgm. of dried epidermis.

We found that there is no marked lowering of serum copper in the majority of vitiliginous than normal.

It was of interest to find that there is a definite rise in serum copper after per-oral meladenine treatment in 25 patients out of 31 cases treated (80%). This rise was from 7-118 microgram percent[24] (Table I).

TABLE I

Serum Copper Of Patients With Vitiligo Before And After Meladenine Treatment

Serial No.	Sex	Before Treatment	After Treatment	Duration of treatment in days	Difference in serum Copper
		Copper	Copper		
1	M.	62	180	219	118+
2	M.	150	171	451	21+
3	M.	125	184	275	59+

4	M.	150	173	49	23 +
5	M.	125	173	425	47 +
6	M.	170	190	93	20 +
7	M.	190	171	64	29 –
8	M.	140	212	39	72 +
9	M.	150	185	94	35 +
10	M.	145	170	105	25 +
11	M.	140	181	105	41 +
12	M.	62	153	69	91 +
13	M.	143	181	107	38 +
14	M.	190	145	64	45 –
15	M.	145	170	104	25 +
16	M.	130	170	63	40 +
Mean values		139	176	Average rise	57 +
Normal mean value		157	157		
17	F.	196	159	77	36 –
18	F.	205	212	100	7 +
19	F.	140	244	162	104 +
20	F.	145	135	120	10 –
21	F.	181	200	41	19 +
22	F.	120	173	60	53 +
23	F.	171	190	274	19 +
24	F.	157	140	57	17 -
25	F.	155	173	38	18 +
26	F.	210	195	62	15 –
27	F.	135	231	378	96 +
28	F.	155	173	58	18 +
29	F.	171	181	62	10 +
30	F.	130	157	377	27 +
31	F.	175	202	74	27 +
Mean values		163	184	Average rise	21 +
Normal mean		158	158		

Serum copper is raised : 7–118 microgram/100 ml. blood.

We found experimentally in albino rats that the blood copper is raised under the effect of 8-methoxypsoralen to a marked degree from 131 to 325 micrograms percent and that of liver copper is lowered. Ammidin-8-isoamylene oxypsoralen is inert and has no hypercuparemic effect. The doses used in this experiment were much above the therapeutic effective doses in order to accentuate the changes for purpose of demonstration. The results are graphically represented in Fig. 1.

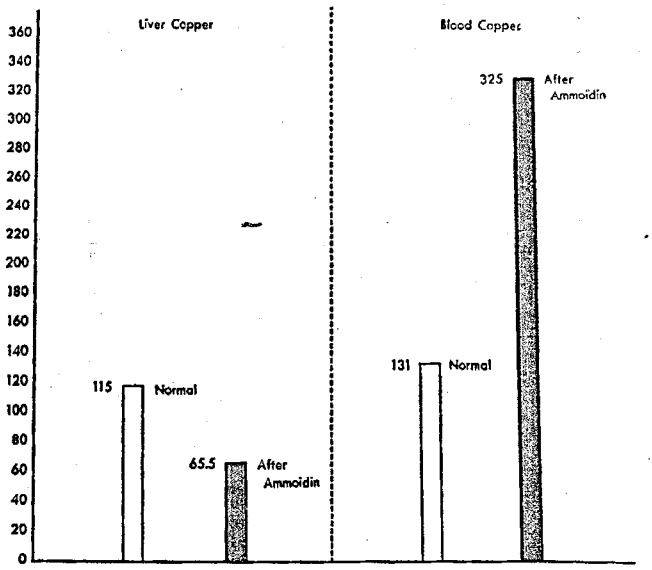

Fig. 1. Effect of Ammoidin on copper levels. Rat

FIG. I : 8-METHOXYPSORALEN RAISES BLOOD COPPER

This hypercupraemic effect of 8-methoxypsoralen is abolished in hypophysectomised rats. (Fig. 2).

