about cancer and clinical trials is when they are well, in anticipation of the fact that a third may develop cancer in the future. In other words it is time the lay public woke up to their responsibility that if they want to enjoy the benefits from clinical trials of the past they also have a responsibility to enter clinical trials in the future. In return the profession must be prepared to work alongside lay groups in the design of the clinical trials because we are all stake holders in these ventures as well As describing these underlying principles, I also wish to describe the pioneering work of the Consumer's Advisory Group for clinical trials which has risen to this challenge.

1011

Structured patient information in radiotherapy departments in Europe

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Purpose: With the help of ESTRO, we performed a survey to evaluate the present status and means of information given to patients treated by radiotherapy. A short questionnaire was sent to 746 European heads of department with a request to send specific documents used for informing the patient. Within 2 months (March and April 1996), we received 290 answers (39%) and 97 centres sent 298 documents.

Methods: Analysis of the questionnaire and the documents was performed quantitatively with usual statistical methods and qualitatively with a socio-anthropological method of content analysis.

Results: Analysis of the questionnaire shows the major role of the radiation oncologist in giving information and writing documents. The 298 different samples sent from 97 centres represent a wide panel with a booklet of general information (59 booklets/57 centres), practical advice and specific explanations (177 documents/49 centres) and informed consent (36 documents/28 centres). The anthropological study was centred on the way information was given, evaluation of the patient's understanding and qualitative analysis of documents sent.

Conclusion: The high rate of response (40%) of this survey shows the general interest for radiation therapy staffs on patient information. However, this preliminary survey needs to be completed by a study, including the patient's point of view and needs, about the information given.

1012

Training oncologists in communication

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Purpose: To develop, run and evaluate communication skills courses for clinicians in cancer medicine.

Methods: 178 senior clinicians from all medical specialties that deal with cancer patients attended $1\frac{1}{2}$ or 3 day residential courses. The teaching model utilised an experiential learner-centred approach. Emphasis was placed on video-taped role-play with trained actors and structured feedback from facilitators working with small groups of 4.

Results: Few participants had received any communication skills training during their medical education. Giving complex information and informed consent were the primary problem areas for the majority of doctors. Confidence ratings in most communication areas improved significantly post-course ($p < 0.01$). At 3 months post-course, 95% of doctors reported significant changes in their practice of medicine, due to their increased awareness of specific new skills and techniques. 78% of participants had already embarked on new teaching initiatives in communication for junior staff. 97% said that they would 'definitely' recommend the course to colleagues.

Conclusion: Doctors recognised that they were hampered by the lack of adequate communication skills training and will, if the format is acceptable, attend courses. Subjective improvements were reported immediately post-course and were maintained at 3 months. Resources for such educational initiatives are important to help both patients with cancer and their doctors.

1013

Cytoplasmic transduction mechanisms of mitogenic signals

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Two fundamental steps in the cytoplasmic transduction of mitogenic signals are: *i*) activation of tyrosine kinases and *ii*) membrane recruitment of cytoplasmic proteins with function of signal transducers.

The transducers are usually substrates of activated tyrosine kinases and transmit their signals to members of the Ras family of small GTPases. Ras proteins regulate fundamental cell functions such as growth and survival (ras), cytoscheleton organization (rho and rac). On their turn, Ras proteins activate a number of serine/threonine kinases.

The mechanism through which the signals are transmitted from the membrane to the nucleus involve a chain of protein-protein interactions which are mediated by protein modules with specific binding properties: the SH2 and PTB domain, which interact with phosphorylated tyrosine residues; SH3 and WW domains which interact with polyproline regions; the EH domain, which interacts with the NPF motif. Structural alteration of proteins involved in signal transduction may confer proliferative advantages and in fact are frequently found in tumours.

Signal transduction pathways in hematopoietic cells and their activation in leukemias will be discussed.

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Growth factor activated MAP kinases: Mechanism of nuclear translocation and role in growth control

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Many extracellular signals are transduced via the activation of a conserved and specific MAP kinase module: MKKK > MKK > MAPK. Growth factors promote nuclear translocation and persistent activation of p42/p44 MAP kinases during the entire G0/G1 period. Whereas the two upstream kinases of the module, RAF and MKK are exclusively cytoplasmic. MAPKs nuclear translocation is controlled by the strict activation of the MAPK cascade indicating that MAPKs are retained in the cytoplasm via a MAPK- sensitive 'anchor'. Relocation of MKK in the nucleus by expression of an NLS::MKK is sufficient to re-address MAPKs in the nucleus in the absence of mitogenic stimulation. This finding, together with the co-immunoprecipitation of the MKK/p42-44MAPK complex, strongly suggests that MKK serves as a regulatable MAPK cytoplasmic anchor. Finally, we conclude that MAPK nuclear translocation is crucial for the growth factor response since preventing p42/p44MAPK nuclear translocation blunts S-phase entry.

1015

Growth factors and ErbB/HER tyrosine kinases: How do they contribute to malignancy?

