Molecular Biology of Leukemia

Thesis

Submitted for Partial Fulfilment of Master Degree

in Clinical Pathology

By

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M.B., B.Ch.

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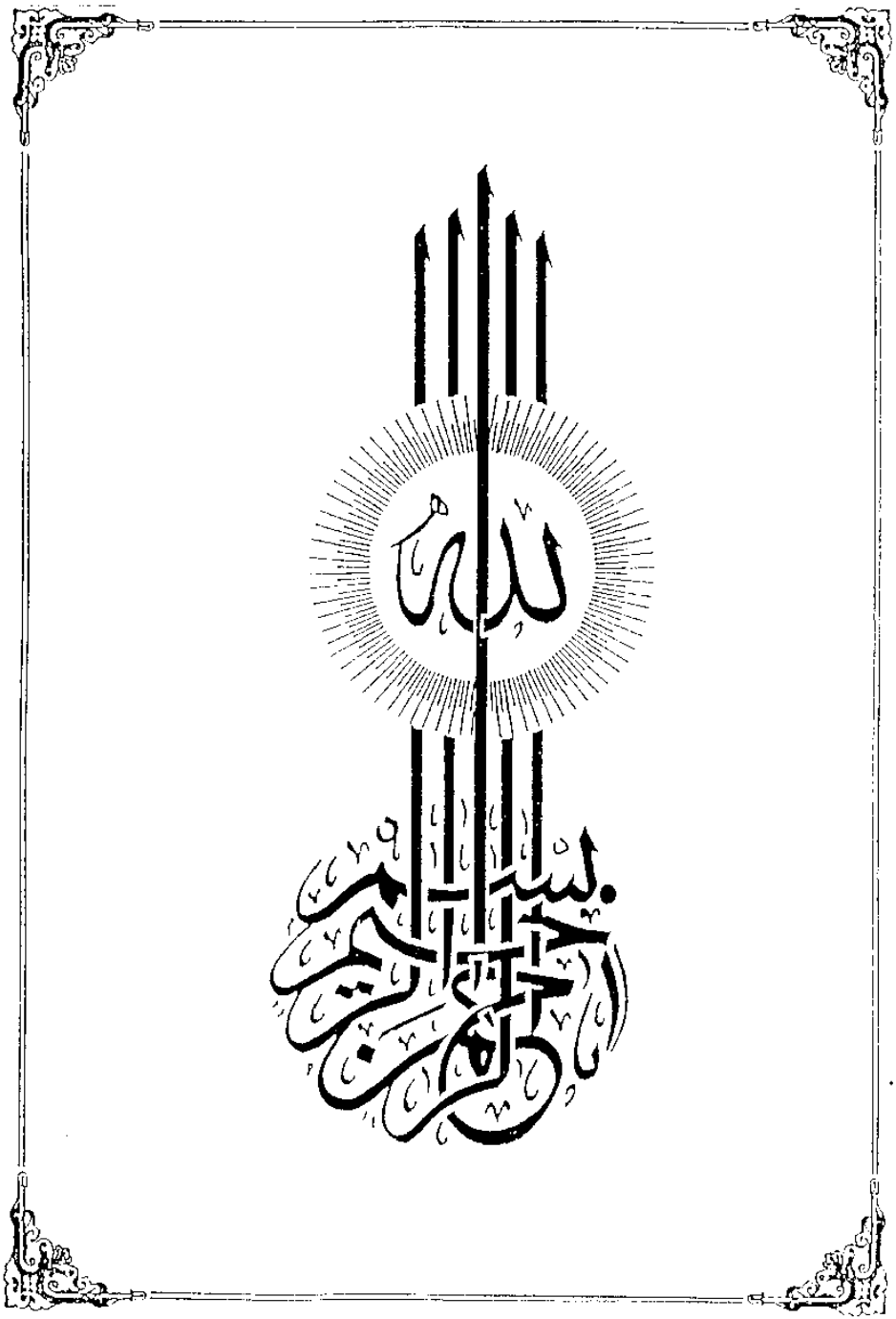

