

# Abstract of Theses from the Nordic Countries

*Abstract 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.*

## **On the effect of degradable starch microspheres in intra-arterial chemotherapy**

H. STARKHAMMAR

Department of Oncology, Linköping University, S-581 85 Linköping, Sweden

Degradable starch microspheres (DSM), injected intra-arterially, induce temporary vascular occlusion without lasting effects. DSM co-injected with a cytostatic drug will increase the regional drug uptake and reduce the systemic concentration.

The effect of fixed doses of DSM injected via the hepatic artery has in previous studies varied considerably between different patients.

In order to analyze the DSM-effect on the kinetics of co-injected substances a method was developed based on continuous measurements of the passage of a low molecular weight radiolabelled marker through the liver into the systemic circulation. The same method was also employed for registration of arterio-venous shunting through the liver into the lungs. The degree and rate of marker passage to the systemic circulation was individually influenced by DSM and was, together with angiography and registrations of shunt blood flow, used to measure the DSM-effect.

Fifty-one patients with liver tumours were treated with DSM and cytostatic drugs. Measurements during the treatment sessions indicated that the dose of DSM must be individualized due to variation in size and vascularity of the liver tumours, arterial blood flow and arterio-venous shunting.

The portal blood flow also had a major influence on the passage of substances given intra-arterially as shown from studies on the liver of the pig.

Arterio-venous shunting increased during the administration of DSM in the majority of the patients.

Two parameters for the kinetics of the passage of the labelled marker—Passing Fraction and Marker Flow Rate—were, together with shunt-measurements, useful for individualization of the DSM-dose.

The retention of drugs, co-injected with DSM, was found to be due to extra-vascular uptake and not to entrapment of the drugs in the vessels.

April, 1987

## **Vascular perfusion characteristics in tumours**

**Experimental studies in induced rat tumours and human renal carcinoma with reference to vascular reactivity and interstitial fluid pressure**

E. TVEIT

Departments of Surgery I and Histology, University of Göteborg, Surgical Clinic, Östra sjukhuset, S-41685 Göteborg, Sweden

Vascularization and blood perfusion is a prerequisite for solid tumour growth, but they also modify the sensitivity of tumour cells for radiation and chemotherapy. It was therefore decided to

investigate whether non transplanted, induced mammary tumours of the rat show similar characteristic perfusion patterns as a human tumour, i.e. renal carcinoma. If the DMBA-tumour can be considered to be a useful experimental model, and if an increased interstitial fluid pressure can be demonstrated then what circulatory consequences might this produce?

Utilizing the microsphere tracer technique, blood flow in vivo and perfusion in vitro were studied in both rat and human tumours in order to characterize norepinephrine sensitivity and to investigate pressure-flow relationships. Micropuncture and 'wick-in-needle' techniques were used for interstitial fluid pressure measurements.

The DMBA-tumours of the rat showed a heterogeneous hypoperfusion and necrosis like the human renal adenocarcinoma and the perfusion of the rat tumour was hypersensitive to norepinephrine. This hypersensitivity could not be verified for the human tumour. A high pressure was demonstrated in the interstitial fluid of the rat tumours probably impairing flow through the capillary bed of these tumours and possibly also of the renal carcinoma at low perfusion pressures.

It was concluded that a compartment syndrome might be involved in the development of tumour hyponutrition and necrosis.

April, 1987

## **Diagnostic imaging in glioma**

**Delineation and classification using positron emission tomography**

M. MOSSKIN

Departments of Neuroradiology, Neurosurgery, Tumour Pathology and Clinical Physiology, Karolinska Institute, Stockholm, Sweden

The present treatment of gliomas is still far from satisfactory. This might at least partly be due to the fact that delineation and classification of gliomas is still inaccurate notwithstanding recently developed diagnostic methods.

The present investigation was carried out in order to compare the more recent method of positron emission tomography (PET) using tracers for glucose kinetics, for amino acid kinetics and for blood brain barrier (BBB) disruption with the well established method of computed tomography (CT) with respect to delineation and classification of gliomas. A preliminary comparative study, with the same intention, including an evaluation of magnetic resonance imaging (MRI) was also carried out. Representative images from the different methods were compared with each other and with histologic examination of stereotaxic biopsy specimens from identified targets in the same images.

Contrast medium used with CT, 68-Ga-EDTA and 11-C-glycine with PET were markers of a disruption of the BBB. After it once had passed the BBB, glycine was accumulated in tumour tissue. 11-C-methionine was the single tracer used, that passed an intact BBB and subsequently accumulated in most gliomas.

