GENIC AND CHROMOSOMAL MARKERS IN SOME SELECTED CHILDHOOD MALIGNANCIES

THESIS

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By

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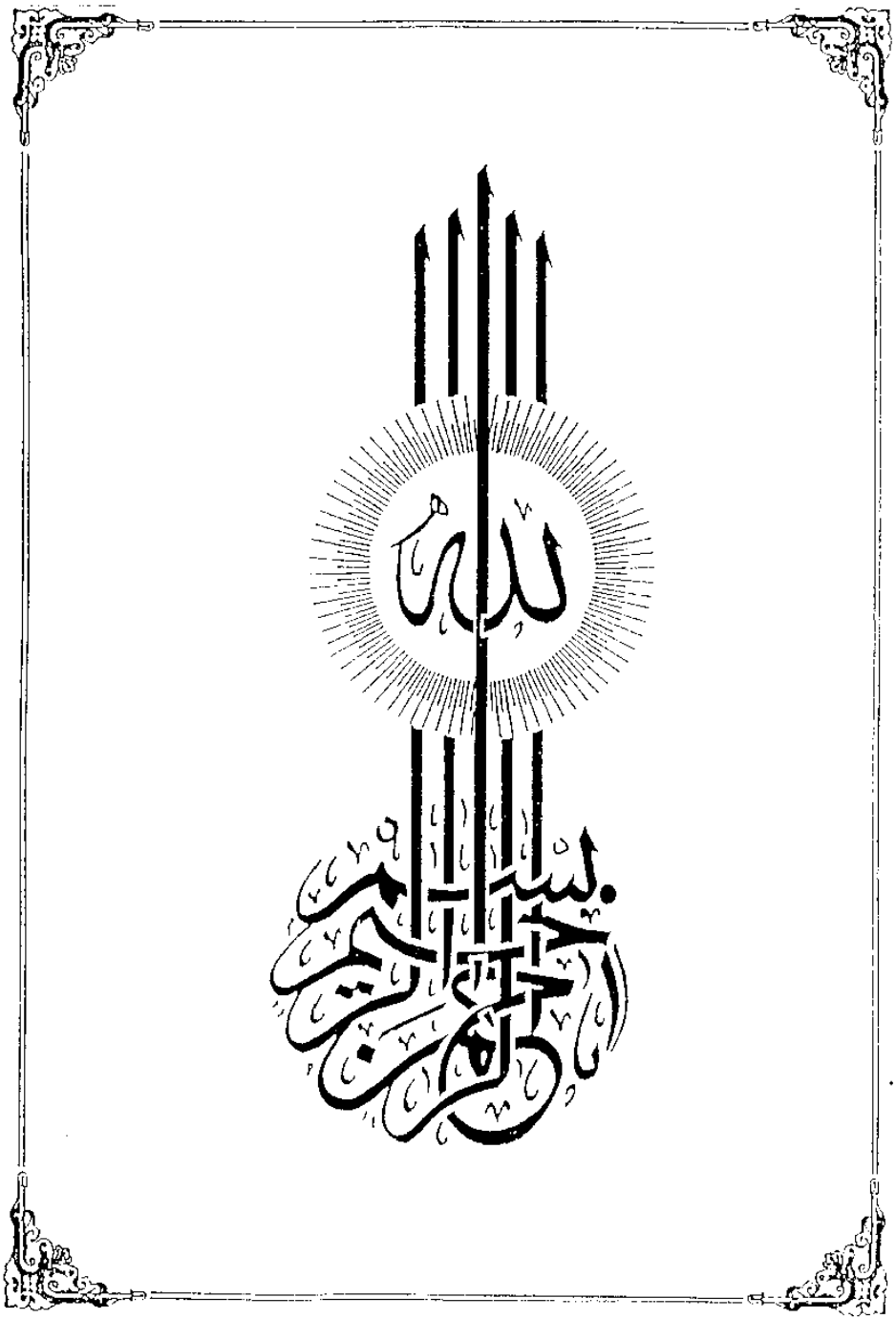

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INTRODUCTION AND HISTORICAL BACKGROUND

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Cancer is defined as a neoplatic tissue which develops through uncontrollable proliferation of malignant cells that had become transformed from pre-existing normal cells and acquired the capacity for autonomous growth (Makino, 1975).

