Abstracts of Theses from the Nordic Countries

Abstracts of Nordic theses on oncologic subjects are published under this heading. The full theses are as a rule published by the universities or as supplements to different journals. They can usually be obtained after contact with the author.

Cytogenetic studies in chronic myeloid leukemia and polycythemia vera

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The onset of chronic myeloid leukemia and polycythemia vera is generally insidious. Both diseases change their character and can terminate in acute leukemia. These diseases are considered to be of clonal origin. The expansion of distribution of a clone can be followed in these slowly progressing diseases if the clone contains a chromosome marker. Cytogenetic examinations have been performed on bone marrow cells and, in some patients, on cells from extramedullary tissue. The study comprised 44 patients with Philadelphia (Ph^1) positive, chronic myeloid leukemia and 73 patients with polycythemia vera. Prospective studies were carried out on 32 consecutive patients with chronic myeloid leukemia and on 57 consecutive patients with polycythemia vera. Chromosomes were prepared either by the direct method or after 48 hours' culture of the cells. The chromosomes were stained for G and Q-band. The frequency of patients with chromosome abnormalities in addition to the Ph^1 in chronic myeloid leukemia increased with the duration of the disease from 13% to 45% in the late chronic phase and to 83% in the blastic phase. Patients with polycythemia vera had chromosome abnormalities in 17% at the initial examination. Abnormalities occurred later during the polycythemic phase in 30% of the patients. Abnormalities were found in 70–80% of the patients when myeloid metaplasia, myelofibrosis or leukemia was evident. The early precence of chromosome abnormalities, in addition to the Ph^1 abnormality in patients with chronic myeloid leukemia predisposed them to terminal leukemia. Early development of abnormalities in patients with polycythemia vera, however, did not predispose to leukemia. The pattern of the chromosome abnormalities was different in the two diseases. The occurrence of +8, +22q–, and i (17q) was common in chronic myeloid leukemia, while +1q, +8, +9, or 9p, and 20q– was common in polycythemia vera. The pattern of chromosome abnormalities may be influenced by the therapy before the development of the terminal leukemia. The risk of development of acute leukemia and chromosome abnormalities was significantly higher in patients with polycythemia vera during the time intervals after myelosuppressive therapy was initiated than in time intervals with the therapy of phlebotom alone. Patients treated with hydroxyurea did not develop +8.

The type of chromosome abnormalities in the extramedullary tissue can differ from and may appear earlier than those present in the bone marrow. Spleen cells from 17 patients in the chronic phase and from 7 patients in the blastic phase of chronic myeloid leukemia have been examined. Abnormalities in addition to the Ph^1 were found earlier in the spleen than in the bone marrow in only 3 patients.

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The surgical treatment of oesophageal cancer

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Resectional surgery gives the best palliation and change of cure to patients with oesophageal cancer. As earlier found, the combination with radiotherapy improves the outcome. A well thought-out technique reduces the operative risks, so that surgery can be offered to more patients. A standardized procedure is described in a review of 86 patients with a median age of 64, range 43–81. It was used for tumours in the middle and lower thirds in 54 patients. The overall morality of 15% and the complications are presented and discussed. Particular attention was paid to the healing conditions of the anastomosis, and only one leakage (non-fatal) occurred after elective resections. A safe method for pyloromyotomy was developed and proved helpful in avoiding tension in the suture. Indications for resection were wide, the finding of a large tumour at computed tomography did not exclude exploration, and resections were performed whenever feasible. Experience with oesophagectomy without thoractomy in 30 cases indicated that it was usable when tumour dissection could be carried out under direct vision from the neck or the abdomen. Morbidity was reduced but not the mortality. Pneumonia was caused by repeated aspirations that occurred unnoticed by some patients with a high anastomosis. In 9 patients submitted to total or subtotal oesophagectomy prospective studies of the swallowing function showed that this had to be checked before these patients are made dependent on normal eating. To evaluate the validity of dysphagia as an indication for major surgery, patients with dysphagia were interviewed. The patient's suffering was realised to be great enough to justify an aggressive surgical approach. Non-resectable malignancies engaging the oesophagus were by-passed in 26 patients. In cases with generalised disease the survival was too short to make this surgery profitable, but when local growth made resection impossible, the operation had a better outcome, especially in patients with a fistula to the airways. Wide indications for oesophageal surgery increases the work load. In a quest for criteria for the procedures, we undertook a multivariant analysis of 66 cases available for the study and treated with the adopted surgical and radiologic regimen, which had yielded a prospective cumulative survival at 5 year of 17.5%. Special reference was made to prognostic indications of a new histopathologic system for classification of epidermoid cancer. No absolute criteria were found, but microscopic tumour-host relations were found to be of greater importance than other factors. Patients classified to have M 1 disease because of nodes in the coeliac or supraclavicular regions, were among the long-term survivors. Surgery, especially when combined with radiation treatment, has much to offer these patients, but in order to make further gains, other treatment adjuvants must be tried.

