21.

CLINICAL AND EXPERIMENTAL STUDIES ON HUMAN TUMOUR METASTASIS

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Recent investigations in this laboratory, on patients with intractable malignant ascites treated by peritoneo-venous shunts, have shown that metastasis is not an inevitable consequence of shedding of large numbers of tumour cells directly into the bloodstream. They have also confirmed that metastases are not ubiquitous in all organs of the human body even where the tumour cells being infused into the circulation have proven themselves to be capable of forming deposits in some sites. These observations directly corroborate the "seed and soil" hypothesis of Paget (1889) as well as showing that earlier results obtained both in this laboratory, with spontaneous neoplasms, and of elsewhere, with transplantable tumours, are applicable to man.

When heterogeneous tumour cell populations such as those in malignant ascites are infused intravenously it can be assumed that, after mixing in the vortex of the blood, more-or-less representative proportions of metastasis-competent and metastasis-incompetent cells arrive in all organs. It follows that in sites where metastases do not form their growth is either suppressed or at least not encouraged. Recent results in this laboratory suggest that normal organs can inhibit or kill cells from other normal organs, that these effects are mediated at least in part by soluble agents and that cells from some mammary tumours can resist the inhibitory effects of organs in which they commonly form metastatic deposits.

22.

IN VITRO CLONOGENIC GROWTH OF OVARIAN TUMOR CELLS FROM DIFFERENT SITES OF ORIGIN.

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We have had the opportunity to examine the different in vitro growth patterns of six ovarian tumors for which cells from different sites of origin were available. After mechanical (+/- enzymatic) preparation of a single cell suspension, the cancer cells were plated in 35-mm bacteriological petri dishes with 0.9% methylcellulose in growth medium containing 5% foetal bovine serum. The dishes were incubated for 21 days at 37°C in a fully humidified 5% CO2 / air atmosphere Colonies were scored with an inverted microscope using a lower size limit of 60 microns. In the following table site 1 indicates ascitic fluid for tumors A, B, D and E whereas site 2 is either the ovary or a solid peritoneal implant. For tumors C and F sites 1 and 2 stand for left and right ovary, respectively.

	COLONIES per 10^5 CELLS PLATED					
	A	B	C	D	E	F
SITE 1	298	1000	11	5	0	5
SITE 2	112	129	1	60	16	10

The differences observed for the plating efficiency of cells from various sites of origin might include the following: different proportion of tumor versus other cells in the initial single-cell suspension, variable modulation of colony-growth by non-malignant cells in the ascitic fluid, etc. However this variation might also reflect true heterogeneity, as shown by striking differences in drug resistance observed in one of our samples.Similar observations have been reported by several other authors.

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23.

FUNCTIONAL PROPERTIES AND CLONING OF TUMOR-INFILTRATING LYMPHOCYTES FROM HUMAN SOLID TUMORS

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To define functional properties of lymphocytes infiltrating solid tumors (TIL), we have obtained preparations enriched in TIL from enzymatic digests of 20 human tumors (8 breast CA, 6 melanomas, 3 gliomas, 2 esophageal CA and colon CA). The number of recovered TIL per gm wet tumor tissue varied from 2×10^4 to 1.7×10^6. The viability of TIL was consistently > 95%, and T lymphocytes (OKT11+ cells usually constitued > 50% (range 10-100%) of recovered TIL. These cells had a morphology of small lymphocytes and did not express the receptor for IL-2 as determined with monoclonal anti-Tac antibodies by immunofluorescence. Their reponse to PHA was decreased (SI=1.3 ± 0.8) while that of enzymatically-treated control PBL was normal (SI > 50).The degree of lymphocytic infiltrations as determined by immunoperoxidase in cryostat sections of each tumor correlated positively with numbers of recovered TIL.
The TIL were plated in a limiting dilution assay (LDA) in the presence of PHA, allogeneic spleen cells, and TCGF as described by Moretta et al. Normal PBL as well as PBL treated with enzymes were plated in parallel with TIL. Th plates were scored on days 20-30 of culture and frequencie of clonogenic T cells determined. In contrast to control PBL's, TIL consistently had a much lower cloning frequency (0% in 6 TIL preparations, and from 0.5% to 17% in others) Among 200 clones that were tested for functional activitie 27 lysed K562 cells, 38 were cytotoxic to P815 cells in th presence of PHA, and 1 clone lysed allogeneic melanoma cel - significantly fewer than in normal PBL clones.
Our experiments indicate that TIL may have altered functio nal capabilities in comparison to normal PBL.

24.

THE MANAGEMENT OF METASTATIC CANCER

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Most patients with solid tumors will eventually die of widespread metastases. In the last years we have learned to differentiate different prognostic factors, which greatly influence the outcome of therapy in the metastatic stage of the malignant disease. The most important prognostic parameter is the intrinsic chemosensitivity of the tumor, which profoundly affect our management: e.g. in very chemosensitive tumors "debulking surgery" is not useful and can even be harmful (testicular tumors), while in tumors slightly less chemosensitive (e.g. ovarian cancer) debulking surgery influences the outcome of the subsequent chemotherapy.
In most tumors another very important prognostic parameter is the tumor burden. In some tumors (e.g. testicular cancer) we may already differentiate between a "minimal" and a "advanced" metastatic stage and this distinction has already influenced our management. In general, tumor burden has a different impact in tumors, which are hormonoresponsive.
Other prognostic parameters will be discussed. It is important to realize, that the metastatic stage of the malignant disease is not a uniforme situation and that a better phenomenological understanding of the differences in metastases should lead to a better management of the patients.