EFFECTS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS ON EXPERIMENTAL TUMOUR CELLS (in mice)

A THESIS

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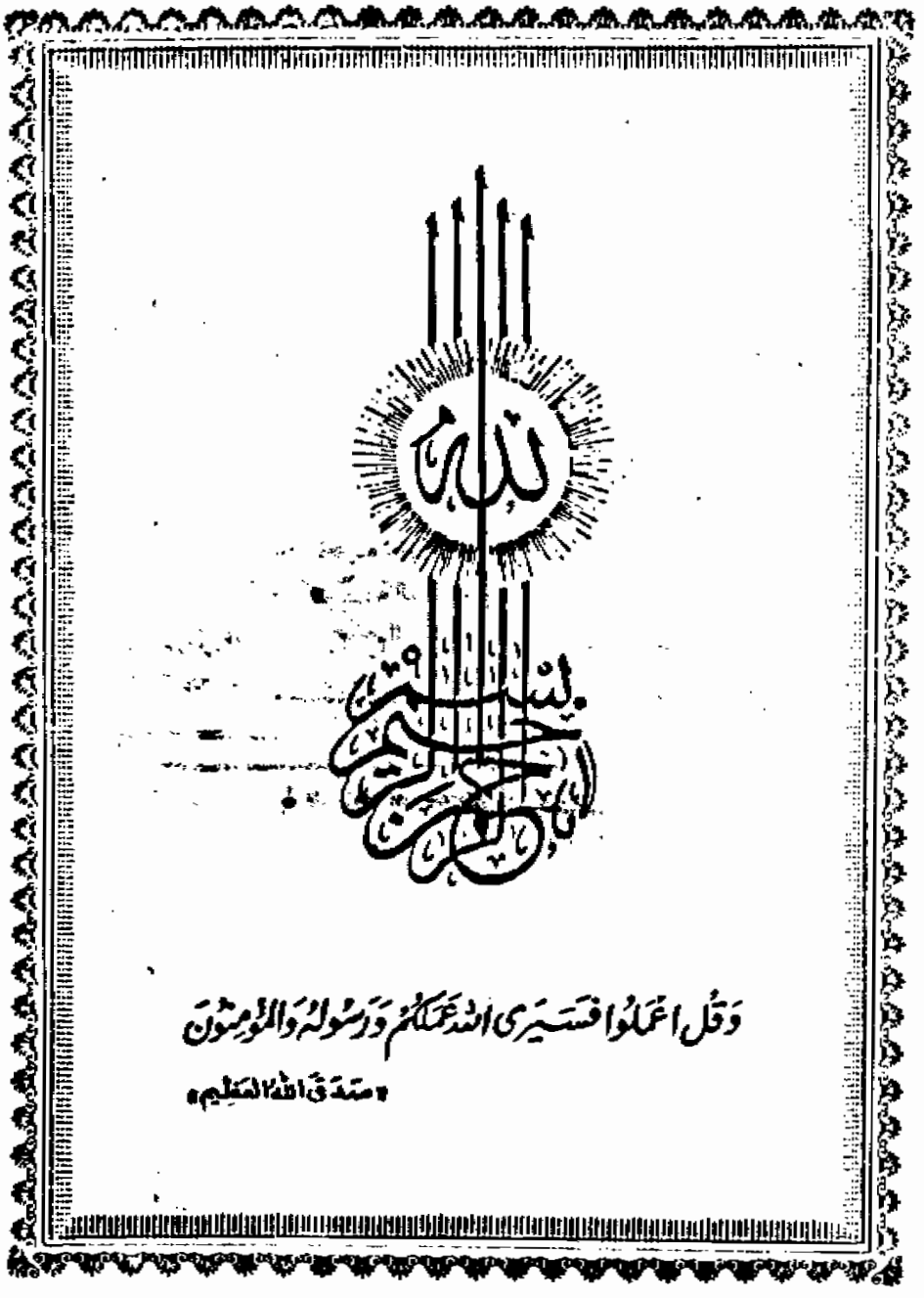

