IMMUNOLOGICAL STUDIES ON PATIENTS WITH CANCER LARYNX AND LARYNGOPHARYNX BEFORE AND AFTER SURGICAL EXCISION OF THE TUMOUR

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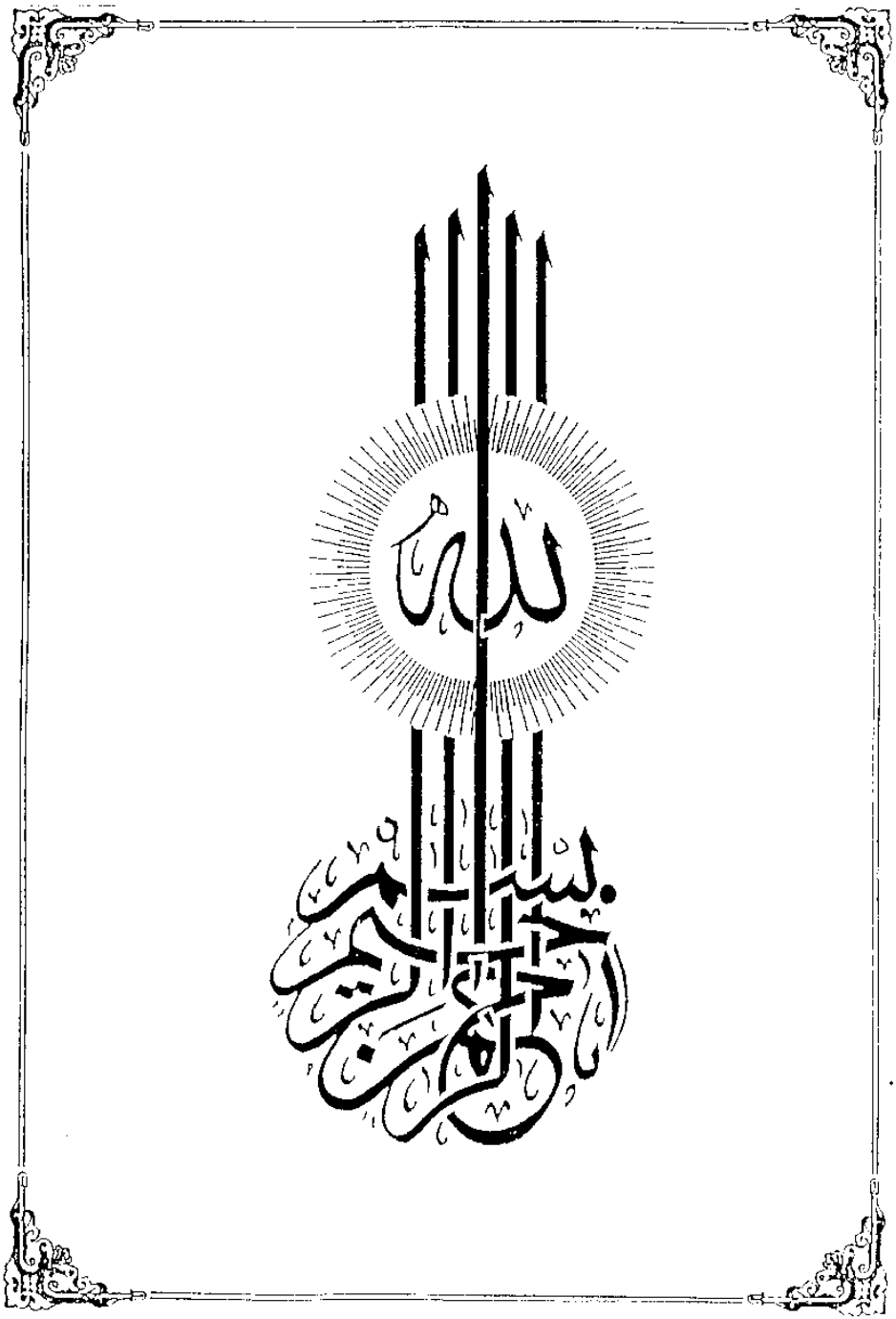
بسم الله الرحمن الرحيم

"قالوا سبحانك لا علم لنا إلا ما علمتنا
إنك أنت العليم الحكيم"

صدق الله العظيم



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Finally, by this work I'm starting to walk in the road illuminated by my father's knowledge and wisdom, for whom I dedicate this work.

