was improved. The overall results thus demonstrated that the biological issue related to hypoxia appears to be a sound rationale, which may impact the outcome of radiotherapy, especially in head and neck carcinoma. Yet, despite this wealth of positive data, "hypoxic modification" still has no impact on general clinical practice.

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Exploiting hypoxia: Bioreductive drugs and gene therapy approaches

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Background: Hypoxia is known to play a major role in determining resistance to conventional therapy of solid tumours. However, hypoxia mediated changes in gene expression can also influence treatment outcome.

Purpose: To develop two complimentary strategies *a)* selectively kill and/or inhibit the function of hypoxic cells in tumours by the use of bioreductive drugs *b)* exploit the presence of hypoxia in tumours to deliver highly selective therapy.

Examples: Tirapazamine kills hypoxic cells via a reductase mediated mechanism. In breast carcinoma cells, cytotoxicity is exquisitely dependent on P450 reductase. Further in human breast tumour biopsies, P450 reductase levels are sufficiently high that tirapazamine should cause substantial toxicity. We have identified a novel hypoxia mediated drug delivery system based on the indoloquinone nucleus. This, under hypoxic conditions will selectively release diffusable cytotoxic species, enzyme inhibitors etc. Exploiting hypoxia is further demonstrated by taking advantage if genetic sequences (HREs) that allow increased gene expression under hypoxic conditions. Therapeutic genes that are controlled by HREs will only be expressed under hypoxic conditions, thus providing a novel method for delivering selective gene therapy of tumours. The transcription factor which binds to HREs to promote gene transcription is HIF-1. Data will be presented to show that inhibition of HIF-1 inhibits tumour growth, thus identifying HIF-1 as a novel therapeutic target.

Clearly hypoxia is still a problem to be overcome but it is also a physiological abnormality of tumours that can be exploited.

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Anaerobic bacteria as a potential tumour gene transfer system

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To have a highly specific vector system for gene therapy in cancer, we propose the use of apathogenic clostridia. This use of strictly anaerobic bacteria as vector for specific tumour targeting is based on several observations. (1) Hypoxic-necrotic regions are unique to solid tumours. (2) Spontaneous and deliberate infiltration of anaerobic bacteria has been shown both in animal and in human tumours. To test the feasibility of using *Clostridium* as a tumour specific transfer system, we have used WAG/rij rats with rhabdomyosarcomas as a model. Our data showed that after intravenous administration of at least 10^8 spores, *Clostridium* could colonise the tumour model; the most efficient species being *Clostridium acetobutylicum* and *C. oncolyticum*. Spores could survive a few weeks in normal tissues, they did not germinate in these tissues. In tumours *Clostridium* spores started germination already after 2 days. We found that *C. acetobutylicum* and *C. oncolyticum* are not sensitive to therapeutic doses of the prodrug 5-fluorocytosine or the drug 5-fluorouracil to be obtained under the influence of the suicide gene cytosine deaminase that we plan to express in *Clostridium*. To this order, we are able to transform *C. acetobutylicum* by electroporation. Furthermore, repeated injections of *Clostridium* do not provoke any change in body temperature. In conclusion, it seems likely to use these bacteria as a selective transfer system. This strategy would be quite tumour specific.

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The biology of Hodgkin's disease

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Due to the scarcity of Hodgkin-Reed Sternberg (H-RS) cells their genetic analysis is difficult to perform. The recent establishment of micromanipulation of single H-RS cells from lymph node biopsies with subsequent gene amplification by polymerase chain reaction (single cell PCR) allows the molecular characterisation of these cells for the first time. Using this new approach analysis of immunoglobulin (Ig) gene rearrangements revealed evidence that Hodgkin's disease (HD) represents a B-cell disorder in the majority of cases. The sequences of rearranged Ig genes contain multiple somatic hypermutations indicating that the H-RS cells are derived from the germinal centre of lymph follicles. Moreover, mutations appear which prevent the expression of the antibody. Physiologically these cells would undergo apoptosis. A possible mechanism to keep the H-RS cells from apoptosis could be the activation of the oncogene bcl-2 which might be induced by EBV infection. The transformation process thus might take place in EBV-infected B-lymphocytes. Loss of EBV after initiation of the malignant transformation could explain the occurrence of EBV negative Hodgkin's lymphomas. Karyotype analysis of H-RS cells revealed a heterogeneous pattern including a broad spectrum of numerical and structural abnormalities. No specific chromosomal marker could be found. Nevertheless the analysis of HD by fluorescence in situ hybridisation (FISH) demonstrated clonal numerical aberrations in 100% of immunophenotyped H-RS cells. In addition the analysis of a recently established H-RS cell line L1236 revealed loss of heterozygosity (LOH) at several chromosomal loci. Newly established methods such as LOH, FISH and single cell PCR will reveal new insights into the molecular structure of H-RS cells. This might help to identify the remaining 20% of patients with a poor prognosis for early aggressive treatment.

