SPOTLIGHT ON THE VIRAL ETIOLOGY OF LEUKEMIA AND LYMPHOMA

THESIS

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By

MAHA MOHAMED TAWFIK EL-ZIMAITY

Supervised by

Professor Dr. **Mohamed Sadek Sabour**
Head of Internal Medicine Department
Faculty of Medicine
Ain Shams University

Dr. **Rasha Yousef Khalil**
Ass. Professor of of Immunology
Microbiology Department
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University

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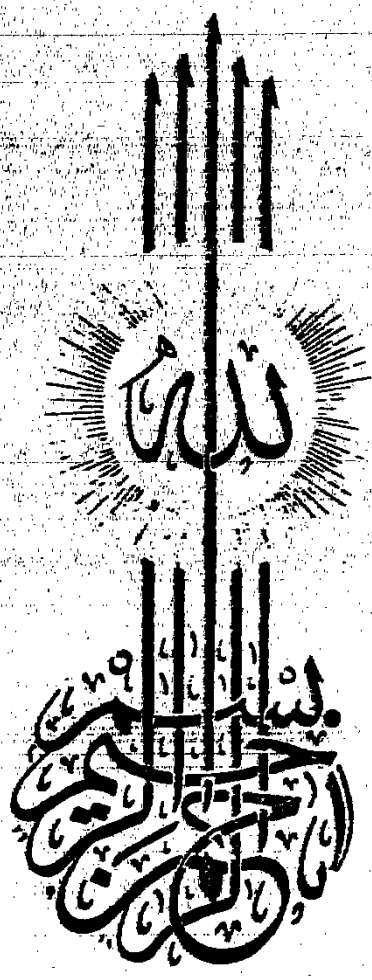