Delineation of viable tumour tissue was done, in the majority of cases, most efficaciously by PET using 11-C-methionine as tracer, although MRI was superior to PET with respect to delineation of the total area of a lesion including tumour and surrounding oedema. PET using 11-C-glucose, 11-C-glycine and 68-Ga-EDTA were of less value in delineating gliomas, as was CT. In a few cases the MRI examination was of value in delineating tumour tissue.

Radiologic classification of gliomas should primarily be based on examination of the (BBB). A disruption of the BBB indicated a malignant glioma of grade III-IV and an intact BBB a glioma of grade II or reactive gliosis. PET using 11-C-methionine could further refine the classification. If the BBB was intact and the methionine accumulation lower than in the ordinary brain, the lesion was an astrocytoma with sparse cells or reactive gliosis.

When the uptake of methionine was higher than that of normal brain and the BBB still intact, the lesion usually was a glioma of grade II. Gliomas with disrupted BBB always had a methionine uptake higher than the rest of the brain. A moderate uptake indicated an anaplastic astrocytoma and a strong uptake favoured a glioblastoma. In this study MRI was of no help in the classification of gliomas.

In summary, the most efficacious diagnostic work-up of patients with suspected gliomas at present seems to be the combined use of CT with and without contrast enhancement and PET using 11-C-methionine, while MRI yet has to find its proper place in diagnosis of gliomas.

May, 1987

#### **The hypothalamo-pituitary-liver axis**

##### **A possible determinant of sex differences in chemical hepatocarcinogenesis in the rat?**

A. BLANCK

Department of Medical Nutrition, Karolinska Institute Stockholm, Sweden

As shown previously, sex differences in rat liver metabolism of steroid hormones are due to a sexual dimorphism in growth hormone (GH) secretion. Liver metabolism of steroids in male rats can be 'feminized' by e.g. implantation of pituitary grafts (PG:s) under the kidney capsule or by continuous infusion of GH from osmotic minipumps. Both these manipulations raise the basic level of serum GH to the female level.

Marked sex differences ( $\sigma^2 > \varphi$ ) in the growth rate of enzyme-altered hepatic foci were observed in rats treated according to the 'resistant hepatocyte model' (RH-model). These foci are considered as precursors for liver cancer. Sexual differentiation of focal growth occurs during selection/promotion of diethylnitrosamine 'initiated' cells with dietary 2-acetylaminofluorene (2-AAF) and partial hepatectomy (PH).

Implantation of PG:s to male rats during the 2-AAF/PH selection in the RH-model decreased the growth rate of foci towards the female level. Whereas continuous infusion of bovine GH to male rats completely feminized the growth rate of foci, no effect was observed after infusion of ovine prolactin.

In a long term experiment hormonally untreated male rats developed cancer with a shorter latency time than PG-bearing male rats and females ( $\sigma^2 < \sigma^2 + PG < \varphi$ ) indicating that the results obtained in short term experiments and relevant also in terms of hepatoma formation.

A sexually differentiated metabolism of 2-AAF might provide a possible basis by which the results obtained *in vivo* could be explained. The very reactive intermediate formed by sulfation of N-hydroxy-2-AAF (N-OH-2-AAF) has been suggested to be an important promoter in 2-AAF carcinogenesis. This sex differentiated metabolic pathway ( $\sigma^2 > \varphi$ ) might be of importance for the observed sex differences in focal growth. Several cytochrome P-450 mediated hydroxylations of 2-AAF as well as N,O-sulfation of N-OH-2-AAF were shown to be sex differentiated and regulated by pituitary and gonadal hormones in a way similar to the hypothalamo-pituitary regulation of steroid metabolism in rat liver.

In conclusion, the present study provides evidence that the pituitary gland modifies the growth of early putatively preneoplastic lesions, possibly via an influence on 2-AAF metabolism. It is reasonable to believe that GH might be the pituitary hormone responsible for the observed effects.

May, 1987

#### **Grenz ray therapy in dermatology**

##### **An experimental, clinical and epidemiological study**

B. LINDELÖF

Department of Dermatology, Karolinska Hospital, and Department of Medical Biophysics, Karolinska Institute, Stockholm, Sweden

Grenz rays (ultrasoft X-rays, Bucky rays) have been used in the treatment of benign skin disorders for more than 60 years. The mechanism of action, the clinical effect, and the potential carcinogenic effect have been mainly unknown, and many of the reported studies are obsolete today. In the present work these concepts have been studied by means of immuno-histological methods, transmission electron microscopy, patch testing, clinical evaluation and epidemiological methods. The results can be summarized as follows.

