AUGUST 1971

The American Journal of Medicine

VOLUME 51

NUMBER 2

EDITORIAL

On the Etiology of Vitiligo and Gray Hair

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The loss of melanin pigment that occurs in patients with vitiligo nearly always poses severe cosmetic problems and in some cases indicates the presence of a systemic disease. At least 1 per cent of the world's population has vitiligo. In countries where people are dark skinned vitiligo is a major health problem. As a result of documenting the clinical findings in hundreds of patients with vitiligo, working with the chemicals that produce depigmentation and studying the advances made in the biology of melanocytes, I want to suggest that in vitiligo and physiologic graying of hair the melanocytes are destroyed by the very factors required for the production of melanin.

CLINICAL PICTURE OF VITILIGO

Hypopigmented areas appear on the skin of a subject with normal pigmentation. Part or all of a body surface may be involved, but the most common sites of pigment loss are (Figure 1) exposed regions—face, backs of hands, upper part of the chest; body folds—axillas and groin; around the orifices—eyes, nostrils, mouth, ears, nipples, umbilicus, penis, vulva and anus; around nevi; areas of trauma and pressure—under watch bands, bra straps, belts, etc.; hair; cutaneous segments supplied by a nerve, in which case the pigment loss is called segmental vitiligo. Varying degrees of hypopigmentation may occur, and in some cases light patches may show hyperpigmented borders.

Vitiligo can begin at any age, but in half of all affected patients its onset is noted before the age of twenty [1]. In more than half there is a family history of vitiligo or early graying of

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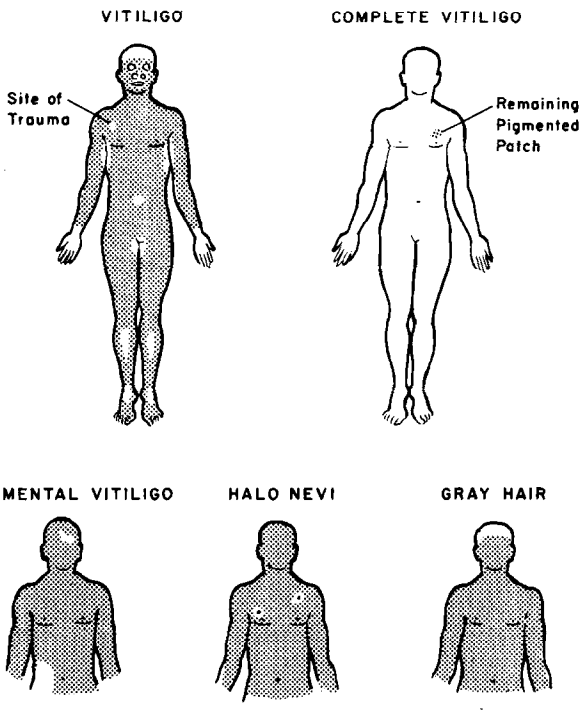

Figure 1. *Clinical forms of vitiligo.*

hair. In people with light complexions it is common for vitiligo to become apparent for the first time during the summer when a suntan accentuates the contrast between depigmented and normal skin. The disorder may occur spontaneously, or it may be precipitated by sunburn or severe physical or emotional trauma. Usually the rate of pigment loss decreases a year or two after the onset of vitiligo. A subsequent stress may trigger another episode of pigment loss. In time the hypopigmentation spreads and the entire body (but not the eyes) may become white. Spontaneous repigmentation is rare. Vitiligo occurs in horses and elephants as well as in man.

Graying of hair is commonly considered a sign of aging. However, patients with vitiligo as well as other members of their family frequently have prematurely gray hair. Ordinary graying of hair, representing as it does pigment loss, can be considered a manifestation of the vitiliginous process; in that sense in everyone who lives long enough vitiligo develops. However, most people with gray hair do not have vitiligo of the skin. Many children and teenagers have halo nevi, i.e., hypopigmented rings surrounding dark nevi. Although in most of these people there is no pigment loss in other areas, halo nevi do develop in 50 per cent of the patients with vitiligo. Sometimes the skin over dark subcutaneous nodules from melanomas becomes white, and the tumors are referred to as halo metastases.