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Plasma steroid hormones in women with epithelial ovarian carcinoma

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Plasma concentrations of steroid hormones were investigated in 51 postmenopausal or bilaterally oophorectomized women with epithelial ovarian carcinoma, but free from other malignant or endocrine disease. All FIGO stages and histologic types IC, IIC, IIIC and V are represented. Plasma levels of progesterone (P), 20α-hydroxyprogesterone (20α-OH-P), androstenedione (A), testosterone (T), estradiol (E_2), sex-hormone-binding globulin (SHBG) and albumin were analysed, and unbound fractions of testosterone (UT) and estradiol (UE) were calculated. Blood samples were drawn for radio-immunoassay prior to and during chemotherapy at monthly intervals on four occasions. Thus, it was possible to study how plasma levels of steroid hormones are influenced by tumor volume, stage, histologic type, effect of

chemotherapy, recurrence of disease, and finally, whether determination of the initial plasma level of any steroid hormone, separately or in combination, may give an indication as to the prognosis of the disease. Plasma hormone levels were also compared with those of a control group of postmenopausal women (PM), a control group of fertile women in early follicular phase of the menstrual cycle (FPh), and finally with a control group of postmenopausal women with a non-gynecologic disseminated malignant disease (DMD). A relationship has been found between tumor volume and plasma concentration of the investigated hormones. Corresponding relationships have also been found vis-à-vis FIGO stage and histologic type, though probably secondary to tumor volume. With reduction of tumor volume during treatment, a concomitant decrease in plasma concentration has been found concerning P, A and E_2. The unbound fraction of T was not influenced by therapy and did not differ from PM controls. With the combined determination of P and A it has been possible to detect recurrence of disease earlier than by clinical means in the majority of cases. Certain combinations of the initial values of P, A, T and A/alb seem to predict prognosis as well as or better than does FIGO stage. In conclusion, a correlation between steroidogenesis and progress of epithelial ovarian carcinoma seems to exist. Steroidogenesis might also reflect the prognosis of the disease.

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The human macrophage system
Effects of antineoplastic agents in vivo and in vitro

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Combined treatment of gastrointestinal (GI) tract cancer is based on surgery, radiotherapy and chemotherapy (CT). The possible hazards of an immunosuppressive effect of perioperative CT are often referred to but are of unknown clinical significance. This investigation was performed to study the effect of common anticancer agents on the fixed and mobile reticuloendothelial system (RES). The effect of vincristine, methyl-CCNU and fluorouracil on RES was studied in vivo in twenty patients, operated for GI cancer. ^{125}I-labelled microaggregated human serum albumin was used. During long-term treatment a transient depression of the phagocytic ($2p=0.08$) and metabolic ($2p=0.006$) functions occurred. Splenectomy performed as part of the cancer operation did not influence the effects exerted by anticancer drugs. The results initiated further systematic studies of CT agents in vitro. In order to test the phagosytic functions of human peritoneal macrophages (HPM), a method to enrich HPM using a Percoll-gradient was developed. By means of a fluorescence-quenching technique, a distinction between the adherence and engulfment steps of the total phagocytic process was obtained. HPM from cancer patients did not differ from normal controls in this respect. However, HPM from uremic patients had a significantly lower phagocytic capacity. The effect on macrophage by some frequently used CT drugs with different modes of action (antimetabolites, antibiotics, spindle poisons and alkylating agents) was tested in following experiments. Addition to HPM of therapeutic and higher concentrations of fluorouracil (F), doxorubicin (A), as single drugs and in combination with mitomycin (M), did not affect the adherence or engulfment steps of the total phagosytic process of HPM.

