# VITILIGO

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THE incidence of vitiligo among Indian population is thought to be about 3% compared to about 1% of world population[1]. There is urgent need for research on vitiligo since very little is known about it and since it affects a large population of India[2-4].

*What is vitiligo*: Vitiligo is hypomelanotic disorder. It is characterised by patchy depigmentation of skin. It may be localised giving rise to focal vitiligo, segmental *i.e.* strictly unilateral, or generalised when more than one area is involved. Although the distribution of depigmentation cannot be predicted, it frequently occurs around the body orifices and in areas of repeated local trauma. Usually vitiligenous macules (or areas) are asymptomatic. Apart from the absence of melanin and identifiable melanocytes, the vitiligenous epidermis appears to be normal. The exception to this conclusion is the recent observation that vacuolated keratinocytes have been observed in the normally pigmented perilesional skin of vitiligo patients[5]. The vitiligo patients can otherwise be healthy but there are certain disorders more often associated with it[4].

Vitiligo is not an infectious disease. Its etiology is far from clear although many theories were put forward. The major theories could be listed as (i) genetic theory, (ii) melanocyte self destruction theory, (iii) neural control theory and (iv) autoimmune hypothesis[1,2,4].

All the theories for the etiology of vitiligo suggest that melanocytes are absent in the vitiligo macule since they are destroyed by different mechanisms in different theories. Yet no microscopic evidence exists for the actual dissolution and disruption of melanocytes in the vitiligo skin. This is a serious drawback of all these theories.

*Existence of inactive melanocytes in vitiligo*: Although identifiable melanocytes are absent in vitiligo patches[6], indeterminate cells or α-dendritic cells are observed in vitiligo macules[7], and the work of Mishima *et al*[8] suggests a dynamic interrelationship between melanocytes and indeterminate cells. According to this hypothesis the indeterminate cells are inactive melanocytes and they increase in proportion to the disappearance of active melanocytes in vitiligo. This theory was supported from various points of view[9-11]. Thus whether melanocytes are destroyed or their active melanising ability is lost in vitiligo, remains yet to be resolved.

## MELANIN SYNTHESIS AND ITS CONTROL

Human skin colour: Normal colour of human skin is mainly due to melanin pigment in the skin, located in a very small granule called the melanosome[11a]. The melanosomes are formed in the melanocytes. They are transferred into the keratinocytes directly by phagocytosis of dendrites containing melanosomes of melanocyte[12-14]. These are distributed throughout the epidermis by the outward movement of the keratinocytes and thus contribute to the colour of the skin. Racial differences in colour among humans are not due to quantitative differences in the number of melanocytes in the skin but apparently due to differences in the number of melanosomes, their size and the distribution within keratinocytes[15]. For instance the melanosomes in Negroid skin are numerous[16], longer and wider than those in caucosoids and unassociated[17]. These differences are responsible for the darker Negroid skin in contrast to the caucasian skin.

*Melanins*: There are two major classes of integumentary melanins. The blackish brown ones are called eumelanins and the yellow to red melanins are called the phenomelanins Melanin

is most conspicuous absorber of visible and longwave ultraviolet radiation and of free radicals in skin[17a–19]. Melanins thus act as a filter for biologically harmful radiations from the sun. The biosynthesis of Eumelanins[20–25] and pheomelanins are discribed in figures 1 and 2. Eumelanins are almost insoluble in all solvents while pheomelanins are soluble in dilute alkali. A protein matrix is a prerequsite for Eumelanin formation in the melanosome while pheomelanin granules develop without an organised protein skeleton[25].

*The chemistry of melanogenesis*: The early stages of mammalian melanogenesis involve the conversion of tyrosine to 3,4-dihydroxyphenyl alanine (dopa) and its further oxidation to dopa quinone. These reactions are catalysed by tyrosinase[26–29] (E.C.1.4.18.1). The first one is called cresolase activity and the later as dopa oxidase activity. The cresolase activity of tyrosinase obtained from many sources has a characteristic lag, it is inhibited by excess tyrosine and has the essential requirement of 3,4-dihydroxyphenylalanine as the hydrogen donor[11,29–37]. These properties disappear when the human skin tyrosinase is partially purified[38]. Further studies on the tyrosinase from human skin and from murine melanoma reveal that these properties can be modulated by pH or pH and tyrosine (Chaya and Ramaiah, Tripathi and Ramaiah—unpublished observations) and may have important implications in the regulation of melanin synthesis. The partially purified enzyme is inhibited by a protein which is present in the cytosol as well as in the melanosomes[38] and by various dialysable factors in the skin homogenate[11]. In addition, the recent reports indicate that there is an additional enzyme involved in the conversion of dopachrome[39] (5th reaction in figure 2). Moreover, factors are isolated which could accelerate or block conversion of 5,6-dihydroxy indole to indole 5,6-quinone[40]. The role of these factors in the regulation of melanin synthesis is yet to be clearly established.

