IMMUNOLOGY AND BIOCHEMICAL CHANGES IN VITILIGO

THESIS

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BY

IMAN ABD EL-FATTAH SALEET

M.B; B.Ch.

Supervised By

Professor Dr. ALI ABD EL-FATTAH

Professor of Dermatology and Venereology

And

Professor Dr. MONA EL-OKBI

Professor of Dermatology and Venereology

Faculty of Medicine

Ain Shams University

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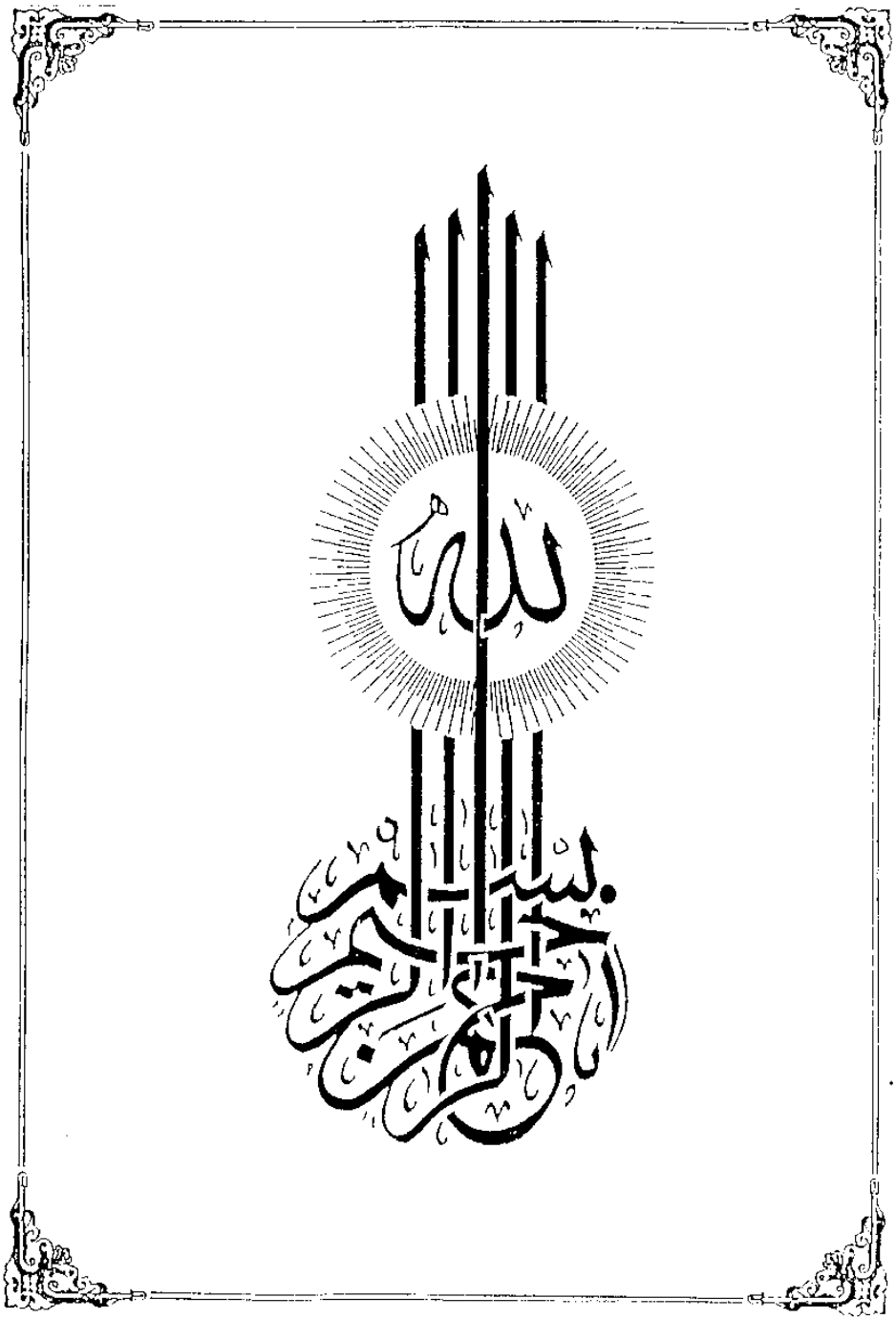

