CANCER TREATMENT RESEARCH

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INTRODUCTION

In recent years the field of cancer treatment has been burgeoning with ever expanding interest and commitments to research and therapy. Besides the large number of specialty journals and publications devoted to cancer related fields, nearly every general medical journal contains one or more articles related to cancer treatment and research. Another example of this expanding commitment and interest is reflected in the Internal Medicine subspecialty of Medical Oncology which, since its recognition as a subspecialty in 1973, has become the secondmost populated subspecialty, second only to cardiology. This burgeoning interest and commitment is obviously appropriate in view of the prevalence and incidence of the various cancers. These diseases constitute, after all, some of the most important and devastating problems of civilized man.

It has been particularly gratifying to those involved with cancer research and therapy to observe the increasing interest in these diseases being translated into real improvements in patient care - improvements in length of survival, improvements in quality of survival, and improvements in palliative care. One need only look at Hodgkin's disease to observe the high rate of cure now routinely obtained whereas, in the past, many patients' disease continued to progress with fatal consequences. Some of these improvements came about through better staging techniques, and other improvements, as will be discussed in the chapter on Hodgkin's, came about from the application of early chemotherapy. Further research in Hodgkin's disease is still going on in order to improve results and decrease treatment related complications.

Another example of the improvements derived in recent years from ongoing treatment research studies has been the realization of improved survival from the application of early or "adjuvant" treatment of micrometastases. Based on solid evidence in the animal tumor systems, the early multimodal treatment of bulk and micrometastatic disease has led to marked improvements in survival of patients with Wilms' tumor, pediatric rhabdomyosarcoma, and osteosarcoma as well as breast cancer. With the principle and the concepts of early treatment of micrometastases firmly established, new studies are being rapidly carried forward on a variety of diseases such as gastric cancer in which active therapy of advanced disease has been identified. In other tumors, such as pancreatic cancer, active drugs and combinations are being sought in the advanced stage of the disease with the aim of eventually applying such active drugs or treatment modalities earlier in the course of the disease.

Parallel to such advances in therapy, a large effort at earlier diagnosis is being made in order to institute therapy of cancer at its earliest and most

potentially curable state. Such diagnostic efforts would also lead to methods which could help evaluate, measure and follow difficult tumors. Thus newer methods or new applications of established methods (such as those discussed in the chapters on mammography) allow for the identification of early cancers. Other techniques such as CAT scans could allow for the identification, measurement and sequential follow-up of difficult tumors such as pancreatic carcinoma, in which measurable disease has been a stumbling block in the past for evaluating potentially active agents or treatments.

This volume, derived in part from a past continuing education symposium held by the Baltimore Cancer Research Program, has brought together a group of medical investigators involved in cancer research to review their respective areas from the standpoint of actual and anticipated advances in cancer treatment. The spectrum of the material thus ranges from basic medical and scientific information necessary for staging and therapy (as discussed in the chapters on non-Hodgkin's lymphomas) to the anticipated changes within the next decade. The chapters on head and neck cancers deal with treatment for this group of cancers for which newer agents and treatment approaches, such as combined modality therapy or pre-operative application of chemotherapy, will hopefully lead to marked improvements. The discussion of abdominal CAT scans naturally leads into discussion of intra-abdominal cancers of the stomach, pancreas and bladder. The discussions of mammography for the early detection of breast cancer lead into the chapters dealing with newer approaches for the primary management of breast cancer with either radiotherapy or lesser surgical procedures. The chapters on the early therapy of micrometastases review the striking success seen in the pediatric tumors as well as the principles involved in the design and management of "adjuvant" treatment programs. Other discussions include cell kinetics and their use in predicting optimal application of therapy, and a discussion of unconventional treatments in cancer. With these reviews of a wide spectrum of cancer diagnosis and treatment, we hope to present a very large body of information in a relatively compact and easily digested format.

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NEW APPROACHES TO THE DIAGNOSIS AND CLASSIFICATION OF THE NON-HODGKIN'S LYMPHOMAS

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INTRODUCTION

Malignant lymphomas have been traditionally classified morphologically. The classification published by Rappaport in 1966 (1), with minor modifications (2,3), has been the one most widely employed for clinicopathologic studies (table 1).

Table 1
CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS (1-3)

Nodular

- Lymphocytic, poorly differentiated
- Mixed lymphocytic-histiocytic
- Histiocytic

Diffuse

- Lymphocytic, well differentiated
- Lymphocytic, intermediate differentiation
- Lymphocytic, poorly differentiated
- Mixed lymphocytic-histiocytic
- Histiocytic
- Undifferentiated (Burkitt's type)
- Undifferentiated, pleomorphic (non-Burkitt's)
- Lymphoblastic

However, with the recognition of malignant lymphomas as neoplastic disorders of the immune system, a new functional approach has been undertaken for the classification and understanding of these tumors. Immunological knowledge and techniques have been brought to bear on clinical and pathological problems. For example, the concepts of homing and "traffic" of normal lymphocytes help to

explain the patterns of spread of these tumors. Likewise, the immunological deficits manifested by these patients relate to which component of the immune system is affected by neoplasia. One major area of investigation which typifies this approach has been the study of the neoplastic cells themselves, both for the presence of cell surface markers as well as in functional assays (table 2).

