REVIEW AND ASSESSMENT OF THERAPY OF LEUKAEMIA.

Thesis

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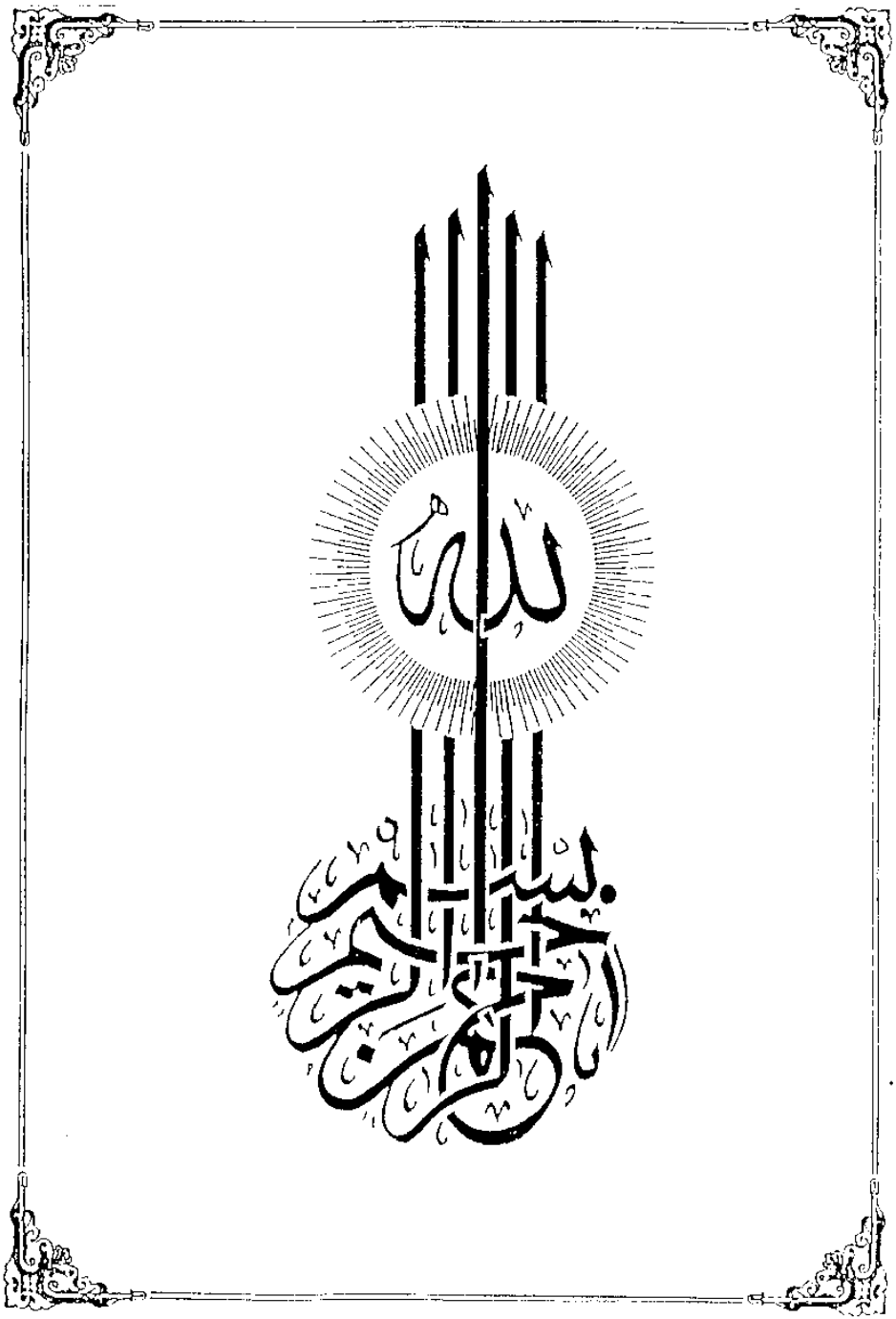

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Etiology and Pathogenisis of Leukaemias

The view on the possible causes of leukaemia are changing without affecting the methods of management to any degree, Many theories and fators are current:-

1. Leukaemia as malignant neoplasm of the white cell forming tissue like other malignant neoplasms.
2. Viruses and mycoplasmas as a possible cause of leukaemia.
3. The role of radiation in relation to leukaemia.
4. Leukaemia as chromosomal and cytogenic abnormalties.

