GENETICS OF LEUKEMIAS

AN ESSAY

Submitted in partial fulfilment for

The Master Degree in

Pediatrics

By

EBRAHIM ABDEL AZIZ MOUSTAFA

(M.B.,B.Ch.)

Supervised By

Prof. Dr. OMAR HELMY ESMAEIL

Professor and Head of Pediatrics Department

Faculty of Medicine

Ain Shams University

Prof. Dr. MOHAMED A. AWADALLA

Professor of Pediatrics

Faculty of Medicine

Ain Shams University

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

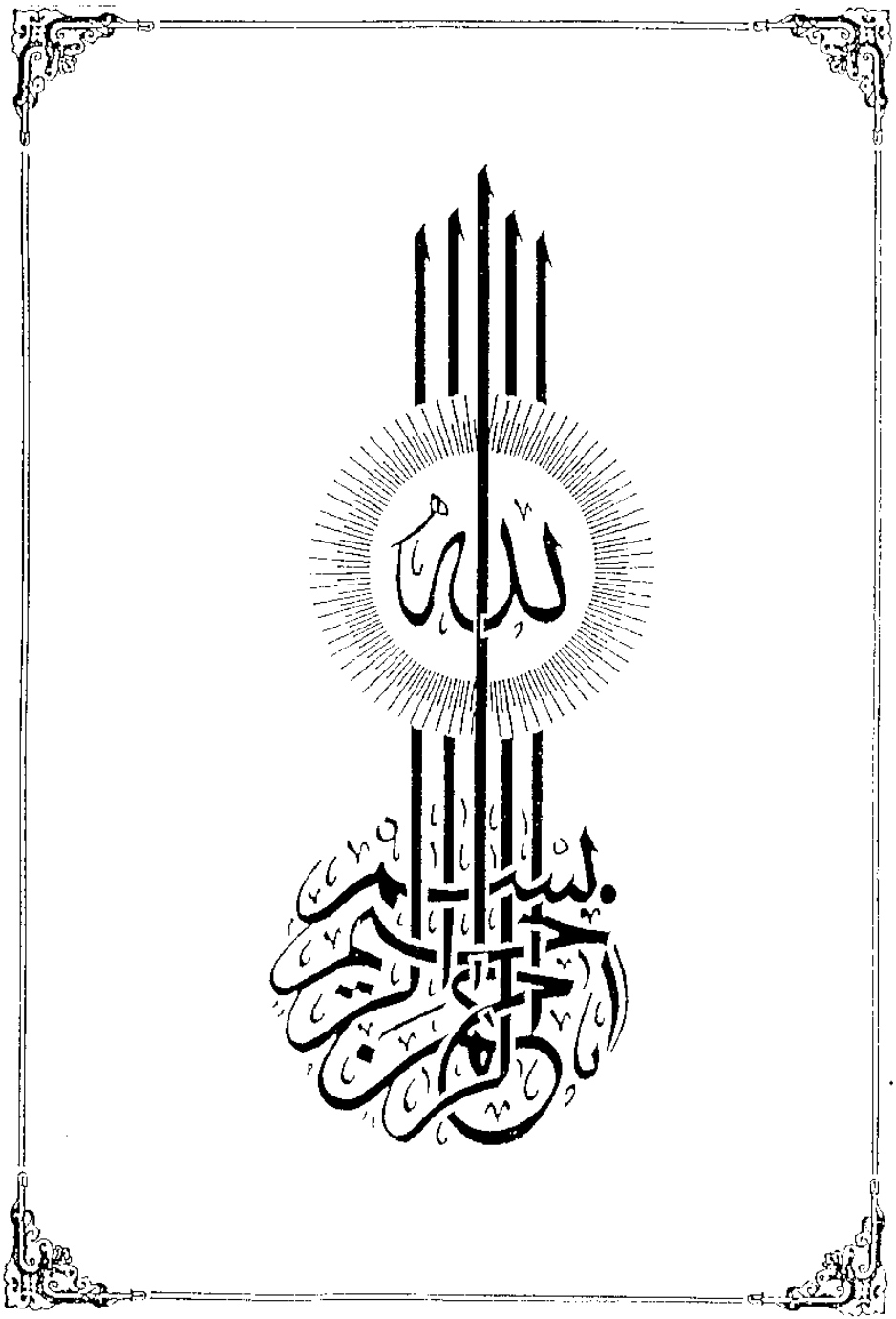
CAIRO

1987

بسم الله الرحمن الرحيم

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ.

صدق الله العظيم



ACKNOWLEDGEMENT

I wish to express my sincere thanks and deepest gratitude to Prof. Dr. OMAR HELMY; Professor and Head of Pediatrics Department, Ain Shams University, for his keen supervision, encouragement and precious instructions.

Also my great appreciation goes to Prof. Dr. MOHAMED AWADALLA; Professor of Pediatrics, Ain Shams University, for his kind and continuous guidance, interest and helpful effort throughout this work.