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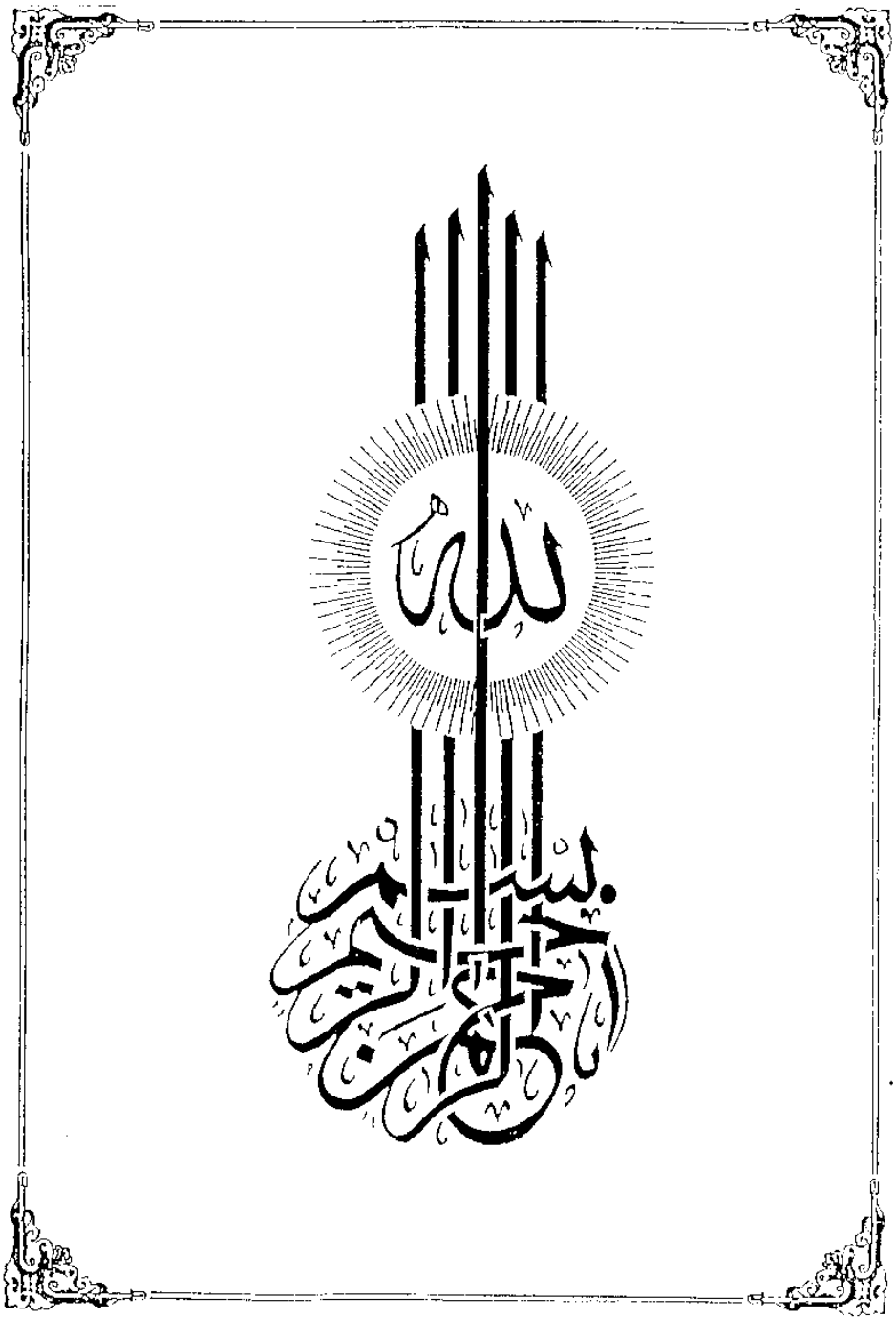

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Cancer means usually a word associated with disease, death and dying. It strikes fear into the hearts of ordinary people because it has been associated with a mysterious illness with no known cause and no known cure. Those who are fortunate enough to escape it themselves will almost certainly face cancer when it strikes a family member or friend.