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Management of early stage Hodgkin's disease (HD) in 1997

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In Europe, exploratory laparotomy and splenectomy is no more considered as a routine staging procedure for early stage HD, so that we will concentrate on the management of clinically-staged (CS) stages I–II HD.

Most groups involved in HD therapy agree that (at least) two subgroups should be defined among those patients; "favourable" (or good prognosis) and "unfavourable" (or good prognosis).

For the favourable group, a competition still exists between subtotal nodal irradiation (STNI) alone and combined modality (chemo-radiotherapy) treatment (CMT), both modalities having been shown to achieve similar long-term survival in several large-scale trials. However, the usually lower event-free survival (EFS) and the late complication risk linked to STNI presently make more and more attractive specific CMT schemes which are both reducing the number of chemotherapy courses (down to 3–4) and the extent of irradiation.

For the unfavourable group of CS I–II HD patients, most data in the literature suggest that the optimal treatment is a combination of chemotherapy and radiotherapy. Nevertheless, the optimal delivery of both chemotherapy (schedule, number of courses, timing) and irradiation (volumes, dose) is still debated.

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The Classification of the non-Hodgkin's lymphomas. Results from the International Lymphoma Classification Project

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The REAL classification (Harris 1994) provides a listing of the clinico-pathologic, lymphoma entities which pathologists can recognise. It represents an attempt to develop a common language between North American and European pathologists which would have obvious advantages in clinical trials of lymphoma therapy.

The ability of pathologists to apply the REAL classification had not been tested prior to publication nor was there any information about the clinical value of this proposal. In order to address these questions the International Lymphoma Classification Project was carried out under the chairmanship of Prof. J.O Armitage (University of Nebraska).

A cohort of 1403 consecutively accrued cases of lymphoma, from nine different study centres around the world was assembled. Five expert haematopathologists visited each site and classified cases using the REAL and Kiel classifications and the Working Formulation. Each expert re-reviewed a random selection of 20% of the cases from each site.

The inter-observer reproducibility was over 85% for most of the major lymphoma subtypes. The intra-observer reproducibility, when clinically insignificant divergences were discounted, was 94%.

The REAL classification could be readily applied and identified clinically

distinctive entities. Further prognostic discrimination could be obtained by application of the International Prognostic Index to most of the clinico-pathologic entities defined by the REAL classification

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Biology and treatment of primary gastric lymphoma

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Most primary low-grade gastric lymphoma (NHL) recapitulate the histopathologic features of mucosa-associated lymphoid tissue (MALT). Therefore they often are called MALT-lymphoma, although this type of NHL does also occur in several other extranodal organs. NHL of MALT type do transform to high-grade NHL, the latter showing both components in about 33%..

Primary gastric lymphoma is a localised disease compared to nodal NHL with 75% being in stage I and II_1 though high grades have a higher tendency for a wider spread and per continuitatem growth into neighbouring organs.

There is a small predominance for the male gender. Clinical symptoms are uncharacteristic. History in low grades is longer than in low grades.

Discussion on the right treatment is still going on, though in the last years authors seem to favour a conservative organ conserving approach, which is backed by preliminary data from a prospective study, which demonstrates no advantage for stomach resection.

A completely new approach in the treatment of gastric NHL was triggered by data showing that Helicobacter pylori (H.p.) is a stimulus for the growth of low grade NHL. In prospective studies complete remissions of lymphomas after eradication of H.p. have been published, though it is to early to evaluate duration of these CRs.

