A CLINICOHISTOPATHOLOGICAL STUDY OF DARIER'S DISEASE

THESIS

Submitted in Partial Fulfilment of
the Requirements for the Degree of
Master Dermatology and Venereal Diseases

By
ADNAN KHAMIS ABU EL-ROUS
M.B., B.Ch.

Supervisor
Prof. Dr. HAFEZ KHAFAGY

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

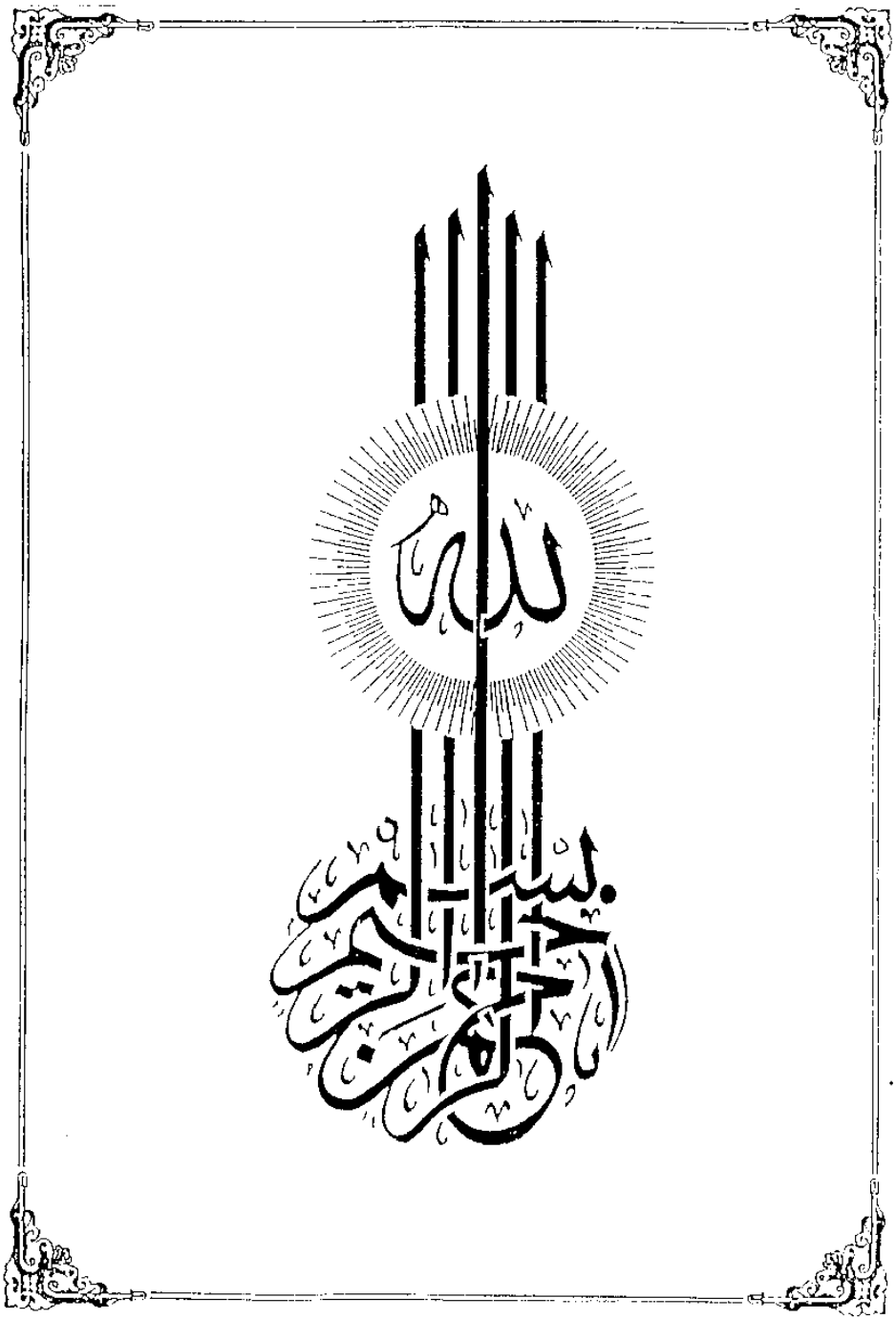
1977

A C K N O W L E D G E M E N T

It is a great honour to me that I take this opportunity to express my great indebtedness and supreme gratitude to Professor Dr. Hafez Khafagy, Professor of Dermatology and Venereal Diseases, Ain Shams University, for his kind supervision, direction and constant encouragement in this work.

It is also a great honour and pleasure to me that I express my deep sense of gratitude to Professor Dr. Mohammed Farid Roaiah, Professor and Head of the Department of the Skin and Venereal Diseases, Ain Shams University, for his precious remarks and instructions. I am very much obliged to all the staff members of the Department of Dermatology and Venereal Diseases, Ain Shams University.

