**Summary**

In Chapter I, a review of the literature is presented, in which attention has been paid to a number of aspects of non-Hodgkin's lymphomas that are relevant for the prognosis of the patient, especially in the relation to the choice of therapy. These aspects are:

1) History
2) Histopathology
3) Immunology
4) Incidence and etiology
5) Cytokinetics
6) Cytogenetics
7) Dissemination patterns
8) Diagnostic critera and disease staging
9) Therapy

In an attempt to improve the therapeutic results, further investigations into some of the above mentioned aspects have been carried out. The purposes of the studies are outlined at the end of chapter I.

Chapters II and II present the studies on the significance of a careful histocytological analysis for estimating the clinical prognosis of patients with low grade non-Hodgkin's lymphomas.

Chapter II describes a cytological subdivision which was made using histologic material of 44 patients diagnosed as having a follicular centroblastic/centrocytic lymphoma (FCC lymphoma), according to the Kiel classification. The subdivision was made, taking into account the predominating neoplastic cell type in the follicle. This resulted in the following classification: small centrocytes with occasional centroblasts (SCC), centrocytes with few (CBCC/A) or many centroblasts (CBCC/B) small and large centrocytes (SLCC), and small and large centroblasts (SLCB). The growth pattern showed marked variability between the subgroups, being predominantly follicular in the SCC group and with a prominent component of diffuse growth in the SLCB group. Bone marrow dissemination did not occur in the SLCC group, whereas it was found in most cases of the other groups. Immunological findings confirmed the B-cell type and demonstrated monoclonality, but did no show any prognostic differences between the various groups. Enzyme histochemical findings were also inconclusive in determining differences between the groups. The cell composition of the neoplastic follicle seems to play a role in the behavior of FCC lymphomas and to be directly related to other parameters as for instance growth and dissemination pattern and clinical behavior.

Chapter III deals with the clinical histories of 30 of the patients described in chapter II, with a diagnosis of FCC lymphoma. Immunological investigations demonstrated that all lymphomas were of the B cell type, but immunophenotyping did not distinguish groups with different prognosis. The latter also is valid for clinical staging, bacause patients with a stage III or IV disease did not behave significantly worse than did patients with a stage I or II disease. The histological material of these patients was reclassified according to the cytological classification presented in Chapter II. The actuarial survival of the whole group of 30 patients was 66% after 5 years. The survival in the five sybgroups, however, varied from 100% in group SCC to 0% in group SLCC. An increased number of centroblasts in the follicles was shown to representt a significantly worse prognosis. The regonition of patients with many centroblasts at the time of diagnosis makes it possible to treat this prognostically bad group earlier with more agressive regimens in order to reach a complete remission, similar to the treatment of high-grade lymphomas.

Chapter IV and V reflect the results and discussions of an investigation into new possibilities for therapeutic intervention in high-grade non-Hodgkin's lymphomas. At the same time the reaction of the individual patient on each cytostatic drug was looked at.

In Chapter IV the results are presented of the treatment of patients with high-grade malignant lymphomas with a new induction schedule. This weekly applicated regimen consists of three drugs: methylprednisolone (Solu-Medrol), cytosine-arabinoside (Ara-C), and vincristine (Oncovin) (SOA-regimen), administered on consecutive days. These are all drugs with short half-lives. Treatment was given for two or three weeks, and apart from one non-responder, all patients showed rapid reduction of the tumour mass. The only side effect demonstrated was a small decrease of the blood counts, without any apparent effect on bone marrow cellularity. In all cases, recovery was rapid, although negatively influenced by the preceding start of consolidation therapy. The SOA regimen resulted in rapid reduction of tumour masses with only minor side affects, thus improving the basis for conventional cytotoxic regimens. It requires further investigations to improve the schedule, for instance by adding other drugs with phase specific actions.

Chapter V gives the results of an investigation into the possibility of using urinary polyamines as a method to study tumour cell kinetics of patients with high-grade malignant non-Hodkin's lymphomas during treatment. Of nine patients, treated for two to three weeks with the SOA regimen as described in Chapter IV, all spontaneous voided urine samples were collected. Polyamines and their metabolites were determined in each sample. In patients with small tumour masses, no response could be observed in polyamine excretions. In

those cases, polyamines were not suitable to measure the effect of treatment of the tumour. Patients with large tumour masses exhibited a clear response 48 to 72 hours after the start of treatment, consisting of increased excretions of the polyamine degradation products spermidine, spermine and isoputreanine. These rapid polyamine responses are important indications concerning the attainment of a complete or partial remission, and can be used for early evaluation of the effect of chemotherapy. Thus, in the absence of a response, it could be judged necessary to change treatment at an early stage.

The curves of the polyamine metabolite concentrations plotted against time, give insight into the tumour cell kinetics during treatment. There appeared to be no direct relationship between tumour load and elevation of polyamine excretion. Further investigation of the polyamine metabolism therefore, seems to be important.

In conclusion, the determination of polyamines in all spontaneous voided urine samples is a non-invasive method, which gives an impression about tumour cell kinetics during therapy.

When no polyamine response is observed 48-72 hr. after the start of therapy, an alteration in therapy has to be considered.