CANCER IN RELATION TO GENODERMATOSES

THESIS

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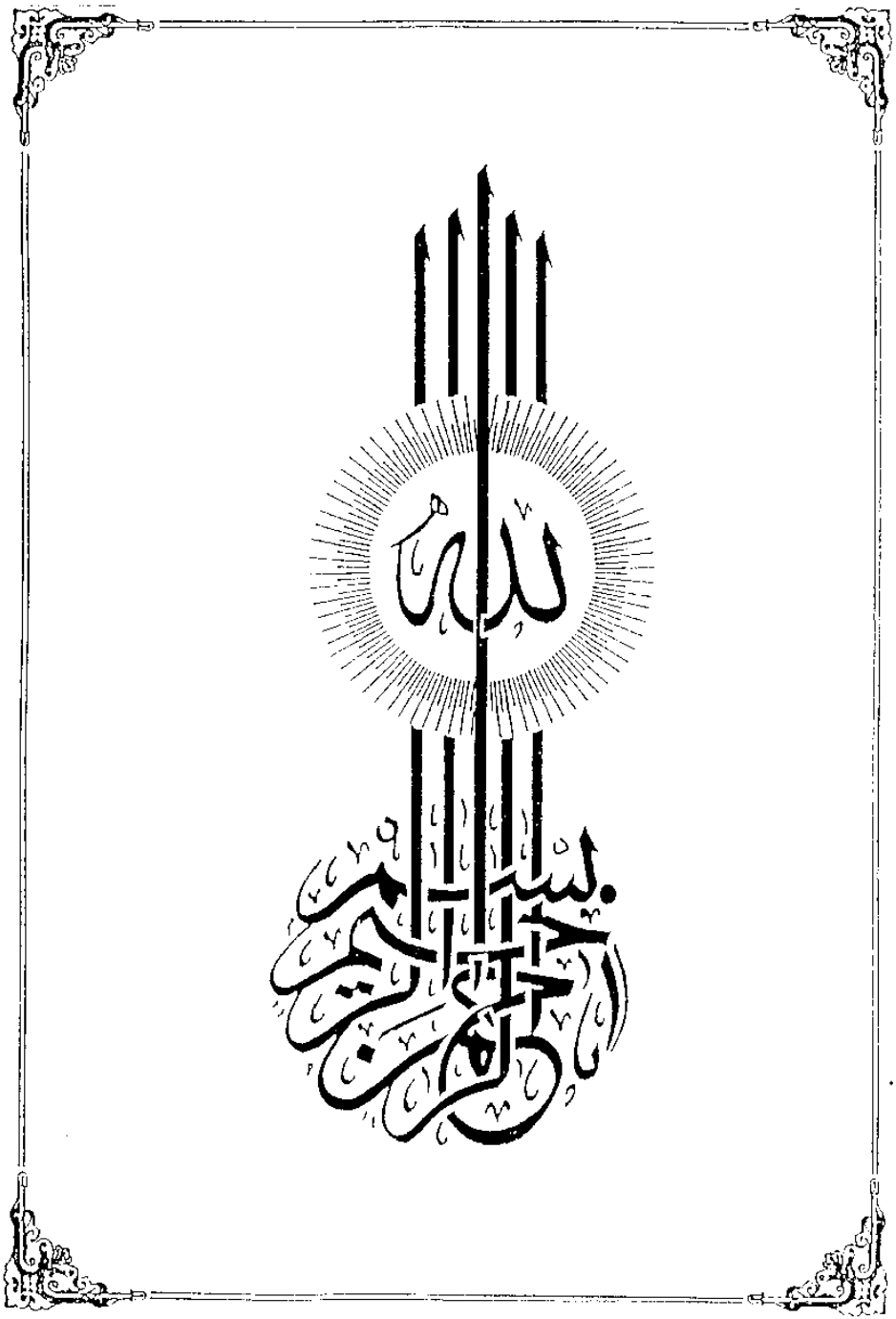

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INTRODUCTION

Scientific developments in the fields of genetics and oncology during the past two decades have been almost explosive, this has been particularly true for the cancer-associated genodermatoses (Lynch, 1972).

Historically, many examples which indicate that clinical predecessors were extremely interested in the cancer-associated genodermatoses, however, because of limitations in the body of knowledge as well as the technology of their times, they were necessarily restricted to primary descriptive approaches to these disorders. This was clearly evidenced by the efforts of clinicians a century ago which led to their recognition of familial aggregation in such cancer-associated genodermatoses as Recklinghausen's neurofibromatosis, tuberous sclerosis, xeroderma pigmentosum (XP), and others (Lynch, 1976).