Examination of biopsy specimens of skin by light and electron microscopy reveals that melanocytes are absent in the vitiliginous areas. In contrast, in generalized albinism melanocytes are present but do not produce pigment.

It is significant that the normally dark areas of the skin surface are the very places that become hypopigmented in vitiligo. Stated differently, the production of melanin can predispose the melanocytes to pigment loss. This thought will be explored later.

DISORDERS ASSOCIATED WITH INCREASED INCIDENCE OF VITILIGO

Most patients with vitiligo are in good general health. However, in patients with the following diseases the incidence of vitiligo is increased: adrenocortical insufficiency, hyperthyroidism, alopecia areata, pernicious anemia, melanoma, scleroderma and morphea.

Addison, in his first description of eleven or possibly twelve patients with adrenocortical insufficiency, noted that in addition to hyperpigmentation two patients had vitiligo [2]. Since that time many physicians have cited the simultaneous occurrence of hyperpigmentation and spreading vitiligo as evidence of Addison's disease. Vitiligo occurs in patients with Addison's disease whether the adrenal insufficiency is idiopathic or a result of tuberculosis. Hyperthyroidism is the only other endocrine disorder in which hyper- and hypopigmentation occur in the same patient.

It is not unusual for physicians to link hyperthyroidism with early graying of hair. In addition, in some patients there is a loss of cutaneous pigment which may progress to total vitiligo. When this happens the patient as well as the physician frequently and incorrectly state that the vitiligo was cured.

Alopecia areata is characterized by round bald patches on the scalp, bearded area and extremities. Hair may be lost from the eyebrow, eyelids and any other part of the body. When the hair grows back it is often white or of a lighter shade than the original. Eventually all the pigment may return. Patients with alopecia areata often have vitiligo in addition to light colored hair. Some of them have total alopecia and total vitiligo. It is not unusual to see the triad of vitiligo, hyperthyroidism and alopecia areata.