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The management of non-Hodgkin's lymphomas ANNO 1997

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An overview will be given on the possibilities and limitations in the current treatment of non-Hodgkin's Lymphomas (NHL) of both low and intermediate/high grade malignancy. Although 50–60% of patients presenting with limited stages of low grade malignant NHL can be cured with involved field radiotherapy, no significant advances have been made in the treatment of patients presenting with advanced disease. In other words, for this special category of patients it has appeared to be impossible to change the natural biology during the past 30 years. However, new perspectives in the treatment of these indolent NHL's will be discussed (interferon, purine analogs, stem cell transplantation).

For the intermediate/high grade malignant NHL's CHOP chemotherapy still remains the standard treatment. At present, prognostic factor tailored treatments are being evaluated in prospective randomized phase III clinical trials. An overview will be given on the current state of affairs, ranging from intensified conventional chemotherapy to marrow-ablative treatment in selected poor risk groups.

Finally, realistic options for the treatment of relapsing patients will be indicated for the various disease categories.

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Role of high-dose chemotherapy and autologous bone marrow transplantation in the treatment of lymphoma

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• The selection of bad prognosis groups is mandatory if BMT is considered in first CR. It is now widely accepted that candidates for prospective studies can be defined as patients less than 55 years old at diagnosis, with at least 2 extranodal localisations or a tumour of at least 10 cm at diagnosis, with a bad Karnofsky score (<70%) or with bone marrow or CNS disease at initial presentation. This group is reported to have an expected survival with conventional regimen of 55% at 3 years. Only prospective and ramdomised studies are acceptable in this field.

• There is no indication for ABMT in primary refractory patients except in prospective experimental studies.

• Partial responders to first-line induction therapy are chemo-sensitive high-risk patients. This is probably the best indication for BMT in NHL.

Pilot studies with ABMT were able to report 71% disease free survival at 90 months, all with proven active lymphomas at time of BMT. These preliminary results should be confirmed, but BMT can be strongly recommended in 1991 for these patients if a biopsy shows active lymphomas after 4 courses of a conventional induction regimen.

• Patients who previously reached CR1 on conventional therapy and then relapsed, and who are not responding to conventional rescue protocols are calls *resistant relapses*. BMT is probably the only chance of cure and can be highly recommended.

Patients who previously reached CR1 on conventional therapy and then relapsed and who are still responding to conventional rescue protocols are called *sensitive relapses*.

A randomised study had shown that BMT is mandatory in theses cases.

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The role of the palliative care specialist. Controversies and definitions

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More than 60% of cancer patients are incurable. Problems of communications, physical and emotional symptoms control, environment and ethical issues are important in the process of dying. Palliative care specialists, with a team of caregivers should offer to those patients a compassionate and a professional help in which the medical role is only 50% of the entire care.

The oncologist professional is mainly bound to the clinical approach and require in several instances an integration with a PC specialist. Such experts may work in a symptom control team or in a special in-out patient unit. A number of university chairs on PC in UK, in USA and in other countries are growing, facing the need of a new approach on the care of cancer and other incurable disease.

WHO recommendations, reports of prestigious medical journals are stressing such needs in view of the fact that hospital death, assisted suicide and euthanasia are presently highly debated.

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Helplessness reduction in a palliative care unit (PCU)

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Introduction: Due to the nature and uncontrollability of the illness and treatment side-effects, cancer elicits different levels of helplessness in medical staff working in PCUs.

Purpose: 1. Identify situations that give rise to staff helplessness in PCUs. 2. Describe behavioral manifestations of staff helplessness. 3. Provide behavioral interventions to reduce staff helplessness. 4. Provide guidelines to prevent the development of staff helplessness in PCUs.

Method: Effective consultation to staff members of PCUs in the context of learned helplessness theory will be reviewed, emphasizing the integration of behavioral medicine principles in the training of medical staff. Participation of symposium attendees may be requested.

Conclusion: The PCU constitutes a setting in which death and lack of control over patient care and survival are experienced on a daily basis. Therefore, identifying and controlling helplessness reactions of medical staff members have important clinical implications and will improve patient care and staff wellbeing significantly.

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No abstract

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How should we assess alternative medicine?

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The term alternative medicine (AM) embraces a variety of therapies that can be sub-divided into two board groups – physical and psychological. Physical therapies include diet, vitamins, herbal remedies and homeopathy, immune stimulants and acupuncture. Psychological methods include meditation, hypnotherapy, relaxation therapy and visualisation. Assessment of the value of AT alone or as a complement to conventional treatment (CT) is complicated. Furthermore the majority of patients using AM use several methods at the same time. Conventional methods of assessing medical