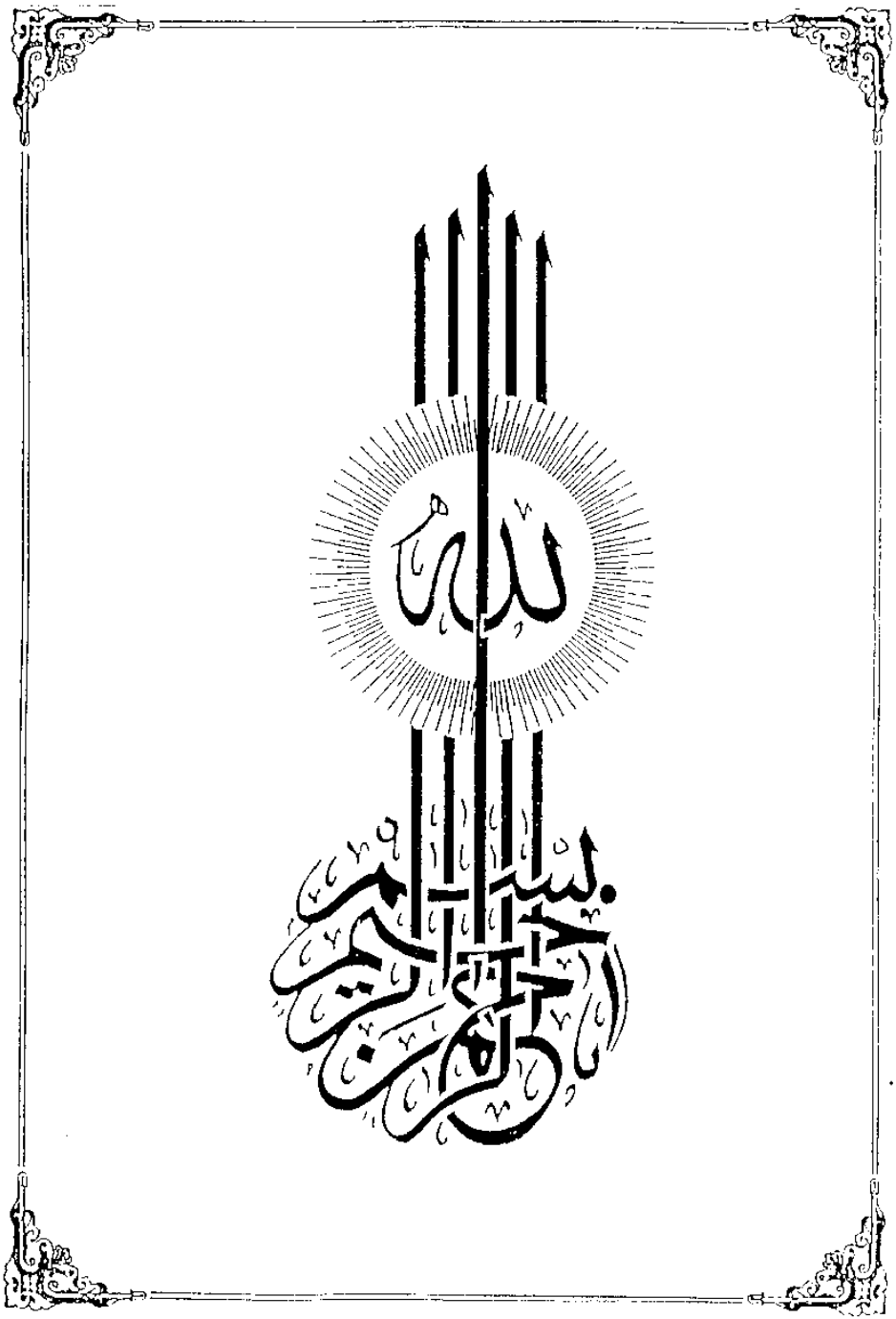

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AIM OF THE WORK

1- To review the viral etiology of leukaemia and lymphoma .

2- Study of some of the viral markers in patients with leukaemia and lymphoma.

INTRODUCTION

SPOTLIGHT ON THE VIRAL ETIOLOGY OF LEUKEMIA AND LYMPHOMA

Leukemia occurs through the world, the annual mortality rates in different countries vary from around 3 to 7 per 100,000 population, being highest in the Scandinavian countries and Israel and lowest in Chile and Japan. Still lower death rates are reported in some developing countries, but this may reflect inadequate medical services. Both leukemia and lymphoma account for 10.6 % of malignant disease registered yearly in Cairo National Cancer Institute and 12.6 % of the cases by Ain Shams Radiotherapy Department.

The etiology of leukemia is still unkown, although there are certain factors which predispose to its development including ionizing radiation, chemical agents, hereditary factors and viruses (Clarkson, 1983).

(a) Ionizing radiation

In doses of 1 Gy (100 rads) or greater, whether from unintentional exposure to nuclear sources or from irradiation therapy, ionizing radiation is clearly associated with an increased incidence

of both acute and chronic myelogenous leukemia. It is still controversial whether a threshold dose exists below which there is no attendant increase in the risk of developing leukemia. There is no convincing evidence that doses employed in radiodiagnostic procedures are leukemogenic in adults, unless the exposure is excessive, as it was for pioneer radiologists working without effective protection. Exposure of the fetus to diagnostic radiographic procedures during pregnancy appears to be associated with a slightly increased risk of leukemia later in childhood, but the extent of the increase is controversial. It is also debatable whether any irradiation of the mother prior to conception increases the likelihood of leukemia in children born later (Clarkson, 1983).

(b) Chemical agents

The leukemias which follow exposure to chemical agents are usually acute or chronic myelogenous leukemia rather than the lymphocytic type. Occupational exposure to benzene and possibly other chemicals is associated with an increased incidence of leukemia. Certain drugs, such as chloramphenicol and phenylbutazone, which are knows to cause bone marrow depression, are probably also leukemogenic, although the risk is not great. There are now numerous reports of an increased incidence of acute nonlymphocytic

leukemia in patients with Hodgkin's disease, multiple myeloma, chronic lymphocytic leukemia, ovarian cancer, and other types of cancer, as well as in patients with non-neoplastic diseases who have been treated with cytotoxic drugs, expecially alkylating agents. Moreover, the risk appears to be greater with combined-modality therapy (irradiation plus chemotherapy). The incidence increases with lengthened survival due to successful treatment of the original disease. Loss of chromosome 5 or 7, or parts of these chromosomes, is common in these secondary leukemias, and they rarely respond satisfactorily to treatment (Clarkson, 1983).