Hereditary (single gene determined) forms of cancer play a primary role in the pathogenesis of approximately 5-10 % of all human cancer, but exogenous and endogenous factors, including suppressor genes, position effect, maternal and cytoplasmic effects, may

temper gene penetrance and expressivity. Less clearly defined genotypes, including polygenic inheritance, predispose to as much as an additional 5-10 % of the cancer load, but again, myriad exogenous and endogenous factors may be influential. It is well recognized that primary genetic factors mediate the nature of the immune response and the susceptibility of individual cell types to viral infection. In the case of immunodeficiency disease, the frequency of malignancy may be roughly 10,000 times greater than that of the general age-matched population. While the skin provides a convenient "looking glass" for the detection of a wide variety of systemic disorders, its significance in cancer-associated genodermatoses is virtually unparalleled. In certain circumstances, cutaneous signs may be recognizable at birth i.e., sebaceous cysts in Gardner's syndrome (Lynch and Frichot, 1978).

Research in the human cancer genetics has revealed a growing consensus regarding the manner in which particular genotypes contribute to the overall cancer burden. Cancer liability can be seen as a combination of genetic susceptibility and environmental exposure (Lynch, 1980).

Attention throughout this thesis will be focused upon a concerted apprasial of those common denominators which best characterize the cancer-associated genodermatoses. Not only should this then aid in providing integration of the seemingly diverse and multifaceted contributions to the field, but it will also assist in syndrome identification, classification, and hopefully, early cancer diagnosis. Furthermore, it should also provide a more enlightened comprehension of current knowledge about the etiology of cancer associated genodermatoses.

AIM OF THE WORK

This work has been performed to review the clinical picture, cancer association, the mode of genetic transmission of the specific disorder, prevention and treatment in some cases of cancer associated genodermatoses.

AUTOSOMAL DOMINANT DISEASES

Autosomal dominant inheritance must fulfil the following criteria :

1. Every affected person has an affected parent.
2. The trait is transmitted by an affected person to half of his children on the average.
3. Unaffected persons do not transmit the trait to their children as they have only normal alleles.
4. The trait appears in every generation with no "skipping".
5. Transmission of the trait is not influenced by sex or by consanguinity of the parents.

A DD(homozygous) person cannot be distinguished from a Dd (heterozygous) person by his phenotype but only by the progeny he produces .

Multiple nevoid basal cell carcinoma syndrome

(basal cell nevus syndrome)

The basal cell nevus is hereditary dysplasia conditioned by an autosomal dominant gene (Sanderson and Mackle, 1979).

The syndrome is a dysgenetic dermatosis characterized by multiple small cutaneous tumors. These are histologically indistinguishable from basal-cell cancer. Malignant supervention is common, generally resulting in multiple basal-cell cancers of the face in young adults. The basal cell epitheliomas are nevoid and occur between puberty and the mid-thirties. The early lesions appear as brownish or flesh-colored papules with a marked tendency for the central facial area, especially the nose, upper lips, cheeks, periorbital regions, and eye lids, but they also occur on the trunk. These nevoid tumors are biologically as destructive and invasive as the regular basal cell epitheliomas and have been known to metastasize to brain and lung. The cutaneous lesions also include palmar and plantar pits, which are 1-3 mm shallow holes. Further cutaneous lesions are milia, epithelial cysts, comedone,

lipomas, and cafe au lait pigmentation. Multiple dental follicular cysts, a bifid sixth rib, a fibroma of the ovary, and a fatty tumor of the left foot as developmental defects are often present . Prophylactic treatment of the nevi as a means of preventing cancer highly desirable especially in the region of the eye lids and nose by cautery, electrosurgery, excision or freezing with liquid oxygen or nitrogen and this is also the treatment of a single basal cell cancer resulting from a basal cell nevus (Howell and Caro, 1959).

Cheilitis glandularis

This rare dominant trait manifests as a diffuse enlargement of the lower lip, with firm nodularity. A mucus substances is exuded from the dilated orifices of the mucus gland. The condition is a hypertrophy of the mucus glands and ducts. Varying amounts of acute and chronic inflammatory processes occur with the resulting damage to tissue (Doku, 1965).

There is controversy concerning the reported 20 % malignancy rate(squamous cell carcinoma) in these patients . Sunlight is an important carcinogen where patients develop actinic damage and squamous cell carcinomas on their protruding lips (Schweich, 1964).

Hidrotic Ectodermal Dysplasia

There are two forms of ectodermal dysplasia, hidrotic type and anhidrotic type. The former is usually dominant in its genetic expression, while the later is usually X-linked recessive (Campell and Keohan, 1966).

This ectodermal defect shows nail dystrophy, a generalized hypotrichosis, and palmo plantar keratoderma. The nail changes are varied (Thick, slow-growing, discolored), the body hair may be sparse or absent and the scalp hair is minimal. The sweat gland and teeth are invariably normal in contrast to the anhidrotic type. Hyperpigmentation of the skin especially of the joints (Gold and Scriver, 1972).

There are many examples of squamous cell carcinoma of the nail bed and hands reported with this disease (Campbell and Keokam, 1966).

Demonstrations of defects in sulphur metabolism of polypeptides, and the formation of proteins of abnormally low molecular weight in the tissue, suggest a defect in structural genes of the matrix polypeptides (Gold and Scriver, 1972).