The number of Langerhans' cells (OKT-6 positive cells) decreases in human epidermis after grenz ray radiation and this reflects a true disappearance of the Langerhans' cells as shown by electron microscopy.

Grenz ray treatment was found to

- suppress the expression of nickel allergy in sensitive individuals.
- have a tendency to suppress irritant skin reactions.
- have a very good effect on psoriasis of the scalp.

Grenz ray therapy cannot be excluded as a risk factor in the development of non-melanoma skin tumors, but this risk factor is small, if any, when certain therapy recommendations are followed.

May, 1987

#### **Neodymium-YAG laser in the treatment of urinary bladder carcinoma and localized prostatic carcinoma**

H. O. BEISLAND

Department of Surgery, Aker Hospital, Oslo, Norway

Neodymium-YAG laser irradiation produces a deep homogeneous tissue coagulation and an instantaneous arrest of blood circulation. The method is well suited for endoscopic management of urologic diseases.

This study, consisting of 100 consecutively treated patients and 122 patients prospectively randomized for laser irradiation or TUR, confirms previous clinical reports on Neodymium-YAG laser in the treatment of urinary bladder carcinoma. Laser is superior to conventional transurethral electroresection in the treatment of superficial bladder tumors. In addition, laser technique makes it possible to treat invasive bladder tumors endoscopically. However, the indications and the limits of laser treatment in such cases remain to be settled.

Laser as a new alternative in the treatment of localized prostatic carcinoma opens exciting perspectives to patients who are reluctant to accept, or unfit for conventional radical operations. The method gives functionally good results and is well tolerated even by high risk patients. The shorttime results obtained from 63 patients are promising, but further observations are necessary for definite evaluation of permanent cure.

January, 1987

# **Benign tumors, tumor-like conditions and preneoplastic lesions of the adult human liver**

## **Epidemiology and pathogenesis in medicolegal autopsies and clinical patients**

P. J. KARHUNEN

Department of Forensic Medicine, University of Helsinki, Helsinki, Finland

This thesis is based on studies of the occurrence and pathogenesis of benign tumors, tumor-like conditions and preneoplastic lesions of the adult human liver. The material for the study comprised retrospective and prospective medicolegal autopsy series and clinical patients. Data on the use of hormones, alcohol, drugs and smoking were obtained, in addition to hospital records and police reports, by interviewing the clinical patients and the collaterals of the deceased.

The results can be summarized as follows:

a) Benign hepatic tumors and related conditions are, contrary to prevailing concepts, common but mostly small in size. Cavernous hemangioma and focal nodular hyperplasia (FNH), usually found in females, were also common in the males of the present study. Benign bile duct microhamartomas and adenomas were the most common lesions in the prospective male autopsy series. Their frequency increased with age, whereas FNH occurred in early adulthood and cavernous hemangioma showed no age dependence.

b) Of the proposed precursor lesions for hepatocellular carcinoma (HCC), hyperplastic hepatic nodules were shown to be associated with risk factors of HCC such as liver cirrhosis or heavy alcohol intake, but liver cell dysplasia (LCD) was not. Hyperplastic hepatic nodules also occurred together with FNH and nodular regenerative hyperplasia (NRH) of the liver, which conditions may also carry neoplastic potential.

c) An association between benign hepatocellular tumors, such as FNH and liver cell adenoma (LCA) and the chronic use of alcohol, found in clinical patients and retrospective autopsy cases, was confirmed in an prospective autopsy series of alcoholic and non-alcoholic males. This association has not been observed previously. Usually, FNH and LCA occur in females in association with the use of oral contraceptives or estrogens. It is suggested that alcohol-induced liver cell hyperplasia or the feminizing effect of alcohol on the male sex hormone metabolism may contribute to the growth of preexisting tumors in males. In support of the first hypothesis, FNH was associated with increase in liver weight. In indirect support of the latter hypothesis, the size of cavernous hemangioma, a third type of tumor, suggested to respond to estrogens in females, correlated with the reported daily dose of alcohol, independently of age or the size of the liver.

Benign bile duct adenomas and biliary microhamartomas were, for the first time, shown to associate both with periportal and bridging fibrosis of the liver, most likely caused by alcohol and by chronic pancreatitis. Bile duct adenoma and microhamartoma were shown to be different types of the same lesion.

d) Hepatic pseudolipoma, present in 0.2% of the autopsy series, was found to be morphologically identical with twisted fat appendages of large bowel, which give rise to peritoneal free bodies.

e) Bile duct microhamartoma was the common histopathologic lesion associated with all types of cystic liver in adults, including solitary hepatic cysts, adult polycystic liver disease (PLD) and liver cysts accompanying adult polycystic kidney disease (APCD) which was, for the first time, shown to occur in most cases independently from adult polycystic liver disease. Bile duct microhamartomas were found to be the most numerous at the early phase, but to disappear at the late phase of adult polycystic liver disease.