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ErbB-2 (also called Neu and HER2) is a cell surface molecule that attracted attention of oncologists because a significant fraction of several types of human adenocarcinomas overexpresses this marker protein. Overexpression was correlated in certain types of solid tumors with poor patient survival and resistance to chemotherapy. Since ErbB-2 has structural characteristics of a transmembrane receptor/enzyme, whose catalytic function is stimulatable by growth factors, initial work aimed at isolating a ligand for this putative receptor. Indeed, by using kinase activation as an assay, we and others isolated a family of novel growth factors, termed neuregulins. However, later studies revealed that ErbB-2 becomes activated by neuregulins only indirectly: these ligands first bind to either ErbB-3 or to ErbB-4, two related tyrosine kinase receptors, which then form heterodimers with ErbB-2. Over the last two years we learned that these inter-receptor interactions are part of an interactive network of signal transduction, that funnels intercellular signaling not only by neuregulins, but also by a large group of EGF-like growth factors. ErbB-2 plays a major coordinatory role in the network, amplifying and diversifying biochemical signals that control cell fate. Our more recent work resolved the molecular mechanism underlying ErbB-2 function: it turned out that all growth factors of ErbB proteins are bivalent; their high affinity arm selects the primary receptor, but the low affinity arm is more promiscuous. Nevertheless, ErbB-2 is the preferred target of the second binding site. Thus, by acting as a low affinity receptor of a group of

approximately 30 different growth factors, and through its potent coupling to the major control route of cell division, namely the Ras-MAP-kinase pathway, ErbB-2 efficiently delivers growth-regulatory signals to epithelial cells, the precursors of carcinomas. Successful blocking of ErbB-2 action may, therefore, prove beneficial in the clinics.

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Specific DNA sequences – A new target?

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Purpose: Agents now exist which can target both the type of damage, and particular DNA sequences with a far greater selectivity than conventional DNA damaging agents. Recent advances will be reviewed.

Methods: Novel DNA sequence selective agents have been rationally designed and synthesised. The novel technique of single strand ligation PCR (ssligPCR) now allows DNA damage by such agents to be mapped at the nucleotide level of single copy genes in intact cells.

Results: As examples oligopeptide based agents will be used to illustrate how sequence selective binding in the minor groove can be altered and enhanced and used to deliver selectively different types of reactive groups. The rational design of sequence selective interstrand crosslinking agents based on the pyrrolobenzodiazepine structure found in natural products such as anthramycin will also be illustrated. Until recently determination of sequence selective binding to DNA was only possible in cell-free systems using highly purified or synthetic DNA. Using ssligPCR binding of sequence selective agents to their target cellular gene sequence can be confirmed. In addition, the sequence selectivity of repair of individual lesions can be measured allowing more precisely the relationship between sequence selective binding and biological activity to be investigated.

1017

Vascular endothelial growth factors and receptors involved in angiogenesis and lymphangiogenesis

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Angiogenesis, the formation of new blood vessels from preexisting ones, and the permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two known receptors Flt1 (VEGFR-1) and KDR/Flk-1 (VEGFR-2). VEGFR-3 does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. We have purified the Flt4 ligand, *VEGF-C*. Transgenic mice expressing VEGF-C under a basal keratin promoter develop a hyperplastic lymphatic vessel network in the skin. VEGF-C is thus a novel regulator of lymphatic endothelia. As VEGF-C is also capable of stimulating VEGFR-2, its effects may extend beyond the lymphatic system, where VEGFR-3 is expressed. Another related novel growth factor, *VEGF-B* was also cloned in collaboration with Dr. Ulf Eriksson's group and found to be co-expressed with VEGF and VEGF-C in heart, muscles and less in other tissues.

Tie, one of the receptor tyrosine kinases we have cloned, is expressed in mouse hematopoietic stem cell fractions and in all studied fetal endothelial cells. Tie is required during embryonic development for the sprouting of new vessels, particularly in the regions undergoing angiogenic growth of capillaries, but it is not essential for vasculogenesis. Our results thus demonstrate an increased complexity of signalling for endothelial cell proliferation, migration, differentiation and survival.

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Functional and proliferative characteristics of neovasculature as potential targets in tumour therapy

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All solid tumours evoke a new network of capillaries. They are usually chaotic, thin walled, poorly innervated and lacking a corresponding lymphatic drainage system. The intercapillary distances are abnormally large and the blood contained within the vessels is nutritionally depleted. The endothelial cells are rapidly proliferating, immature, more procoagulant, sticky and leaky than in normal vessels. The vessels lack musculature and innervation.

As a consequence tumour cells are poorly supplied with nutrition and in large tumours extensive death due to starvation may almost balance the rapid production of new cells. Most tumour cells are totally dependent on a single capillary and have no access to an alternative collateral circulation if that vessel closes. Thus vessel occlusion or collapse can lead to an avalanche of secondary ischemic cell death. If the neovasculature is viewed as a target for anti-proliferative therapy, or for functional alteration e.g. of coagulation or permeability, the differences can be used to cause specific occlusion or destruction of newly formed vessels. This already happens sometimes with hyperthermia, photodynamic therapy, certain cytokines e.g. TNF and some cytotoxic drugs. However, little effort has been made to maximise the indirect effect mediated via vascular damage instead of direct killing of tumout cells. New approaches include targetted antibodies and inducible gene therapy using altered endothelial function to induce clots or blood stasis.

The changes in tissue architecture, especially nutrient gradients, also provide pathophysiological pO_2 and pH conditions which may be viewed as additional helpful factors in targetting either tumour endothelium or the tumour cells themselves.