Early graying of hair also occurs in pernicious

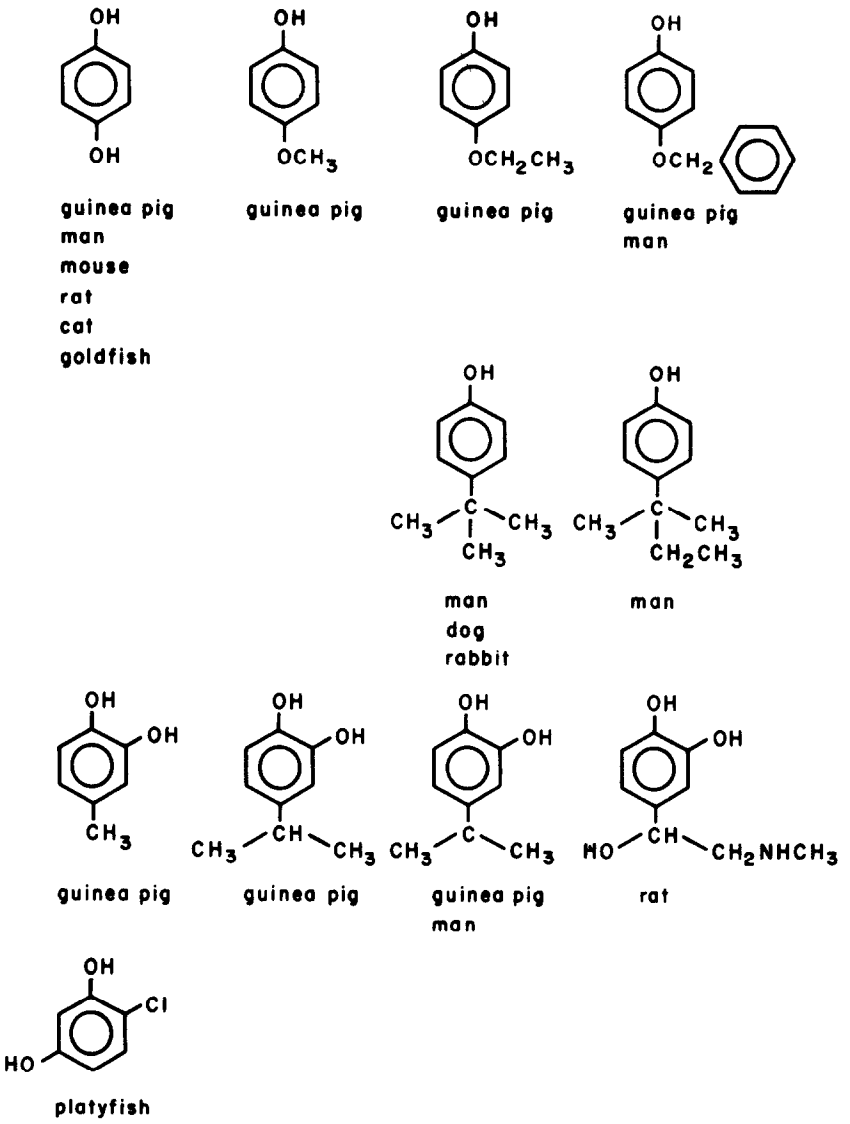

Figure 2. A variety of phenols and catechols can produce depigmentation in the animals indicated. Hydroquinone and monobenzyl ether of hydroquinone are used clinically to depigment patients with vitiligo. The chemicals are as follows (left to right): Top row: hydroquinone, monomethyl ether of hydroquinone (hydroxyanisole), monoethyl ether of hydroquinone and monobenzyl ether of hydroquinone. 2nd row: p-tertiary butylphenol, p-tertiary amylphenol. 3rd row: 4-methylcatechol, 4-isopropylcatechol, 4-tertiary butylcatechol and adrenaline. 4th row: 4-chlororesorcinol.

anemia, and the incidence of vitiligo in that disease is at least 8 per cent. Unlike hyperthyroidism and vitiligo, alopecia areata is not associated with pernicious anemia.

In patients with melanomas originating from the skin or eye the incidence of vitiligo is high, and halo metastases may occur in the skin.

Hyperpigmentation followed by hypopigmentation is common in generalized scleroderma. Except for numerous small islands of normal, perifollicular pigment throughout the depigmented areas on the trunk and upper parts of the arms, the hypopigmentation in scleroderma, although striking, does not resemble ordinary vitiligo. Morphea or localized scleroderma, unrelated to generalized scleroderma, also is associated with an increased incidence of ordinary and/or segmental vitiligo.

CHEMICAL DEPIGMENTATION

The chemicals that stop melanin production in man and animals and thereby produce depigmentation are almost without exception phenolic or thio compounds. Of these two groups the phenolic substances, both mono- and dihydroxyphenyl derivatives, are of far greater significance today. Numerous phenolic compounds used industrially have been responsible for loss of pigment in workers who come in contact with them [10–13] (Figure 2). Two phenols are used therapeutically to produce total depigmentation in patients with extensive vitiligo in order to achieve uniform coloring. In this discussion only the hydroxylated phenyl compounds will be examined in detail.

