DETECTION OF HETEROPHILE ANTIBODIES IN LYMPHADENOPATHIES

THESIS

Submitted in Partial Fulfilment
For The Master Degree
Clinical Pathology

By

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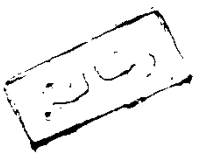

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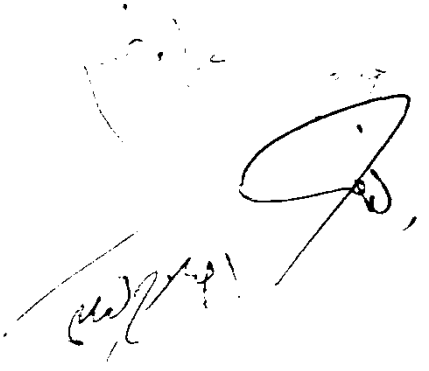

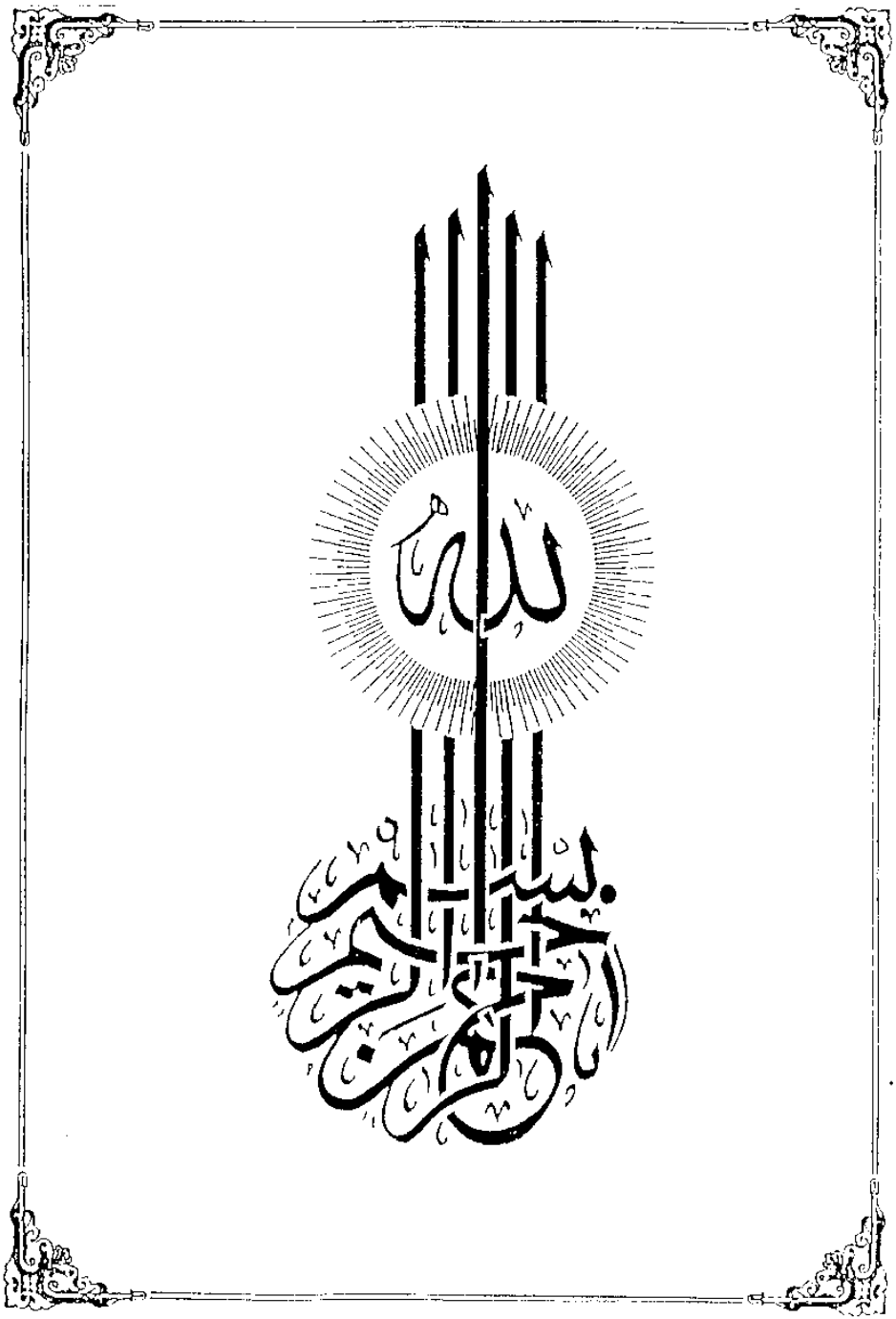

ABBREVIATIONS

1. I.M. Infectious mononucleosis.
2. E.B.V. Epstein Barr virus.
3. DNA Deoxy ribonucleic acid
4. EBVCA Epstein Barr viral capsid antigen
5. MA Epstein Barr virus determined cell membrane antigen.
6. EBEA Epstein Barr virus induced early antigen.
7. EBNA Epstein Barr virus associated nuclear antigen
8. B.L. Burkitt's lymphoma
9. GPK Guinea pig kidney antigen
10. BRC Bovine red cell antigen
11. GVHR Graft versus host response.

CONTENTS

REVIEW OF LITERATURE
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AIM OF THE WORK

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The virus causing infectious mononucleosis and which has a special predilliction for lymphatic tissue was first described by Epstein and Barr (1964) from a case of Burkitt's lymphoma. This virus was also demonstrated by Stewart et al. (1969) in a cell line tissue culture derived from Hodgkin's tissue.

In 1969 I.M. was suggested to be a self limiting form of acute lymphoblastic leukaemia (Dameshek, Carter and Penman 1969) and Epstein Barr virus was reported to confer a malignant growth potential on normal cell by stimulation of deoxy ribonucleic acid synthesis (Smith 1972).

Case reports describing the appearance of acute leukaemia, Burkitt's lymphoma (Stevens, Davis, 1970), Hodgkin's disease (Massey, 1953) and lymphosacroma (Price and Davies, 1969) shortly following I.M. provide clinical support for a contribution of E.B.V. to human oncogenesis.