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Introduction
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Vitiligo is an acquired cutaneous achromia characterized by variously sized and shaped, single or multiple patches of milk white colour usually presenting hyperpigmented borders and a tendency to enlarge peripherally (Ormsby and Montgomery, 1954). Absence of pigment is the only symptom and the skin presents no textural changes and is clinically normal in every way except for a sensitivity to solar irradiation (Dawber, 1970).

It affects both sexes equally and 35% of cases give a positive family history (Dawber, 1968). Its peak of incidence is in the second or third decade of life. It occurs in approximately 1% of the general population and it is 5 to 10 folds greater in patients with autoimmune diseases such as Hashimoto's thyroiditis, Graves' disease, diabetes mellitus, adrenal insufficiency and pernicious anaemia. In addition, vitiligo has been associated with lymphoid malignancy and with thymectomy. It is, therefore, suggested that the pathophysiologic mechanism for vitiligo might be a systemic process.

This common disease, although benign in character, produces a marked degree of disfigurement in those afflicted and thereby unpleasantly influence the lives of other members of household.

Our aim in this thesis is to review the literature on vitiligo as regards the aetiological factors, pathogenesis, immunology and biochemical changes.

VITILIGO-A RETROSPECT

Vitiligo is one of the commonest and most disfiguring cutaneous disease. From its early description down to modern textbook accounts, it was thought to be a disease only of the skin (Nordlund and Lerner, 1982).

The description of the disease was probably detected 1,500 B.C. in Ebers Papyrus where two types of diseases affecting the colour of the skin were mentioned. One of them associated with swellings and recommended to be left alone, is probably leprosy. The other, presented only by a change of colour of the skin, is likely to be vitiligo, as it is recorded to be responding to treatment (Ebbel, 1937). Also, in the ancient vedic scritpure of India, Atharvaveda, (Circa 1,500 B.C.) there was a mention of a disease "Kilas". The sanskrit word kilas is derived from kil meaning white;as meaning to cast away. Therefore, kilas is most probably vitiligo, where the colour is casted away resulting in a white patch (Nair, 1978). At a later period, Whitney (1905) in his English translation of Atharavaveda also interpreted kilas as

white patch on the skin.

In the early classics of the Far East, there were also references to diseases with whiteness of the skin. In Makatominoharai, a collection of shinto prayers, dating back to about 1,200 B.C., there was a mention of a disease "Shira-bito", which Later on meant white-man. As only dead white spots could make a mongolian appear white, this could have been vitiligo (Feeny, 1964).

Other terms used for vitiliginous patches in ancient Indian medical treatises like "Charaka Samhita" is svitra, (Circa 800 B.C.). At 600 A.D. and according to Sanskrit lexicon Amarakosa, svitra means spreading whiteness; an apt description for vitiligo (Goldman et al., 1966).

Though vitiligo was recognized in the ancient past, it was often confused with leprosy. Even Hippocrates (460 to 335 B.C.), did not differentiate these two conditions and included lichen, leprosy and leuce under one category (Adams, 1848). This confusion was perpetuated when the Bible was translated into Greek by the order of Ptolemy 11 (250 B.C.).

Therefore, the term vitiligo was derived from many words according to different authors.