Adnan Abu EL-Rous.



C O N T E N T S

INTRODUCTION

Historical Review:-

Keratosis follicularis first described by Prince Morrow in 1886. It is a genodermatoses inherited as an irregular autosomal dominant in which there is a slight male predominance, later White 1889 reported a similar case. Two months later 1889 Darier described his first case and accepted White's case as belonging to the same group.

Porter et al. (1947) prefer the synonyms "Darier's disease" and "Darier's dyskeratosis". The term "Keratosis follicularis" has been avoided by Porter et al. because the disease is not primarily a follicular disease (Ellis F.A. 1944).

Sometimes lesions of Darier's disease are present in the proximity of or actually surrounding a hair follicle. This fact led Darier (1889) as well as White (1889) to the idea that the process was follicular (Beerman 1949).

Darier's disease is also known as (1) Keratosis follicularis (2) Ichthyosis follicularis (3) Pseudospermosis (4) Acne sebacee cornee (5) Ichthyosis sebacea cornea and (6) Keratosis vegetans, (J.C. Wright 1962).

Darier's disease becomes manifest at any age, but usually begins in childhood (Svendsen & Albrectsen).

The early stages are described as papules of varying numbers which become crusted and produce vegetating growths which become foul-smelling particularly in the intertriginous areas.

The distribution of the lesion may be wide spread involving the face, torso and extremities particularly the palmar and planter surfaces. Occasionally the mucous membranes may be involved (Weathers et al. 1969).

Nail changes are very consistent and characteristic (Ronchese, F. 1965).

Darier (1920) considered the disease clinically as "papulo crusts, often follicular". The typical eruptive lesion is a papule covered with a grayish brown crust.

Pels and Goodman reported the case of a patient with Darier's disease in whom vesicle formation was a prominent feature, (1939).

Ellis (1950) prefers to call the syndrome Darier's disease and to separate the two variants as dry and wet

and called them vesicular and non-vesicular Darier's disease. He further concluded after detailed study of 22 cases that Benign chronic familial pemphigus is a variant of Darier's disease. He suggested that the two variants must be called vesicular and non-vesicular Darier's disease.

Montogomery (1948) in his notes on benign pemphigus of Hailey and Hailey stated that "There are several dermatologists who still believe that the condition is a form of Darier's disease with which view, I am not in accord." Warty dyskeratoma (Szymanski 1957) and isolated Darier's disease (Graham and Kelwig 1958) have been regarded as solitary lesions of Darier's disease because of their pathological resemblance.

The hereditary background of Darier's disease seems to be widely accepted (Svendsen & Albrectsen 1959).

Because of the close resemblance between the morphologic criteria of Hailey - Hailey disease and of Darier's disease, some authors feel that these two disorders are related, the Hailey - Hailey disease being a bullous varient of Darier's disease (Ellis 1950).

Genetic studies by other investigators indicate, however that Hailey - Hailey's disease and Darier's disease occur independently in the involved families and are not known to be associated genealogically or to overlap (Svendsen, Albrectsen 1959 and Reymann & Raaschou 1959).

The simultaneous occurrence of Darier's disease, Hailey - Hailey's disease and acrokeratosis verruciformis in one patient was reported by (Niordson 1965).

ETIOLOGY

1) Heredity:

Fischer (1924) found a total of 97 publications describing a total of 120 cases of Darier's disease. Thirtytwo of these cases were familial and 88 solitary cases. (Svendsen & Albrectsen).

Arnold Sorsby (1953) stated that Darier's disease is due to a single dominant gene. He stated further "Isolated cases are commoner but the disease has often occured in several members of a family. The pedigrees are small, however, and seldom extend to more than three generations. This may be caused by social selection in marriage."

Svendsen & Albrectsen (1959) have found the prevalence of Darier's disease to be 1 pr. 100,000 population in Denmark. They stated "since the condition is a result of mutation, a possible increase in the incidence might point to the existence of mutation provoking factors such as an increase in radioactivity."

They claimed that Darier's disease is aggravated if the patient perspired a great deal or underwent nervous strain. They further stated that exposure to sunshine had been found to be a provokating factor. They concluded

that the mode of inheritance of the disease appears to be simple dominant heredity.

According to Ford (1942). Darier's disease results from two different types of genetic disturbances. In some families it is inherited as a sex-linked dominant and in others as an autosomal dominant. It was supposed that one genetic type might account for the responsiveness to vitamin A and the other genetic type for the refractoriness. But this supposition is ruled out by the behaviour of 4 patients with Darier's disease reported by Carleton & Steven (1943), Since in one member of each family the disease was refractory and in the other it was responsive.