بسم الله الرحمن الرحيم

" وقل رب زدني علما "

صدق الله العظيم

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LIST OF ABBREVIATIONS

IDs	:	Acquired immunodeficiency syndrome.
LL	:	Acute lymphocytic leukemia.
MV	:	Avian myeloblastic virus.
NLL	:	Acute nonlymphocytic leukemia.
TL	:	Adult T-cell leukemia.
:l	:	B-cell lymphoma leukemias.
CR	:	Breakage cluster region.
ALLA	:	Common ALL antigen.
GL	:	Chronic granulocytic leukemia.
LL	:	Chronic lymphocytic leukemia.
ML	:	Chronic myelogenous leukemia.
oncs	:	Cellular oncogenes.
-SF	:	Colony stimulating factor.
:l	:	Deletion.
MS	:	double minutes.
BV	:	Epstein-Barr virus.
BVNA	:	Epstein-Barr virus nuclear antigen.
AB	:	French American British Company.
SR	:	Homogenously staining regions.
TLV	:	Human T-cell lymphotropic virus.
	:	Isochromosome.
	:	Immunoglobulin.
H	:	Immunoglobulin heavy chain.
L	:	Immunoglobulin light chain.
v.	:	inversion.
).	:	Kilobase pairs.
uLV	:	Murine leukemia virus.
CNA	:	Proliferating cell nuclear antigen.
CR	:	Polymerase chain reaction.
FG	:	Pulsed field gradiant gels.
ı'	:	Philadelphia.
HA	:	Phytohemaglutinin
PO	:	Pluripoietin.
FLP	:	Restriction fragment length polymorphism.
	:	Translocation.
CR	:	T-cell receptor.
dT	:	Terminal deoxy transferase.
oncs	:	viral oncogens.

CONTENTS

Introduction & Aim of the Work

INTRODUCTION AND AIM OF THE WORK

Leukemia, indeed cancer in general, is a disorder of growth and proliferation that occurs when the normal function of one or more of growth affecting genes is disrupted.

The mechanisms by which these gene disruptions may occur are not just of intellectual interest, but of profound clinical import as well, because it is now becoming clear that one or more of these disruptions have occurred in every patient with cancer *(Kirsch, 1988)*.

The tumor-specific markers, that would distinguish a tumor cell from the normal cell background, in which it arises, are precisely the specific genetic alterations which occur at the level of DNA within cancerous cells. Most importantly is the DNA rearrangement of immunoglobulin gene creates a tumor specific marker capable of establishing the clonality cellular lineage, and stage of development of hematologic malignancy *(Bishop, 1985)*.

Oncogenes are genes coding for proteins in malignant transformation. Classically defined "oncogenes", cancer causing genes carried in the genome of certain tumor viruses *(Bishop, 1985)*, exist as cellular homologues "proto-oncogenes" with normal human DNA *(kirsch, 1988)*.

In light of a possible pathogenetic significance of proto-oncogenes for the development of cancer special attention has been paid to the normal function of the proteins coded for by the proto-oncogenes. These proteins were found to be involved in an information pathway from the cell surface to cell nucleus, which regulates cell growth and differentiation *(Bjergaard et al., 1986).*

The techniques of molecular biology involve the analysis, or manipulation of DNA,RNA and protein at the molecular level *(Worwood and Wagstaff, 1990).* These molecular genetic analysis hold the promise of improving the classification schemes, providing sensitive and specific approaches, following the clinical course and providing in sights in pathogenesis that will prompt improved therapy *(Korsmeyer, 1988).*

This study aimed to review some of the important concepts and techniques of molecular biology applied to the field of leukemia.

Introduction to Molecular Biology and its Significance

INTRODUCTION TO MOLECULAR BIOLOGY AND ITS SIGNIFICANCE

Two decades ago concepts were developed to exploit cell kinetic differences of normal and malignant cells to selectively damaged cancer cells *(Klein et al., 1976)*.

