Part V
Clinical Applications of Psoralens, and Related Materials

VITILIGO—WHAT IS IT?*

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When I first became interested in vitiligo in connection with psoralen therapy, the answer to the question: what is vitiligo? seemed to be very simple. Every textbook gives a clear-cut definition.

DEFINITION

To quote Ormsby-Montgomery (1): "Vitiligo is an acquired cutaneous achromia characterized by variously sized and shaped single or multiple patches of milk white color, usually presenting hyperpigmented borders and a tendency to enlarge peripherally." The authors add to this: "Absence of pigment. . . is the only symptom in vitiligo". . . . "The skin. . . presents no textural changes and is normal in every way except a sensitiveness to solar irradiation". . . "the cause of vitiligo is unknown". . . "the treatment of the disorder is unsatisfactory".

Other books offer similar definitions, all of them almost completely negative, except for that one positive fact: acquired loss of pigment with a general progressive tendency.

The attribute "acquired" differentiates vitiligo from partial albinism which is congenital. The attribute "progressive" also sets it apart from albinism in which the white areas do not enlarge, and from leukodermas following injury, such as superficial burns, or inflammatory dermatoses, such as syphilis or psoriasis. These secondary leukodermas generally are transient and decrease rather than increase with time.

Now, several years later, after observing numerous cases of vitiligo closely, following their

course with and without therapy, and reading whatever could be found in the literature, the picture has become more diversified and even more puzzling.

CLINICAL MORPHOLOGY

Concerning the clinical picture and course, it is certainly true that most lesions show a complete absence of pigment and a tendency to progress. However, some patients report that every summer, on exposure to sunshine, there is some repigmentation from the borders, and small pigmented, freckle-like spots may appear in the center of white areas, only to disappear again during the winter. The difference is a real one and is not due to enhanced color contrast between tanned and vitiliginous skin in the summer. Repigmentation of some degree occurs in 50% of patients according to Lerner (2).

Other patients exhibit what Siemens (3) recently has called "vitiligo gradata", a graded, step-wise diminution of pigment. This feature is especially noticeable in colored skin, but may be observed in whites. Between the normal and the totally depigmented skin, there are zones of varying width exhibiting an intermediate hue. The borders always are sharp, not shading gradually. The German term "Stufen-Vitiligo" (vitiligo by steps) expresses this phenomenon. While Siemens describes this as a secondary development due to partial repigmentation, I have seen it also in progressing lesions as a step-wise depigmentation.

Another peculiar experience is that patients under treatment with methoxsalen may show repigmentation of the majority of areas, while others may progress. New areas even may appear.

The hyperpigmented border, mentioned by many authors, has been explained as an optical illusion by others. We will see later that there is histologic evidence that hyperpigmentation is indeed present. It is often quite prominent when repigmentation occurs under therapy.

Another point worth mentioning is the behavior of hair color. In some vitiliginous patches, the hairs retain their natural color, even in large areas of long standing. In other cases, the hairs become white sooner or later. In this connection, it has been a general experience that the freckle-like pigment spots, which appear within vitiliginous areas spontaneously or under therapy, almost always are perifollicular and seem to occur only where the hairs have preserved their color. It is quite rare for new centers of pigment to appear on the non-hairy surfaces. Prognosis for repigmentation is better if the color of the hair is preserved because each hair may then serve as a center from which pigmentation spreads. On the other hand, the epidermis of relatively small areas may become repigmented from the borders even though the hairs remain white. In rare cases, white hairs may turn dark again under treatment.

The pigmentary systems of epidermis and hairs thus seem to be under independent control. Similarly Iijima and Kanazawa (4) observed that a blue nevus did not depigment and retained a positive dopa reaction when the epidermis above it become vitiliginous. Another peculiar observation is the "halo nevus" or leucoderma acquisitum centrifugum (Sutton (5)). Here a brown mole becomes surrounded by a depigmented halo that has all the earmarks of vitiligo and may be associated with other vitiliginous patches in the same patient. It happens not infrequently that eventually the central nevus also becomes depigmented. It may even disappear completely, being destroyed or absorbed by inflammatory infiltrate.

ASSOCIATED LOCAL CHANGES

The statement that absence of melanin is the only symptom in vitiligo has been challenged repeatedly. Even Ormsby-Montgomery write that histologic evidence of mild inflammation is found in the border of the lesions. Cases have been reported in which there was a narrow inflamed edge around the enlarging areas of vitiligo (Habermann (6)).