2) Dyskeratotic-Acantholytic Theory:

Caulfield & Wilgram (1963) stated that the changes common to basal cells and prickle cells namely separation of the tonofilaments from desmosomes with subsequent disintegration of their attachment plates, produce most of the classically accepted histological alternations ascribed to Darier's disease.

3) Vitamin-A-Deficiency:-

Peck in (1938) studied a case of Darier's disease in a man aged 25 y. He postulated that since the chief

pathologic change is a follicular dyskeratosis, the disease might possibly be due to vitamin-A-deficiency. He therefore tried the effect of large doses of this vitamin and obtained considerable clinical improvement. He suggested that the disease is due to a hereditary defect in absorption of vitamin A or in conversion of provitamin (A) manifesting itself in the skin as dyskeratosis.

Carleton and Steven (1943) descided that there is no resemblance between the picture seen in cases of a vitaminosis A and that observed in Darier's disease.

Also they postulated that there is no reliable link between dyskeratosis and vitamin deficiency, since dyskeratosis with the production of grains and corps ronds is seen in a number of dermatoses such as molluscum contagiosum, Paget's disease, Bowen's disease and certain types of papilloma and epithelioma, in which vitamin deficiency doesn't play any etiologic role. But they stated that "It is difficult to dismiss the vitamin factor entirely, as a clinical response is seen in a disease which had previously remained unchanged for years."

In spite of improvement following treatment with vitamin-A- in so many cases, it is clear that the disease is

not a simple deficiency state. (Porter et al. 1947). Vitamin -A- when given in large amounts and over long periods, seldom leads to disappearance of Darier's disease manifestations entirely (Porter et al. 1947).

The only patients reported as having recovered completely one the 2 cases described by Carleton & Steven (1943) and a case reported by Newman (1943).

Two laboratory methods used to detect deficiency of vitamin -A- . Firstly, the vitamin A and caroten levels in the plasma, secondly, dark adaptation tests. Moore (1946) found the mean average level to be within normal limits in 3 cases, although individual estimation revealed subnormal levels in 2 of them.

Carleton & Steven (1943), however reported normal levels in all their 4 cases. Porter, Godding and Brunauer (1947) found the figures within normal limits in all 4 cases reported by them before vitamin -A- therapy was begun.

Porter et al. (1947) postulated that the most satisfactory hypothesis is that the epithelial cells of the skin are unable to make use of the vitamin -A- available

in a normal manner. This idea is consistent with the common finding of normal amounts of vitamin -A- in the plasma as mentioned previously.

Six patients suffering from Darier's disease were observed by Leitner and Moore (1948) who concluded that Darier's disease is probably not due to a simple avitaminosis. They postulated that vitamin -A- may be directly or indirectly connected with the eruption of the disease. They suggested the possibility of impaired liver function which might interfere with the utilization of the vitamin.

Liver function tests were carried out on six cases of Darier's disease by Porter & Brunauer (1949) in an attempt to evaluate the aetiological significance of vitamin A. Although minor abnormalities occurred, no sure evidence of hepatic failure was obtained in any case of the disease.

4) Viral Theory:-

Ikada (1971) postulated that Darier's disease may be a new type of chronic viral infection of the skin on the basis of results from epidermologic studies. Zaias et al. (1973) stated that "A surprising finding was the presence

of bizarre multinucleate epithelial giant cells, mostly in the nail bed, which bear a striking resemblance to the giant cells in the epidermis of measles.

Preliminary electron microscopic studies utilizing paraffin sections reembeded in epoxyresin, show bodies similar to RNA-type-C-Viral particles. Perhaps Darier's supposition was correct: An infectious agent may be involved in the pathogenesis of Darier's-White disease.

Graham & Helwig (1958) stressed that single isolated lesions of Darier's disease may be viral. Shelley et al. (1959) concloded that there is no evidence supporting viral theory, furthermore they failed to find any transferable causal agent.

CLINICAL PICTURE

The distinctive lesion of Darier's disease is a greasy crusted papule, skin-coloured, yellow-brown or brown.

If the adherent crust is removed acentral , funnel-shaped orifice may sometimes be exposed. Coalescence of papules produces irregular warty plaques or papillomatous masses which in the flexures become vegetating and mal-odourous. The sites of predilection are the seborrheic areas of the trunk, the flanks, the face particularly the temples, fore head, ears, nasolabial furrows and the scalp. The flexures notably the anogenital region, the groins and the natal cleft, are often involved. The dilated follicular openings may become infected. with ulecration and purulent discharge.

Darier(1920) considered the disease clinically as "papulocrusts, often follicular". The typical eruptive lesion is apapule covered with agrayish brown crust. The crust when removed leaves a red weeping surface which may bleed.