Paul and Bunnel (1932) reported the presence of sheep red cell agglutinins in sera of I.M patients and the diagnosis of the disease is based on the detection of these heterophile antibodies.

Davidsohn in 1939 described a differential test which can distinguish antibodies of I.M.

The aim of the work is to detect heterophile antibodies in case of I.M and in other varieties of lymph adenopathy as Hodgkin's disease, leukaemia, lymphosarcoma, tuberculosis and to assess the significance of their presence.

GENERAL FEATURES OF INFECTIOUS MONONUCLEOSIS (I.M.)

History: Glandular fever is a peculiar disease which affects only human beings. This clinical syndrome was first described by Emil Pfeiffer (1889) in Germany. However, it seems propable that this condition was already described by Filatow (1885), in Russia. Turk (1907), noticed a peculiar lymphoid picture in the disease and later on the alternative name of infectious mononucleosis was suggested by Sprunt and Evans (1920).

Clinical features of I.M.:

The disease is an ill defined clinical syndrome but in most cases it presents as an acute infectious disease characterized by fever, lymphadenopathy, especially in the posterior cervical region, splenomegaly, acute abdominal symptoms and slight jaundice with rash usually of the rubella type are sometimes observed. A distinctive palatal enanthem at the junction of soft and hard palate usually develops between the fifth and the seventh days of illness (Paul, 1929 ; Caird and Holt, 1958). Hepatitis was also regarded by Burnet (1963), as a constant feature. These signs and symptoms do not appear equally in all cases but some may predominate while others may be absent.

The duration of the disease is variable but usually two to three weeks and relapses are common. Severe complications may occur but fatal cases are very rare (Chessin et al., 1968).