Table 2
TECHNIQUES USED IN THE INVESTIGATION
OF LYMPHORETICULAR MALIGNANCIES

1. Membrane bound immunoglobulins - SIg
   individual light and heavy chains
   in vitro synthesis
2. Intracytoplasmic immunoglobulin
   immunofluorescence
   immunoperoxidase
3. Complement receptors - EAC rosettes
4. Receptors for cytophilic antibody - IgGEA rosettes
5. Spontaneous SRBC binding - E rosettes
6. *In vitro* phagocytosis
7. Cytochemical markers
   "non-specific" esterases
   acid phosphatase
   beta-glucuronidase
   alkaline phosphatase
8. Terminal deoxynucleotidyl transferase (TdT)
9. *In vitro* culture of neoplastic cells

By analogy with normal cells, many of the tumors have been classified according to their presumptive cells of origin: T lymphocyte, B lymphocyte, or monocyte-macrophage (table 3).

Table 3
SUMMARY OF CELL SURFACE MARKERS IN
LYMPHORETICULAR MALIGNANCIES

Well-differentiated lymphocytic malignancies Chronic lymphocytic leukemia Well-differentiated lymphocytic lymphoma Waldenstrom's macroglobulinemia	B lymphocytic
Lymphocytic lymphoma, intermediate	B lymphocyitc
Nodular (Follicular) lymphoma	B lymphocytic
Burkitt's lymphoma	B lymphocytic
Mycosis fungoides Sezary syndrome	T lymphocytic
Lymphoblastic lymphoma Acute lymphoblastic leukemia (25%)	T lymphocytic
Histiocytic lymphomas	Heterogenous
Malignant histiocytosis	Histiocytic

LYMPHOMAS ORIGINATING FROM B LYMPHOCYTES

Most non-Hodgkin's lymphomas in adults appear to be of B lymphocytic origin. However, different B-cell populations display subtle variations in their surface markers and have thus permitted the assignment of some lymphomas to particular subpopulations. The cells of the lymphoid follicle are characterized by abundant surface immunoglobulin (SIg) and avid complement receptors, but as a B cell differentiates towards a plasma cell there is a loss of both of these surface membrane markers. Of course, intermediate stages also are present in which SIg is reduced in density and complement receptors are sparse.

Nodular lymphomas are cytologically and immunologically tumors composed of follicular B lymphocytes (4-6). These tumors are a major category of non-Hodgkin's lymphomas in adults, representing approximately 50% of all cases. Clinically these tumors are most often generalized at diagnosis, presenting as stage III or IV disease. Peripheral lymph node groups are frequently involved as are mesenteric nodes, bone marrow and liver (7). However, in spite of its

widespread dissemination, this disease may be compatible with relatively long survival, even without aggressive therapy (8). This favorable prognosis appears to be particularly true of the nodular lymphomas of poorly differentiated lymphocytic type, in which the tendency of these tumors to disseminate seems related to the capacity of the neoplastic lymphoid cells to migrate or home like normal lymphoid cells (9). The large cells or "histiocytes" within these tumors represent the proliferative component and, when such cells are present in increased numbers, as in nodular lymphomas of mixed or histiocytic type, the disease is associated with a more aggressive clinical course (10), especially if one does not achieve a complete remission.

Cytologically nodular lymphomas reflect the composition of a normal germinal center (11-12). Immunologically, these tumors also have the characteristics of follicular B lymphocytes. We have previously published on the surface membrane markers of nodular lymphomas and have shown avid complement receptors on the neoplastic cells, also a feature of normal follicular B lymphocytes (4). Other authors have found easily detectable SIg, usually of the IgM class with or without IgD (5,6). Our studies have now been expanded to include a total of 49 specimens from 36 patients and earlier observations have been confirmed (table 4). Strong binding of erythrocyte-antibody complement rosettes (EAC), both in suspensions and on frozen sections, was seen in 48 of the 49. Thirty-two studied for SIg had bright staining of the neoplastic cells in all but one. Fifteen were evaluated for individual light and heavy chains, i.e., k and λ, as well as IgM, IgG and IgA. In all instances the SIg was monoclonal with only a single light chain. IgM was the heavy chain in 13 of the 15. Only kappa light chains were found in two, but these were not studied for IgD. Two of five specimens studied for IgD were positive and in one of these both IgD and IgM were identified with only kappa light chains. The coexistence of surface bound IgD and IgM has been reported in other B lymphocytic tumors, most commonly in chronic lymphocytic leukemia, and does not contradict the monoclonality of these neoplasms (13). When an anti-idiotypic antibody was prepared, the IgD and IgM were shown to be of the same idiotype and even to share the same antibody specificity.