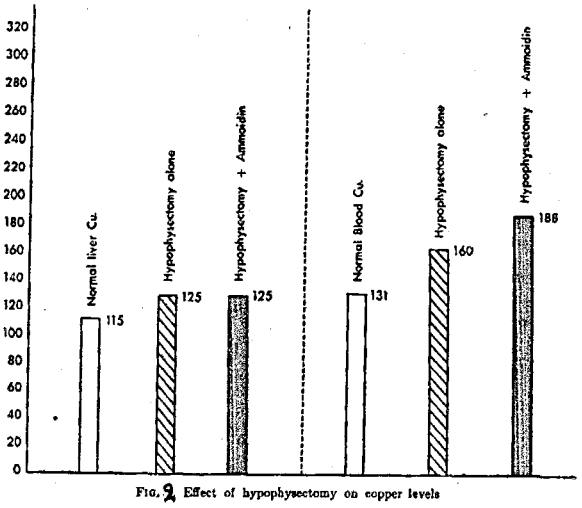

Fig. 2 Effect of hypophysectomy on copper levels

FIG. II : HYPOPHYSECTOMY ABOLISHES THE EFFECT OF 8-METHOXYPSORALEN ON BLOOD COPPER

HYPOPHYSECTOMY + 8(MOP)=NO RISE IN BLOOD COPPER AND NO CHANGE IN LIVER COPPER

Fig. 2: Effect of hypophysectomy on copper levels in blood and copper.

A difference of 20–30 microgram per 100 c. c. blood may be due to dehydration.

Adrenalectomy in rats was found to mobilise copper from liver to blood from 131–262 denoting that adrenals has a restraining role over the hypercupraemic action of the pituitary [26].

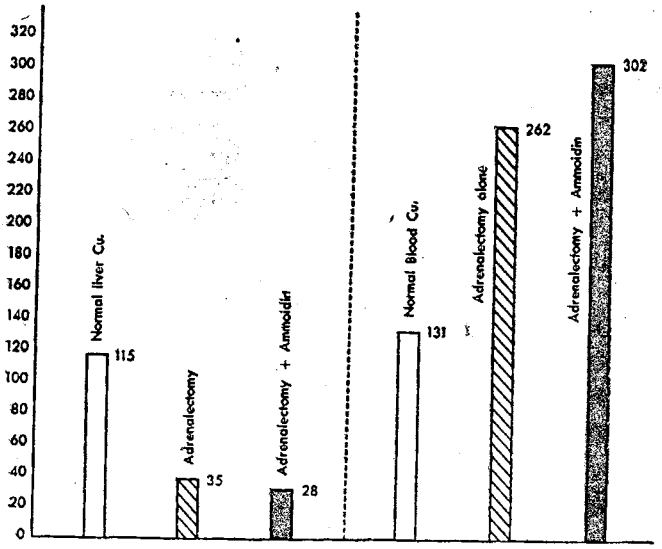

Fig. 3. Effect of adrenalectomy on copper levels

FIG III ADRENALS HAVEA RESTRAINING EFFFCT OVER THE HYPERCUPRIMIC ACTION OF THE PITUITARY

Fig. 3: Adrenals have a restraining effect over the hypercupraemic action of the pituitary.

The adrenals physiologically perform a restraining effect on the pituitary action on copper mobilisation preventing mobilisation of copper from liver to blood.

The role of copper metabolism in vitiligo is not yet clear. The studies of Behl, Agarwal, and Gurdas Singh [21] investigating the different nutritional factors in the etiology of vitiligo in India, proved that there was no significant deviation from normality except in copper level of serum of vitiligo skin. In their patients they estimated copper content of vitiliginous skin and found it to be much less, (26 microgram per 100 mgm of dried epidermis) in comparison to the pigmented skin of the same patient (30) having 65 micrograms of copper per 100 mgm of dried epidermis[30]. All factors known to lead to defective melanin formation including nutritional factors as lack of vitamins, trace metals, various hormonal and neural imbalance, could finally be traced to a disturbance in the physiologic balance between the two opposing factors namely the copper tyrosine activity and the sulphydryl content.