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INTRODUCTION

INTRODUCTION

From around the turn of this century, the notion that cancer results from some immunological disarrangements has intrigued many investigators.

One of the major advances came in 1947 when R.T. Prehn and J.M. Main demonstrated that, while the mice would reject a tumour graft, they would accept skin graft from the same animal in which the tumour originated. This was the first demonstration that the antigens involved in immunization were tumour specific.

Sir McFarlane Burnette (1957) had postulated in his Noble winning Colonel theory, that cellular immunity was a surveillance system to guard against continually occurring neoplastic transmutations.

In mid-1950s, Mitchinson in England demonstrated that it was the lymphocyte which mediates the immunologic response to normal transplantation antigens and, more importantly, that one could adoptively transfer lymphocytes from one animal to another animal, making the latter immune also (Kennedy, 1975).

All works in this time laid stress on the cellular response and

tended to disregard the humoral circulating antibodies as possibly part of the immunological surveillance system involved in recognition and destruction of tumour cells in the body.

With new techniques, many workers have been able to demonstrate that tumour cells are found in blood in the veins draining from areas of carcinoma in almost 100 percent of cases, furthermore, in all cancer patients studies on the peripheral blood have yielded detectable cancer cells in from 10 - 40 percent. This suggests that the body has a good immunological surveillance system for most tumours and that the cancer eventually by some escape mechanism, overwhelms the surveillance system. Perhaps this is by pure bulk of tumour cells as opposed to the number of cells of the surveillance mechanism. Wilson (1972) was able to demonstrate in vitro experiments that the ability of lymphocytes to kill tumour cells is dirfectly dependant on the number of lymphocytes present as compared to tumour cells. A second alternative is that there is a blocking antibody produced, as Hellestrom suggested, but this would not explain fully the paucity of melastases seem in this group of patients (Kennedy, 1975).

Immune responses to tumour associated antigens in the tumour-bearing host can be detected using in vitro techniques, these have the advantage of being directly applicable to human cancer patients. These studies, initiated by Hellestroms' (1970 - 1974) introduction

of in vitro lymphocytotoxicity tests, represent a major development in the study of immunity to human cancer and conclusively establish that the tumour bearing patient responds to neo-antigens associated with the autologous tumour.

AIM OF THE WORK

To study the affect of surgery and its extent on the immunological status of the patients and what is the role of serum factors on this status.

REVIEW OF LITERATURE

IMMUNE SURVEILLANCE

A significant development in contemporary tumour immunology was the theory immune surveillance, which proposed that malignant cells expressing specific transplantation antigens are constantly arising in the host, the host's immune system is continually monitoring the body and destroying such cells. In other words, it states that the normal function of the immune system or more precisely the cell mediated immunity carried out by the thymus derived T-lymphocytes is to recognize and destroy newly appearing tumour cells in situ (Byers, 1982).

The concept of surveillance was initially proposed by Ehrlich (1909) who further suggested that during cell differentiation abnormal cells arose but kept inactive by the host's immune response. Later Thomas (1959) proposed that a reaction against histocompatibility antigens actually developed to defend the body against neoplasia. Burnet (1971) further expanded the idea suggesting that the role of natural immunity was not to eliminate established tumours but to destroy subclinical tumours.

The concept of surveillance is accepted by many oncologists although some serious challenges of this theory have recently been

made. There is considerable evidence for some form of serveillance, particularly the observation that most tumours passes antigens which are capable of arousing a cytotoxic or cytostatic reaction in autochthonous hosts. Certainly most chemically induced tumours are immunogenic but the quantitative responses vary widely from one tumour to another and occasional tumours initiate no immunity at all. Such non-reactivity may result from serum inhibitory factors although some tumours have been shown to lack surface antigens (Castro, 1978).