As far back as 1890, pathologists agreed on one common predominating feature of cancer which is the occurrence of chromosomal and mitotic irregularities. Since cell growth and differentiation is under genetic control, malignant transformation can be ultimately taken as a result of modified structure and function of chromosomal DNA. Hence, it is probable that the sequence of chromosome aberrations in cancer is intimately associated with the etiology of malignant transformation of cells. The notion that abnormal cellular events could produce intracellular imbalance leading to cancer was first enunciated by the german cytologist Von Hansemann (Triolo, 1965).

However, as early as 1914, the Flemish cytologist Theodor Boveri, suggested that an etiological relationship exists between chromosome abnormalities and

carcinogenesis interms of the mutation theory i.e. mitotic irregularities result in changes of chromosome number in individual cells and these cells acquire new properties, one of which could be malignancy (Boveri, 1929).

This theory stimulated the continuing interest in attempting to relate neoplastic growth to hereditary factors. Many subsequent investigators demonstrated the trans-generational transmission of tumors in inbred strains of mice and that several genes influence the susceptibility of the mouse to tumor development (Strong, 1958). Hence at present, the main question of genetic factors in neoplasia is how is cancer hereditarily transmitted? (Jackson et al., 1979).

It has been estimated that single genes play a major role in the pathogenesis of approximately 5-10 % of all human cancer. However, exogenous factors, such as irradiation effects and other known carcinogens, must be assessed in concert with certain endogenous factors, including suppressor genes, chromosomal-gene position effects, maternal and cytoplasmic effects, all of which may influence gene penetrance and expressivity.

Polygenic inheritance may as well predispose to as much as an additional 10 - 15 % of the overall cancer load (Lynch, 1982).

The understanding of the malignant transformation of cells requires a full insight into cytogenetic principles, since the growth of cells and tissues is ultimately related to the mechnism of cell division and the behaviour of chromosomes (Makino, 1975). It became evident that malignant transformation involves loss of chromosomal stability which results in the appearance of cells with new functional properties, one of which seems to be the capacity for autonomous growth (Levan, 1969).

Technical facilities are defining cytogenetic aspects of tumors to be considered useful as criteria for the consideration of the etiological, pathological and clinical aspects of neoplasms. Hence the study of chromosomes in cancer is, and have been for the last twp decades an urgent and meaningful undertaking (Makino, 1975).

The recently advented new staining techniques allow the identification of individual chromosomes by

recognizably differential banding patterns along the chromosomes at different meiotic and mitotic cell division phases than that done by conventional methods. In addition to being useful in detecting any excess or loss of any chromosomal material, these characteristic banding patterns are unchanged by structural chromosomal rearrangements such as translocations (Miller et al., 1972) . Hence banding analysis of chromosomes aids in elucidating karyotypic changes beyond merely morphological criteria, in terms of numerical or structural analyses of altered or affected chromosomes in such cell populations.

AIM OF THE PRESENT STUDY

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The aim of the present study on cancer genetics, is to formulate the basis for establishment of an early screening program for high risk subjects with cancer-prone genotypes or cancer-predisposed carriers of karyologic errors.

Though different varieties of biological markers can be looked for in search for proneness to neoplastic diseases, the markers searched for in the present study comprise two of these biological markers.

1. Chromosomal markers looked for through karyotypic analysis of peripheral blood lymphocytes and, if available, of tumor tissue from the same index subject.
2. Genic markers looked for through HLA-typing of the same index subject through a lymphocytotoxicity test employing lymphocytes isolated from subject's peripheral blood.

The simultaneous study of these two markers, the cytogenetic marker and the immunogenetic marker, is obviously more relevant than the study of any of them alone, and if in specific combinations could signal

prevalent types of childhood neoplasia or genetically determined diseases which predispose to neoplasia, then the search in early life for these two marker i.e. karyotype and HLA type, could provide an operational effective means, towards cancer prevention, if an establishment of a screening program based on these two markers is achieved.

Early identification of individuals prone to cancer would ensure their follow-up with appropriate medical care so as to save them the deadful consequences of cancer development.

REVIEW OF LITERATURE