(c) Hereditary factors

Patients with Down's syndrome, a defect characterized by trisomy of chromosome 21, have approximately a twentyfold higher incidence of acute leukemia than expected in comparable age groups of the general population. A number of other congenital condition are also associated with an increased incidence of leukemia, although the risk is less than in Down's syndrome. These include Fanconi's aplastic anaemia, ataxia-tetangiectasia and Wiskott-Aldrich syndrome. Although there is no common specific chromosomal lesion, most of these syndromes are characterized either by chromosomal aneuploidy or by a tendency to chromosomal breakage.

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Familial leukemia is rare, but a few otherwise normal families have been reported in which multiple cases have occurred during one or more generations. Otherwise normal siblings and fraternal twins of leukemic children have a slightly higher than normal risk of developing leukemia, and although the overall incidence is not increased in twins, if one monozygotic twin develops acute leukemia, the other has about a 20 percent chance of developing it also. Because the majority of concordant leukemias in identical twins occur during the first few years of life and because they are often diagnosed simultaneously or within a short time interval, these cases probably represent only one occurrence of leukemia and not two. Unlike the situation in dizygotic twins, the in utero circulatory systems of monozygotic twins are united by shared placental vessels, and if the initial leukemic transformation occurred in one twin before separation of the placental circulation, the other would almost inevitably be colonized by the progeny of the transformed cell. In confirmation of this hypothesis, an identical karyotypic marker was found in leukemic cells of both monozygotic twins with near simultaneous development of acute leukemia (Clarkson, 1983).

(d) Viruses

It is firmly established that viruses may cause leukemia in fowls, rodents, cats, and monkeys. The viruses are leukemogenic when initially inoculated, but infected animals may harbor the virus for their lifetimes often without themselves developing leukemia. They can pass virus to their offspring through the ovum or shed it in milk or other secretions and thereby transmit it to uninfected animals. There are many environmental and genetic factors which determine whether and what type of leukemia an infected animal will develop. Among the most important are quantity of virus, differences in susceptibility of different strains, age, sex, hormonal and immunologic influences, and exposure to external agents such as irradiation or chemical carcinogens which can release or trigger the virus and cause full expression of the disease. Most of the viruses which are leukemogenic in fowls and mammals are RNA viruses (type C or B); type C virus, have been shown to cause lymphomas or myelogenous leukemia in subhuman primates. Exception to this rule are Marek's disease (neural lymphomatosis) in chickens and malignant lymphoma in owl monkeys which are caused by DNA viruses of the herpes group.

Several time space clusters or microepidemics of leukemia have been reported, which might suggest an infectious etiology.

However, prospective epidemiologic studies in situations that might reflect an infectious mode of spread have failed to support this suspicious (Clarkson, 1983).

Despite intensive and arduous efforts, credible candidate retroviruses were not detected in human leukemias and lymphomas until very revently. Their remarkable elusiveness may be due in part to the circumstance that the expression of human retroviruses is strongly repressed.

Recently, however, the persistent efforts of some groups have begun to be rewarded. A retrovirus-like particle was found to be produced spontaneously by a human diffuse histocytic lymphoma cell line, SU-DHL-1. Although it contained a typical viral reverse transcriptase and a p 28 core protein distantly related antigenically to those of certain subhuman primate retroviruses, it was not infectious and did not yield enough high molecular weight RNA to permit its molecular cloning or genomic characterization.

Gallo and his collegues have obtained evidence for the association with cutaneous and other T cell lymphomas and leukemias of a novel type C retrovirus, designated HTLV, and for the consistent presence of antibodies reactive with the p 24 core protein of HTLV in the sera of patients with an unusual form of adult