In 1936 it was reported that hydroquinone fed to black cats produced gray hair [3]. Subsequently

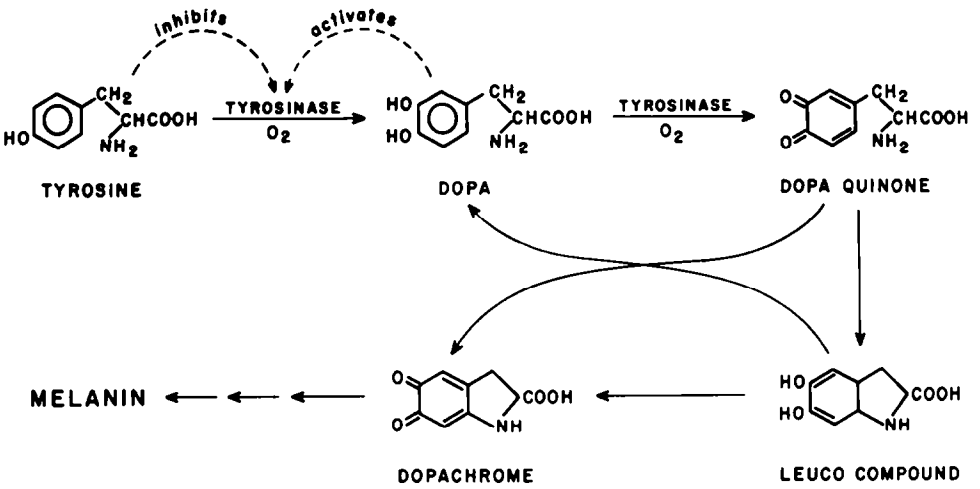

Figure 3. Tyrosine and dopa are the normal precursors of melanin. Tyrosinase, a copper containing enzyme located in melanosomes, catalyzes the hydroxylation of tyrosine to dopa and then the dehydrogenation of dopa to dopa quinone. Several peculiarities about the process stand out. To start the reaction tyrosinase must be activated by dopa. Increasing the amounts of tyrosine blocks the priming by dopa. This situation is opposite that of most enzymic reactions in which an excess of product slows the reaction and an excess of substrate speeds it up. Even though dopa is rapidly dehydrogenated to dopa quinone, dopa is kept in the system to activate tyrosinase by being reformed in a subsequent step in which some dopa quinone is reduced back to dopa. Very large quantities of dopa, unlike small amounts, have an effect like that of tyrosine. In cultured melanocytes dopa can slow both protein and DNA synthesis.

it was shown that exposure to hydroquinone caused depigmentation of pigment cells in mice, rats, black goldfish, guinea pigs and man [4–9]. In 1939 industrial workers in contact with monobenzyl ether of hydroquinone observed loss of skin color [10]. Within the past few years phenols, used as germicides in detergents or in the manufacture of resins, and catechols, used as antioxidants in industrial oils, have been found to produce depigmentation in man [11–13]. Adrenaline, a catechol derivative, induces graying of hair in rats [14,15]. The most common phenols and catechols that prevent melanin formation are listed in Figure 2. As a general rule all phenols and catechols can cause depigmentation.

Two separate approaches have been used to determine how the hydroxylated phenyl compounds operate. In one the effect of these compounds on the enzymic conversion of tyrosine to melanin in vitro has been studied. In the other cytologic changes in melanocytes in vivo and in tissue culture have been investigated. From the first approach it was learned that most of these chemicals block the hydroxylation of tyrosine to dopa [5,16]. It is not clear whether or not the next step, the enzymic oxidation of dopa, is affected. Excess of the natural substrate tyrosine, a monophenol, inhibits the tyrosine-tyrosinase reaction (Figure 3). Dopa, which is needed to prime tyrosinase so that the enzyme will work with tyrosine, administered in large amounts can slow the reaction in vitro. It would appear that pigment loss results from inhibition of tyrosinase by phenols or catechols and the subsequent cessation of melanin formation.

However, from microscopic examination of pigment cells another picture emerges. The phenols and catechols named in Figure 2 were found to have a rapid and profound effect on melanocyte structure [6–9,11,12,17–19]. For example, injection of small quantities of hydroquinone into black goldfish produces cytologic changes in one to two hours [6]. All experimental topical applications of these compounds to man or animals produced some degree of melanocyte destruction. In human beings histologic or electron microscopic studies of depigmented skin revealed changes similar to those found in vitiligo. Melanocytes were altered and missing in varying degrees.