On this basis it was found advisable to supplement the meladenine therapy with copper salts in the doses used in haematinic preparations, i. e. 15 mgm. of copper sulphate or copper gluconate given in three divided daily doses.

Toxicity of the Psoralens :

The psoralens are safe drugs that can be given for a long time. They can be tolerated for years without any toxic symptom or sign. Jaundice has never been reported in psoralen treatment carried for many months. In an analysis of symptoms in 100 patients for 3 months, only three persons complained of gastrointestinal disorders. No nausea or vomiting or diarrhoea occurred in the other 97 subjects. Elaborate liver function tests have been carried out for a group of twelve persons taking 30 mgm. of the 8-methoxypsoralen before treatment and at monthly periods for 3 months-using bromsulfalein retension, cephalin cholesterol floculation, zinc and thymol turbidity tests. No subject had a change in liver funtion indicating liver damage [27]. It has no diabetogenic action at all. This has been proved by animal experiments giving up to 800 mgm/kg i. e. 16 times the therapeutic dose-that it does not raise blood sugar or interfere in any way with carbohydrate metabolism[28]. The question has been studied on volunteers, in no one, did hyperglycaemia or glycosuria occurred. It was proved that they have no bad effect on the kidnies, blood forming organs, or any of the visceral organs.

The Combined Psoralen and Quinoline Derivatives Treatment of Vitiligo [31].

Our last trial with oral meladenin therapy was the combination of its administration with some members of the quinoline group of antimalarials namely amodiaquin and chloroquine diphosphate. I am going to give a preliminary report of some of our data under publication[31].

Fifty five patients suffering from vitiligo, have been studied for the effect of the combined treatment.

The duration of vitiligo before treatment varied from 1.5 months and 28 years.

The duration of treatment, before the beginning of repigmentation varied from 4 weeks to 13 weeks.

The dose used is one tablet daily for 3-4 weeks, gradually diminished to half a a tablet twice weekly.

Higher doses have been tried early in the work and were abondoned as they proved not to be superior to smaller doses used. High doses stimulated a marked degree of tanning of normal skin especially of the face and exposed parts prior to initiation of pigmentation of vitiliginous areas.

Results Obtained :

The combined meladenine and antimalarials evoked repigmentation in 50 out of 55 cases and failed in 5. The results could be summarised in the following :

Complete cure	13 cases	24%	69%
Excellent response more than 75% cure	25 cases	45%	
Good response more than 50% cure	8 cases	15%	
Weak response less than 50% cure	4 cases	7%	
No response	5 cases	9%	
Total	55	100%	

— Initiation of repigmentation is prompt irrespective of duration of disease.

— The amount of success of repigmentation depended on the duration of exposure to sun or ultraviolet irradiation.

— Tanning of the uncovered areas of healthy skin was observed in all cases. This was considered as a disadvantage in dark skin individuals. High doses of the quinoline derivatives caused great degree of tanning.

— Reduction of the dose was followed by reduction of the tan of the skin.

— The striking observation was the prompt initiation of repigmentary response in relatively short time average 1–3 months. 12 days in one case.

— All patients who strictly followed the treatment showed marked repigmentation of the vitiliginous areas.

— Amodiaquin in general is more effective but it causes more tanning of the exposed healthy skin. It is of interest to mention that the storing capacity in the epidermis to dermis is 15: 1 in amodiaquin and is only 5: 1 in chloroquine [32].

— Whether the treatment needs, maintenance doses or not, it is too early to judge but it seems that maintenance doses are needed in some cases.

— A hint in treatment was to postpone exposure to irradiation 2–3 weeks after beginning of combined treatment and to encourage exposure to sun and ultraviolet when the follicular repigmentary spots appear..

— There is a definite benificial synergestic action between meladenine and quinoline derivatives in treatment of vitiligo.

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