EDITORIAL

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ETIOLOGY OF VITILIGO — A PROBLEM

Vitiligo continues to be a global problem due to its universal incidence in all races[1], affecting 0.38%[2] to about 1%[3,4] or even more[5] of the general population. It poses a great socio-medical challenge because there is probably no other disease which can cause so much of disfigurement with so little morbid change, and which is so easy to diagnose yet so difficult to cure.

As ancient as Leprosy, Swetakustha of Atharva Veda (1500-1000 B. C.) has been confused with leprosy from biblical times till today. In India, the problem is intensified by the social stigma and misconcept amongst lay people.

The precise cause of vitiligo remains an enigma. Studies on the etiopathogenesis of the disease through clinical, genetic, physiological, biochemical, histological, immunological and experimental methods especially during the last three decades can be compared with the blindman's study of an elephant documenting isolated but significant facts on the various patho-physiological aberrations. The bits of the jigsaw puzzle remains to be arranged coherently for attaining a comprehensive concept of the disease as a whole.

Genetic concept of vitiligo evolves from positive family histories in 7.5-21% in India[6-12] and 33-38% in Western countries[13-15], occurrence in mono-zygotic twins[16], ABO blood group studies[17,18] and secretory state of patients[19] and in recent years by the electron microscopic demonstration of a pattern of pigment loss and eventual disappearance of melanocytes[20]. In the absence of a precise location of the gene of vitiligo, the disease is thought to be transmitted through an autosomal dominant gene[3]. It is however, possible that in a common disease like vitiligo, the higher familial incidence recorded by later workers[9,12-14] as compared to earlier observers[6] might only indicate a rising incidence of the disease.

Various sorts of gastro-intestinal ailments with or without parasitic infestations are by far the commonest associations of vitiligo in Indian patients[9-11,22,23]. Though its etiologic significance is not established, treatment of such ailments has been a routine pre-requisite to Psoralen therapy in India [24]. That these ailments could cause malabsorption or 'toxic' absorption affecting liver cells and melanocytes would be conjectural without sufficient scientific proof.

Trauma induces vitiligo by Koebner's isomorphic phenomenon as has been reported after severe sunburn[13], onset at sites of rubbing and vaccination[4], sari and dhoti injuries at the waist[25], and gingivitis, herpes simplex, fixed drug rash and heavy smoking predisposing vitiligo of the lips[24]. Higher incidence in tense and nervous individuals[6,12], onset and spread following menopause, mental shock, surgical treatment and miscarriage[4] indicate that vitiligo subjects are prone to develop depigmentation reaction in

response to various physical and mental injuries. Similar depigmentation reaction to inflammation is very common in normal infants and children[26] as might have been noticed by many clinicians.

All mysterious diseases have been linked with auto-immunity and it has indeed been so in vitiligo due to circumstantial association of other auto-immune diseases with demonstrable organ-specific antibodies, viz., Addison's disease[27], hypo and hyper-thyroidism[28], pernicious anaemia[29], halo naevus[30,31]; as also diabetes mellitus[32], alopecia areata[33], morphoea[34] and melanoma[35,36]. Demonstration of adrenal, thyroid and gastric antibodies[37], antimelanin antibody[35], in vitiligo and antibody to parietal cells with increased serum gastrin level in hypochlorhydric achlorhydric vitiligo patients[38] strengthen the auto-immune concept. Rare association of vitiligo with clinical thyroid disease[39], failure to demonstrate anti-thyroid antibodies in Indian patients[40] and absence of pernicious anaemia in India would make one sceptic about auto-immunity as the main cause of the disease in this country. Even with direct evidence of demonstrable anti-melanocyte antibody, its genesis from degeneration of melanocytes could not be ruled out[41] and would rather be considered as the result and not the cause of vitiligo.

