Pergamon

European Journal of Cancer Vol. 30A, No. 13, p. 1911, 1994

0959-8049/94 $7.00+0.00

0959-8049(94)00380-7

Introduction

N.R. Lemoine and H.C. Hurst

THESE ARE exciting times for those involved in cancer research and for those who care for cancer patients. Our understanding of the molecules and genetic events involved in human tumorigenesis increases daily, with the flood of new reports from laboratories all around the world, and the pace of discovery is truly dazzling. Identification of the *BRCA1* gene involved in inherited breast/ovarian cancer and the mutation repair genes involved in hereditary non-polyposis colorectal cancer (as well as a variety of sporadic cancers) are amongst the most impressive events in recent months. We have moved from appreciation of cancer as a genetic disease to consideration of genetic intervention for the prevention and therapy of the disease in little more than a decade, and it is, therefore, timely to review the whole field of cancer genetics and consider the options and applications for the future.

Inherited predisposition to cancer has been a critical area for research, not only for the understanding of the genetic basis of individual syndromes, but also because discoveries have proved to have implications for the wider spheres of sporadic tumorigenesis, cell cycle control and even morphogenesis. For instance, the identification of *RB1* as the tumour suppressor gene involved in inherited and sporadic retinoblastoma was followed by the observation of its involvement in other types of sporadic tumour, understanding of its role in checkpoints of the cell cycle and insight into its function during embryonic development through transgenic experiments. More recently, familial adenomatous polyposis was shown to be due to inherited mutations in the *APC* gene (whose product associates with catenins and may be involved in microtubule organisation), and loss of function mutations also occur in a variety of other gastrointestinal neoplasms. As well as genes associated with predisposition to site-specific malignancies, other classes of genes whose products are involved in the critical process of maintaining the fidelity of DNA replication and DNA repair, as well as xenobiotic drug metabolism, may be associated with predisposition to a wider variety of tumour types. Elucidation of the mechanisms of these processes is changing the way in which we think about the interaction of the environment and cells at risk of cancer development, and will have a major impact on the development of strategies for cancer prevention.

Although cancer has typically been regarded as a disease of uncontrolled proliferation, it is now clear that failure of the normal controls of programmed cell death are at least equally important. Induction of apoptosis has become a key goal for conventional chemotherapy and radiotherapy, while the natural checks and balances of this system include many potential targets for rational therapy with molecular mimics and informational drugs, such as nucleic acids and their derivatives.

Another aspect of cancer, which is attracting more attention at the genetic level, is the metastatic phenotype. This is a complex field and our understanding is fragmentary, but some general themes have emerged, particularly the central importance of genes encoding cell adhesion molecules and their control circuits.

Genetic intervention for the prevention and therapy of cancer has now become a technological reality and raised important social, commercial and ethical issues which need to be considered at the international level. Such genetic intervention encompasses the counselling of individuals in kindreds affected by cancer predisposition for family and lifestyle planning, *in vitro* fertilisation and pre-implantation diagnosis, and gene therapy. Which, if any, of these are appropriate for individuals with cancer (or at risk of cancer) and how they should be delivered will need to be debated in both the scientific and general communities.

The unprecedented publicity which has accompanied the recent flurry of papers reporting discoveries in cancer genetics and gene therapy reflects the level of excitement generated by the potential power of this technology. We share that excitement and are pleased that the contributors to this special issue have helped us to present a comprehensive and up-to-date perspective.

Correspondence to N.R. Lemoine
The authors are at the ICRF Oncology Group, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, U.K.