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CANCER GENETICS

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Cancer is essentially a somatic evolutionary process. Its fundamental understanding depends on identifying the individual genetic steps in this process and their functional significance, which determines their effective selective advantage. Enormous strides had been made in identifying specific genetic changes in cancer, starting from the dominant oncogenes identified through the oncogenic viruses. Tumour suppressor genes, whose normal function is knocked-out in tumours, have been identified through positional cloning of familial susceptibility genes, or through studies of loss of heterozygosity in tumours, again followed by positional cloning.

It has become clear that tumour growth is a complex balance between the control of cell division and the control of programmed cell death, together with selection for independent growth ability rather than high growth rate. Models of the carcinogenic process which take into account all these various factors can explain the development of benign tumours, and the long lag period of a characteristic of many carcinomas.

Award lecture

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OVARIAN CANCER FROM THE LABORATORY TO THE CLINIC—CHALLENGES FOR THE FUTURE

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Over the past 20 years ovarian cancer has provided a vivid illustration of the successes, failures and challenges for the medical oncologist. During that time the results of treatment have substantially improved; in the West of Scotland for example, for women aged under 55, 3 year survival rates have increased from 36% to 50% (*Lancet*, 337: 611–612, 1991). One reason for this was probably the introduction of effective agents such as cisplatin in the mid-1970s and then carboplatin in the mid-1980s. The recent introduction of taxoids promises further improvement in the future. Nevertheless, the majority of patients still die from the disease; when relapse occurs, clinical drug resistance eventually proves fatal despite further treatment. What are the fundamental mechanisms by which this resistance develops, and what means are available to attempt its circumvention?

Factors involved could be described as pharmacological or cellular. Pharmacological resistance might best be addressed by increasing the doses of the drugs used, particularly cis- or carboplatin. Three years ago we published the results of a randomized trial of 2 doses of cisplatin in 179 patients. At that stage a highly significant median survival advantage for the higher dose (100 mg/m^2) of cisplatin was seen (*Lancet*, **340**: 329–333, 1992). However, a recent updated analysis with a median follow-up of 4 1/2 years shows that the survival curves for the 2 doses have come closer together with 4 year overall survival rates for high and low dose cisplatin of 32.4% and 26.6% respectively. This suggests that a population of drug resistant ovarian cancer cells will eventually emerge despite the use of initial higher doses of cisplatin. A more dose-intensive approach is being pursued with carboplatin, but it seems unlikely that circumvention of drug resistance would be achieved by using higher doses of existing drugs alone.

Cellular factors will probably probe to be crucial; it seems probable that multiple genetic events are involved and these will need to be examined in relevant clinical material. Limited information available so far from sequential tumour biopsies indicates a possible role for increased P-glycoprotein expression, particularly in respect of taxoid resistance; on the other hand a lack of correlation between various detoxifying enzymes, e.g. glutathione S-transferase, and clinical response has been found. Further information is needed on the role of certain oncoproteins, and of the transport proteins, lung resistance protein (LRP), as well as various repair enzymes.

After DNA damage induced by a range of cytotoxic agents has taken place in ovarian cancer cells, the key to sensitivity/resistance may well be the ability of these cells to engage the process of apoptosis. Several genes are involved in control of this process, these include the p53 gene, mutations of which have been linked to cisplatin resistance *in vitro* (*Int. J. Cancer* 55: 678–684, 1993) as well as to a lack of clinical response to carboplatin. A thorough understanding of these mechanisms may lead to the rational development of therapeutic means for circumventing drug resistance in ovarian cancer; clues to these could emerge from parallel studies of the less common, but extremely drug-sensitive ovarian germ cell cancer.