The neurogenic theory of vitiligo rests on the clinical observations of occasional neural distribution, association of itching and burning sensations and vaso-motor disturbance[6,12]; common origin and morphology of melanocyte, demonstration of alpha and beta adrenergic receptors respectively stimulating lightening and darkening of skin of frogs, chemical similarity of DOPA and noraderenaline, lightening effect of neurochemical agents like acetylcholine, noraderenaline, adrenaline and melatonin in animals[13,42,43]; histochemical studies suggesting melanogenesis as a process of biological oxidation under neural control[44] and pigment retention studies in homografts[10,45-47]. Various dermato-physiological studies, viz., skin temperature gradient[48], altered peripheral physiological adjustment to local and general thermal stimuli[49], demonstration of enhanced cholinergic activity[50], diminished axon-reflex sweating with nicotine[51] and other altered physiological phenomena, e. g. sudo-motor reaction, blister resorption, adrenaline induced blanch reaction, focal bleeding time, etc[52-54] as well as electron microscopic observation of mild degenerative changes in the peripheral nerve endings[55] lend further support to the theory. However, these studies do not give definite clue to the role of "neuro-autonomic" changes in the genesis of vitilgo.

Of the histological findings, increase of Langerhan's cells in the basal layer of epidermis in vitiligo[56] and electron-microscopic observations[57] suggest the probability of an active role of these cells in the genesis of vitiligo.

Relative or total loss of functional melanocytes being the basic morbid change, a hypothesis of self-destruction of melanocytes was considered a probable etiopathogenetic mechanism[34]. Overfunctioning of melanocytes of exposed skin was likely to exhaust them to premature death due probably to accumulation of toxic melanin precursors synthesized by the melanocytes themselves. Though such toxic products have not been demonstrated, experimental studies on the depigmenting effect of substituted phenols[58-61] and their selective melanocyte destructive power[59,62] led to the demonstration of a reactive free radical[62] and suggest that the substituted phenol or catechol, after diffusion into the cytoplasm of the melanocyte, is oxidised by tyrosinase to a semiquinone free radical that leads to destruction of lipoprotein

membranes of cytoplasmic organelles through a chain reaction of lipid peroxidation.

Biochemical studies indicated normal serum copper with little variations[63-65] and high caeruloplasmin values[66]; high sulphydryl content with low ascorbate in vitiliginous skin[67] with an upset in the balance between the two[68] and raised serum tyrosine and other phenolic compounds in blood and urine[68]. Routine liver functions were normal[10,23,25] with increased levels of transaminases[22]. Gastric function studies indicated histamine-fast hypochlorhydria and achlorhydria[13,69] with increased serum gastrin and normal serum B_{12} in vitiligo[38]. Indian observers noted hypoacidity in the majority with hyperacidity in some[70]. Detailed biochemical and radio-isotope studies for evaluating liver and thyroid functions in vitiligo[71-73] showed statistically significant rise of aspartate and alanine transaminases, lactate dehydrogenase, aldolase and alkaline phosphatase, with hypercholesterolaemia of a moderate degree and decrease in butanol-extractable iodine; significantly low values of 2 and 24 hours thyroid uptake and 48 hours PBI^{131} and subnormal patchy uptake and delayed clearance of I^{131} Rose Bengal by the liver in majority of the cases. The findings suggested damage to hepatic parenchyma, increased cellular permeability, impairment of excretory function of the liver and a hypoxic state, co-existent with a hypometabolic subclinical hypothyroidism in vitiligo. Increase in serum lactic acid and lactic/pyruvic ratio[74] confirmed the hypoxic state. Could these parameters be interpreted as a clinical replica of the experimental studies[58-62] with substituted phenols?

While both melanin and thyroxine are derived from tyrosine by oxidation-reduction system, biosynthesis of melanin involves quinones and that of thyroxine involves semiquinone intermediates[75]. If semiquinone radicals remain free within the cells, they may act as initiators of lipid peroxidation which sets free lytic enzymes from lysozomes with consequent cell damage[76,77]. They would also prevent conversion of tyrosine to T_3, T_4 and melanin. The tyrosinase system remaining normal, in vitiligo it may be quite probable that melanin production from tyrosine is blocked at the quinone system due to a hypoxic state and the semiquinone system may be the modus operandi. Vitiligo thus would appear to be a basic metabolic disease. The precise role of the various factors, either singly or in combination, will await further exploration.

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