Habermann (6) writing in *Jadassohn's Handbuch* in 1933 quotes a variety of contradictory observations that the vitiliginous skin is either more or less susceptible to irritants such as croton oil or mustard, and shows hyperreactivity or hyporeactivity when tested with old tuberculin, diphtheria toxin and other allergens.

Diminution of spontaneous sweating and of sweat response to pilocarpin has been reported by several authors, but has been denied by others (7). Among recent authors, Halter (8) found heat sweating absent in vitiliginous skin although response to pilocarpin was not disturbed. Lerner (9) reports that under resting conditions, more sweat occurs in areas of vitiligo than on adjacent normal skin and that the electrical resistance is decreased in the vitiliginous areas (2). Lerner (9) also quotes reports that blood vessels are constricted in patches of vitiligo and that vitiliginous skin does not become yellow during jaundice or on ingestion of atabrine. Hypesthesia has been claimed occasionally to occur in cases in which leprosy could be ruled out. Habermann wonders whether such cases may not have been incipient tabes dorsalis in which according to him, vitiligo is found not infrequently.

ASSOCIATION WITH SYSTEMIC DISEASE

This brings up the much discussed question of systemic diseases associated with and perhaps causative of vitiligo. Habermann listed the following:

Vitiligo and Systemic Disease

A. Diseases of the Nervous System
   a. psychic disturbances and neuroses
   b. disorders of sensory or motor nerves
   c. disorders of the vegetative nervous system
B. Endocrine Disorders
   a. thyroid (hyper- or hypo-)
   b. adrenals
   c. ovaries
   d. others (parathyroid, thymus, pituitary)
C. Infectious Diseases
   a. syphilis
   b. tuberculosis
   c. others (typhoid, scarlet fever, etc.)
D. Other Systemic Diseases
   a. pernicious anemia
   b. alcoholism
   c. liver, kidney, gastro-intestinal

Most of these reports are based on few or even individual cases in which the association certainly could have been coincidental. Among the few correlations that seem to be more valid, is that with thyroid dysfunction, especially with thyrotoxicosis in which figures as high as ten per cent have been reported (Habermann). Allison and Curtis (10) found an association of pernicious

anemia and vitiligo in 22 cases out of 801,670 hospital admissions. Chance would have accounted for only one case of this combination. Lerner (2) found a tendency to hypochlorhydria in a study of 25 patients. Excretion of noradrenaline and melanocyte stimulating hormone was normal in the same group of patients. So were liver and thyroid function tests. Agarwala *et al.* (11) found 17-ketosteroid excretion increased.

The relationship of vitiligo to syphilis deserves a few comments. It is well known that secondary syphilis may give rise to a characteristic and long lasting leukoderma, which should not be confused with true vitiligo. Tabes dorsalis, formerly of very widespread occurrence, was implicated because it is a nervous disorder, and the influence of the nervous system on pigmentation has been discussed by many and for a long time. Lerner (2) recently proposed the hypothesis that vitiligo may result from increased activity of the sympathetic nerves in the skin. It seems that the causative role of syphilis had proponents especially in France. Habermann wrote that in France, even in 1933, most cases of vitiligo were subjected to thorough antisyphilitic treatment (pg. 933).

HISTOPATHOLOGIC CHANGES

In this confusion of opinions it is tempting to turn to histopathologic examination for some solid ground. Unfortunately, histologic data are not too numerous. Many of the older ones must be discounted because in a disease affecting the pigment forming mechanism of the skin, exact knowledge of that mechanism under normal conditions is essential for correct interpretation of its pathology. It has not been too many years that the melanocyte has been recognized as the sole pigment forming cell and its extra-epidermal derivation acknowledged by the great majority of investigators. Becker, Jr. *et al.* (12) have demonstrated the presence of junctional cells, corresponding to melanocytes, but lacking the ability of forming pigment, in sections of vitiligo. They used gold impregnation for this purpose. These "clear cells" or "white melanocytes" can be seen at the dermo-epidermal junction in H and E sections. All that is lacking is enzyme activity when the sections are treated with dopa or tyrosine, and of course there are no melanin granules in melanocytes or epidermal cells. On the other hand, one often sees unusually large, highly dendritic, and highly melanized cells at

the border of the vitiliginous area. Here, one also finds melanin-carrying macrophages in the cutis, and often there is more or less inflammatory infiltrate around blood vessels of the upper corium. These changes probably are responsible for the clinical impression of a hyperpigmented areola.