Two current reports of tissue culture experiments bear on this topic. In one the monomethyl ether of hydroquinone (hydroxyanisole) as well as two catechol derivatives produced severe damage to normal guinea pig melanocytes carried in culture [20]. In the second investigation malignant melanocytes from the Harding-Passey mouse mel-

anoma showed a decrease in leucine and tyrosine incorporation when grown in the presence of dopa [21]. These investigators concluded that the oxidation products of dopa inhibited protein synthesis within the cultured melanocytes. Increasing the opacity of the cells, i.e., increasing melanin formation, was associated with a decrease in the rate of cellular DNA synthesis as followed by thymidine incorporation.

From the results of both the enzymic and cytologic investigations it is reasonable to conclude that substances that block the tyrosine-tyrosinase reaction directly or indirectly exert a cytotoxic effect on melanocytes.

SELF DESTRUCTION OF MELANOCYTES

From clinical studies we know that people with vitiligo are predisposed genetically to pigment loss. The gradation of pigment loss depends on the number of surviving melanocytes. The areas that most frequently lose pigment are those that are normally hyperpigmented. A classic example is the halo nevus: not only do the melanocytes around the nevus disappear but also the nevus itself may vanish. The more pigment produced by a given group of melanocytes, the greater the tendency for the cells themselves to disappear.

Patients with decreased adrenocortical function have an increased output of pituitary melanocyte stimulating hormone (MSH) that results in skin darkening. MSH in turn increases the level of cyclic 3′,5′ adenosine monophosphate (cAMP) within the melanocytes, and then the cAMP probably induces tyrosinase synthesis [22,23]. After these events the patients become predisposed to vitiligo. Again, the increased pigment forming capacity of the melanocyte seems to lead to its own destruction. The skin of patients with hyperthyroidism also can become dark. Whether hyperpigmentation results from an increase in pituitary MSH or a separate thyroid darkening factor has not been established. Vitiligo occurs in association with hyperthyroidism whether or not the patient's skin darkens. The increased responsiveness of hyperthyroid patients to adrenaline may play a role in predisposing them to vitiligo. Some patients with hyperthyroidism also have alopecia areata. When new hairs grow in the bald area they may be lighter in color than the original because melanocytes probably regenerate more slowly than keratin forming cells.

The lemon yellow coloring in patients with pernicious anemia results from heme products, not melanin, so the explanation for the high incidence of vitiligo in these patients cannot be the same as that in patients with thyroid or adrenal disease. However, the basic neurologic defect in pernicious anemia may affect more than one kind of nerve cell, including melanocytes which are derived from neural tissue. Although the subcellular lesion in the melanocytes of patients with pernicious anemia may not be the same as that in the melanocytes of patients with ordinary vitiligo, the end effect could be the same.

In patients with metastatic melanomas functioning tyrosinase and tissue levels of melanin precursors are increased. The incidence of vitiligo also is high, and some patients exhibit halo metastases. Again, increased melanin production is associated with vitiligo.

Several salient points bear reiteration. The greater the pigment producing activity of a melanocyte the less likely are its chances for survival. Most phenol and catechol derivatives of either natural or synthetic origin can in the proper concentration inhibit the tyrosine-tyrosinase reaction. The same substances also can produce lethal changes in melanocytes. It is possible that pigment cells are exquisitely sensitive to phenols, catechols or the phenol-tyrosinase complex but under ordinary circumstances have a protective mechanism against them. The protective process must be a labile one because of the ease with which it is disrupted. When disruption does occur the amino acids, tyrosine or dopa, or other melanin intermediates destroy the melanocyte.

In what other disorders can one evoke a mechanism in which cells destroy themselves? Perhaps idiopathic adrenocortical insufficiency is one. Cortisol causes atrophy of collagen by suppressing fibrocytes. Maybe the adrenal cortex also is sensitive to cortisol but has a built-in method to avoid self destruction. Once the protective mechanism were lost the entire cortex could atrophy. Other kinds of disease states thought to be autoimmune in nature might belong in a cell self destruction group.