The most important hematological changes in I.M. are:

1. Absolute lymphocytosis from 4500 - 5000 lymphocytes/ cubic mm. of blood or more (Hoagland, 1967).
2. Relative lymphocytosis from 70 - 90 % occurs during the first two weeks of illness and returns to normal during third or fourth week.
3. Presence of atypical lymphocytes at least 20 % or more (Bender, 1958). These cells are known as Downey cells (Downey and McKinlay, 1923), or glandular fever cells. By Leishman's strain these atypical cells appear with oval or horse shoe shaped nucleus and abundant bluish grey cytoplasm which may contain granules. Indentation in the periphery of these cells occurs whenever they come in contact with other cells whether red or white blood cells or even platelets. This phenomenon is known as "Scalloping" (Downey and McKinlay, 1923).
4. The red blood cells are usually normal and anaemia is not a feature of I.M. (Cameron and Mac Bean, 1973).

5. The total white cell count is usually normal or slightly increased.

6. Cameron and Mac Bean, (1973), have found a mild degree of reduction in platelet count in at least 50 % of patients.

7. Coagulation time, bleeding time and sedimentation rate are usually normal (Whitby and Britton, 1963).

Etiology of I.M.:

History: Schmidt and Nyfeldt (1938), have isolated listeria monocytogenes from the blood and cerebrospinal fluid of 5 cases with I.M. Agglutinins to listeria monocytogenes together with sheep red cell agglutinins of Paul-Bunnell reaction were also detected by Stanely (1949), but many workers failed to prove any relationship between listeria monocytogenes and I.M. Wising (1942) also failed to cultivate this organism from blood of patients with I.M.

A second view as regards the etiology of I.M. is an organism related to rickettsia group. Misao and Kobayashi (1955), in Japan have isolated an agent from the blood of a suspected I.M. patient. This agent was retained by Seitz filter and gave rise to a fatal disease characterized by generalized swelling of the lymph nodes and atypical lymphocytes in the blood when this agent was inoculated intracerebrally

in mice. Its relation to I.M. is suggested by its ability to set up a febrile illness with generalized enlargement of lymph nodes in monkey (Shishido, 1965), and glandular fever in human volunteers (Kisao et al., 1957). By the help of the electron microscope Tanaka and Haneoka (1961) studied this agent and it was given the name of Rickettsia sennetsa.

The third view of the cause of I.M. suggested that the disease is caused by a virus having special predilection for lymphatic tissue. This virus was described by Epstein and Barr (1964), from Burkitt's lymphoma and was named as Epstein-Barr virus(E.B.V). It is of herpes group of viruses measuring about 150 - 200 nm. in diameter and viral genome composed of double stranded deoxyribonucleic acid (DNA) and it contains lipid in the envelope.

The etiologic relation between E.B.V and I.M. is based on the experimental success in transmission of infection to monkeys and man by Wising (1942) who succeeded in the production of the disease in monkey's inoculated intra-cerebrally intraperitoneally or subcutaneously with fresh lymph node suspension from patients in the acute stage of I.M. He also succeeded in transmission of the disease to female volunteer by inoculating her with heparinised blood from a patient in the acute stage.

Taylor (1953) and Evans (1960) have also reported successful transmission of I.M. by inoculation of pooled sera from patients with acute stage of the disease into patients with acute leukaemia as a therapeutic effort to induce remission. It was also noticed that cases of monocytic leukaemia resemble severe forms of I.M. and infection by the benign condition exerts a diversionary influence on the malignant leukaemic process.

Epidemiology of I.M.

Prevelance and incidence:

The prevelance of antibodies to E.B.V has been determined in many countries and many age groups. In developing and tropical areas, most children have been infected by the age of 6 years. Porter et al. 1969) have reported a prevelance rate of more than 80 % with the age of 2 - 4 years. Nafuko et al., 1972) have reported a 90 % positive rate by the age of 3 years in the west nile district of Uganda. In these developing countries the infections are usually mild and asymptomatic. But in developed countries and in high socioeconomic groups the prevelance of antibodies to E.B.V. in the childhood period is lesser. Porter et al., (1969) reported a prevelance rate of about 50 % among high socioeconomic