Conclusions:
TP-1 can be given safely daily i.m. to man in single doses of 1 mg/kg.

IFOSFAMIDE (IF) WITH THE UROPROTECTIVE AGENT MESNA (MS) IN THE TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE LUNG

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Ifosfamide has been reported to possess a definite activity in non-small cell carcinoma of the lung (Harrison et al. 1979) although its dosage is limited by urotoxicity. This toxic effect can be effectfully prevented by the concomitant use of the uroprotective agent MS (Scheef 1979). The aim of this study is to define the response rate for higher IF-doses under MS-protection. 24 patients (pts) with advanced, histologically or cytologically proved squamous cell ca. of the lung have been treated with IF 1.8 g/m2 iv daily on 5 consecutive days repeated every 4 weeks. MS was given after each IF-dose at 0^h, 4^h and 8^h either iv (0.36 g/m2) or po (0.72 g/m2). No patient had previous chemo- or radiotherapy, all had objectively assessable tumour parameters. A total of 54 treatment courses has been applied. Reversible gross hematuria has been observed in 5/54 courses (9 %), WBC 1'000 - 2'000/mm3 in 15/54 (28 %) and WBC $<$ 1'000/mm3 in 5/54 (9 %). Other toxic effects included generalized weakness, nausea, vomiting and alopecia. Presently 15 pts are evaluable ($>$12 wks) for response (median age: 63; Karnofski 70 - 100). So far 1 CR and 1 PR (CR+PR = 13.3 %) have been noted for a duration of 213+ respectively 68+ days. Nine pts showed NC after 3 courses and 4 were progressive. Since these preliminary data show some activity of IF in squamos cell ca. of the lung, patient accrual will continue. At the schedule used hemorrhagic cystitis is effectfully prevented by MS while leukopenia is the major dose limiting factor in this previously untreated population.

COMBINATION HORMONOTHERAPY WITH TAMOXIFEN AND FLUOXYMESTERONE IN PATIENTS WITH ADVANCED BREAST CANCER RELAPSING ON HORMONOTHERAPY

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Twenty-six patients were treated with a combination of tamoxifen (TAM) and fluoxymesterone (10 mg t.i.d. each) after disease progression on prior hormonotherapy (HT) (in only two cases prior HT did not include TAM). The patient population was characterized by a high median age (65 years, range 41 to 82 years) and by a high median time interval between diagnosis and entry into the trial (4,5 years, range 10 months to 25 years). Five of 19 patients (26 %) exhibiting a partial response (PR) or stable disease (NC) on previous HT responded to the combination (median time to relapse 7 months, range 3 1/2 to 17+ months). Nine patients (47 %) maintained NC (median duration 5 months, range 1 1/2+ to 9 1/2 months). Six non-responders had subjective improvement with a median duration of six months although two of these patients had objective progressive disease (PD). No response has been seen in seven patients who experienced PD during prior hormonal manipulation or who were non-evaluable for response to prior HT. Median overall survival was 10+ months (range 2 1/2+ to 19+ months): 17+ months for responders (6 to 18+ months), 8+ months for patients with NC (2 1/2+ to 19+ months, all alive) and 10+ months for patients with PD (3+ to 17+ months). The drug combination was well tolerated with virilization, weight gain and hemoglobine increase as predominant side effects. Based on our findings the role of combination HT as a secondary endocrine manipulation in metastatic breast cancer is discussed.

THE MODIFICATION OF EXPERIMENTAL PANCREATIC CANCER BY DIETARY FAT

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Dietary fat has been implicated in the development of human pancreatic cancer. Since the pancreatic cancer model developed by us shows remarkable similarities to pancreatic cancer in man in its biological and morphological patterns, we tested the effect of dietary fat on the induction of pancreatic cancer with an experimental design in order to determine in which phase of carcinogenesis (initiation or promotion) dietary fat is effective. A semisynthetic diet of corn oil was fed at three levels (4.5, 9.0 and 18.0 gm/385 Kcal) to Syrian golden hamsters either before (3 - 8 weeks of age) or after (8 weeks until death) single treatment with a pancreatic carcinogen. The high fat diet enhanced the incidence, multiplicity and size of pancreatic tumors when fed after carcinogen treatment, especially in male hamsters. However, the level of fat fed before carcinogen treatment appeared to have little effect on pancreatic

cancer induction. Benign preneoplastic lesions were found in all groups. The number per animal, however, increased with higher levels of dietary fat, particularly when the diets were fed after carcinogen treatment. Moreover, some carcinogen-treated hamsters also developed acinar cell nodules when fed the semisynthetic diet. This did not occur after being fed the commercial diet. These studies indicate that dietary fat has a promoting effect on pancreatic carcinogenesis.