Through scientific research over the last 25 years our ordinary understanding of this disease has been greatly increased which represents the initial step towards a cure. Therefore, research is the only hope to solve this problem (Prescott, 1984).

At the clinical level, the word cancer is used to describe a group of diseases with related clinical features which, if untreated, results in death from overgrowth by the cancer cells (Calmon and Paul, 1978). At the cellular level, cancer is a disease process which may affect multicellular organisms and which is characterized by the uncontrolled multiplication (Roe , 1975).

All cancerous cells are descended from normal cells. The conversion of a normal cell to a cancerous cell is a

slow genetic process that usually takes many years. Therefore, cancer takes years to develop, and the person may not be aware of the disease until it begins to interfere with the normal functions of his body. But even before the appearance of pain which is a late symptom of the cancer, there are painless symptoms that may indicate the presence of cancer in the body such as change in bowel or bladder habits, unusual bleeding or discharge, thickening or lump in the breast or elsewhere (Prescott, 1984).

About 20 years ago , much cancer research was concerned solely with the uncontrolled multiplication of cells. It is now widely appreciated that in many normal tissue cell replication takes place more rapidly than in most cancers. It is therefore, obvious that the selective elimination of cancer cells cannot be achieved by treating a patient with a drug which indiscriminately damages all dividing cells.

Tumours are classified as benign and malignant; benign tumours tend to remain localized, are often surrounded by a capsule and rarely give rise to serious effect . Malignant tumours, on the other hand do not remain localized but invade other tissues and give rise to secondary tumours in other parts of the body.

The progress of a tumour from being benign to becoming malignant sometimes follows quite well-defined stages and it

was found that many tumours have their own natural history (Roe, 1975).

There are more than 100 different types of Cancer: some originate in the muscle and bone (Sarcoma), some in the skin or in the lining of organs (Carcinoma), some in the blood (leukemia) and some in the lymphatic system (lymphoma) (Levih and Guralnick, 1984).

Cytological studies (Koller, 1978) of the chromosome consitution of cells in tumours of varying kinds have revealed that abnormalities in number and structure of chromosomes are of common occurence. Also, it has been found that, tumour tissue is composed of a heterogenous cell population, the structure of which can change under environmental influences.

But these studies failed to demonstrate the existence of a stable chromosome pattern which would be characterstic of the malignant cell.

Certain genetic disorders increase significantly the risk of cancer. Such disorders could result from radiation, viral infections or exposure to chemical carcinogens. Also, tumours occur with increased frequency in patients with congenital deficiencies and also in patients with acquired or induced immunologic deficits (Frei and Bodey, 1974).

Cell surface modifications play a major role in regulating mechanisms essential for malignancy. It was found that the tumour cells are more readily separated from each other than normal epidermal cells, suggesting that the surfaces of the tumour cells are less adhesive (Ambrose, 1975).

The external factors that determine a cells pattern of growth e.g. substratum, adjacent cells and growth stimulating compounds must first impinge on the cell surface (Pardee, 1982).

The biochemical approach to tumour metabolism represents the most promising approach to the understanding of the neoplastic growth. It is well known that tumour tissues, either in the form of solid tumours or ascitic cells, have a higher rate of aerobic and anaerobic glycolysis. Warburg (1956) stated that a normal cell becomes malignant as the result of impairment to its respiratory processes and that in order for these cells to survive they must derive the energy that was once provided by respiration from other metabolic processes. Thus he proposed that the increased rate of glycolysis serves to provide energy for its survival. However, it has never been shown experimentally that tumour cells are dependent on glycolysis for survival.