Again, some support for this concept has come from the demonstration of increased predisposition to cancer growth in patients with variety of immunologic syndromes. A frequency of cancer development which is 15 - 30 times greater than that in the general population may be observed in conditions such as congenital X-linked agammaglobulinemia, late onset immunedificiency and the severe combined immunedificiency syndrome (Southam, 1974). Patients with various types of hypogammaglobulinemia appear to have an increased predisposition to lymphocytic leukemia (Gatti, 1971). In addition, the family members of patients with chronic lymphocytic leukemia manifest an increased incidence of hypogammaglobulinemia.

In human patients taking immune suppressive drugs after renal transplantation, there is an increased incidence of tumours. In

such patients Penn (1975) reported an overall corrected incidence of 5.6 % compared with 0.058 % for a normal aged matched population. The histological types of these tumours are markedly different from the normal population, for nearly 50 % of the tumours were mesenchymal in origin and many were reticulum cell sarcomas. This suggests that the mechanisms operating in immune suppressed patients maybe different from those involved in normal patients. The observations may be explained by the suggestion that immunesuppressive agents may themselves by oncogenic or that the antigenic drive of an allogenic organ graft in combination with immunesuppressive drugs may initiate tumours of lymphoid system and account for high incidence of such lesions.

In patients suffering from diseases like Wiscott-Aldrich syndrome or ataxia talengectasia (both of which affect cell mediated immunity), there is increased incidence of tumours. Again ageing which is well known to be associated with depression of immunity (Snyderman, 1975), is also accompanied with increase incidence of tumours.

Measures adapted in order to investigate immune surveillance through interfering with immunologic reactivity by neonatal thymectomy or irradiation or immunesuppressive drugs, gave confusing results. Nehlson (1971) reported no increase in the incidence of tumours following the injection of rabbit antimouse thymocyte serum (ATS), on the other hand mice given ATS and exposed to an oncogenic

virus showed marked increase in the incidence of tumours. The finding that mice deprived of cell-mediated immunity and exposed to an oncogenic agent developed more tumours is a definite evidence in favour of surveillance. The only convincing evidence for surveillance in a spontaneous tumour system is the lung adenoma of mice where immunosuppressives are associated with marked increase of tumours (Castro, 1976).

The failure to demonstrate tumour antigens may be an evidence against surveillance, but the lack of immunegenicity may by the very reason for the clinical occurrence of such tumours and may be an evidence in favour of the hypothesis.

At a time when the only known function of T lymphocytes was to destroy foreign grafts, immune surveillance gave a satisfactory explanation. Today we know from numerous observations that the main function of T lymphocytes is to defend an individual against otherwise lethal microbial (mainly virus and parasitic) infections. Thus the previous need to find a normal biological function for T cell is no longer pressing, but the concept of immune surveillance still persists and has been unchallenged until recently. It has for several years been regarded as dogma in tumour immunology.

Evidence Against Surveillance (Escape From)

Today it is scientifically acceptable to question immune surveillance which never rested on concrete experimental support and it has been critically reviewed by several authors.

Cellular Origin of Tumours:

The first clear observation of the cellular origin of tumours came from studies of myelomas. These tumours arise from B cells which are capable of synthesizing and releasing immunoglobulins and it was shown that sera from patients with myeloma contained a very typical homogeneous peak of immunoglobulins (Miller, 1968). In individual patients all the immunoglobulins belonged to the same class and had identical variable regions, indicating that the myelomas were derived from a single cell. Since each B lymphocyte has a unique immunoglobulin receptor, the inescapable conclusion is that myelomas start from one individual cell. By the use of immunoglobulin markers it has been found that myelomas are not unique in this respect for a variety of lymphatic tumours have been studied and monoclonal origins have been reported for example Waldenstrom's macroglobulineamia and chronic lymphatic leukemia. Monoclonality