Turner (1714), the 'First British Dermatologist', recognized vitiligo in our sense of the word that it signifies any white spot or mark in the skin only and is usually of several sorts....a third sort, named melas, seuMorphea nigra. According to Bateman (1813), the white and glistening appearance bearing some resemblance to the Flesh of Calves (Vituli) seems to have given rise to the generic term vitiligo. In 1868, Addison recognised the non infiltrated nature of the condition. He noted that: "Certain insular portion of the integument presenting a blanched or morbidly white appearance.....From an actual defect in colouring matter in these parts". Fitzpatrick (1964) and El-Mofty (1968) suggested that the term is derived from the latin word "vitelius" which means "the Calf" from the resemblance of the white patches of the disease to the white patches of a spotted calf. Leider and Rosenblum (1968) said that the word was derived from "vitium", a fault or blemish. Therefore, one would

have been reasonably happy to compromise with all these interpretations, as they all indicate a white blemish of the skin. However, the following passage pointed out by Sutton, Jr. (1965) from the lexicon of latin language by Facciolati and Forcellini made the interpretation of the term more difficult. He mentioned that "Vitiligo (Vitium) - kind of leprosy or cutaneous eruption consisted of spots sometimes black, sometimes white, is called the morphea, alphus, melas, or leuce".

Indeed, there were great number of diseases with white spots. These might be broadly classified into five categories:

1. White spots perse,
2. White spots associated with regrowth of hairs which turn white,
3. White spots associated with inflammation,
4. White spots associated with scaling,
5. White spots with atrophy.

Accordingly, the first two most probably are vitiligo, while the others are not vitiligo (Nair, 1978).

AETIOLOGY

The many aetiological hypotheses which have at one time or another found supporters can conveniently be considered under the following headings:

AUTOIMMUNE HYPOTHESIS:

The autoimmune nature of vitiligo, at least for a certain number of patients, seems to be more and more likely. There is increased incidence of vitiligo associated with presumed autoimmune disorders (Harsouli et al., 1978; Lerner and Nordlund, 1978). El Mofty (1968) found the incidence to be 10-15% as compared to the 1 % representing the disease incidence in general population, while Nordlund and Lerner (1982) recorded that 20-30% of patients with vitiligo had an associated autoimmune endocrine disorders. Moreover, organ specific antibodies i.e., antithyroid, antismooth muscle or antinuclear antibodies, had been detected in these diseases, as well as in vitiligo (Bor et al., 1969; Carter and Jegasothy, 1976 and Nordlund and Lerner, 1982).

In 1979, McBurney mentioned that an increase of $HLAB_{12}$ in patients with vitiligo prior to the age

twenty five and increase of $HLAB_{13}$ in patients with antithyroid antibodies (30.8%) as compared with controls (4.1%), will add further support.

The autoimmune theory has been strengthened by the detection of circulating antibodies, of IgG immunoglobulin type that bound itself to normal melanocytes in human skin, nevus cells, and melanoma cells intracellularly and not to the cell surface. Hertz et al. (1977) and Harsoulis et al. (1978) detected these circulating antibodies in two patients with vitiligo, alopecia totalis, mucocutaneous candidiasis, and multiple endocrine insufficiencies, using an immunofluorescent complement fixation test. This suggests that these antibodies may be a result of melanocytic injury rather than a cause of its destruction (Betterle et al., 1979).

However, Koga in 1977 was not satisfied with the current theory that the autoimmune hypothesis was responsible as it could not explain many phenomena concerning the dysfunction of autonomic nervous system in the vitiliginous areas.

MELANOCYTE SELF-DESTRUCTIVE HYPOTHESIS:

This hypothesis proposed that an intermediate or a metabolite in melanin synthesis causes disapearance of melanocytes (Nordlund and Lerner, 1982), or that the normal mechanism for melanosome destruction proceeds unchecked to cause melanocyte dysfunction or death (Fitzpatrick et al., 1979). In 1971, Lerner suggested that melanocytes have an inherent protective mechanism which leads to successful elemination of toxic precursors that are synthesized by melanocytes but toxic to them. Disruption of this labile destructive process causes vitiligo.

Husain et al. (1982) postulated that pigment cells synthesize melanin by oxidation of tyrosin to dopa and then of dopa to dopaquinone. The latter spontaneously oxidizes through a multistep reactions into a variety of indoles and, possibly, free radicals. Moellmann et al. (1981) added that all the intermediates in the biosynthesis of melanin are monophenols or polyphenols that would injure or kill the cell if in excessive production or accumulation. Therefore, catechols and phenols have a toxic effect