CONTENTS

LIST OF ABBREVIATIONS

AGL : Acute Granulocytic Leukemia

ALL : Acute Lymphocytic Leukemia

ALs : Acute Leukemias

AML : Acute Myelogenous Leukemia

AMMoL: Acute Myelomonocytic Leukemia

AMoL : Acute Monocytic Leukemia

ANLL : Acute Non Lymphocytic Leukemia

APL : Acute Promyelocytic Leukemia

ATL : Adult T-cell Leukemia

CALLA: Common, Acute Lymphoblastic Leukemia

CD : Cluster Differentiation

CD_w : Provisional Cluster Differentiation

c-fra: constitutive fragile site

CIgM : Cytoplasmic Immunoglobulin M

CLL : Chronic Lymphocytic Leukemia

CML : Chronic Myelogenous Leukemia

DAT : Distal Axial Triradii

del : deletion

DNA : Deoxyribonucleic Acid

EBV : Epstein-Barr Virus

FAB : French American British

FdU : Fluorodeoxy-Uridine

FIWCL: First International Workshop on Chromosomes in Leukemia

Hex : Hexosaminidase

h-fra: heritable fragile site

HLA antigens: Histocompatibility antigens

Ig : Immunoglobulin

inv : inversion

MDS : Myelodysplastic Syndromes

MHC : Major Histocompatibility Complex

MZ twin: Monozygotic twin

5'NT : 5 Nucleotidase

p : short arm of the chromosome

Ph^1 : Philadelphia chromosome

PLL : Prolymphocytic Leukemia

PNP : Purine Nucleoside Phosphorylase

q : long arm of the chromosome

RNA : Ribonucleic Acid

SmIgM: Surface membrane Immunoglobulin M

SIWCL: Second International Workshop on Chromosome in Leukemia

t : translocation

TdT : Terminal deoxy-nucleotidyl Transferase

TIWCL: Third International Workshop on Chromosome in Leukemia

INTRODUCTION AND AIM OF WORK

INTRODUCTION AND AIM OF WORK

Leukemia is the most common form of childhood cancer (Behrman and Vaughan, 1983). Being a serious and fatal disease, it is important to study the probable genetic predisposition in childhood leukemias.

A question that concerns all parents of leukemic children is whether there is a risk that their other children might develop the disease. Several studies have demonstrated that siblings of leukemic children do have a higher incidence of leukemias, the relative risk being 2.3 to 4 times that the general pediatrics population (Altman and Schwartz, 1978).

In this essay, the aim of work is to review genetics of leukemia and how genetics and environmental factors could predispose to the development of leukemia.

REVIEW OF LITERATURE

DEFINITION

Dameshek and Gunz in 1964 defined leukemia as a generalized neoplastic proliferation, slow or rapid, of one of the leucocytopoietic tissues often associated with abnormal white blood cell counts and leading eventually to anemia, thrombocytopenia and usually death.

Leukemia is a malignant neoplasm characterized by disorderly seemingly purposeless proliferation of blood cells or their precursors. Leukemia is a disease of blood forming tissues and the bone marrow is always involved. Abnormalities in the peripheral blood reflect marrow dysfunction but the circulating leucocytic count is not always elevated (Linman, 1975).

CLASSIFICATION OF LEUKAEMIAS

Leukemia occurs in a number of forms which differ in their clinical, pathological and haematological features. Numerous terms, based on many different characteristics of the disease, have been used in the past to describe the different forms of leukemia. This has resulted in some confusion in the terminology. The two main criteria used in classification are; the clinical course of the disease, and the type and maturity of the predominant leukemic cell. Leukemias are therefore classified into:-

(1) Acute and chronic, according to the clinical course; and

(2) Lymphocytic and non-lymphocytic according to the predominant leukemic cell type (Kay, 1974).

CLASSIFICATION OF ACUTE LEUKEMIA

A French, American and British cooperative group (FAB) has proposed a classification of acute leukemias based on morphological and cytological criteria (Bennett et al., 1976). In the FAB classification acute leukemia can be diagnosed morphologically into lymphocytic (ALL), and non-lymphocytic (ANLL) categories (Bennett et al., 1976).

1- ACUTE LYMPHOCYTIC LEUKEMIA (ALL)

On morphologic grounds, ALL may be subdivided into three types: L_1, L_2 and L_3, according to the occurrence of individual cytologic features and the degree of heterogenicity in the distribution of these features among the leukemia blast cells population (Altman and Schwartz, 1978).

According to FAB classification, approximately 84% of childhood ALL is L_1, and 14% is L_2, and 1% is L_3. L_1 are patients whose cells are fairly uniform in size and relatively small. Nuclear shape is regular, but indentation, clefting or folding may be present, and the cytoplasm is scanty and less basophilic than in L_2 or L_3. L_2 refers to patients in whom most lymphoblasts are more than twice the size of normal small lymphocyte. Nuclear shape is irregular, with frequent indentation, folding and clefting. The amount of cytoplasm is variable as is the degree of basophilia. In L_3 type, cells are large, the nuclear chromatin appears dense, and cytoplasm is moderately abundant and intensely basophilic, and vacuolization is more common and more prominant than in L_1 and L_2 (Bennett et al., 1976).

It is now well-recognised that morphology alone can not distinguish the various clinical types; and special techniques utilizing the electron microscope, cytochemistry, surface markers, biochemistry and cytogenetics have been developed to supplement morphological classification. These classifications have both prognostic and therapeutic significance (Catovsky, 1977).

- Cell markers and classification of ALL:

Recently, the classification of leukemia has been based on the recognition of cell markers which proved to be essential to reach a precise diagnosis of subclasses of acute leukemia with different biologic and prognostic characteristics. These markers are of special importance in classification and management of ALL and to less extent AML (Thiel et al., 1980).

I- Membrane and immunologic markers:

The availability of monoclonal antibodies directed against specific surface antigens of ALL should refine the current immunological classification (Coccia et al., 1979).

Six major subtypes of ALL are now recognised including: Unclassified or null ALL, common ALL (c-ALL), pre-B ALL, B-ALL, pre T-ALL and T-ALL (Thiel et al., 1980).