EXOCRINE PANCREAS ALTERATIONS AND RELATED NEOPLASIA IN SELECTED AUTOPSY MATERIAL

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Eighty three pancreata from autopsy material obtained from the Omaha, USA Veteran's Hospital, and from neighboring county hospitals, were thoroughly examined histologically, and the exocrine and endocrine tissue alterations recorded according to their zonal distribution. Hyperplasia, metaplasia and dysplasia affecting the ducts and the ductules were found in 47 (57 %) and 32 (39 %) of the cases, respectively. Of major interest was the occurrence of squamous cell metaplasia of the ductules in 7 (8 %) of the samples, some showing atypical patterns. Carcinoma in situ of the ducts was found in 1 (1 %) case and that of the ductules in larger numbers (5 %). There were three cases of early cancer, definitely of a ductular origin, and 3 of invasive cancer; 2 of these were clinically known adenocarcinomas and 1 was adenosquamous cancer with metastases of squamous cell components to the lungs. (This case had been mistakenly diagnosed as primary squamous cell cancer of the lung with metastases to the pancreas.) These 3 cancers also seemed to be of ductular origin. Most of these lesions were multifocal, and most were found in the pancreas head. In addition, endocrine tissue alterations were found in many of these samples.
It was concluded that in man, as in experimental animals, the ductular cells are the primary source of pancreatic exocrine cancer, including squamous cell carcinoma. The morphology and the histogenesis of individual lesions will be outlined and the possible reasons for the predilection of pancreatic tumors to occur in the head region will be discussed.

HUMAN MONONUCLEAR CELLS PRODUCE INTERFERON IN COCULTURE WITH TUMOR CELLS

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Ficoll Metrizoat separated, human mononuclear cells (MNC) were induced to produce interferon (IFN) by short term culture on viable or glutaraldehyde-fixed monolayers of the mammary carcinoma cell line, BT20. The amounts of IFN in the supernatants of both types of coculture were comparable for single MNC donors. Interferon production by MNC of 12 normal blood donors resulted in widely divergent IFN titers when cocultured with viable BT20 ($<$10-320 units/ml/24h/10^6MNC). From two donors, MNC were collected four times over a two week period and IFN production was induced on glutaraldehyde-fixed BT20 of the same passage. Again, a wide range of IFN titers were observed, similar to that seen for single donors.
Our results suggest that the IFN producing potential of MNC varies considerably between donors as well as in single donors on repeated bleeding. Furthermore it is clear, that glutaraldehyde-fixed tumor monolayers are useful "solid phase" IFN inducers without metabolic activity and may be employed to determine the IFN producing capacity of human MNC from different sources under constant conditions.

NAUSEA, VOMITING AND CANCER CHEMOTHERAPY

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With modern aggressive treatment approaches to tumor patients nausea and vomiting are an increasing, often dose limiting problem. Before vomiting is attributed to treatment other causes such as brain metastases, gastrointestinal obstruction, endocrine and metabolic abnormalities should be excluded. Pathophysiology of vomiting is incompletely understood. Vomiting is controlled by the vomiting center in the medullary reticular formation. Input from three major sites, i.e. the chemoreceptor trigger zone, the so called periphery and higher central nervous system structures, can produce vomiting. Although most of the anticancer agents do not pass the blood - brain barrier they can induce nausea and vomiting. This is probably due to the fact that capillaries of the area postrema consist of a leaky fenestrated endothelium allowing close chemical communication between blood and the chemoreceptor trigger zone. None of the currently used antiemetics like sedatives, antihistamines, phenothiazines, butyrophenones and metoclopramide is very satisfactory in treating chemotherapy induced vomiting. The better use of currently available agents represents an alternative to the search for new, more effective antiemetic agents. In a phase I