Pathological changes of myelinated and nonmyelinated nerve fibers have been claimed by some old and recent investigators, but these findings need confirmation. Histamin (Quiroga *et al.* (13)) and sulfhydryl groups (Lajmanovich and Magnin (14)) have been reported present in normal quantity.

DISCUSSION

Vitiligo seems to be an achromia of the skin, due not to any marked anatomical disturbance, but purely to a functional abnormality of the melanocytes. If the literature offers any hint to an underlying systemic disturbance, this may be in the neuro-endocrine field. Familial incidence is common (Lerner (2)).

There have been several attempts to elucidate the seat of the disturbance in the skin by exchange transplantation between normal and vitiliginous areas. Results have been somewhat contradictory. Haxthausen (quoted by Tolmach (15)) found that split skin grafts changed color quickly. Comel's (16) pedicle grafts preserved their original color for several months, then assumed the character of the surrounding skin. Spencer (17) and Spencer and Tolmach (18) found that full thickness grafts preserved their original characteristics for as long as 16 months. Kato (19) confirmed this difference in the behavior of thin and thick grafts. There is, however, in the work of Gillman *et al.* (20) some indication that the epidermis of split skin grafts may be replaced by hair sheath cells of the host site even after the graft seemingly has taken successfully. This line of experimentation thus has not been too helpful. If anything, the results seem to argue against any immediate neural control of pigmentation.

There are a few clinical peculiarities which make one wonder what the actual mechanism of melanocyte inhibition is. In most cases, there is an all-or-nothing effect. Not only clinically, even under the microscope, the transition from normal to abnormal skin is abrupt. Also, if repigmentation takes place spontaneously or under therapy, it does not come in the form of gradual darkening of the entire area, but by creeping extension of pigment from the borders or from perifollicular
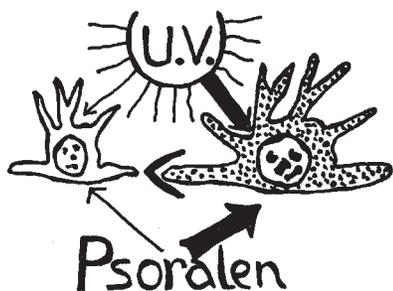
FIG. 1

foci. As the latter form only where the hair is pigmented, it seems a fair assumption that melanocytes in the hair bulb serve as a source of new pigment.

Theoretically, two mechanisms seem plausible at the cellular level. Either, there is in vitiligo a heritable change of melanocytes in certain foci, and these abnormal achromatic melanocytes multiply and push back the normal ones. In repigmentation the tide of battle turns and the abnormal cells are crowded out. Or, the cells stay where they are and there is an "infectious" spread of inhibition of pigment formation from cell to cell. Inhibition may result from some kind of blockage of the enzyme or from actual loss of the enzyme forming mechanism. Repigmentation then would take place by a similar "infectious" spread of either the enzyme mechanism or an "unblocking" agent. Examples for either cell migration or infectious spread of pigment forming ability are present in experimental work in animals.

In any case, the therapeutic action of the psoralens in vitiligo seems to require the presence of four cooperating factors: The drug, photochemical energy, the presence of achromatic "diseased" melanocytes, and last but not least, the presence of normal melanocytes in contact with the diseased ones. It seems open to argument whether the drug and ultraviolet exert their influence on the diseased cell, or perhaps rather on the normal one, if not both (Fig. 1).

SUMMARY

(1) Vitiligo is an acquired progressive achromia due to loss of function of the tyrosinase system of the melanocytes at the epidermo-dermal junction.

(2) Clinical peculiarities and systemic associations of vitiligo are reviewed.

(3) The importance of the presence of functional melanocytes in contact with the diseased

ones is emphasized in the explanation of spontaneous and therapeutic repigmentation, and the question is raised whether the psoralens exert their action on the normal melanocyte rather than on the diseased one.

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Psoralen (also called psoralene) is the parent compound in a family of naturally occurring organic compounds known as the linear furanocoumarins. It is structurally related to coumarin by the addition of a fused furan ring, and may be considered as a derivative of umbelliferone. Psoralen occurs naturally in the seeds of Psoralea corylifolia, as well as in the common fig, celery, parsley, West Indian satinwood, and in all citrus fruits. It is widely used in PUVA (psoralen + UVA) treatment for psoriasis