In addition, this study revealed that about half of the males

over 35 years, subjected to medicolegal autopsy, may be classified alcoholics or heavy drinkers (over 80 g of alcohol daily). This result casts serious doubt on the general epidemiologic value of medicolegal autopsy series, but offers good possibilities to study alcohol-related diseases.

December, 1986

## **Lung cancer in males**

### **An epidemiological study in northern Sweden with special regard to smoking and occupation**

L. DAMBER

Department of Oncology, University of Umeå, S-901 87 Umeå, Sweden

In a case-control study comprising 589 cases of male lung cancer in northern Sweden longitudinal data concerning occupations, employments and smoking habits were collected by questionnaires.

Pipe smoking was as common as cigarette smoking and gave very similar relative risk. The pipe smoking cases, however, had significantly higher mean age and mean smoking years at the time of diagnosis than the cigarette smoking cases. In ex-smokers, the relative risk gradually decreased from 5 years after smoking cessation but this decrease was much less pronounced in ex-pipe smokers than in ex-cigarette smokers. High relative risks were obtained for small cell and squamous cell carcinomas. For adenocarcinoma the relative risk was considerably lower but still significantly increased. The population etiologic fraction attributable to smoking was about 80% in this series.

Some occupational groups (underground miners, copper smelter workers, electricians and plumbers) exposed to previously known lung carcinogenic agents had considerably increased odds ratios, which persisted after adjustment for smoking. A slightly elevated odds ratios was observed in a group of blue collar workers potentially exposed to lung carcinogenic agents but this elevation generally disappeared after adjustment for smoking. For two specific subgroups, asphalt and concrete workers and pulp workers, the overrisk persisted after adjustment for smoking. Farmers and foresters had strikingly low odds ratios, which could only partly be explained by their more moderate smoking habits. The population etiologic fraction attributable to occupation was in the reported material assessed to 9 per cent.

Professional drivers had higher average tobacco consumption than non-drivers, which explained the slightly increased crude odds ratio found for the occupational group as a whole. Smoking drivers in an upper age group (70 and over), however, had a high relative risk of lung cancer, while in a lower age group (under 70) no significant increase was found. The results in the older age group suggested a multiplicative effect between smoking and the occupational exposure.

The study clearly verified the increased lung cancer risk in underground miners. An obvious dose-response relation was found with high risk after long time exposure. All analyses concerning underground miners suggested an interaction of a multiplicative type between underground mining and smoking in the causation of lung cancer. The cases of small cell carcinoma among the underground miners had shorter average latency time and in contrast to the other part of the material, shorter average age than the cases with epidermoid cancer.

May, 1986

**Flow cytometry in squamous cell carcinoma of the uterine cervix**

P. STRANG

Department of Oncology, Uppsala University, Akademiska sjukhuset, S-751 85 Uppsala, Sweden.

Flow cytometric measurements of the DNA content and the S-phase rate were performed in a prospective study of totally 172 women with invasive squamous cell carcinoma of the uterine cervix. Thirty-five per cent of the tumors were peri-diploid (1.8–2.2c), of which 21 per cent were diploid (2.0c). In 22 per cent of the cases multiple stemlines were found.

With increasing age a successive shift from a dominance of peri-diploid (1.8–2.2c) and peri-tetraploid (3.8–4.2c) values to marked aneuploidy was found. Aneuploid values were significantly more frequent in post-menopausal than in premenopausal women. The proportion of aneuploid values also increased with advancing stage. Aneuploidy was associated with diffuse tumor growth, vascular invasion and weak or no plasmolymphocytic response of the host. No correlation was found between blood group antigens and DNA patterns. Loss of blood group antigen expression did not influence short-term survival.

The mean S-phase rate for the material was 18 per cent, range 6 to 35 per cent. The mean S-phase rate increased with increasing age and advancing stage. For each of the eight histopathologic parameters according to a malignancy grading system the mean S-phase rate was higher for the histopathologically more aggressive 3-point tumors than for the 1-point tumors, although the differences were not statistically significant.