There are several observations which together suggest that leukemia is a neoplasm of the leucopoetic tissue in the bone marrow:

1. The proliferation of the leucopoeetic elements in leukemia is usually unlimited with ultimately fatal result.
2. The occurrence of leukemic infiltrations in the different organs late in the course of most leukemias with disturbance of the proper function of these organs.
3. The occurrence of apparently increased mitosis in the marrow and even in the blood.

It has been found that the rate of increase of leucocyte - doubling time in chronic myeloid leuckemia follow as exponential curve and if the leucoyte doubling time is calculated for a group of patients a definits correlation emerges between this time and the survival of the patient, the quicker the leucosytes increases the shorter is the peroid of survival.

4. The precepitation of leukemia and radiations(to be discussed later).

However there meny other observations against the malignant theory as the only explanation of the leukemic process.

1. The leukemic cells apparently simulates normal cells in structure without the presence of the characters of malignancy i.e. hyperchromatic nuclei, invasion of the capsule of the lymph nodes and disturbance of the architecture of the organs involved.

As regards the reports on leucocyte doubling time . When the technique of thymidin labelling in applied to the bone marrow in chronic myloid

leukamia the rate of labelling turns out to be lower than in normal marrow, which suggests that there is in fact a slowing rather than a quickining of actual cell division.

Surprisingly this slowing of cell division noted in chronic myloid leukamia has also been found in acute leukamia also the experimints show that the blast cells in acute leukamia are not dividing cells. These results suggest that the blast cells have actually prolonged life span. Supporting observation is that the rate of DNA labelling increases befor a remission appears. The present view of acute leukemia is therfore quite different from the classical idea of the replacement of normal marrow cells by malignantly prolcferating mass of blast cells, instead we have the picture of limited blast cell proliferating population producing cells which fail to mature, becomes smaller and aatypical and probably loose their capacity to divide, these non dividing cells released into the blood and accumulate in the tissue.

2. The start of the leukemic process throughout the bone narrow all over the body at the same time suggest that leukemia may be related to a systemic factor rather than a local neoplastic change.

3. There are few reports of epidemics of leukemia in certain areas.

Radiation in relation to leukaemia:

It is the most firmly established leukaemogenic agent in man the relation between radiation dosage and incidence of leukaemia has been studied in the survivors of atomic bomb explosions at Hiroshima and Nagasaki. In these population the incidence of leukaemia has been approximately five times greater than that which would have been expected to arise spontaneously. There are many examples which support the relationship between erradiation and leukaemia:

1. Patients with ankylosing spondylitis who have been given a high dosage of x-ray to the spine have raised incidence of leukaemia . (Court, Brown and Doll, 1957).

2. Children who have had x-ray therapy for thymic tumours have also raised incidence of leukaemia.

3. The ingestion of radioactive iodin is associated with an increased susceptibility to leukaemia.
4. Treatment of polycythemia vera with P^{32} increased the tendency to leukaemic change. Watkins, Fairley and Bodely Scott (1967), in reporting their own experiences conclude that acute leukamia is very rare complication of polycythemia rubra vera unless P^{32} have been used when the incidence usually exceeds 15 per cent.

Viruses and mycoplasmas as cause of leukaemia:

During the post 50 years it has been demonstrated that leukaemia in certain laboratory and domestic animals, is initiated by viruses. A viral etiology of leukaemia in certain species warrants the search for such an etiology in human leukaemia. The search for viruses in human leukaemia is often conducted by indirct methods, for those methods which have been so successful in animals i.e. injecting the agent into newborn or compatible animal of same species is impossible. Viruses can be stuicded for their effect on tissue cultures for their antigenicity, immunological neutralization, electron microscopic appearance and for their

leukaemogenic properties in animals, there have been a considerable number of reports of virus like particle in the blood and cells of leukaemic patients (Anderson 1965, Dmochourski (1965). There particles are far too thin to be considered as possessing a viral nucleoid, these particles can not be said to be a viruses on morphological grounds alone, other points which make the problem more difficult is that animal experiments have shown that oncogenic (tumour forming) and non oncogenic viruses have a very similar appearance and they cannot be distinguished by electron microscope. So far the injection of human leukaemic products (cells and extracts of the serum) has failed to induce leukaemia in experimental animals. These reports of "virus particles" even if they indicate genuine viruses do not prove that are the aetiological agents in leukaemia. The virologist Bryan 1968, points out the viruses of fawel and mouce leukaemia are RNA viruses which differ in their propertier form the viruses responsible for infection most of which are D N A viruses. R N A viruses donot kill the infected cells but stimulate growth and proliferation. The technique for detecting and assaying D N A viruses often fail when applied to

RNA viruses. New and more modern techniques have to be discovered to become able to detect the viruses that may cause leukaemia.

