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EDITORIAL

Cancer and Immunology

Macfarlane Burnet's little gem, "The integrity of the body" was published thirty years ago.[1] He lamented that it had taken 30 years for immunology to develop from a little niche into a significant part of biology. Burnet discussed the various aspects of immunology and stressed that the subject must be regarded as having wider bounderies and depth than the popular view at the time. Immunologists were mainly concerned with infection, but cross border interests in genetics, biochemisty and transplantation were emerging. Burnet viewed immunology as part of the maintenance and the processes by which the structural and functional integrity of every complex organism is sustained, the cohesion of separate living parts into an independent organism. Allergic and autoimmune diseases were discussed but rather surprisingly, the old enemy, cancer, was not even mentioned. Burnet must have been aware of the potential role of immunology in cancer therapy as attempts to produce passive immunotherapy with serum and active immunization with tumour cells were made nearly a hundred years ago. Burnet's theory of immune surveillance which suggests distinct clones of malignant cells, was published a little later[2] but was not universally accepted. Experimental work in the 1940s and 1950s established tumour immunology on a more secure basis. These experimental studies illustrated antigenicity and immunogenicity of chemically induced tumours. Since then a large number of experimental neoplasms have been produced using viral, chemical and physical agents. Many methods have also been employed to try to induce immunity experimentally. These include induction of tumour necrosis by ligation of the blood supply, injection of tumour cells and administration of intracellular fractions of tumour cells. The better understanding of the virus induced neoplasms in animal experiments and the association of Burkitt's lymphoma and the Epstein-Bars virus have given more impetus to cancer immunologists. Now a number of neoplastic conditions such as human leukemia and urothelial cancer are suspected of having viral association.

Doctors have been treating cancer from the dawn of recorded medical history and methods of combating the disease have not altered significanty. Cutting, burning and poisoning tumours are still practised today but in the guises of aseptic surgery, radiotherapy and chemotherapy. The addition of hormone therapy helps in the minority of malignant diseases and is only paliative. The recent introduction of immunotherapy has given fresh enthusiasm to physicians concerned with fighting cancer. The philosophy and underlying principles satisfy all disciplines and appear to tackle the very basic problems of treating malignant diseases. The modality of treatment is actually based on the fundamental immunological principles of natural host defence mechanism against cancer cells. There are many biological components, mostly polypeptides, which are capable of affecting cancer growth; these include the cytokines, monoclonal antibodies, immuno-modulating agents (eg.thymic hormones) and certain vaccines.

The processes of anti-tumour immune response are now better understood and they involve the roles of macrophages, lymphocytes and antibodies. The entire network involves processing the tumour antigens by the macrophages, activation of T cells into T_H cells. Cyto-

kines and antibodies are produced to kill tumour cells. The factors for the host's failure to destroy tumours are more perplexing. The probable reasons range from lack of appropriate tumour antigens to tumour secretory products suppressing macrophage functions. Many attempts at treating cancer using immunobiological principles have been made. The results of immunization using BCG have been disappointing. Adoptive immunotherapy in which cells with anti-tumour reactivity are given to a tumour bearing host, has however, a limiting factor. It is the inability to produce an adequate number of cells with anti-tumour activity for systemic application. Recent studies are encouraging but the therapeutic efficacy of this method needs well controlled clinical trials. [3,4]

The other specific approaches are serotherapy and the use of biological response modifiers. The former requires monoclonal antibody technology and pure immunoglobulins have been used in large quantities. Both animal and human trials have been carried out in different types of cancer. The inherent problems of this therapy are its effectiveness against a large tumour mass, localization in sanctuary areas, the failure against antigen-negative tumour cells and tumour cell heterogeneity. This therapy is, however, associated with low toxicities. It is also very useful to "mop up" autologous bone marrow prior to bone marrow transplantation, and in leukemic patients. [5-9]

Biological response modifier is a simple substance which can influence the immune response by modifying a variety of cell types and their functions. They are mostly cell-cell regulators. This type of therapy has been made possible because of recent advances in biotechnology and genetic engineering. The approach entails the stimulation of the natural host defence system against tumour cells. Some biological response modifiers interact with the lymphocyte killer cells enhancing their ability to lyse cancer cells; some act via both macrophage and lymphocyte. The most widely used biological response modifiers so far are the interferons. Interferons act by influencing the B, T, natural killer cells and macrophages; they also have anti-proliferative activity. The three main types of interferons, alpha, beta and gamma produced by fibroblast, B lymphocyte and T lymphocyte respectively, have given an added dimension to the tretment of cancer. Claims of improved responses have been made in many areas of malignant conditions, particularly in hairy cell leukemia. Benefits in other areas, such as melanoma, head and neck, colorectal, and ovarian cancers have been reported. The results still, however, require extensive trials under controlled settings for evaluation and the most likely application and usefulness are in the management of residual and minimal disease conditions. [10-14]

The next logical step in the treatment of cancer is to combine cytotoxic drugs with immunotherapy. Chemo-immunotherapy is based on the general principles of cytotoxic drugs acting effectively against large volume disease and immunotherapy against microscopic residues. Mixed results have been published. Interferons and 5-FU have been tried in gastro-intestinal cancers and preliminary reports of both oesophageal and colo-rectal tumours are encouraging. [15-18]

Recent advances in the management of cancer would not have been possible without progress in other directions. Immunohistochemistry is now part of routine diagnostic techniques. Origins of poorly differentiated tumours can be accurately traced. It is also of considerable interest to be aware that some human tumours show cross-activity with embryonic tissue antigens. These oncofetal antigens are probably the products of dedifferentiated cells. Carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) are examples of oncofetal antigens. In clinical practice CEA is associated with endodermal tumours such as carcinoma of the colon; AFP is produced by fetal liver and the elevation of this protein is observed in hepatoma. HCG is of germ cell origin and is associated with trophoblastic tumours. Other oncofetal antigens, such as CA-125 for ovarian cancer, have been introduced in clinical practice to improve diagnostic or prognostic accuracy.

All areas of medical science have been expanded at an explosive pace and as a result many subjects are less well defined. Physicians interested in trauma, sepsis, metabolic response to stress, starvation and cancer need to be aware of the macro-endocrine systems as well as less familiar agents such as cytokines, tumour necrosis factors and prostaglandins. Purified mediators and growth factors are now available for clinical use. Immunology has provided a common ground for many different specialties and these areas of mutual interests should help to generate a more effective approach to the treatment of cancer. It is also very easy to be overwhelmed by ultra-modern advances; the orthodox and traditional methods are still the basis of cancer management. It is futile to try to treat a cachectic patient with powerful anti-cancer drugs unless malnutrition is reversed; practially all organs suffer and the immune system is no exception. Animal experiments demonstrate that within a short period of starvation the normal thymic pattern begins to alter and the structure of this immunologically important organ almost disintegrate if starvation is prolonged. The changes are similar in chronic diseases such as diabetes. [19-21] Good and basic principles must still be observed.

On the oncological horizon more rational combinations of cancer

treatment are emerging. Mutilating surgery and radiotherapy will continue to "spear-head" cancer treatment but with more effective chemotherapy and precise immunotherapy oncologists can look towards the future with greater confidence. It is certainly not over ambitious to plan routine treatment of notoriously aggressive tumours such as oesophageal cancer with pre-operative chemotherapy, surgery, and post-operative immunochemotherapy.

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