The predictive value for short-term prognosis (24 months after initial therapy) was evaluated. There was no significant difference in recurrence rate between patients with peridiploid and aneuploid tumors. High S-phase rates, defined as S-phase rate  $\geq 20$  per cent, were significantly associated with early relapses. The significant association prevailed after consideration had been taken to staging. Thus evaluation of the S-phase rate yielded additive prognostic information.

May, 1987

**DNA flow cytometry in neoplasms of the thyroid with special reference to preoperative diagnostic methods and prognostic factors**

H. JOENSUU

Department of Radiotherapy, Turku University Central Hospital, SF-20520 Turku, Finland

Survival rate, prognostic factors, occurrence of DNA aneuploidy as determined by flow cytometry, and the diagnostic and prognostic value of DNA aneuploidy were investigated in thyroid neoplasms. In the material of 200 patients with thyroid carcinoma treated during the 18-year period from 1966 to 1983 at the University Central Hospital of Turku, the crude survival rate at 10 years

after the diagnosis was 74% in papillary, 62% in follicular and 6% in anaplastic carcinoma of the thyroid, and the corresponding figures corrected for known intercurrent deaths were 87%, 66% and 6% respectively. Seventeen of the 18 patients with anaplastic carcinoma died within 24 months after the diagnosis.

By multivariate analysis, the most important prognostic factor in papillary and follicular thyroid carcinoma was age at diagnosis. Tumor penetration beyond the thyroid capsule and follicular histologic type were also independent prognostic variables. Misdiagnosed intercurrent deaths do not explain the adverse effect of age on prognosis.

DNA aneuploidy was found in 24% of the 82 papillary, 56% of the 36 follicular and 57% of the 7 medullary thyroid carcinomas studied. In differentiated thyroid carcinoma, DNA aneuploidy was found to be more common in the elderly, in moderately and poorly differentiated carcinomas, and in tumors infiltrating beyond the thyroid capsule. The probability of DNA aneuploidy did not increase steadily with age, but increased more rapidly after the age of 45, which may partially explain the earlier clinical observation that prognosis in differentiated thyroid carcinoma becomes less favorable in patients older than 45 years at the time of the diagnosis. Patients with aneuploid carcinoma had a less favorable survival rate ( $p < 0.007$ ) as compared with diploid carcinoma in univariate analysis, but in Cox's multivariate analysis DNA ploidy was not an independent prognostic factor.

In all 19 studied cases of large cell or spindle cell anaplastic carcinoma of the thyroid, evidence of DNA aneuploidy could be found, but in 4 (21%) cases only after subserial analysis of all histological material available. Because in paper II all material available was not analysed for DNA content, the above figures of occurrence of DNA aneuploidy in differentiated carcinoma should be regarded as minimum numbers. In anaplastic carcinoma, patients with a DNA index  $> 1.3$  may have a poorer prognosis as compared with those with a DNA index  $< 1.3$ .

Eighteen (27%) of 67 follicular adenomas investigated were aneuploid. In none of the 12 aneuploid adenomas or 40 diploid adenomas followed up for more than 5 years did distant metastases develop after surgical removal of the adenoma. Subserial sectioning of the aneuploid adenomas did not change the histopathological diagnosis. Two of the 20 adenomatous goiters studied were aneuploid, but DNA aneuploidy was not found in non-neoplastic or histopathologically normal thyroid tissue.

DNA flow cytometry can be successfully combined with routine fine needle aspiration biopsy (FNAB). DNA aneuploidy can be used to indicate the presence of a neoplasm. Calculation of the percentage of S- and G2/M-phase cells aids in the differentiation of malignant from benign tumors, because benign lesions rarely contain  $> 6\%$  S-phase cells or  $> 9\%$  G2/M-phase cells. The presence of cell debris, nuclear doublets, or a limited number of aspirated cells may make cell cycle distribution analysis unreliable. Despite these shortcomings, DNA analysis in combination with FNAB was found to improve the diagnostic potential of the FNAB technique. It may lead to increased diagnostic accuracy and deserves further study.

June, 1987

## Notice

The 6th San Rocco symposium for Cancer Research will be devoted to THE RATIONAL USE OF IMMUNOMODULATORS IN TUMOR THERAPY at the University of Pavia on September 8–10 (or 11–12) 1988. Traditionally an invitational meeting, a limited number of proffered *FREE PAPERS ARE*

*HEREBY CALLED FOR*. Abstracts (no form) to be sent to Dr. A. Porwit, Division of Hematopathology, Karolinska hospital, S-10401 STOCKHOLM, SWEDEN, before June 30, 1988. Authors of accepted papers will be awarded free lodging and waived congress fee.