Lazo and Sols (1980) found that elevated glycolysis was related directly to the tumour growth rate. Also, the activities of the key glycolytic enzymes increased in parallel with tumour growth rate and this is accompanied by a decrease in the levels of the key glucogeneogenic enzymes (Weber and Lea, 1967; Harrap, 1975).

The liver of the tumour hosts are known to exhibit a variety of biochemical abnormalities including quantitative changes in the activity of several enzymes (Lazo and Sols, 1980).

However, blood enzyme disturbances showed no diagnostic value for detecting early malignant diseases. With the exception of the usually raised serum acid phosphatase in spreading cancer of the prostate gland, no specific enzyme changes can be found for advanced cancer (Baron, 1979).

Also, there would appear to be a progressively enhanced activity of anabolic enzymes in association with a decreased activity of catabolic enzymes of pyrimidine metabolism, correlating with the tumour growth rate. The production and processing of RNA do not seem to be different in normal and neoplastic cells; yet changes in methylation of t-RNAs of tumour cells have been reported (Pardee, 1982).

Treatment and Management of Cancer

The philosophy underlying all cancer treatment is to improve the quality and /or length of life of the patient. The ideal is to achieve a long term cure, which is possible in some cases, but in many others, the nature and stage of the neoplastic disease clearly preclude this objective. Presently, the possibility of curing most malignant diseases lies in early detection.

The treatment of cancer is a complex process and requires the knowledge and skills of multiple disciplines. It can be carried out through several procedures which include, the surgical therapy; which is the primary therapeutic modality used for most solid tumours. It is based on the concept that malignant tumours remain localized to the point of origin for a time then progress systematically to involve adjacent structures, blood vessels, and regional lymph nodes.

The older view that surgical therapy had to remove every malignant cell from the body in order to be curative has been modified; modern view is that surgery should remove every cell if possible, but in most cases few cells remain which host defences can destroy. Therefore, cancer

surgery may be viewed as a form of immunotherapy (Schronck, 1982). No appropriate surgical intervention can be undertaken without a preliminary assessment of : the exact extent of the disease, the biologic growth rate of the tumour, and the patient's general condition.

The palliative treatment of cancer, that is, treatment without the prospect of cure has certain important aims which includes elimination of the most burden some symptoms, prevention of complication, prolongation of life and psychologic uplift.

Veronesi (1982);stated that surgery with a cooperative effort with radiotherapy and chemotherapy can give the best treatment.

Radiotherapy is the second important modality in the treatment of malignant diseases as a curative procedure,as a palliative procedure and as a junct to other forms of treatment. It selectively destroys or alters the growth potential of the neoplastic cells without significantly compromising the normal tissues within which the tumour is located (Hazra, 1977).

Radiotherapy has been used as adjuvant therapy with surgery or chemotherapy. Pre-operative radiation may reduce the size of certain tumours, thus facilitating

the surgical removal and providing a greater opportunity for cure (Frei and Bodey, 1974).

Radiation injury in normal tissues and in tumours differs because of the ability of the normal tissue to respond to injury with physiologic mechanisms of adaptation. Such adaptation allows shortening of cell cycle and recruitment of cells into the cell cycle from the tissue itself or adjacent tissues, so that the production of new clonogenic cells may be rapidly increased over that present in steady-state situation.

Tumours that lack such control mechanisms may show increased proliferation at certain stages following radiation. This generally occurs as tumour cell number is reduced, allowing a better supply of nutrients and oxygen for the surviving cells, thus more rapid proliferation with short cycle times and higher growth fraction and lower cell loss during the period of tumour regrowth following treatment (Philips, 1982).

Tumours which arise in endocrine-sensitive tissue may retain some endocrine control of growth (Powles, 1982). It has been appreciated that some human malignancies may respond to manipulation of the endocrine milieu. Essentially, all of the endocrine manipulation which are effective against neoplastic disease involve alterations in concentrations of steroid hormones or interference with their activity.