AUTOIMMUNE AND NEURAL CONCEPTS OF VITILIGO

Vitiligo was a disorder without a plausible etiology until a decade ago. Two hypotheses evolved, one based on an autoimmune and the other on a neural interpretation of vitiligo [1,24–27]. According to the autoimmune theory, antibodies to melanin or a melanocyte structure form and de-

stroy the pigment cells [24–26]. Halo nevi, halo metastases from melanomas and vitiligo in patients with melanomas are thus easily explained. Autoimmune disorders such as hyperthyroidism, Addison's disease and pernicious anemia would by some unknown mechanism produce antibodies to melanocytes. The same would hold true for the few patients who manifest a generalized exfoliative dermatitis from a drug allergy and in whom total alopecia and total vitiligo subsequently develop. The finding of increased levels of antibodies to melanin in patients with vitiligo [28] is consistent with either an autoimmune or a cell destruct system. But the timing would differ: in one case antibodies cause melanocyte loss, whereas in the other antibodies are produced following cell damage.

Although the autoimmune concept of vitiligo is attractive it fails to account for several facts. For example, vitiligo may be associated with adrenocortical insufficiency of either the idiopathic autoimmune or the tubercular variety. The hypothesis does not account for segmental vitiligo. The rapid action of phenols and catechols in fish and in cultured mammalian melanocytes does not support an autoimmune concept. A different mechanism for the action of these chemicals on melanocytes must be formulated. The presence of an inflammatory infiltrate in the dermis of halo nevi and about the pilosebaceous apparatus in alopecia areata has been used to support an autoimmune etiology for both conditions. However, the common denominator in these cases as well as for the infiltrate observed in skin following the application of phenols and catechols may simply be the tissue response to damaged melanocytes and not to an antigen-antibody reaction.

The neural hypothesis focuses on the fact that melanocytes are nerve cells. Accordingly, hypopigmentation occurs when excessive amounts of a neurocytotoxic agent are released near or within melanocytes [27]. This concept in which the action of phenols and catechols would mimic the neural factor is useful for understanding segmental vitiligo as well as vitiligo associated with hyperthyroidism and pernicious anemia.

TESTING THE HYPOTHESIS

If the sites that lose pigment are those that most actively metabolize phenols and catechols to melanin, it should be possible to anticipate several events as well as design experiments to test the hypothesis. One frequently hears the following question. "Because dopa can form melanin, do patients ingesting L-dopa turn dark?" From the proposed theory the opposite would be expected, namely, in patients receiving L-dopa the incidence of vitiligo and graying of hair should be high. Clinical observations should reveal that although the incidence of vitiligo in patients with melanoma is high, segmental depigmentation does not occur. It might not be appropriate to expect people with dark skin and hair to lose pigment more easily than those with light coloring because the protective mechanisms against melanocyte destruction may be greater in those with darker coloring. On the other hand, a person with hair of mixed shades should, when he begins to gray, lose pigment from the darker hairs first.

MSH and cAMP in vivo and in vitro darken melanocytes. They also should make these cells more sensitive to damage by phenols and catechols. That is, MSH and cAMP could be used to prime melanocytes for destruction. In addition the hydroxyindoles that result from the conversion of dopa to melanin would be expected to retard melanocyte growth. The appearance of Langerhans cells following disappearance of melanocytes must be studied to determine whether or not parts of melanocytes evoke the proliferation of Langerhans cells.

SUMMARY

From an analysis of the clinical features of vitiligo and of the chemicals that cause depigmentation, a melanocyte self-destruct hypothesis for the etiology of vitiligo and graying of hair can be derived. A melanin precursor, one that is either a phenol or a catechol derivative or the phenol-tyrosinase complex, is lethal for melanocytes. When the natural mechanism that protects against the precursor is lost, the melanocytes are destroyed.

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