PROSPECTS FOR IMMUNOTHERAPY

P. ALEXANDER

Conflicting evidence for immune reactions by the patient with cancer. Immune reactions have been invoked to explain the very rare instances of complete spontaneous regression of malignant tumours and the more frequent spontaneous disappearance of some, but not all, metastatic deposits which is most readily observable with melanomas. The curability by chemotherapy of aggressive and metastatic choriocarcinoma and the occasional cure of Burkitt's lymphoma by a single treatment with cytotoxic agents has also been ascribed to a contribution by immune factors, as has the precipitation of cancer by stress, if indeed this is a real phenomenon. Changes in the histological appearance of nodes which drain a tumour, but which are not involved with tumour and the presence within tumours of leukocytes, especially macrophages, are consistent with an immunologically mediated host response in certain cancers. The clinical and pathological data is not decisive and much of the attention which has been devoted to tumour immunology stems from studies of experimental tumours in animals in which tests involving transplantation provide definitive proof of the existence of tumour specific antigens for some but by no means all of the cancers studied. Such transplantation tests can not be applied to man and the in vitro tests for anti-tumour antibody and cytotoxic lymphocytes are for most human cancers conflicting and, in general, cannot be interpreted because of confounding factors. The one example of a truly tumour specific antigen in human cancer is the B-cell lymphoma which produce an immunoglobulin molecule which is unique to each tumour.

The increased incidence of malignant disease in immune depressed individuals is largely caused by an excess of some rare malignancies such as non-Hodgkin's lymphomas and Kaposi sarcomas and relatively benign skin cancers. The incidence of the common carcinomas which constitute 80% of cancer is not increased by immune suppression. The available data
is consistent with the hypothesis that immune suppression in general promotes the occurrence of cancers in the aetiology of which a virus is implicated. It is the virus and not the cancer which is under immune surveillance.

The most satisfactory evidence for an immune response to cancer would be effective immunotherapy. Within the last fifteen years there have been hundreds of claims that immunological manoeuvres based on augmenting or inducing an immunological host response alone or in conjunction with other therapies, are therapeutically useful but almost none of the claims made have withstood the test of prospective randomised controls and, there is as yet, no role for any of the immune procedures tested in the treatment of cancer except in an investigational setting. Well conducted randomized trials have failed to support earlier claims made for immunotherapy in the treatment of melanoma (except for the destruction of superficial tumours by intra-lesional injection of agents which cause inflammation), lung cancer, colon cancer and gynaecological cancers. In the acute leukaemias immunotherapy during remission may be better than no treatment at all, but do not equal the results of intensive chemotherapy and other measures such as total body irradiation and bone-marrow grafting. The exceptions are the B-cell lymphomas in which therapy which uses the idiotypic immunoglobulin as a highly specific target is both logical and promising.

New immunological approaches to cancer treatment
Recent developments in immunology provide a solid basis for new types of passive immunotherapy which do not rely on the presence of tumour specific antigens and their recognition by the host. It is now well worth testing whether a useful response may be induced by laboratory produced monoclonal antibodies - and more in the future by clones of specific T-cells grown in vitro - that are directed against antigens which are associated with the cancer cell but which do not evoke a host response because they are not novel to the host. Such antigens can provide a target for therapy if they are present in cancer cells in much larger amounts than in normal cells or if the antigen is only present in normal cells which are capable of replacement. For example, a differentiation antigen present both on lymphomas and on mature lymphocytes would constitute a good target since the loss of the mature lymphocytes