Blood monocytes were exposed to therapeutic concentrations of vincristine, vinblastine and vindesine. The phagocytosis was significantly inhibited by all three substances, mainly due to inhibition of the engulfment phase. Since the drugs are microtubule antagonists it was assumed that the phagocytic mechanism is partially a microtubule-dependent process. CCNU had no effect in therapeutic concentrations but impaired the phagocytic functions in higher concentrations. Monocytes incubated in F, A and M as single drugs and in combination (FAM) showed a depressed engulfment step and total phagocytosis. No further decrease was found by FAM. The adherence step was significantly depressed only by A. The results from these in vitro studies initiated a comparative investigation in vivo. Thus the effect on monocyte phagcytosis of FAM treatment was studied in nine patients operated for gastric cancer. The engulfment step and the total phagocytosis were significantly impaired one hour after the treatment, probably due to a direct effect on the monocytes. The inhibition was of the same magnitude as that found in vitro. The phagocytosis was normalized after 24 hours but once again impaired after one week, probably due to bone marrow toxicity. Similarities between the functional impairment of CT on macrophages in vitro and in vivo were found in the resent investigation. The results underline the importance of careful monitoring of the manifold effects of chemotherapy on the immune defence in patients with malignant disorders and may encourage further studies on CT effects on the human macrophage system.

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Carcinoid tumors
Clinical studies and the use of tachykinins as tumor markers

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Carcinoid tumors are slowly growing neuroendocrine neoplasms with a malignant potential which may give rise to characteristic symptoms of diarrhea, flush, asthma and cardiac valve disease—the 'carcinoid syndrome'. A prospective study was performed on 103 patients with metastatic carcinoid tumors. The annual incidence of metastatic carcinoid tumors was 0.7 patients/100 000 population, and the annual incidence rate of the carcinoid syndrome was 0.5 patients/100 000. Most patients had tumors of mid-gut origin, which gave rise to symptoms at an average age of 59 years. Fifty-five % of the patients were women. Diarrhea was the most frequent clinical symptom (84%), followed by flush (75%) and ileus/subileus (45%). Carcinoid syndrome, with flush, diarrhea and high urinary 5-hydroxyindoleacetic acid (5-HIAA) was found in 67% of the patients. Tricuspid valve disease was present in 45% of the patients with carcinoid syndrome. Elevated concentrations of various tumor markers were seen in 92%. Thus, elevated urinary 5-HIAA was found in 88%, plasma neuropeptide (NPK) in 66%, pancreatic polypeptide (PP) in 43% and human chorionic gonadotropin alpha subunit (HCG α) in 28% of the patients. 5-HIAA was of value as a tumor marker in patients with carcinoid tumors, irrespective of origin. NPK was predominantly found in patients with mid-gut carcinoid tumors. HCG α and PP were often observed in high concentrations in patients with carcinoid tumors in the bronchi. Using novel radioimmunoassay and a number of different chromatographic techniques, several 'new' members of the tachykinin peptide family were demonstrated in carcinoid tumor extracts as well as in plasma from the patients. These included NPK and neurokinin A and B. Furthermore, the results indicated that other tachykinins might be present in carcinoid tumors. Tachykinins are produced in carcinoid tumor cells, and the same molecular forms are found in tumor extracts, in plasma from carcinoid patient, and in media from carcinoid tumors in culture. The release of tachykinins is increased during spontaneous and pentagastrin-stimulated flush. Since the biological effects of tachykinins closely mimic the symptoms in patients with carcinoid tumors, tachykinins may play an important role in the pathogenesis of the carcinoid syndrome.

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