Today an increased understanding of the biology of cell division is emerging in the context of growth regulation by growth factors and specific genes *(Pardee et al., 1985; Baserga, 1986)*.

A few years ago it was simpler to conceive an article devoted to the impact of molecular biology on the diagnosis, understanding and treatment of the leukemia. Then it may have still been possible to distinguish a separate field of molecular biology distinct from other fields and branches of medicine *(Kirsch, 1988)*.

Genetic Principles and Molecular Genetics

All the information required for the development of a complete adult organism are contained in a single cell the zygote. It contains the information required for the formation of cells, the regulation of their proliferation, their assembly into tissues and the development of these tissues into organs. Understanding how this massive amount

of information are coded has been one of the major advances of modern biology. The information are all contained in polynucleotides, deoxyribonucleic acid (DNA) *(Beutler, 1990).*

Structure of the DNA (Fig. 1 and 2)

The DNA contains only four different bases Adenine (A) Guanine (G),Thymidine (T),and Cytosine (C). DNA exists as a double helix in which A is always paired with T, and G is always paired with C. The nucleotides that make up each strand are linked to each other through a molecule of phosphoric acid, attached to the 3' carbon of the deoxyribose of one nucleotide and to the 5'carbon of the next one *(Beutler, 1990).*

A linear strand of DNA then, has one end in which the hydroxyl group attached to 5' carbon is free at the other end it is hydroxyl group to the 3'carbon that is not involved in a link. The 5' end is drawn on the left and is called up stream end, and the 3'end called downstream. The two strands form a stable double-stranded helix only when they are arranged in an anti-parallel fashion. In other words,one strand in the 3'5'polarity is bound to its complementary strand with a 5'3' polarity *(Maxam and Gilbert 1977; Barrie et al., 1981).*

The two complementary strands of DNA are stabilized in a double helical configuration by the formation of hydrogen bonds between the nucleotides on the opposing strands *(Kirsch, 1988).*