*Approaches to the problem*: Whether the lack of

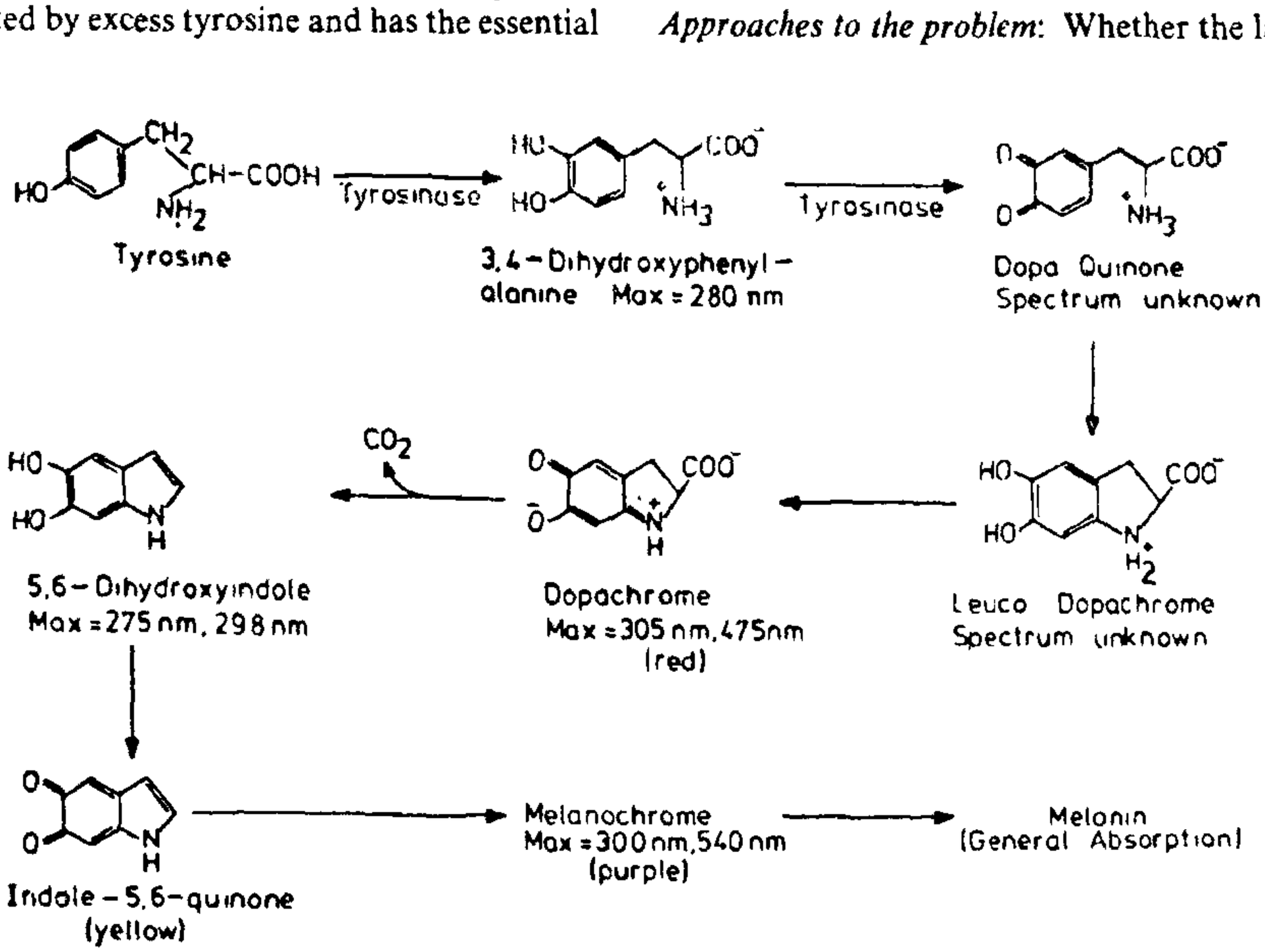


**Figure 1.** Schematic representation of Eumelanin biosynthesis.

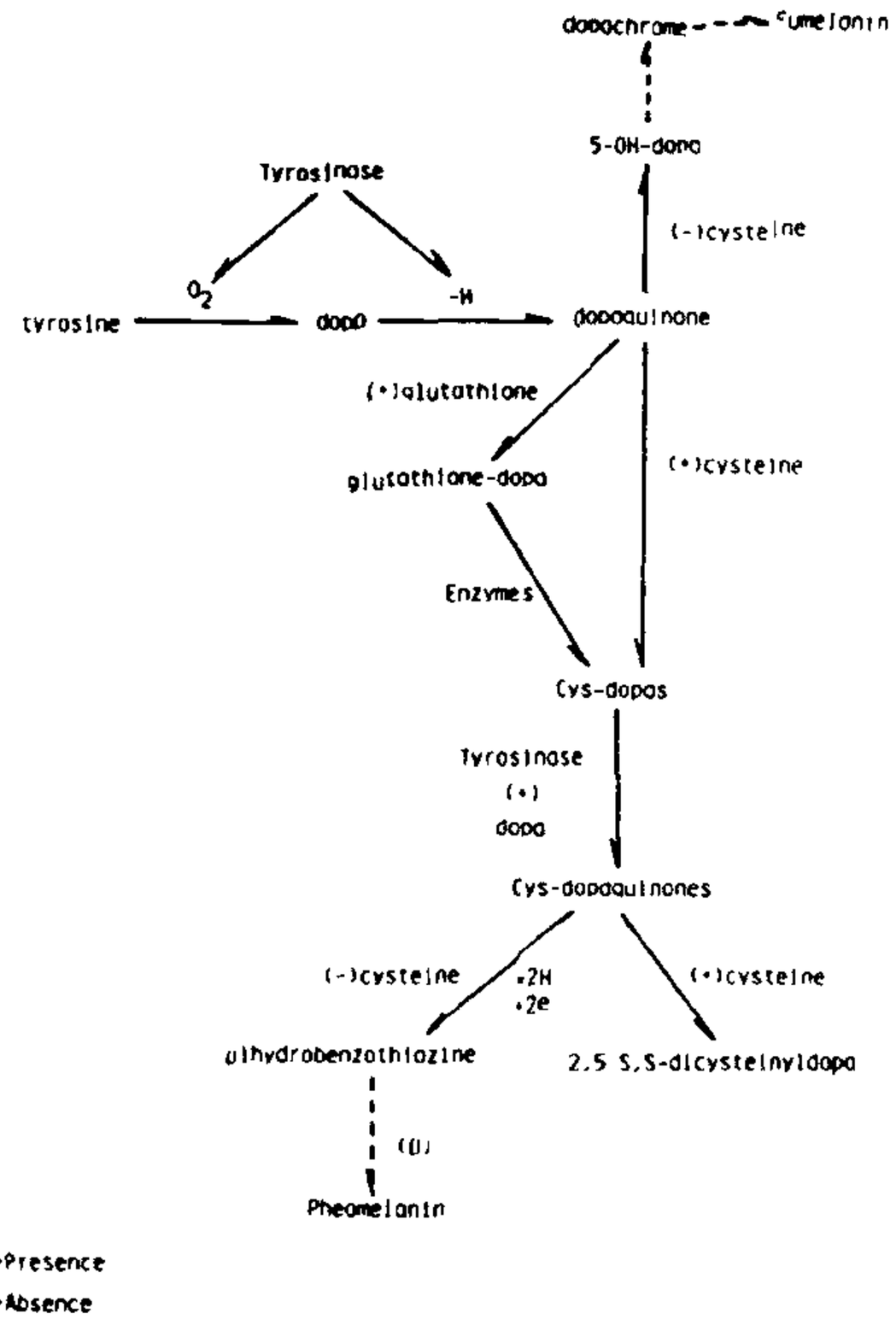


**Figure 2.** Schematic representation of Pheomelanin biosynthesis.

melanin in vitiligo skin is due to the lack of melanocytes or due to the inhibition of melanin synthesis and consequent conversion of melanocytes to inactive melanocytes is an important question to answer, before a clear understanding of vitiligo and its cure is accomplished. The most recent report[41] identified a hypothalamic growth factor, from Bovine hypothalamus which specifically stimulated growth of melanocytes in vitro. Such a growth factor may also be present in hypothalamus of human beings and alteration of its level or its modification may lead to the decrease or elimination of melanocytes from the epidermis. Answers to these questions can now be obtained with the recent successful developments of methods for culturing of melanocytes *in vitro*[41,42]. In absence of melanin synthesis the melanocytes cannot be unequivocally identified by the existing methods. In tissue culture, in the presence of cholera toxin and phorobol ester, melanocytes were shown not only to multiply but also to synthesize melanin. Under these conditions or in presence of the hypothalamic growth factor which stimulates melanocyte multiplication, the inactive melanocytes, if present in vitiligo skin could be stimulated to synthesize melanin and thus be identified. These experiments are already in progress in our laboratory.

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