Recently two approaches to the problem of viral aetiology of leukamia have given most interesting results. The first is the work of Negroni 1964 who isolated an infective agents from the bone marrow in human leukaemia. This agents caused cytopathic changes in human embroynic cells cultures and these cytopathic effects could be prevented by antibodies present in the serum of leukaemic patient. At first this agent was thought to bea virus but later it was demonstrated that pleuropneuomnia like organism , a mycoplasma was present in Negorn's material (Grist & Fallon 1964).

However there is no proof that the agent plays a part in etiology. The association of mycoplasms wiyh leukaemia has been confirmed (Giradi et al 1965) and they have also been found in the lymphoid tissue of patients with reticulosis, so mycoplasms are an important group of micro-organism that must be investigated for Oncogenic properties.

Chromosomes and Cytogenetics in leukaemia :

Chronic myeloid leukaemia is especially interesting from the cytogenic point of view as in high proportion of cases there is specific abnormalties in chromosomes Nowell & Hungerfard (1960) are the first who demonstrated an abnormal chromosome named philadelphia chromosome (Ph). It is 21 chromosome with half its long arm missing. In the marrow Ph chromosome appears to be present in the myeloid erythroid and megakaryocytic cell lines but not in the lymphocytic cell line.

The Ph chromosone is unique to chronic myloid leukamia and is not present in other myeloproleferative disorders i.e. polycythemia and myelofibrosis even when chronic myloid leukaemia complicate there diseases. A small proportion of male patient with chronic myloid leukamia who are Ph +ve have an additional chromosomal abnormalties, loss of Y chromosome in the bone marrow cells (ATKIN & Taylor 1962. Speed & Lawler (1964).

There are a small proportion of patients, who have undoubted chronic myloid leukamia and remains Ph negative.

No chromosomal abnormalties are detected in patients with chronic lymphatic leukamia.

An interisting line of invisigation has been the study of abnormalities of chromosome 21 in Downcs syndrome. In this disease there is 20 fold increase in the incidence of acute leukaemia, as compared with the general population. Chromosome 21 has been thought to be associated with the gene loci for the control of alkalin phasphatase in the myloid cells. Chronic myeloid leukaemia patients have low alkaline phosphatase scores (Valentine & Beck 1951). In the non leukaemic myeloproliferative disorders (Ph) negative there is no reduction of alkaline phosphatase (Hayhoe 1960).

No specfic abnormality has been detected in acute leukaemia that is unique to this disease. But in the majorty chromosome abnormalties are present. In some series of invisigation in acute lymphoblastic leukaemia cells were frequently hyperdiploid and in acute myeloblastic leukaemia hypodiploid.

The reflection of these abnormalites on the understanding of the pathegenesis of leukamia needs further clarification.

Lekaemia as an "Immuno - proliferative disorder :

This is too much accepted in chronic lymphatic leukemia. Studies of mitotic cycles and RNA and DNA changes shown that as in acute leukaemia cell division is slower than normal. The disease now described as accumulative rather than proliferative disease.

Auto Immune haemolytic anaemia is common complication to this disease which support the idea that this type of leukaemia is immune proliferative disorders.

Now we can see that the pathogenesis of acute leukemia is far from clear and needs further investigations. There are pross and cons for each possibelity mentioned. Leukemia as a malignant disease does not solve the problem of aetiology. The role of virus and mycoplasma in human leukemia is probabely anrelated to aetiology and the presence of virus particle inside the leukemic cells may just represent what is called passenger virus , The same applies for chromosomal abnormalities. Perhaps the future may prove that all these factors are contributing to the pathogenesis.

WHY WE TREAT ACUTE LEUKAEMIA

The changes in the treatment of acute leukaemia reflect the altered atitude towards the malignant diseases in general. The idea that malignant disease is ulttimately fatal is now liable to question.

Even of leukemia is ultimately fatal ethically we dont have the right of leaving patients to die for any economic burden on the family or the state.

For prolongation of the patient life may give the chance of any future advances in the management of their disease. So the question which arise is every patient with acute leukaemia should be treated??

The study of (Burchenal 1967) will answer this question.

Burchenal has collected from the entir world literature 157 cases of acute leukaemia of all types of whom 103 are alive and free of disease between 5 and 17 years later.