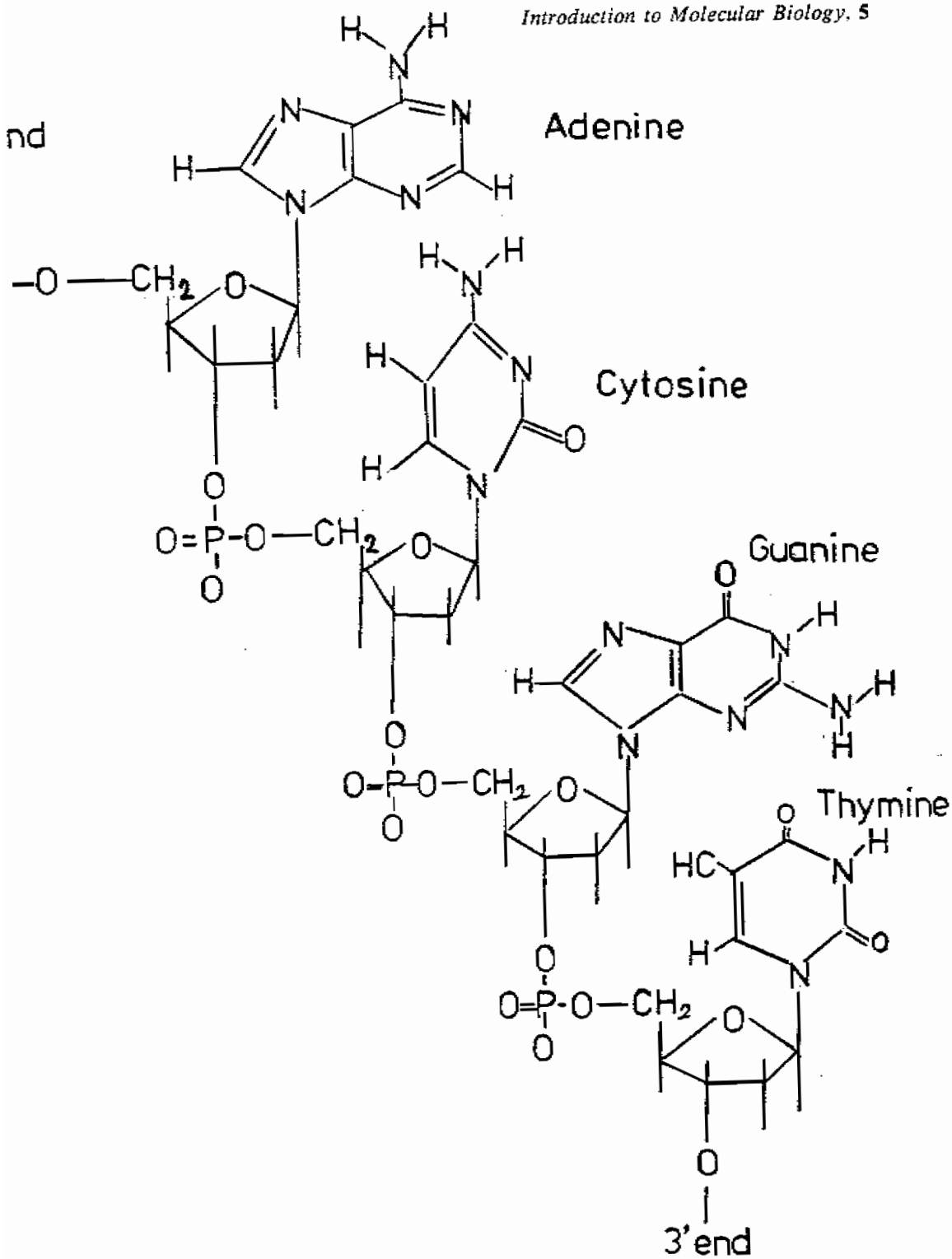

Fig. (1): Chemical Structure of Deoxyribonucleic Acid
(High and Benz, 1985)

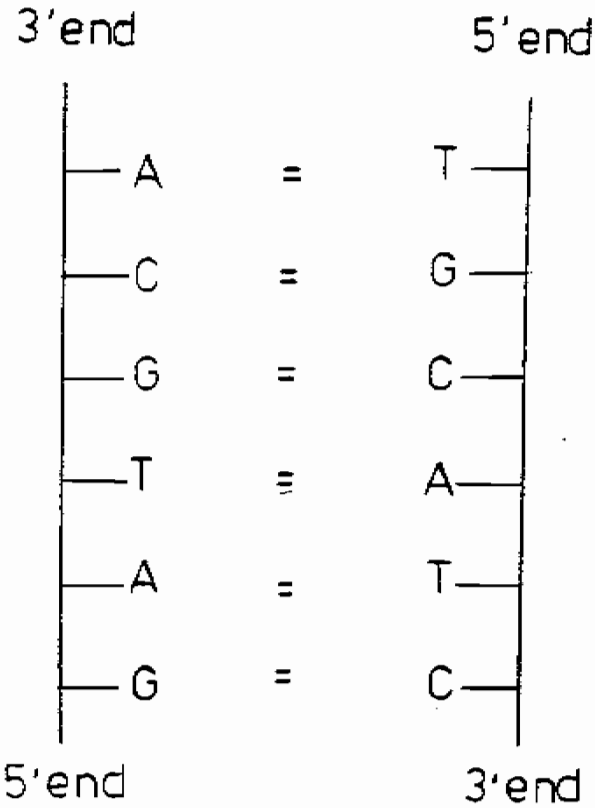

Fig. (2): Complementary Base-Pairing *(High and Benz, 1985)*
(A = T or U, G = C)

Organization of DNA Molecules into Genes

Virtually, eukaryotic and prokaryotic species differ significantly in the manner in which DNA sequences are organized into functional units which are called genes *(High and Benz, 1985)*.

This means that eukaryotic cells contain their DNA within the nucleus in the form of nucleoprotein complexes called chromosomes. Human cells contain 23 pairs of chromosomes. all available evidence suggests that each chromosome consists of a single, long molecule of DNA. The